DIASTEMATOMYELIA AND THE KLIPPEL-FEIL SYNDROME

Relationship to Hydrocephalus, Syringomyelia, Meningocele, Meningomyelocele, and Iniencephalus

W. JAMES GARDNER, M.D.
Department of Neurological Surgery

TWO hundred years ago Morgagni[1] was unencumbered with the knowledge that the sac of a meningomyelocele consists of an open neural tube and, therefore, must represent failure of closure of the embryonal neural groove. From his observations, he naïvely concluded that these watery tumors of the vertebrae result from the pressure of fluid descending from the hydrocephalic head through the tube of the spine and pressing the bones asunder. The purpose of this presentation is to reexamine this hydromyelic theory of Morgagni in the light of present-day information, particularly in regard to diastematomyelia, a condition related to meningomyelocele in which the bones likewise are pressed asunder. The appearance of the divided spinal cord in diastematomyelia clearly indicates that this split develops not from failure of closure of the embryonal neural tube but because the lateral plates of this tube, following closure, have been pushed apart as a result of overdistention of its lumen.

Von Recklinghausen,[2] in 1886, certainly was correct when he pointed out that the sac of the meningomyelocele is formed by an open portion of the neural tube. His assumption that this represents failure of closure has since been confirmed, albeit by investigators whose observations were based on this preconceived idea. It is now fitting that Morgagni's disruption hypothesis receive similar consideration.

The Hydromyelic Theory

Immediately after its closure the neural tube of the normal embryo becomes distended because fluid forms within it more rapidly than it can escape through the semipermeable rhombic roof. As a result, the head of a six-week human embryo resembles a translucent bubble (*Fig. 1A, B, and C*). Since this distention affects the central canal of the cord as well as the cerebral ventricles, it follows that both hydrocephalus and hydromyelia are physiologic in embryonal life. The single term *hydrocephalomyelia*, therefore, more adequately describes this physiologic state. This hydrocephalomyelia normally becomes compensated by virtue of increasing permeability of the rhombic roof long before it perforates to form the foramens. Here, however, exists a situation fraught with grave danger to the developing embryo. As Weed[3] pointed out, if for any reason the roof of the fourth ventricle does not become adequately permeable during the critical six to eight week period, fluid will not filter through it in a quantity sufficient to dissect open properly the

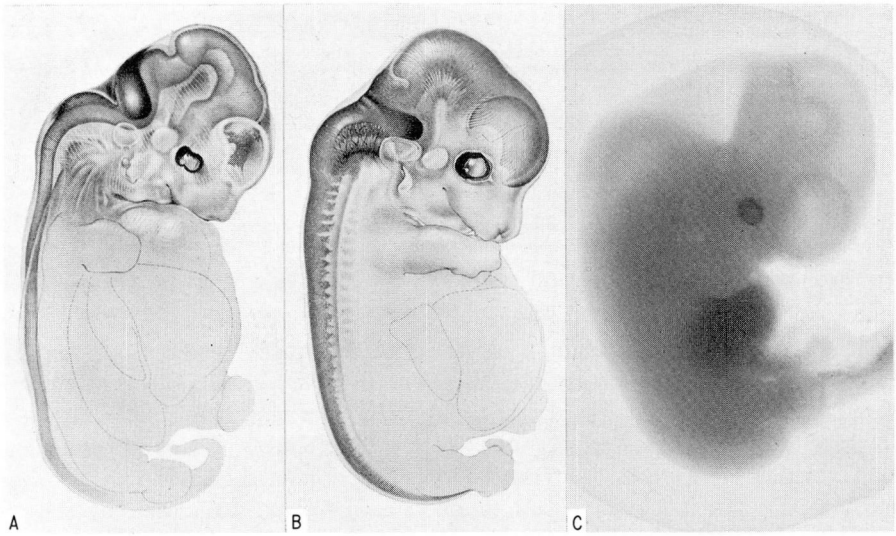


Fig. 1. A, An 18-mm., and B, a 26-mm. pig embryo reduced to the same overall length in order to depict the increased distention of the neural tube in the older embryo. This illustrates the degree of hydrocephalus and hydromyelia that is physiologic in embryonal life. Neural tubes outlined by precipitated crystals of Prussian blue. (Courtesy of The Carnegie Institution of Washington: Weed, L. H. Contributions to Embryology, vol. 5, No. 14, Ins. Pub. No. 225, 1917, 116 p.) C, Six-week human embryo in its amniotic sac, corresponding in development to the pig embryo shown in A. Note the large size of the translucent head. The small globule at the eye level represents primitive forebrain. The bulging prominence between it and the triangular hindbrain area represents the future aqueduct.

developing subarachnoid space. In this case even though the roof subsequently does perforate, communicating hydrocephalus may prevail. Thus in 1917, Weed explained not only the mechanism of congenital hydrocephalus, both obstructive and communicating, and why both forms frequently coexist, but his illustrations also depict why hydrocephalus developing in embryonal or fetal life must be accompanied by hydromyelia. Therefore, if hydrocephalus with hydromyelia is present in the newborn, and particularly if the outlets of the fourth ventricle are found to be unperforated, this represents not some new condition but the pathologic persistence of a state that is normal in the embryo. That these facts are not generally recognized is a striking example of the time lag that so often separates laboratory demonstration and clinical acceptance.

The central canal of the cord takes off from the floor of the fourth ventricle beneath the obex. In the normal adult with patent fourth ventricle foramens the central canal is narrow, if not entirely closed. Contrariwise, in individuals in whom it is dilated, the foramens will be found to be obstructed.[4] This reciprocal relationship suggests that normally the central canal narrows because the foramens open, and, conversely, that it dilates if they do not. This is logical, for if the foramens fail to open, although the mean intraventricular pressure may be normal, the

central canal will continue to receive the full thrust of the ventricular fluid pulse wave generated by the beating of the choroid plexus.[5] On the other hand, when the foramens open, this water-hammer effect is shunted past the central canal into the subarachnoid space. Here its effect, exerted on the outer surface of the spinal cord, will tend to compress the lumen (*Fig. 2*).

Greenfield has described the essential sameness of hydromyelia and syringomyelia, and stated that cases are apt to be assigned to one or the other category

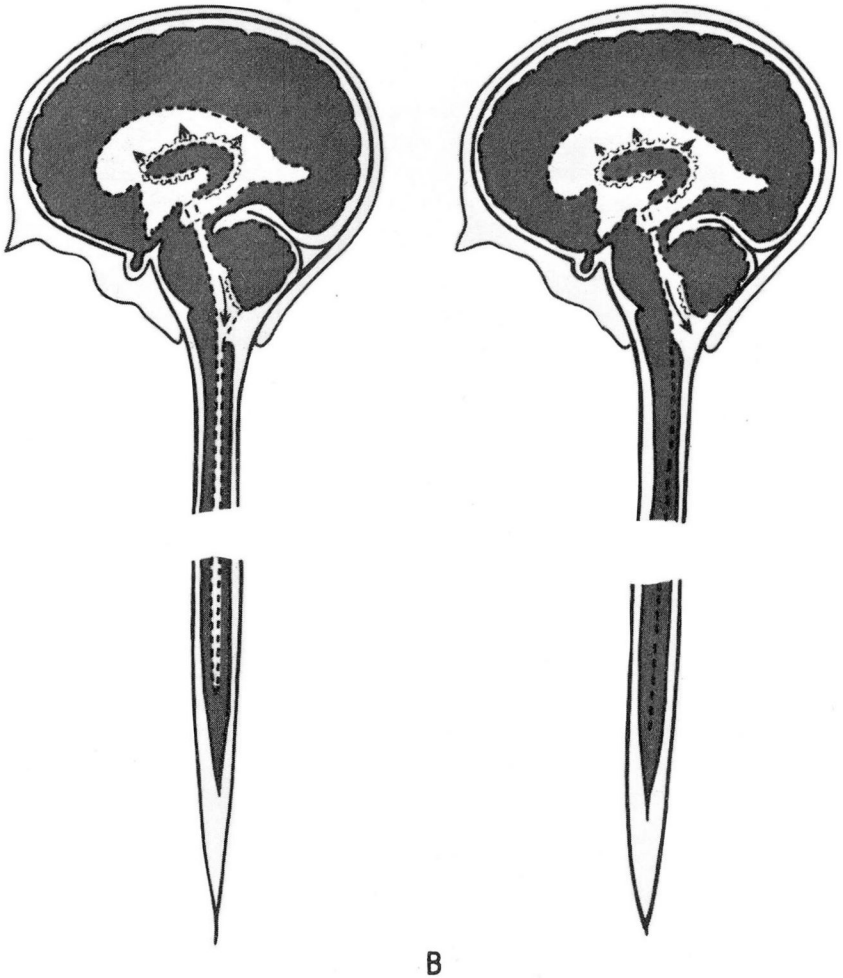


Fig. 2. Cerebrospinal fluid spaces represented diagrammatically. A, Until the foramens perforate, the central canal constitutes a long diverticulum of the fourth ventricle whose lumen receives the pulsations of the ventricular fluid (arrow). B, After the foramens perforate, the ventricular fluid pulse waves are shunted into the subarachnoid space (arrow). The central canal subsequently is compressed to a vestigial remnant.

according to whether or not the cavitation of the spinal cord has produced the typical symptoms of syringomyelia during life.[6] This fact has been confirmed at operation in many cases of clinical syringomyelia.[4] The syrinx is not a slit or cleft as frequently described at autopsy. It is an enormously dilated central canal, distended with ventricular fluid that continues to enter it because the rhombic roof did not perforate as it normally should (*Fig. 3*). This failure is attested by the fact that in many cases of syringomyelia there are membranes enclosing the fourth ventricle foramens that represent persisting portions of the embryonic rhombic roof. In addition, invariably there is a deformity of the hindbrain, generally a mild Arnold-Chiari herniation, although in a few instances, it will prove to be the so-called "Dandy-Walker syndrome."[7] The presence of these hindbrain malformations associated with hydromyelia in adults, and the presence of these same anomalies in infants with meningomyelocele[8] suggest that hydromyelia of adulthood (i.e. syringomyelia) and meningomyelocele of infancy may have a common embryonal origin.[9, 10]

In the Dandy-Walker syndrome, the copious membranes enclosing the dilated fourth ventricle offer histologic proof that the rhombic roof has failed to perforate.[11] In the Arnold-Chiari malformation, histologically similar membranes frequently enclose the foramens but are obscured by their impaction in the hindbrain hernia.[9] Therefore, in the Arnold-Chiari as in the Dandy-Walker malformation, in addition to hydrocephalomyelia, there is anatomic proof that the rhombic roof has failed to perforate.

