EMBRYOLOGICAL STAGES IN THE ESTABLISHING OF MYELOSCHISIS WITH SPINA BIFIDA

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TWENTY-THREE FIGURES

INTRODUCTION

Used in a strict sense the term spina bifida indicates merely an unfused condition of the neural arches. This may occur without any involvement of the spinal cord. Such cases, because of the absence of any externally visible malformation and the absence of neurological symptoms, are characterized as *spina bifida occulta* (fig. 1 A). More commonly spina bifida is accompanied by disturbances in the development of the meninges or the spinal cord, or both. If the meninges are involved in the formation of a saccular enlargement, without distortion or displacement of the cord, the condition is called *spina bifida with meningocele* (fig. 1 B). If the spinal cord is distorted or displaced in the formation of the meningeal sac the condition is designated as *spina bifida with myelomeningocele* (fig. 1 C). A more radical disturbance is that in which an area of unclosed neural plate lies spread out on the surface of a fluid-filled meningeal sac. This latter condition (fig. 1 D) is best characterized as *spina bifida with myeloschisis*.[1]

[1] The term rachischisis is frequently employed to cover the condition here designated as myeloschisis with spina bifida. This is not a desirable usage since *rachis* is the Greek word for spinal column rather than spinal cord. Rachischisis is, therefore, more nearly synonymous with spina bifida. If one were concerned about the conjoined use of Latin and Greek words the condition in question could quite properly be taken over entirely into Greek and called *myelorachischisis*.

Both from the clinical standpoint and from the standpoint of pathological anatomy, the various types of spina bifida have been extensively studied. The relative frequency with which defects within this group as a whole are encountered is well indicated by the fact that Ingraham and Swan ('43) were able to collect a series of 546 cases of spina bifida and cranium bifidum that had been seen at Children's Hospital in Boston

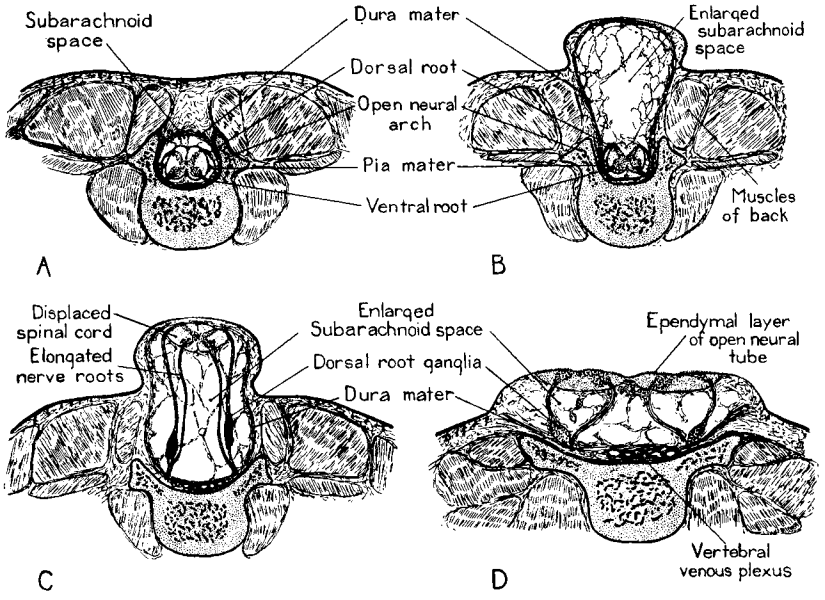

Fig. 1 Diagrams showing different types of spina bifida. A, spina bifida occulta; B, spina bifida with meningocele; C, spina bifida with myelomeningocele; D, spina bifida with myeloschisis. (Slightly modified from Patten, "Human Embryology," courtesy of The Blakiston Co., Philadelphia.)

in a period of 20 years. The incidence in this series was one case among each 4150 new patients observed during this interval. This survey, together with 4 other related papers by Ingraham and his coworkers (II, Ingraham and Hamlin, '43; III, Ingraham and Lowrey, '43; IV, Ingraham and Matson, '43; V, Ingraham and Scott, '43) which originally appeared separately in the New England Journal of Medicine, were collected and reprinted under the auspices of the Mas-

sachusetts Medical Society with the addition of a bibliography of some 2500 references arranged in chronological groups. For the history of the development of our knowledge of these conditions, and the clinical aspects of the problems they present, reference should be made to this outstanding work. More recently Fisher, Uihlein and Keith ('52) reported on a series of 530 cases of spina bifida and cranium bifidum seen at the Mayo Clinic in the 36 years from 1910 through 1945. Their tabular summaries of the regions involved cover 471 cases of spina bifida with varying degrees of involvement of the meninges and cord. Spina bifida occulta was excluded from this series.

In spite of the frequency with which spina bifida accompanied by varying degrees of involvement of the spinal cord is seen postnatally, there are relatively few contributions dealing with the embryology of malformations of this type. In most of the cases that have been reported the preservation of the embryos was not sufficiently good to make detailed studies feasible. The accession to the University of Michigan Embryological Collection of three well fixed human embryos with spina bifida and concomitant involvement of the spinal cord offered an unusually favorable opportunity of studying the genesis of such conditions. Following my preliminary report on this material at the Anatomists' Meetings (Patten, '46), Dr. Paul B. Sawin generously sent to me a term fetus of a rabbit exhibiting the same type of defect. Being developmentally older than any of the three human embryos mentioned, it formed an interesting 4th stage in the series. Only when the serial sections from these embryos were ready for study did we realize the full extent of our good fortune. Not only did the 4 embryos afford a nicely graded series developmentally, they also exhibited basically the same type of anomaly — myeloschisis accompanied by spina bifida. This paper will, therefore, deal specifically with the genesis of that combination of defects.

MATERIAL AND OBSERVATIONS

Eight-millimeter human embryo. The youngest of the human specimens was only 8 mm in crown-rump length, its presumptive fertilization age being just a little more than 5 weeks. Its external appearance (fig. 2 A) was essentially normal except for the open defect of the neural tube in its lumbosacral region (fig. 2 B). Like the other two human embryos which form the basis of this study it was, unfortunately, sent in without any clinical history.

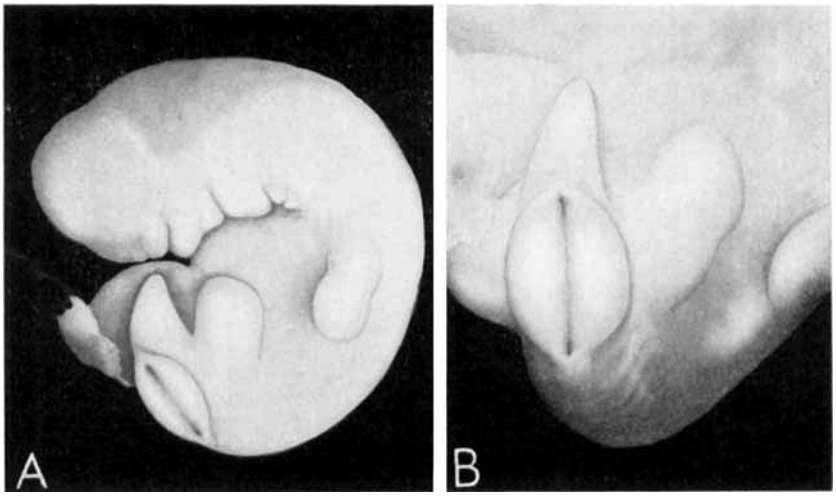

Fig. 2 Two views of an 8-mm human embryo with myeloschisis. (Univ. of Michigan Coll., EH 260.) A, lateral view; B, direct caudal view, more highly magnified.