The clinical diagnosis of syringomyelia may be confirmed in many cases by the roentgenographic demonstration of a dilated spinal canal.[12] In these instances there exists the combination of a distended tube of neural tissue within an expanded tube of bone. This association suggests a cause and effect relationship; namely, that overdistention of the neural tube occurring in embryonal life has resulted in expansion of the developing spinal canal during its soft malleable stage. Holtzer[13] demonstrated experimentally that the diameter of the developing spinal canal is determined by the diameter of the neural tube that it encloses. He states that " . . . migrating precartilage cells respond in a discriminatory and stereotyped fashion to the presence of any neural tissue by maintaining a characteristic distance from the neural tissue. The precartilage cells are deployed in such a fashion that a lumen will eventually be formed in the cartilage whose size is a function of the enclosed nerve bundle." Holtzer did not point out that if lateral displacement of the paired precartilagenous sclerotomes occurs because of hydromyelia, these cell masses may fail to unite, not only posteriorly but anteriorly as well, resulting in combined anterior and posterior spina bifida (hemivertebra) (*Fig. 4*). Holtzer also did not point out that such transverse stretching of the sclerotomes will result in their longitudinal shortening and approximation so that their cell masses may coalesce in the longitudinal plane to form fused vertebrae. Thus, the stretching that

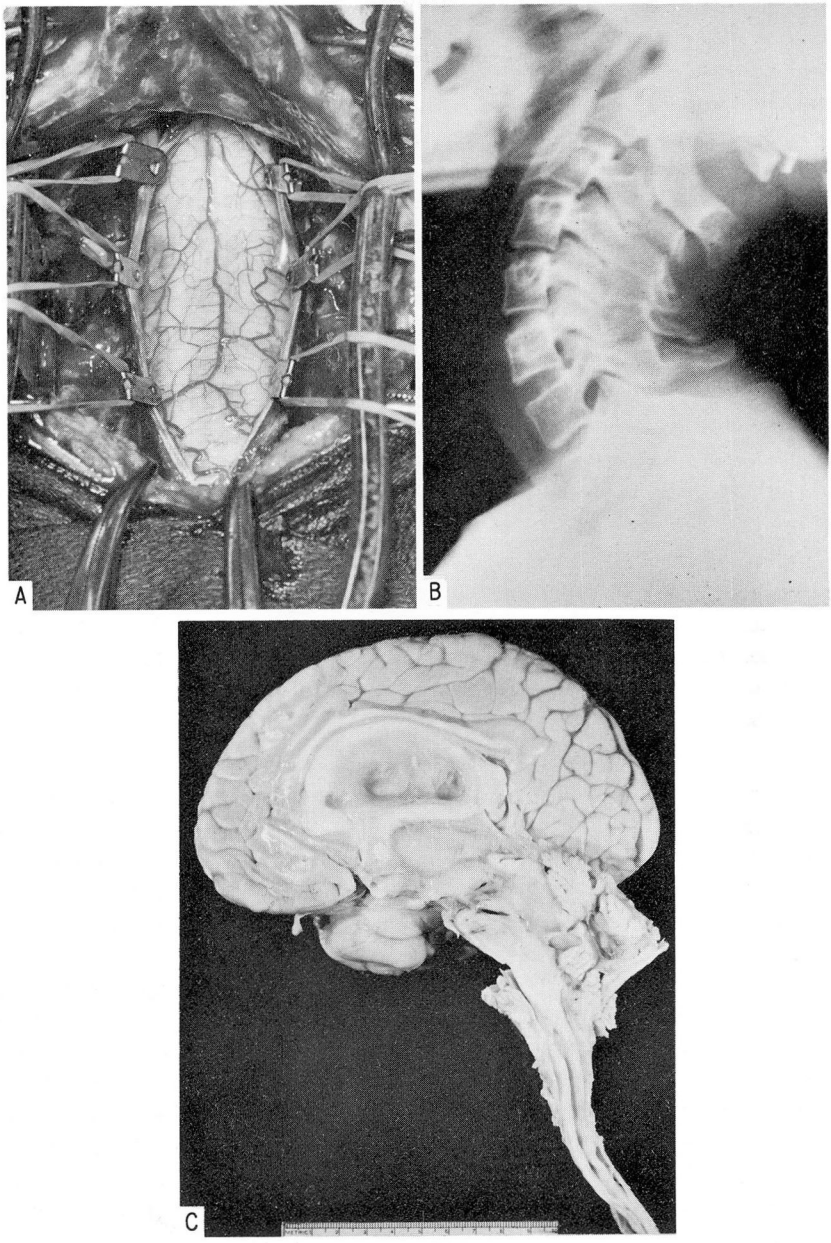
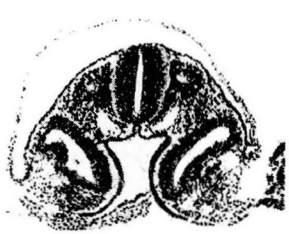
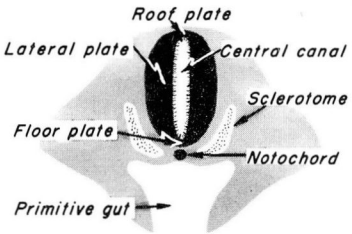


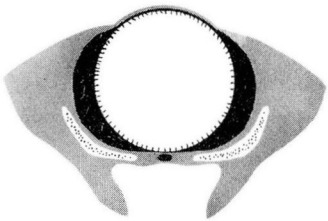
Fig. 3. A, The distended spinal cord of syringomyelia exposed by cervical laminectomy. B, Roentgenogram of same case showing the expanded spinal canal. C, Postmortem specimen of same case. The syrinx has collapsed despite efforts to prevent it by embalming of the body before autopsy. (A and B republished through courtesy of *Cleveland Clinic Quarterly* **26:** 126, July 1959.)



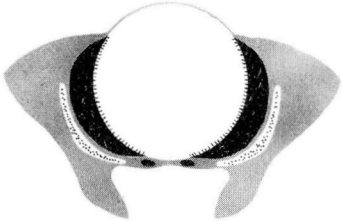
Photomicrograph of
16-somite human embryo



Photomicrograph
shown diagrammatically

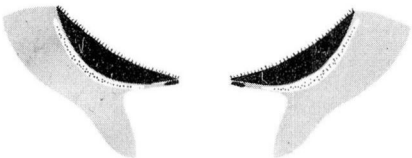


Dilatation of neural tube
First Stage



Separation of roof and floor plates
Second Stage

External rupture
Third Stage



External and internal rupture
Fourth Stage

Fig. 4. Effect of overdistention of the neural tube on the surrounding germ layers. The photomicrograph represents a transverse section of the upper thoracic region of a 16-somite human embryo. The proximity of primitive epidermis and gut to the thin roof and floor plates of the neural tube is well shown. (Courtesy of Sensenig, E. C., Contributions to Embryology. Institution Pub. No. 583, vol. 33, February 28, 1949, Carnegie Institution of Washington, Washington, D. C., Figure 11, Plate 2.)

prevents normal fusion in the transverse axis of the spine may be accompanied by shortening with abnormal fusion in its long axis. Also, as a result of overdistention of the tube, coalescence may occur between neural ectoderm and the neighboring mesoderm, endoderm, and cutaneous ectoderm, with resultant "tethering" of these layers. Such tethering with subsequent incomplete separation may explain the

fragments of displaced glial tissue in the meninges that constitute the glial heterotopia of Cooper and Kernohan[14] in cases of syringomyelia and meningomyelocele.

Ordinary occult spina bifida is limited to the lower lumbar or sacral vertebrae. It is not accompanied by a widened canal, affects only the posterior arch, and obviously is due to inadequate osteogenesis. Applying Morgagni's[1] hypothesis, the pathologic form of spina bifida that occurs at any level, and always is accompanied by a widened spinal canal, is the result of osteogenesis rendered inadequate because the sclerotomes have been pressed apart by an overdistended neural tube. In the pathologic form, the posterior spina bifida may be accompanied by an anterior spina bifida constituting the condition known as hemivertebrae.

A hydromyelic cord within a dilated spinal canal is present in diastematomyelia, in syringomyelia, in tethered cord, in meningocele, in meningomyelocele, in Arnold-Chiari and Dandy-Walker malformations, and in Klippel-Feil (short neck) syndrome. The additional bony anomalies that constitute the Klippel-Feil syndrome (bifida, shortening, fusion, and scoliosis), also may accompany each of the aforementioned congenital conditions and they may affect any portion of the spine.[15] Iniencephalus, the most severe form of the Klippel-Feil syndrome, exhibits the most severe distention of the upper spinal canal usually with tethering of the foregut at this level.[16]

Report of Cases

The individual cases described below were selected to illustrate the anatomic progression from syringomyelia to asymptomatic diastematomyelia, to symptomatic diastematomyelia, to diastematomyelia associated with hydromyelia and meningocele, with hydromyelia and meningomyelocele, with iniencephalus accompanied by meningomyelocele, and finally a "blighted ovum."

Case 1. Syringomyelia

Chief complaint: "All kinds of trouble."

A 44-year-old man had experienced a gradual progression of loss of feeling in the right hand for 20 years, change in voice for 17 years, trouble in swallowing for 10 years, difficulty in walking for five years, and impaired bladder and bowel control for two years. He had burned his right hand without realizing it.

Examination disclosed complete astereognosis in the right hand and loss of appreciation of temperature and pinprick with preservation of touch over the right side of the neck, shoulder, upper chest, and right upper extremity. There was an area of similar dissociated sensory loss over the anterior aspect of the left thigh. There was atrophy of the small muscles of the hands. There were exaggerated reflexes in all four extremities with the presence bilaterally of the Babinski sign. There was impaired function of the right fifth, ninth, and tenth cranial nerves, and nystagmus on lateral gaze. Roentgenograms of the entire spine showed evidence of normal structures except for scoliosis of the thoracic portion. The clinical diagnosis was syringomyelia with Arnold-Chiari malformation.