After being photographed, this embryo (EH 260) was serially sectioned in a plane that would pass directly across the open area of the neural tube. Figure 3 A is a photomicrograph of a section from this series showing the general relations at the level of the defect. Figure 3 B shows the open neural tube and immediately adjacent tissues at a higher magnification. Even casual inspection shows the excessive amount of neural plate tissue present in the defective region. This is a matter that will be returned to in more detail in the discussion.

Histologically the open neural plate does not show any striking differences from the conditions seen in the cord cephalic to the defect. It is in the phase of rapid expansion of the mantle

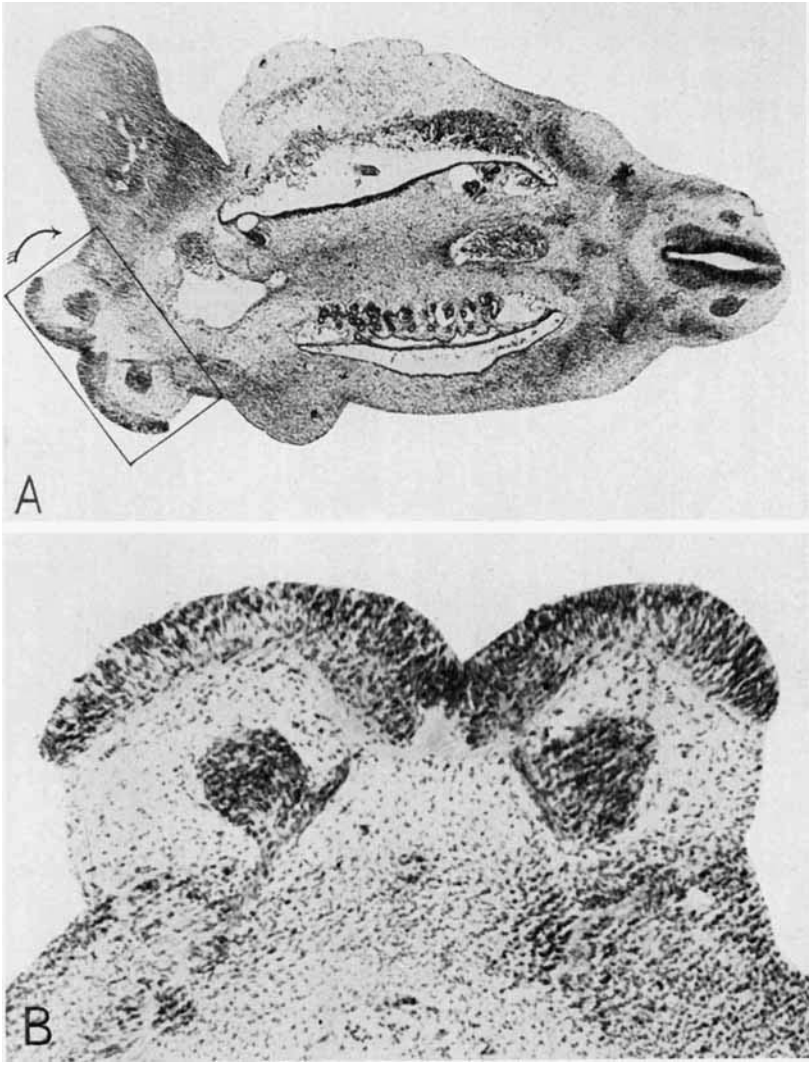

Fig. 3 (A) Section passing through the center of the defect in the embryo illustrated in figure 2, low magnification for general topography.