In an attempt to demonstrate the anticipated connection between an imperforate fourth ventricle and the syrinx, 3 ml. of Pantopaque was introduced into the lateral ventricle and thence maneuvered into the fourth ventricle. Roentgenography showed evidence that the Pantopaque was held in the fourth ventricle except for a fine trickle that passed through the central canal and came to rest within the syrinx opposite the tenth thoracic vertebra (*Fig. 5*).

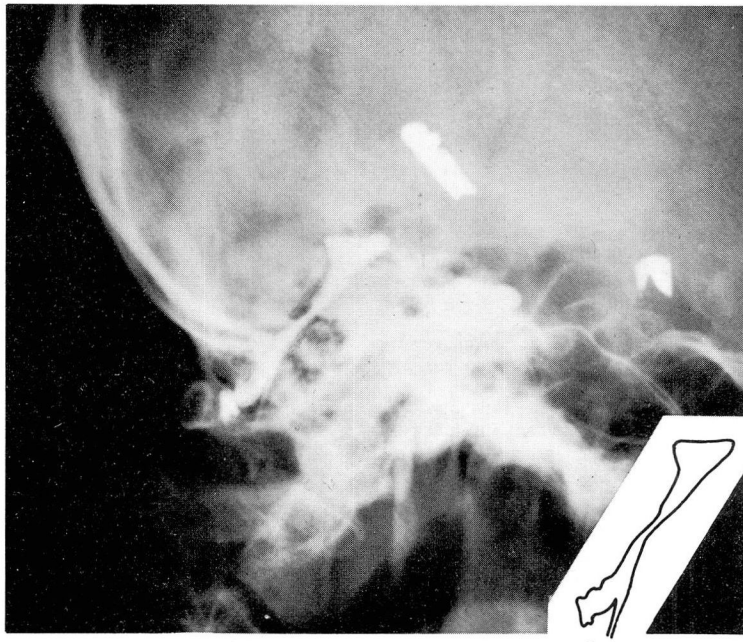


Fig. 5. Case 1. Syringomyelia. Pantopaque ventriculogram with the head erect. The blob of radiopaque material reaching to the level of the first cervical vertebra is trapped between the adherent cerebellar tonsils. Anterior to it a fine line of Pantopaque outlines the narrow upper end of the central canal as it passes down to enter the syrinx. This portion of the central canal is small because of its compression in the hindbrain hernia.

The hindbrain and the upper cervical cord were exposed at operation. The cerebellar tonsils were found to be protruding through the foramen magnum, and were bound firmly together and to the upper cervical cord by a band of dense piarachnoidal adhesions that completely sealed the foramen of Magendie. The second cervical nerve roots pursued an upward course to the foramens of exit, evidence of a downward displacement of the brain stem similar to that seen in the infantile form of Arnold-Chiari malformation. The foramen of Magendie was dissected open by separating the cerebellar tonsils, and a small muscle plug was introduced into the funnel-shaped upper end of the central canal beneath the obex in order to seal it off from the fourth ventricle.

Postoperatively the patient was gravely ill with aspiration pneumonia, and has derived little neurologic benefit other than some improvement in his sensory loss. There has been no further progression of symptoms, however, in the three years that have elapsed since his operation.

Comment. This case was selected from a large personal series of cases of syringomyelia because of the excellence of the radiographic demonstration of the connection between the fourth ventricle and the syrinx. Although in this case the bony changes were limited to scoliosis, other cases, in addition, have shown widening and shortening of the cervical canal, fused vertebrae, spina bifida, hemivertebrae, large skull, and basilar impression. Wells, Spillane, and Bligh[12] described the sagittal diameter of the cervical canal in lateral roentgenograms of 32 patients with the syringomyelic syndrome. They found the canal to be wider than normal in 14 of 17 patients whose symptoms began before the age of 30 years, and in only 1 patient of 15 patients whose symptoms began after the age of 30 years.

Walker[17] described the case of a four and one-half year-old girl in whom a stiff, painful neck developed after a fall, and who three months later was admitted with "complete motor and sensory paralysis below the second cervical dermatome." Anteroposterior roentgenograms showed a marked dilatation of the cervical and upper thoracic spinal canal. At the first thoracic vertebra the width between the pedicles was 4 cm. Operation disclosed spina bifida occulta from the third cervical to the fourth thoracic vertebrae. The spinal cord was tremendously dis-

tended with fluid, and in the middle of the exposed field it was seen to split into lateral halves. Caudally the halves reunited, and the cavity between them continued into the central canal of the cord. Walker's description leaves little doubt but that this was a case of syringomyelia in combination with diastematomyelia.

Case 2. Asymptomatic diastematomyelia

Chief complaint: "Pony tail" between the shoulder blades.

A 17-year-old girl, the first child of healthy parents, was born with a dense growth of long black hair between the shoulder blades. She was otherwise healthy, developed normally and had never shown any neurologic symptoms. The patch of hair between the shoulder blades grew luxuriantly so that the mother shaved it about once a week.

On examination the patient was found to be a healthy, apparently normal girl except for a patch of hairy skin, 3 by 6 in., between the scapulae. There was unsustained nystagmus on lateral gaze. Roentgenograms of the cervical and lumbosacral vertebrae showed no abnormality. Roentgenograms of the thoracic vertebrae disclosed a widened interpedicular distance, —30 mm. at the seventh thoracic vertebra as compared with 25 mm. at the fifth and ninth vertebrae. There was partial fusion and flattening of the bodies of the sixth and seventh thoracic vertebra with a midline bony spur and slight scoliosis. There was anterior and posterior spina bifida of the seventh thoracic vertebra. The roentgenographic interpretation was congenitally deformed midthoracic vertebra with diastematomyelia (*Fig. 6*).

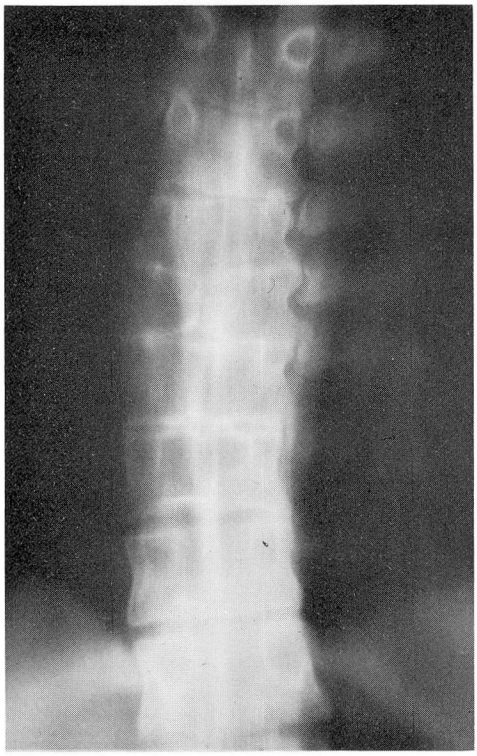


Fig. 6. Case 2. Asymptomatic diastematomyelia. Tomogram showing evidence of widening, shortening and fusion of the involved vertebrae with a poorly visualized bony spur just to the right of the vertebral body cleft.

Comment. This case demonstrates that, though diastematomyelia usually manifests itself by symptoms developing during or before adolescence, the symptoms may appear later or perhaps

not at all, as is true also of syringomyelia. The hairy skin in these cases may represent a phylogenetic reversion due to physical distortion, i.e., stretching of cutaneous ectoderm in embryonal life.

Case 3. Symptomatic diastematomyelia

Chief complaint: Weakness of the right leg.

A five and one-half year-old girl was first noted to have, at the age of three years, an imperfect gait. Subsequently she complained of pain in the right leg and was not able to run as well as other children. Examination disclosed a tuft of hair in the lumbar region. The right thigh and calf were slightly smaller than the left, and the right patellar and Achilles reflexes were absent. A roentgenogram disclosed widening of the spinal canal from the twelfth thoracic to the third lumbar vertebrae. There was a midline bony spur at the first lumbar vertebra. The lamina of the widened lumbar vertebrae were not ossified.

Operation disclosed spina bifida of the twelfth thoracic to the third lumbar vertebrae inclusive. The midline bony spur was fused to the lamina of the first lumbar vertebra and attached to the body of the vertebra by a fibrous stalk. The split dural sac surrounding the bony spur was opened, disclosing a divided spinal cord, the left portion being larger. Embedded in its upper part was a small nodule presumed to be a hamartoma. It was not disturbed (*Fig.* 7). The bony spur was removed and the dura closed both anteriorly and posteriorly. The patient's convalescence was normal, the leg pain was relieved but the gait was unaltered.

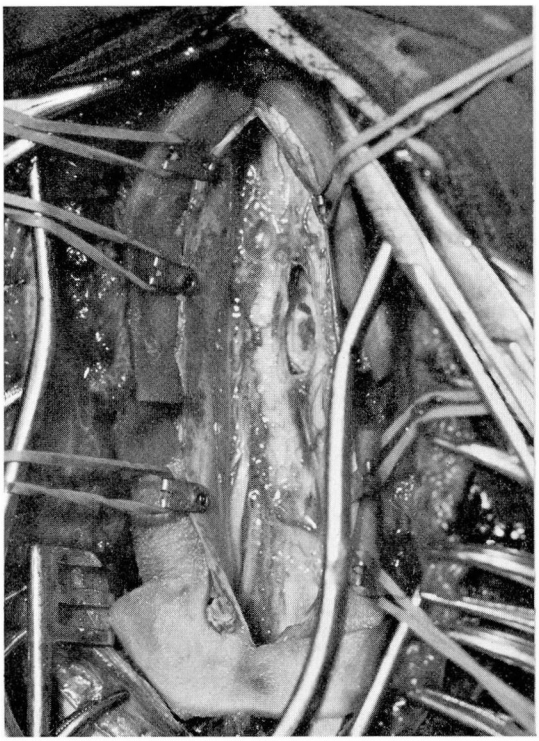


Fig. 7. Case 3. Operative photograph in diastematomyelia. The bony spur is at the first lumbar vertebra. Note the hamartoma in the upper portion of the left hemicord. Because of the tethering, the conus extends well below the level of the spur.

Comment. This case illustrates the usual operative findings in diastematomyelia. Hydromyelia, though undetected at operation in these cases, may be disclosed at autopsy, as shown for example in the case reported by Herren and Edwards.[18]

Case 4. Diastematomyelia with hydromyelia and meningocele

Chief complaint: Weakness of the left leg.

A 12-year-old girl, the younger sister of the patient in case 2, was born with a meningocele in the thoracolumbar area, which had been removed when she was three and one-half weeks old. Her subsequent development was said to have been perfectly normal until two and one-half months before examination when she suddenly noticed that she could not run well because the left foot would turn in and she became aware of numbness of the left leg below the knee. Within a week she was unable to run; the numbness was pronounced, and there was aching in the anterolateral aspect of the left thigh and knee. Roentgenography of the lumbar spine disclosed evidence of diastematomyelia. A pneumoencephalogram showed that air had failed to enter the ventricular system. The subarachnoid spaces were normal except for narrowing of the pontine cistern and a filling defect in the cisterna magna, characteristic of an Arnold-Chiari malformation. The air myelogram disclosed a doubling of the dural sac at the first lumbar vertebra. Because of my interest in the problem, her surgeon, Dr. E. W. Shannon transferred the patient to my service.

Upon examination the patient was found to have scoliosis in the thoracolumbar region. There was a scar where a meningocele had been excised, with some hair surrounding the scar. There was mild atrophy of the left leg with equinovarus deformity, foot drop and some weakness of the left psoas and quadriceps. There was a steppage gait with the left foot, and absence of the left patellar and both Achilles reflexes. There was loss of proprioception in the left foot with impairment of pain, touch, and temperature in the entire left leg, more pronounced in the distal portions. The optic discs were normal; there was nystagmus on lateral gaze; on red glass testing there was mild diplopia on looking straight ahead and downward.

A roentgenogram of the lumbar spine disclosed scoliosis with widening of the interpedicular distances, posterior spina bifida from the eleventh thoracic to the fifth lumbar vertebrae, hemivertebra of the twelfth thoracic vertebra; the smaller half was on the right side and in large part responsible for the scoliosis. There was a midline bony spur at the first lumbar vertebra with partial fusion of the bodies of the twelfth thoracic and the first lumbar vertebrae, with narrow disc spaces above and below. There was decrease in height of the bodies of the twelfth thoracic

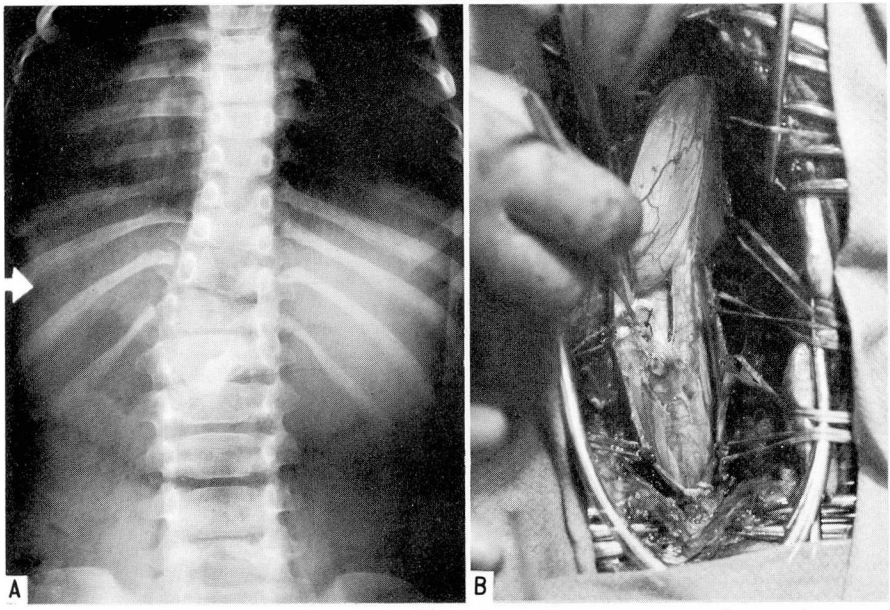


Fig. 8. Case 4. Diastematomyelia with hydromyelia. A, Roentgenogram taken at the age of five years illustrates the vertebral changes more clearly than do later films. B, Operative photograph. The spinal cord above the spur and the left hemicord are hydromyelic. The left hemicord is retracted to disclose the site of the removed bony spur marked by a dural suture.

and the first lumbar vertebrae (*Fig. 8A*). A roentgenogram of the cervical spine disclosed severe widening of the canal. The clinical diagnosis was postoperative meningocele with underlying diastematomyelia, associated Arnold-Chiari malformation and syringomyelia. Operation for removal of the midline bony spur was advised.

Thoracolumbar laminectomy disclosed a wide spinal canal with a midline bony spur at the first lumbar vertebra fused to the overlying lamina. A divided dural sac surrounded the spur. The dura was opened, revealing above the split, a tremendous hydromyelia that involved also the left hemicord. The right hemicord was not obviously distended with fluid (*Fig. 8B*). The midline bony spur was removed, and microscopically proved to be dense bone with no cellular inclusions. A small nodule attached to the cord at the upper level of the diastematomyelia was excised and proved to be a dermoid cyst. The anterior and posterior incisions in the dura were then closed so as to reconstitute a single dural sac.

The postoperative convalescence was satisfactory. The aching in the left thigh and knee and the sensory loss in the left lower leg were relieved immediately. She was discharged on the eleventh postoperative day, at which time the left leg was definitely stronger than before operation.

Comment. Colorless fluid aspirated from the hydromyelic cord at operation in this patient had a total protein content of 23 mg. per 100 ml. while that of the lumbar fluid was 47 mg. per 100 ml. This ratio, comparable to that normally existing between ventricular and lumbar fluid, also may be demonstrated between the fluid of a syrinx and the lumbar fluid of the adult with typical syringomyelia.[4]

This patient was the younger sister of the patient in case 2. Her chromosome count was 46. The karyotype was that of a normal female, 46 XX. A number of broken chromosomes were seen for which there was no explanation. This study was interpreted as showing no specific abnormality.

In the surgical treatment of a simple meningocele, as had been true in this case, the surgeon seldom is able to inspect the spinal cord through the narrow neck of the sac. Doran and Guthkelch,[19] however, demonstrated diastematomyelia in five cases of meningocele, and stressed the importance of a proper exploration of the spinal canal in every case of spina bifida subjected to operation. They did not mention hydromyelia in their patients, but it has been an almost invariable finding at necropsy in cases of diastematomyelia.

Case 5. Diastematomyelia with hydrocephalus, hydromyelia, meningocele, and meningomyelocele

Chief complaint: Two watery tumors of the vertebrae.

A full-term infant with a large meningomyelocele in the upper lumbar region and above that a separate smaller meningocele covered with normal skin, had partial paralysis of the legs, bilateral clubfoot, and enlargement of the head. A roentgenogram disclosed widening of the entire spinal canal, most pronounced in the lumbar region, with hemivertebrae of the entire thoracic spine.

A repair of the meningocele and meningomyelocele was performed. This operation disclosed a midline bony spur located between the meningocele and meningomyelocele, separating the dural sac and cord into halves. The right hemicord together with the entire cord cephalad to the spur was notably hydromyelic; this hydromyelia became increasingly severe as it progressed caudally to where it constituted the sac of the meningomyelocele (*Fig. 9A and B*).

Comment. This meningomyelocele was the type known as a syringomyelocele, that is, a dilatation and posterior bulging of the central canal. A similar case of hydromyelia progressing to diastematomyelia and syringomyelocele was described and illustrated by Humphrey[20] in 1886. In the cases in which hydromyelia progresses to diastematomyelia, the appearance suggests that the splitting of the cord is the result of hydromyelic distention. A similar cause-and-effect relationship is even more obvious where hydromyelia progresses caudally to syringomyelocele, as it did in this case.

Case 6. Iniencephalus with meningomyelocele

A stillborn female fetus of 30 weeks' gestation was delivered by cesarean section; it was a younger sibling of the patients in cases 2 and 4. The enlarged head was severely dorsiflexed with the occiput resting at about the level of the first lumbar vertebra. There appeared to be no neck. The skin of the chin joined that of the anterior chest wall, and the skin of the occiput passed over to that of the lower back which was the site of a meningomyelocele.

Autopsy disclosed tetralogy of Fallot, atrial septal defect, closing ductus arteriosus, atresia of the left diaphragm, nonrotation of the intestine, meningomyelocele and internal hydroceph-

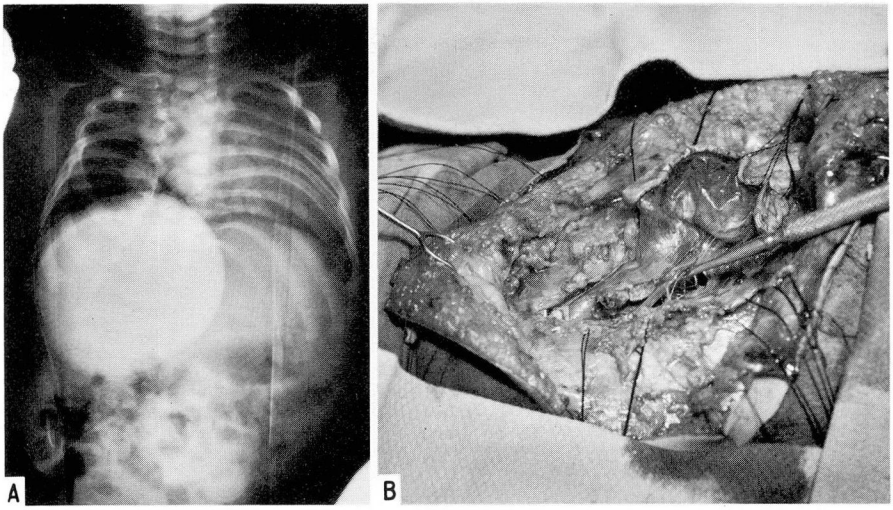


Fig. 9. Case 5, A, Roentgenogram revealing evidence of bilateral hemivertebra of the thoracic spine. The round pale area represents the meningomyelocele. The meningocele is poorly outlined above it. B, Surgical exposure, case 5. Patient's head is toward the left. A spatula is elevating the left hemicord and stretching its nerve roots. The end of the instrument touches the midline bony spur. Note how the hydromyelic right hemicord expands to constitute the sac of the syringomyelocele, its skin edge retracted by sutures. The pale area at the upper end of the exposed hydromyelic cord indicates the level of the neck of the meningocele.

alus. The brain was soft, and the gyri quite small. The cerebellum could not be positively identified and was presumed lost during removal, although pons and brain stem were present. The lateral ventricles were dilated and formed practically one cavity with the third ventricle. The average thickness of brain tissue was 1 cm. The aqueduct of Sylvius was not visible.