(B) Region enclosed by the rectangle in A, showing the area of the defect at higher magnification.

layer with the marginal layer still very thin. The particular section photographed for figure 3 B passes through the ventral nerve roots and shows the more ventral portions of the dorsal root ganglia. The more dorsal parts of the ganglia and the dorsal roots of the spinal nerves, because of the angle of cutting, lie in neighboring sections, and so could not be included in the same photomicrograph. For some reason that is not apparent the dorsal roots at the level of the defect

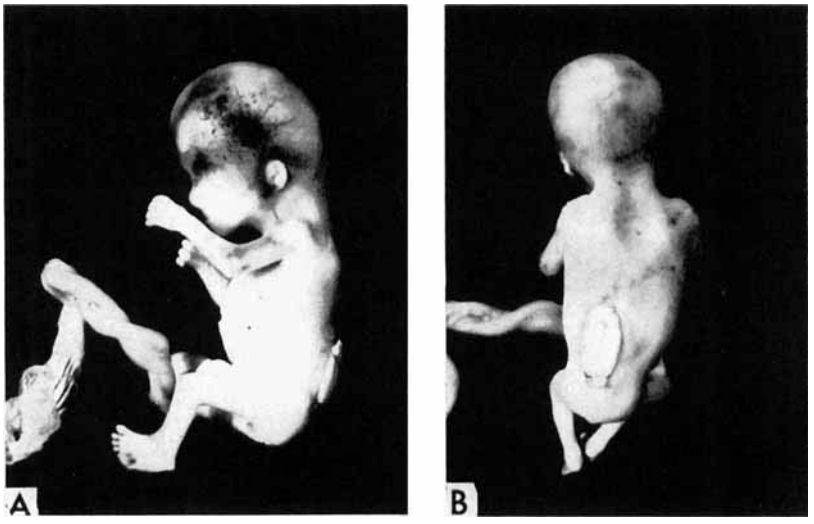

Fig. 4 Lateral view (A) and dorsal view (B) of a human embryo of 49 mm crown-rump length with spina bifida and myeloschisis in the lumbar region. (Univ. of Michigan Coll., EH 220, photographed natural size.)

were less well developed than they were either cephalic or caudal to the abnormal area.

The relatively undifferentiated condition of the vertebral primordia is worthy of comment. There are, in this 8-mm embryo, only slight concentrations of mesenchymal cells about the notochord representing the primordia of the centra of the vertebrae. No suggestion of mesenchymal aggregations presaging the appearance of the primordia of the neural arches could be identified.

Widely open areas in the neural tube of young human embryos, more or less similar to the case here described, have been reported by a number of workers. Wrete ('24) reported on an embryo of 11.5 mm in which practically the entire length of the neural tube was involved by a myeloschisis. In spite of the fact that he characterized the specimen as partially macerated his figures and descriptions satisfactorily portray the general character of the defect. Ingalls ('32) used as one of his examples of dorsal mid-line defects a 7-mm embryo with an open sacral defect of the neural tube which, judging from his figure, must have resembled our case. His embryo (W. R. U. No. 83), however, had other defects and was received in very poor condition. Ingalls apparently found the sections unsatisfactory to work with and makes no mention of the possibility that local overgrowth might be involved. Another closely similar case was reported by Tourneux and Martin (1881). This embryo was also in unsatisfactory condition for critical study. They interpret the defect as being the result of a developmental arrest although, as far as it is possible to judge from their illustrations, the overgrowth of neural plate tissue in this specimen must have been just as conspicuous as it was in ours. Still another case, similar except that the defect is in the cervical region, was reported by Sternberg ('29). Holmdahl ('25-'26) in his study of the development of the caudal part of the embryonic body includes an illustration (fig. 84) of a 7-mm sheep embryo with its neural plate still unseparated from the superficial ectoderm, which seems to accord well with the above-mentioned descriptions of human embryos.

Forty-nine-millimeter human embryo. The second human embryo in our group of three measured 49 mm in crown-rump length, indicating a presumptive fertilization age of just under 10 weeks. It exhibited a myeloschisis in the same location and of the same general type (fig. 4) as that shown in an earlier stage by the 8-mm embryo just described. Sections through the affected area (fig. 5) again show a very large spinal cord, open to the outside. In the groove overlying the thin

floor plate the ependymal layer is well preserved (fig. 6), although on the exposed surfaces on each side it has been somewhat eroded.