There were 12 ribs on each side, but 12 thoracic vertebrae could not be identified because of fusion and shortening of that portion of the spine (*Fig. 10A and B*). The cervical spine and the spinal cord were not described. The autopsy protocol and roentgenograms in this case were made available through the courtesy of Dr. James E. Slivka who also had attended the previous births in this family.

Comment. Gilmour[21] had identified iniencephalus as a severe form of the Klippel-Feil syndrome in which the essential osseous defect is a tremendous distention of the upper spinal canal with combined anterior and posterior spina bifida (*Fig. 11*). In these cases attention has been focused on the obvious vertebral defects at the expense of the central nervous system, which generally is poorly preserved because of intrauterine death. Hydrocephalus, hydromyelia, diastematomyelia, meningomyelocele, hindbrain hernia,[22] and cranioschisis,[16] however, have all been described in association with iniencephalus.

Case 7. Blighted ovum

During her fourth pregnancy, the mother of the patients in cases 2, 4, and 6, underwent a dilatation and curettage performed by Doctor Slivka for an incomplete spontaneous abortion. No fetus was found, and the diagnosis of "blighted ovum" was made. In view of the progression in each of the three previous pregnancies, it is suspected that this embyro may have died of an even more serious defect, perhaps cranioschisis.

Discussion

The above cases, four of which occurred successively in one family, are cited as examples of increasingly severe anatomic expressions of a single embryonal defect; namely, inadequate permeability of the rhombic roof. Relative to this theory

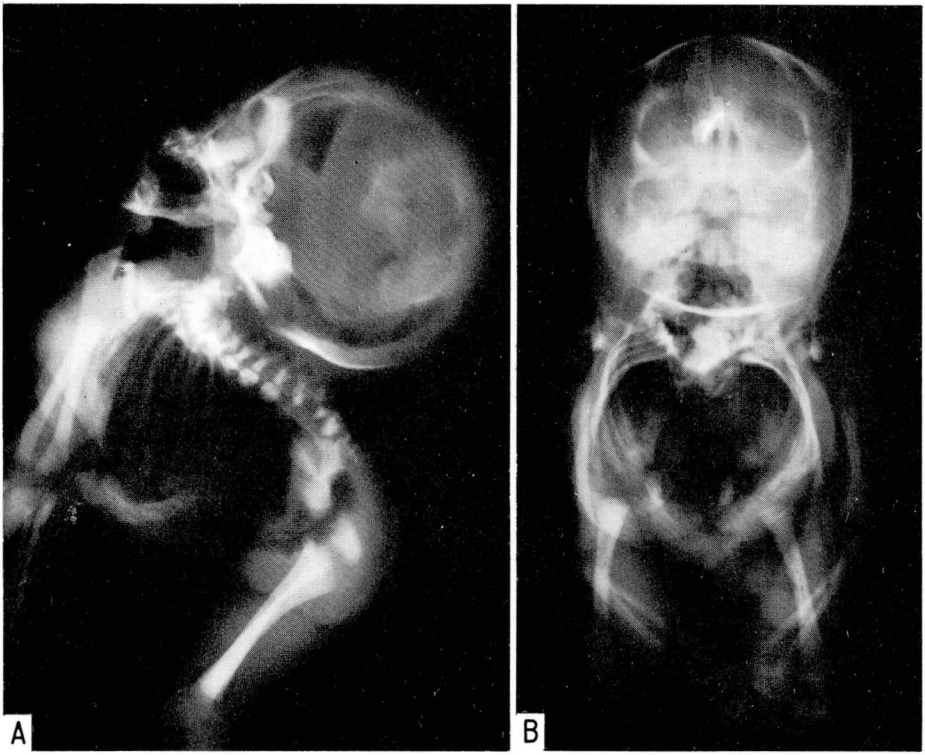


Fig. 10. Case 6. Stillborn sibling of cases 2 and 4. Iniencephalus with meningomyelocele. A, Lateral view illustrating the severe shortening of the spine and hyperextension of the neck. The dorsiflexion is due to greater shortening posteriorly than anteriorly. B, The tremendous dilatation of the cervical and upper thoracic spine in the anteroposterior view gives one the impression of gazing down a funnel.

it is important to recall that the central nervous system, arising from ectoderm, is composed almost entirely of neuroepithelium. It has been suggested[23] that the virtual absence of interstitial spaces in the brain is a reflection of the fact that the primary function of epithelium, wherever it occurs, is to prevent the passage of interstitial fluid. The imperviousness of the brain to interstitial fluid has been advanced to explain the phenomenon of the blood-brain barrier* and also of the blood-cerebrospinal fluid barrier.[23] Because of its ectodermal origin, the developing rhombic roof necessarily must alter its primordial epithelial character in order to allow fluid to pass; that occasionally it may "forget" to do so at the proper moment, is rather to be anticipated. Considered from this viewpoint, one no longer wonders at the frequency of congenital hydrocephalus but rather at its relative rarity.

**It is an interesting coincidence that trypan blue, one of the first dyes employed to demarcate the blood-brain barrier, is one of the most effective agents in producing experimental hydrocephalomyelia and myeloschisis.*[24]

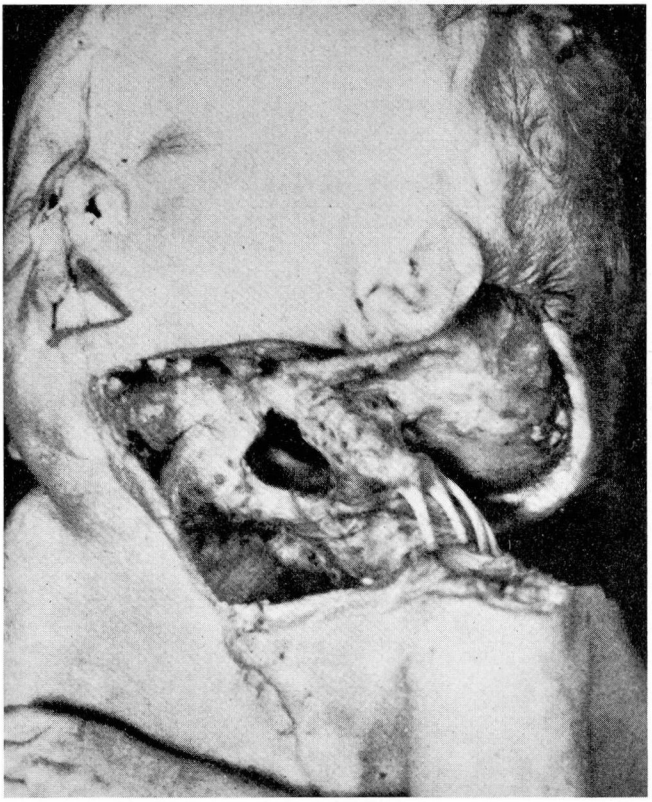


Fig. 11. Case of iniencephalus with the pharyngeal structures removed so as to disclose the anterior spina bifida. The halves of the divided vertebra bound a roughly circular opening through which are seen the base of the skull and the enlarged foramen magnum. An expanded portion of the spinal cord occupied this opening. (Courtesy of author and publisher—Dodds, G. S.: Anterior and posterior rhachischisis. Am. J. Path. **17:** 861-872, Nov. 1941).

To produce a normal embryo there must be extremely accurate time relationships between closure of the neural tube, onset and rate of formation of fluid within it, and onset and rate of attenuation of the rhombic roof. In hydrocephalomyelia of pathologic degree these relationships obviously have been disturbed. Now let it be assumed that a teratogenic agent such as trypan blue administered to the pregnant rat, instead of retarding closure of the neural tube as is generally believed, should hasten it. Other factors remaining the same, this would lengthen the time interval between closure of the tube and the attenuation of the rhombic roof, and thus lead to overdistention. Trypan blue also may act by delaying the onset or by slowing the rate of differentiation of the rhombic roof or by advancing the onset or accelerating the rate of fluid formation. In any event, any of these mechanisms could aggravate the physiologic distention of the neural tube and produce a bulging syringo-

myelocele at the most yielding part. The latter, proceeding to rupture, would be followed by immediate collapse of the overdistention.[25] The time interval between bulging and rupture could be so brief, and the bulging wall so delicate as to make its detection unlikely: thus the belief that myeloschisis is due to failure of closure rather than to rupture after closure. This rupture theory is supported by the work of Fowler[26] who produced the typical picture of myeloschisis in the chick embryo by slitting open the roof plate of the closed neural tube.

To pursue this theory further, it is obvious that while a severe degree of embryonal hydrocephalomyelia would eventuate in rupture, a mild or moderate degree would tend to become compensated by the same mechanism that results in compensation of the physiologic degree. On the other hand, once rupture has occurred, the process of compensation will be interrupted because the hydrostatic dissecting force no longer exists.

The final picture produced by pathologic overdistention of the neural tube will be determined by the somite stage at which it occurs, by its severity, and by whether, when, and to what degree it becomes compensated (*Fig. 12 through 14*). If overdistention is early and severe, a bulging hernia of the forebrain (encephalocele) may develop and progress to rupture (cranioschisis, exencephalus, anencephalus). The embryo then dies and is resorbed (blighted ovum). Under other circumstances, the overdistention may be most severe at the foramen magnum and adjoining cervical portion of the neural tube, and the fetus dies in utero of iniencephalus. In this case the severe overdistention of the cervical portion of the neural tube may result in coalescence of the underlying germ layers with tethering of the gut, or in some instances, actual perforation so that the neural and gut tubes communicate. The tethering interferes with the normal descent of the foregut, so that a portion of it remains in the chest cavity and interferes with the development of the left leaf of the diaphragm. The entire hindbrain may be herniated through the enlarged foramen magnum into the enormously dilated cervical canal as in Chiari's type III malformation.[27]

Occurring later, the pressure of fluid descending in the tube of the spine may cause a posterior herniation of the central canal (syringomyelocele), followed by external rupture (myeloschisis), and the infant may survive with a meningomyelocele.* The rarity of syringomyelocele as compared with meningomyelocele in the newborn, may be a reflection of the delicate and fleeting character of this bulging stage in the embryo. In and above the meningomyelocele there frequently is diastematomyelia, and above that, hydromyelia, hydrocephalus, and hindbrain hernia.[28]

If the development of the arachnoid villi has been retarded because of an obstructive hydrocephalomyelia, but the rhombic roof becomes permeable before this eventuates in rupture, communicating hydrocephalomyelia will result. The pressure of the fluid in the spinal subarachnoid space then may cause the meninges

**Overdistention at the lumbar level, may result in distortion (dysplasia) of the preaxial mesoderm, and thus account for the associated maldevelopment of the kidneys.*

(rather than the central canal) to bulge posteriorly. The contained subarachnoid fluid however is able to continue its process of dissection so that rupture does not occur; the hydrocephalus becomes compensated and the infant is born with a meningocele covered with normal instead of cicatrized skin. The meningocele may be accompanied by diastematomyelia resulting from yielding of the attenuated roof and floor plates because of the preexisting internal hydrocephalomyelia. There may be an associated hindbrain hernia.

If the internal overdistention is more transient, it may compensate after splitting the neural tube without causing a meningeal hernia. If the splitting includes the notocord, this likewise will be double. Depending on the time and degree of com-

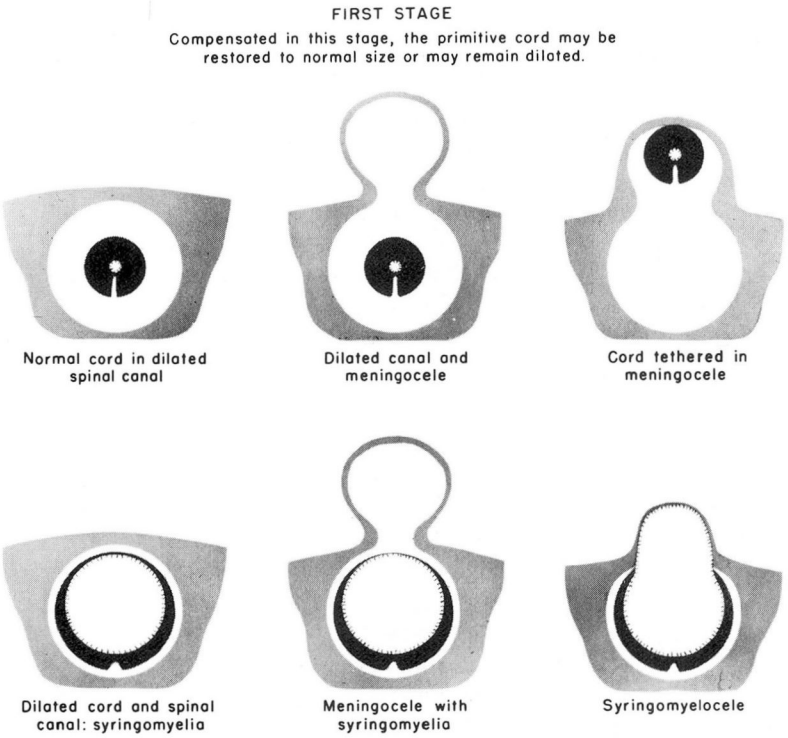


Fig. 12. If overdistention of the neural tube becomes compensated early in stage one (see *Figure 4*), it is possible that both the primitive cord and the spinal canal may be restored to normal size. If the spinal canal remains dilated, the spinal cord may be restored to normal within a dilated dural sac as in the upper row of diagrams, or the spinal cord may remain distended and fill the dural sac as shown in the lower row.

Stage 1. Stretching and attenuation of the thin roof and floor plates cause similar changes in neighboring structures. The roof plate, having less reinforcement, stretches more so that the developing posterior columns are attenuated. Compensated at this stage, a hydromyelic cord within a distended bony canal may result, and symptoms of syringomyelia will appear in adulthood.

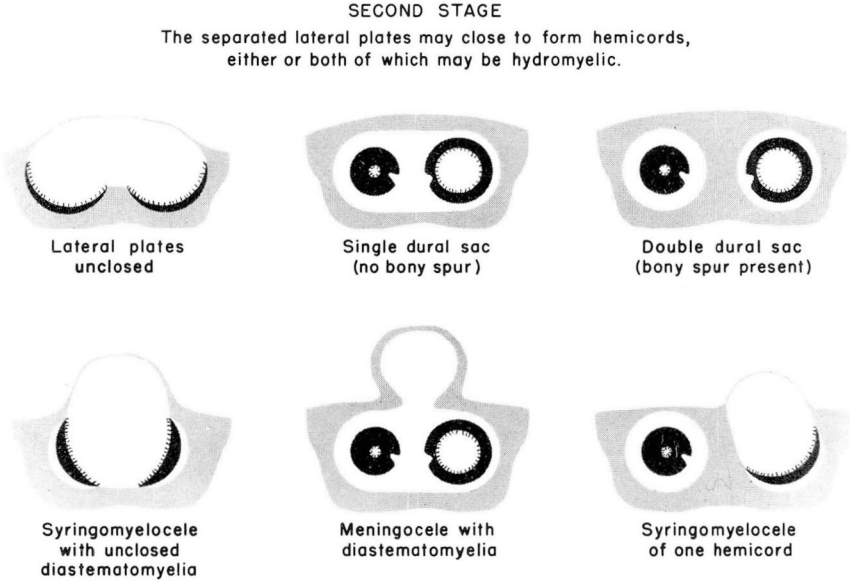


Fig. 13. If overdistention of the neural tube becomes compensated in stage 2 (see *Figure 4*), any of these situations may prevail.

Stage 2. Yielding of roof and floor plates allows the lateral plates to separate from one another. The roof plate yielding more allows the lateral plates to open like a book. This may spread the sclerotomes so widely as to prevent their subsequent union; the notochord also may split. Compensated at this stage, diastematomyelia will result with occult spina bifida. Symptoms appear in adolescence.

pensation, each lateral plate of the neural tube may remain open as in the case of Walker described above or they may close with the formation of two central canals, one or both of which remain dilated in varying degree as in case 4 described above. In accomplishing this closure, the ependyma exhibits its primordial epithelial function of sealing off the interstitial spaces by growing until it meets itself. The anterior fissures of two imperfect cords face each other because of the almost 90-degree rotation of the lateral plates incident to the process of splitting. In diastematomyelia the symptoms usually become apparent in adolescence, and here again there may be a hindbrain hernia as was demonstrated at encephalography in case 4.

If the overdistention compensates before such splitting, the hydromyelia may express itself in adult life as syringomyelia, or may remain asymptomatic to constitute an incidental finding at necropsy. Operation in syringomyelia will disclose in every instance, incompetence of the foramens of the fourth ventricle, usually because of a hindbrain hernia.

Finally, the overdistention may compensate so quickly and adequately that the primitive spinal cord is restored to normal size, but the sclerotomes, having taken a cartilagenous set, will go on to form a dilated canal. The spinal cord, as a result

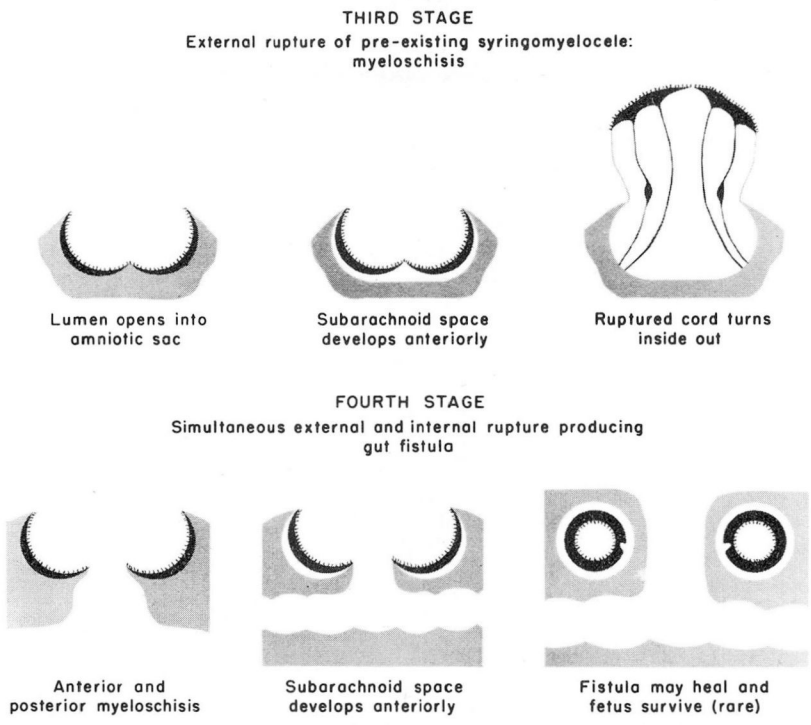


Fig. 14. If overdistention of the neural tube fails to compensate (see *Figure 4*), either posterior myeloschisis or combined anterior and posterior myeloschisis may result. The diagrams in *Figures 12* through *14* obviously do not represent all of the possibilities.

Stage 3. Rupture through the roof plate into the amniotic sac results in myeloschisis, the anatomic forerunner of meningomyelocele. Hydromyelia and diastematomyelia frequently are present cephalad to the rupture.