This specimen is enough older than the first so that the vertebrae have been well molded in cartilage. Beneath the open neural tube the neural processes of the vertebrae flare out to the sides in a very striking manner. Due to difficulty in handling these large sections involving the tough tissue

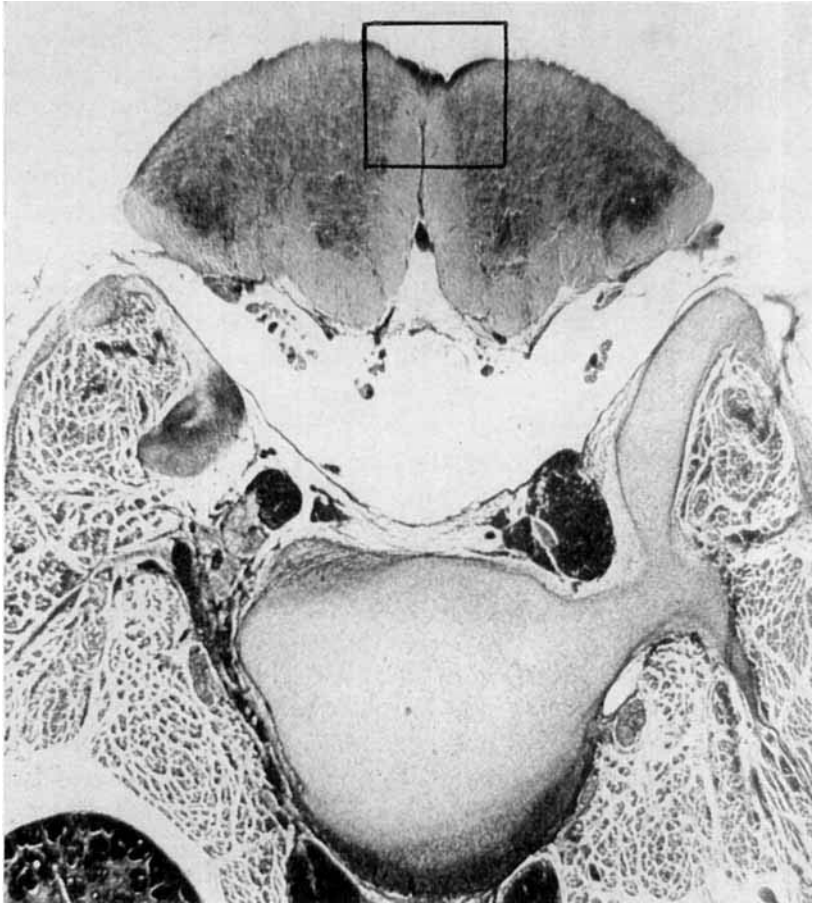

Fig. 5 Photomicrograph of section from the center of the defect shown in figure 4.

of the developing spinal column, the meninges were somewhat torn. Their general relations, nevertheless, were still quite clearly discernible.

An interesting feature of this specimen which was unsuspected from the external study, or even from sections near the center of the affected area, was a doubling of the neural tube. This appeared in the sections just cephalic to the open area. The shapes of the two tubes were somewhat irregular and the configuration of the developing white and gray areas