Stage 4. Rupture through both roof and floor plates results in anterior and posterior myeloschisis with a gut fistula occurring between the separated lateral plates. The result is death in utero.

of fusion of germ layers during the period of overdistention, may be tethered in its dilated canal as in the case described by Walker.[17] Hindbrain hernia is a common accompaniment of a tethered cord.

Innumerable case reports attest to the fact that cephalad to a meningomyelocele the cord frequently is diastematomyelic, and above that there is a progressively decreasing degree of hydromyelia. This can be accounted for by the fact that at the time of the rupture the somites above are progressively more mature, and therefore the results of the overdistention are progressively less devastating. Since closure of the neural tube begins in the cervical region and progresses in a zipper-like fashion both cranially and caudally, the seam is apt to be more yielding at the two ends.

Stretching of living tissues stimulates cellular reproduction. This is most obvious in epithelial structures such as skin, and particularly in growing subjects. Therefore, an increased rate of reproduction of embryonal neuroepithelium would be anticipated from a distention of the neural tube. Thus the increased bulk of nervous tissue at and above the site of a myeloschisis which Barry, Patten, and Stewart[29] considered to be the cause of *failure of fusion*, may represent a cellular response to stretching preceding a *rupture*.

When overdistention does not eventuate in rupture, the developing neural pathways will find their accustomed way around the overdistended lumen. Therefore, the infant with hydrocephalus, hydromyelia, or even diastematomyelia, may exhibit no neurologic deficit. In this case, however, the increased length of the encompassing fiber tracts will contribute to an increased bulk of nervous tissue in the expanded portion. In congenital hydrocephalus, therefore, the degree of ventricular dilatation is not an index of atrophy. As a matter of fact, in congenital hydrocephalus, the brain may be heavier than normal.

Compensation of the physiologic degree of hydrocephalomyelia depends upon attenuation, not anatomic perforation of the rhombic roof. Compensation of a pathologic degree of overdistention likewise may be complete without anatomic perforation of the rhombic roof. However, in this case, although the mean pressure is normal, the ventricular fluid pulse waves throughout life are imprisoned within the lumen. The brain tissue, surrounded by rigid skull, resists this water-hammer effect and funnels it toward the central canal. The central canal, lacking the external reinforcement of rigid walls, responds by stretching and by progressive neuronal atrophy and gliosis. As is true in the hydrocephalic ventricles, the distended central canal may lose its ependymal lining over large areas or may develop a diverticulum that parallels its lumen. Because of the mildness of the hydrodynamic forces, the dilatation is slow, accounting for the long-delayed appearance of neurologic symptoms in syringomyelia. In diastematomyelia the symptoms appearing generally in adolescence are attributed to traction on the tethered cord because of disparity of growth between the cord and the spine.

The Hindbrain Deformity

Any theory that attempts to explain the above anomalies also must explain the deformity of the hindbrain which so often accompanies them. In the Dandy-Walker malformation, attributed to failure of opening of the foramens of Magendie and Luschka, the bulging membrane of the unperforated rhombic roof is obvious. It is seldom pointed out that similar membranes enclose these foramens in the impacted hernia of the Arnold-Chiari malformation, which suggests that it is due to the same cause.[10] In discussing the so-called Dandy-Walker syndrome, Brodal and Hauglie-Hanssen,[30] and recently Portugal and Brock,[31] have objected to statements attributing it to "failure of opening of the foramens of the fourth ventricle" because the shape of the cerebellum proves that the deformity must have developed long before

these foramens were due to perforate. However, these authors overlook the fact that the difference between a permeable and a perforated membrane is merely the size and the number of the holes.[32] Since the permeable rhombic roof in the embryo serves in place of these perforations, inadequate permeability is the equivalent of failure of opening of the foramens and "embryonal atresia of the fourth ventricle" is a properly descriptive term.[7, 32]

In the Dandy-Walker syndrome the posterior fossa is too large for the hindbrain because the transverse sinus with its attached tentorium is too high.[33] In the Arnold-Chiari malformation the posterior fossa is too small because the transverse sinus is too low.[34] The anlage of the transverse sinus originates far rostrally at about the sixth week and is pushed posteriorly by the expansion of the primitive forebrain. As shown by Padget's[27] studies, this excursion is fairly well completed by the twelfth week. The final position of the posteriorly migrating transverse sinus in the embryo is determined by the relative expansion of the forebrain as compared with that of the hindbrain. During the period of migration of the primitive transverse sinus, the intracranial contents consist largely of ventricular fluid contained by a relatively thin layer of cerebral tissue. Therefore, it is an increase of fluid volume rather than brain volume that provides the force responsible for this migration.

During intraamniotic life, the pressure within the cerebrospinal fluid system is exerted equally in all directions. Therefore the relative expansion of the forebrain as compared with that of the hindbrain is determined not by differences in intraluminal pressure but by the relative yielding qualities of the coverings of the forebrain and of the hindbrain. In a hydrocephalic embryo the covering of the forebrain is apt to yield even more than in the normal. The resulting overexpansion of the forebrain, if severe, will cause a severe reduction in the size of the posterior fossa, and therefore the cerebellar hernia developing early will consist of the earlier developing vermis. If the size of the posterior fossa is reduced to a lesser degree, the hernia developing later will consist of cerebellar tonsils and resemble an ordinary pressure cone.

If, in a given case, the coverings of the hindbrain happen to be more yielding, the resulting overexpansion of this portion of the neural tube will prevent adequate posterior migration of the transverse sinus. This will result in an abnormally large posterior fossa as seen in the Dandy-Walker malformation.

At this point it is pertinent to recall that the title of Chiari's[35] original article was "Concerning Changes of the Cerebellum Because of Hydrocephalus of the Cerebrum." In this paper published three years before Arnold's[36] inadequate account of a single case, Chiari's type I deformity of the hindbrain was a pressure cone of the cerebellar tonsils. In his type II, subsequently referred to as "Arnold"-Chiari malformation, he described herniation of the vermis, fourth ventricle, and medulla through the foramen magnum, posterior bulging of the medulla, upwardly directed nerve roots, *hydromyelia* and *diastematomyelia*. His type III almost certainly was a case of iniencephalus in which the entire cerebellum was displaced through the large foramen magnum into the dilated and bifid cervical canal.

The Hydrodynamic Mechanism

Increased pressure within the lumen of the neural tube may be relieved in one of three ways; by physiologic compensation, by rupture of the tube, or by death of the embryo. In the latter event formation of ventricular fluid suddenly ceases. Then because of the low colloidal osmotic tension of this fluid,[37] its volume is spontaneously reduced by absorption into the tissues, interstitial spaces, and blood. Such reduction accounts in part for the sunken fontanel of the infant who has died from hydrocephalus. In the hydrocephalic embryo in addition to this spontaneous absorption, fluid is withdrawn from the neural tube during fixation by the hypertonicity of the fixing fluid. Thus, the unusual plication of the neural tube that Patten[38] observed in pathologic embryos may have been wrinkling due to a shrunken head.

If the caudal end of the neural tube bulges posteriorly (syringomyelocele) and ruptures (myeloschisis) from overdistention, the escaping cerebrospinal fluid may cause hydramnios, the hydrocephalus suddenly will be relieved, and the collapse of the head will cause excessive plication (microgyria) of the thin cerebral mantle. Similar though less severe plication may be anticipated from physiologic compensation of a pathologic degree of overdistention.

If overexpansion of the forebrain has reduced the size of the posterior fossa to a pathologic degree, the subsequent expansion of the growing hindbrain will cause it to herniate through the foramen magnum. This mechanism is illustrated by the fact that none of Warkany, Wilson, and Geiger's[24] trypan blue treated rats with myeloschisis when sacrificed on the seventeenth day had Arnold-Chiari malformation, while those sacrificed on the twenty-first or twenty-second day did have it. Also, none of their rats with myeloschisis had hydrocephalus, while many litter mates without myeloschisis had it.

Impaction of the growing hindbrain in the foramen magnum will cause compression of the rhombic roof before it is time for it to perforate, while in severe cases the accompanying telescoping of the dislocated cervical cord will occlude its central canal. This results in a reestablishment of the obstructive hydrocephalus, which then further aggravates the hindbrain hernia. This hydrocephalus of the forebrain also may push the midbrain through the incisura where it will be compressed along with the hindbrain. Lichtenstein,[39] in considering cases of Arnold-Chiari malformation, has attributed this associated caudal dislocation of the midbrain to traction exerted by the caudally dislocated hindbrain. His explanation is untenable since the cause of the hindbrain dislocation is not traction but pulsion. The expansion of the growing hindbrain in the small posterior fossa would tend to extrude it in both directions; that is, upward through the incisura, as well as downward through the foramen magnum.[34] Therefore, in cases in which the midbrain is found herniated into the posterior fossa, the displacement must have resulted from reestablishment of hydrocephalus of the forebrain. Such displacement

of the midbrain into the crowded posterior fossa will result in compression and longitudinal wrinkling of its previously distended lumen (aqueductal "forking" of Russell[40] and of MacFarlane and Maloney[41]) and in some instances squeeze it shut. In this case, the secondary hydrocephalus of the cerebrum is the cause and not the result of stricture of the aqueduct. Thus the anatomic features associated with meningomyelocele can best be explained on the basis of obstructive hydrocephalomyelia in embryonal life, arrested by rupture, followed by recurrent hydrocephalus of the forebrain in fetal life because of compression of the fourth ventricle.