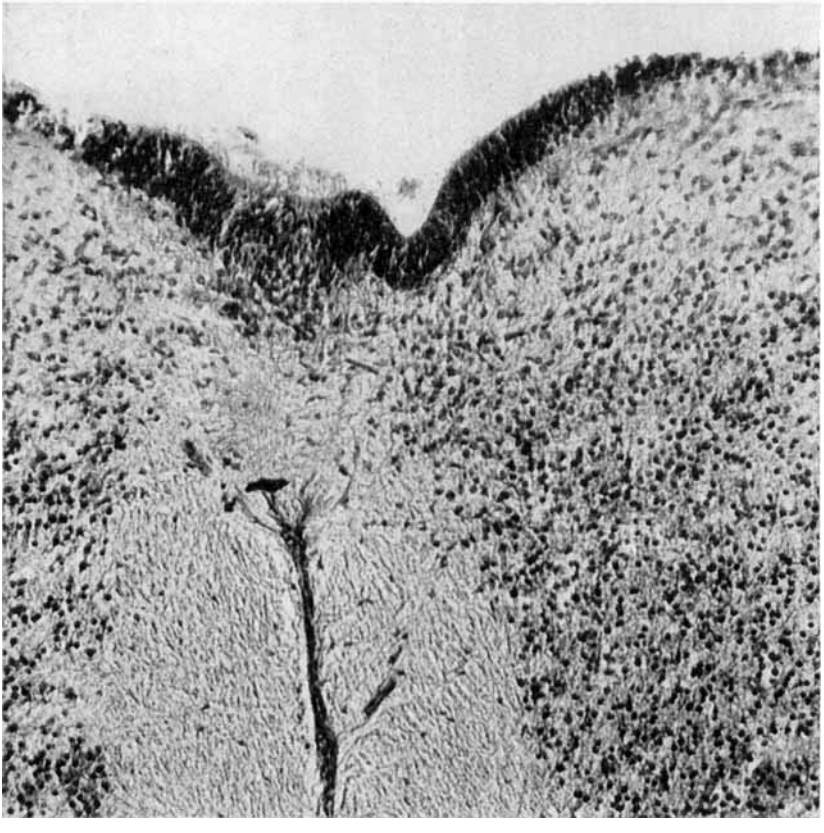

Fig. 6 Photomicrograph, more highly magnified, of area of open spinal cord indicated by rectangle in figure 5. Note especially the clearly defined ependymal layer on the open surface, and the well differentiated marginal and mantle layers on either side of the ventral fissure.

was difficult to interpret. It was not possible to say with certainty whether the condition represented a true doubling of the entire cord, or a halving of the available neural plate material and its partial reorganization into two moieties. The two central canals around which the neural plate tissue was organized were unmistakable because of their clear-cut ependymal linings. Their slit-like lumina were oriented with their ventral

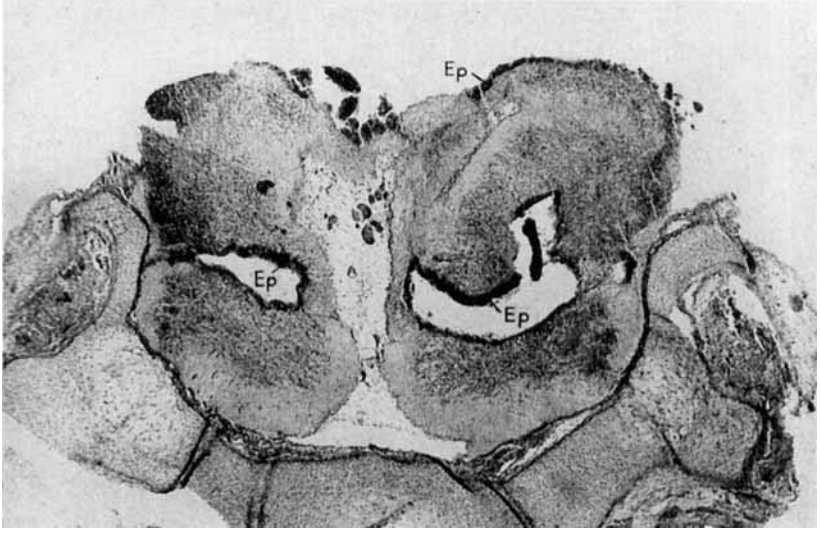

Fig. 7 Double lumen of spinal cord adjacent to area of myeloschisis shown in figures 5 and 6. Notice that there is an ependymal layer (Ep) on the open surface of the neural tissue mass as well as lining the two neural canals.

sides inclined toward the mid-line and their dorsal aspects slanted out to either side (fig. 7).

This doubling of the spinal cord in the neighborhood of a myeloschisis has been reported a number of times (Herren and Edwards, '40; Lichtenstein, '40; Dodds, '41; Gruenwald, '41; Maxwell and Bucy, '46; Kapsenberg and Van Lookeren Campagne, '49; and case no. 17 of Russell, '49, to mention a few of the more recent papers). It is an interesting variant of the overgrowth shown in the adjacent undoubled areas. Schumacher ('27) illustrates in his figure 14 a tripling of the

neural canal in an 8-mm human embryo. This condition was not associated with myeloschisis but it is, nevertheless, of interest in connection with the cases here reported because of the strikingly large amount of neural tube tissue present in the abnormal region.

One-hundred-sixty-millimeter human embryo. The oldest human embryo in the group showing myeloschisis measured

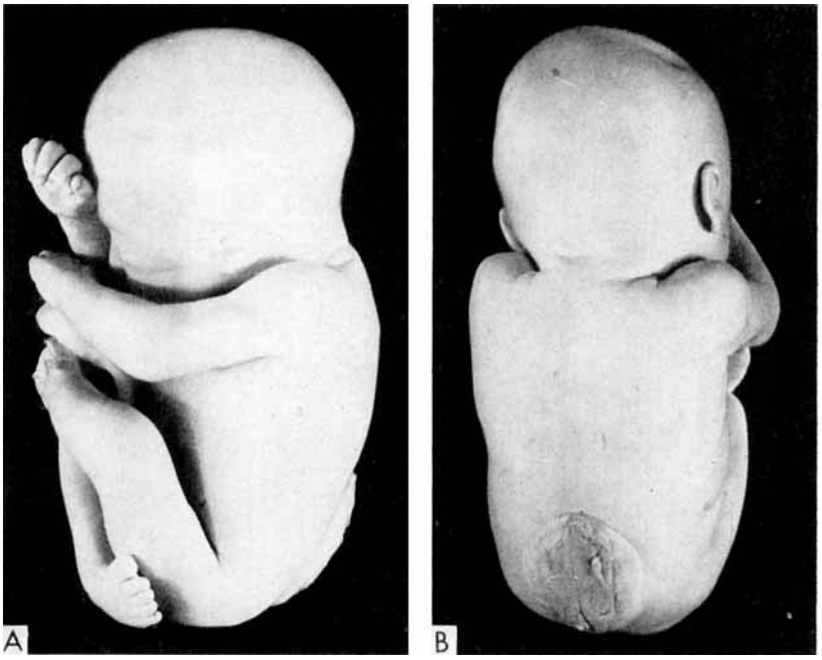

Fig. 8 Lateral view (A) and dorsal view (B) of a 160-mm human embryo with spina bifida and myeloschisis. (Univ. of Michigan Coll., EH 213.)

160 mm in crown-rump length, indicating a probable fertilization age of about 18 weeks. Externally (fig. 8) the general configuration of the defective area was a miniature of conditions seen all too frequently in newborn infants. Sections across the affected area showed the same kind of wide-open neural plate that was exhibited by the two younger specimens. The time intervening between fetal death and fixation was apparently greater in this case than in either of the others

for neither the fixation nor the stainability of the tissues was quite as good. The topography of the sections, however, could be made out without difficulty. A semischematic drawing of a characteristic section is reproduced as figure 9. Such landmarks as ventral horn motor cells, dorsal and ventral nerve roots, and a dorsal root ganglion are clearly recognizable. Very striking are the large subarachnoid spaces. The fluid tension which must have existed in these spaces in the living condition undoubtedly accounted for the way the open cord