In meningomyelocele, the usual sequence of events according to this concept briefly is as follows: inadequate permeability of the rhombic roof causes a pathologic degree of embryonal hydrocephalomyelia. This overdistention, accompanied by hypertrophy of neural tissue, is most pronounced at the two ends where closure is more recent and the tissues, therefore, more yielding. Fluid overdistention of the forebrain accelerates and exaggerates the migration of the primitive transverse sinus, causes spotty aplasia of the membranous calvarium (craniolacunia), expands (syringomyelocele), perhaps splits (diastematomyelia), and then ruptures (myeloschisis) the neural tube. The collapsing cerebral mantle becomes wrinkled (microgyria), and the pressure remains relieved until such time as the hindbrain, enlarging in the small posterior fossa, obstructs the escape of fluid from above to cause a second stage of hydrocephalus. The reexpansion of the forebrain will push the compressed hindbrain farther caudally, will kink the cervical cord and, in some cases, will displace the midbrain partly into the crowded posterior fossa. Below the telescoped portion of the cervical cord, the central canal remains dilated. As this recurrent hydrocephalus progresses, the fissures described by Cameron[28] develop in the compressed rhombic roof while the expanding walls of the lateral and third ventricles become more attenuated and more permeable to fluid. With the increasing filtration of fluid through the walls of the ventricles, dissection of the spinal subarachnoid space will be resumed. The edges of the neural tube at the point of the rupture are fused (tethered) to the skin so that the pressure of subarachnoid fluid anterior to the open neural tube causes it to herniate to form the sac of the meningomyelocele. A leak of subarachnoid fluid may develop in the everted, frequently diastematomyelic, portion of the neural tube as it is undergoing scarring and epithelialization. In this case the recurrent hydrocephalus once more may be relieved, which explains the lack of ventricular dilatation in the occasional infant born with meningomyelocele, Arnold-Chiari malformation, and craniolacunia.

The familial occurrence of cranioschisis, anencephalus, hydrocephalus, meningomyelocele, hydromyelia, diastematomyelia and other "dysraphic" states in humans, and their occurrence also in litter mates of pregnant rats treated by a variety of teratogens, indicates that they have a common cause. Retardation of the blastopore,[28] an accessory neuroenteric canal,[42] persistence of the primitive streak, and doubling of the notochord[16] have all been invoked to explain meningomyelocele and diastematomyelia. However, it is difficult to see how any of these theories

will explain simple meningocele, syringomyelocele, cranioschisis, anencephalus, hydrocephalus, or an encephalocele covered with normal skin, which conditions are surely related to meningomyelocele and to diastematomyelia. Nor will they explain how either an Arnold-Chiari malformation or the Dandy-Walker syndrome may be associated not only with meningomyelocele in the newborn but also with syringomyelia in the adult. Also, it is awkward to explain how the neural tube can become overdistended in cases in which it never has closed. To the mechanically oriented mind of a surgeon, Morgagni's[1] 200-year-old hydromyelic theory seems more logical.

References

1. Morgagni, J. B.: The Seats and Causes of Diseases Investigated by Anatomy, 3 vol. Translated by Benjamin Alexander, London: A. Millar and T. Cadell, 1769.
2. von Recklinghausen, F.: Untersuchungen über die Spina bifida. Arch. f. path. Anat. **105:** 243; 373, 1886.
3. Weed, L. H.: Development of Cerebro-Spinal Spaces in Pig and in Man, Contributions to Embryology, vol. 5, No. 14, No. 225, Carnegie Institution of Washington, 1917, 116 p.
4. Gardner, W. J., and Angel, J.: Mechanism of syringomyelia and its surgical correction. Clin. Neurosurg. **6:** 131-140, 1958.
5. Bering, E. A., Jr.: Choroid plexus and arterial pulsation of cerebro-spinal fluid; demonstration of choroid plexuses as cerebrospinal fluid pump. A.M.A. Arch. Neurol. & Psychiat. **73:** 165-172, 1955.
6. Greenfield, J. G.: *In* Greenfield, J. G.; Blackwood, W.; McMenemey, W. H; Meyer, A., and Norman, R. M.: Neuropathology. London: Edward Arnold (Publishers) Ltd., 1958, 640 p.
7. Gardner, W. J.; Abdullah, A. F., and McCormack, L. J.: Varying expressions of embryonal atresia of fourth ventricle in adults. Arnold-Chiari malformation, Dandy-Walker syndrome, "arachnoid" cyst of cerebellum, and syringomyelia. J. Neurosurg. **14:** 591-605; discussion, 605-607, 1957.
8. Benda, C. E.: Developmental Disorders of Mentation and Cerebral Palsies. New York: Grune and Stratton, 1952, 565 p.
9. Gardner, W. J.: Anatomic anomalies common to myelomeningocele of infancy and syringomyelia of adulthood suggest common origin. Cleveland Clin. Quart. **26:** 118-133, 1959.
10. Gardner, W. J.: Anatomic features common to Arnold-Chiari and Dandy-Walker malformations suggest common origin. Cleveland Clin. Quart. **26:** 206-222, 1959.
11. Taggart, J. K., Jr., and Walker, A. E.: Congenital atresia of foramens of Luschka and Magendie. Arch. Neurol. & Psychiat. **48:** 583-612, 1942.
12. Wells, C. E. C.; Spillane, J. D., and Bligh, A. S.: Cervical spinal canal in syringomyelia. Brain **82:** 23-40, 1959.
13. Holtzer, H.: Experimental analysis of development of spinal column. I. Response of precartilage cells to size variations of spinal cord. J. Exper. Zool. **121:** 121-147, 1952.
14. Cooper, I. S., and Kernohan, J. W.: Heterotopic glial nests in subarachnoid space: Histo-

pathologic characteristics, mode of origin and relation to meningeal gliomas. J. Neuropath. & Exper. Neurol. **10:** 16-29, 1951.

15. Gardner, W. J., and Collis, J. S.: Klippel-Feil syndrome. Syringomyelia, diastematomyelia, and myelomeningocele—one disease? Arch. Surg. **83:** 638-644, 1961.
16. Saunders, R. L. deC. H.: Combined anterior and posterior spina bifida in living neonatal human female. Anat. Rec. **87:** 255-278, 1943.
17. Walker, A. E.: Dilatation of vertebral canal associated with congenital anomalies of spinal cord. Am. J. Roentgenol. **52:** 571-582, 1944.
18. Herren, R. Y., and Edwards, J. E.: Diplomyelia (duplication of spinal cord). Arch. Path. **30:** 1203-1214, 1940.
19. Doran, P. A., and Guthkelch, A. N.: Studies in spina bifida cystica. I. General survey and reassessment of problem. J. Neurol. Neurosurg. & Psychiat. **24:** 331-345, 1961.
20. Humphrey, F. R. S.: Six specimens of spina bifida with long projections from bodies of vertebrae into vertebral canal. J. Anat. & Physiol. **20:** 585-592, 1885-6.
21. Gilmour, J. R.: Essential identity of Klippel-Feil syndrome and iniencephaly. J. Path. & Bact. **53:** 117-131, 1941.
22. Avery, L. W., and Rentfro, C. C.: Klippel-Feil syndrome; pathologic report. Arch. Neurol. & Psychiat. **36:** 1068-1076, 1936.
23. Gardner, W. J.: Blood-brain barrier: expression of absence of interstitial spaces in ectodermal tissue? Perspectives Biol. & Med. **4:** 169-176, 1961.
24. Warkany, J.; Wilson, J. G., and Geiger, J. F.: Myeloschisis and myelomeningocele produced experimentally in rat. J. Comp. Neurol. **109:** 35-64, 1958.
25. Gardner, W. J.: Rupture of neural tube: cause of myelomeningocele. A.M.A. Arch. Neurol. **4:** 1-7, 1961.
26. Fowler, I.: Responses of chick neural tube in mechanically produced spina bifida. J. Exper. Zool. **123:** 115-151, 1953.
27. Padget, D. H.: Development of cranial venous system in man from viewpoint of comparative anatomy. Contributions to Embryology (No. 247) **36:** 79-140, 1957. Carnegie Institution of Washington, Publication 611.
28. Cameron, A. H.: Arnold-Chiari and other neuro-anatomical malformations associated with spina bifida. J. Path. & Bact. **73:** 195-211, 1957.
29. Barry, A.; Patten, B. M., and Stewart, B. H.: Possible factors in development of Arnold-Chiari malformation. J. Neurosurg. **14:** 285-301, 1957.
30. Brodal, A., and Hauglie-Hanssen, E.: Congenital hydrocephalus with defective development of cerebellar vermis. (Dandy-Walker syndrome.) J. Neurol. Neurosurg. & Psychiat. **22:** 99-108, 1959.
31. Portugal, J. R., and Brock, M.: On pathogenesis of Dandy-Walker-Brodal syndrome. Zentralbl. f. Neurochir. **23:** 80-97, 1962.
32. Gardner, W. J.; McCormack, L. J., and Dohn, D. F.: Embryonal atresia of fourth ventricle. Cause of "arachnoid cyst" of cerebellopontine angle. J. Neurosurg. **17:** 226-237, 1960.
33. Matson, D. D.: Prenatal obstruction of fourth ventricle. Am. J. Roentgenol. **76:** 499-506, 1956.
34. Daniel, P. M., and Strich, S. J.: Some observations on congenital deformity of central nervous system known as Arnold-Chiari malformation. J. Neuropath. & Exper. Neurol. **17:** 255-266, 1958.

35. Chiari, H.: Über Venräderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns. Deutsche med. Wchnschr. **17:** 1172-1175, 1891.

36. Arnold, J.: Myelocyste, Transposition von Gewebskeimen und Sympodie. Beitr. path. Anat. **16:** 1-28, 1894.

37. Ortiz, H.; Gardner, W. J., and Kolff, W. J.: Demonstration of colloidosmotic effect of blood on cerebrospinal fluid. Cleveland Clin. Quart. **27:** 232-234, 1960.

38. Patten, B. M.: Overgrowth of neural tube in young human embryos. Anat. Rec. **113:** 381-393, 1952.

39. Lichtenstein, B. W.: Atresia and stenosis of aqueduct of Sylvius; with comments on Arnold-Chiari complex. J. Neuropath. & Exper. Neurol. **18:** 3-21, 1959.

40. Russell, D. S.: Observations on pathology of hydrocephalus, p. 19, *in* Medical Research Council, Special Report Series No. **265**, London: His Majesty's Stationery Office, 1949, 138 p.

41. MacFarlane, A., and Maloney, A. F.: Appearance of aqueduct and its relationship to hydrocephalus in Arnold-Chiari malformation. Brain **80:** 479-491, 1957.

42. Bremer, J. L.: Dorsal intestinal fistula; accessory neurenteric canal; diastematomyelia. A.M.A. Arch. Path. **54:** 132-138, 1952.