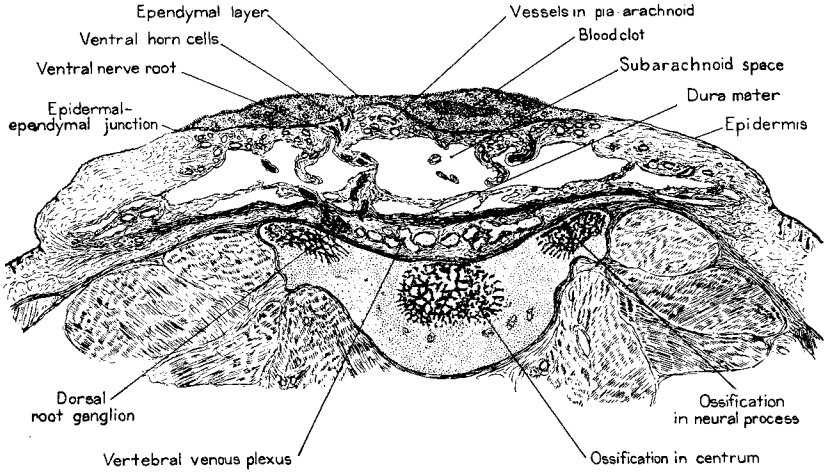

Fig. 9 Semidiagrammatic drawing of a section through the center of the defect shown in figure 8.

bulged out above the general body surface. Of interest also is the way the epidermis becomes thinned out and poorly developed as its junction with the ependymal layer of the cord is approached. In the open neural plate there were evidences of degenerative changes over and above those due to delay in fixation. A few large motor cells are still readily recognizable in the ventral horns of the gray matter (fig. 10, MNC). Except for these the nervous tissue was obviously deteriorating and in large areas there were masses of extravasated blood cells (fig. 10, Bcl). The connective tissue underlying the neural plate shows a maze of engorged blood vessels

(fig. 10, Bv) and evidences of the accumulation of a considerable amount of fluid in its interstices.

The development of the vertebrae has progressed well beyond the stages shown by the younger embryos. In the 8-mm specimen the mesenchyme about the notochord was just beginning to concentrate, foreshadowing the formation of the primordia of the centra (fig. 3 B). There was no suggestion whatever of such concentrations in the regions of the neural

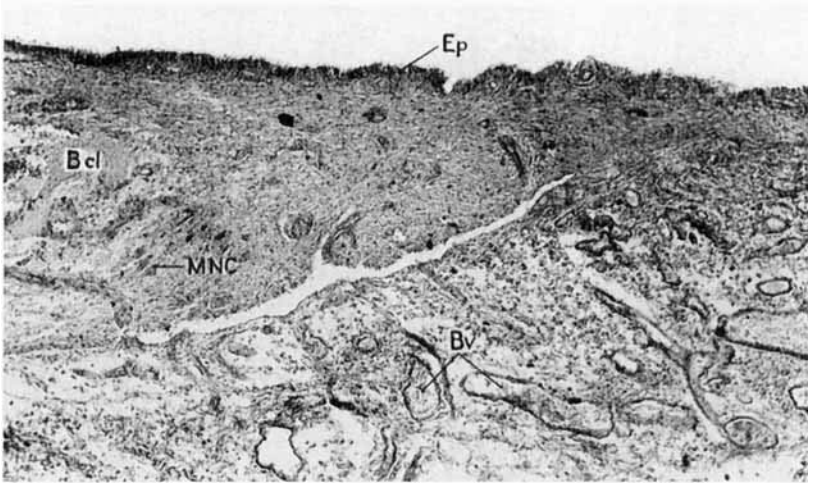

Fig. 10 Photomicrograph through the right side of the open neural tube, the topographical relations of which are shown in figure 9. Some of the motor nerve cells (M N C) and the cells of the ependymal layer (Ep) are still clearly recognizable although there has been considerable deterioration of the neural plate tissue as a whole. Note the engorged blood vessels (B v) of the pia-arachnoid, and the area of clotted blood (B cl) within the cord.

arches. In the second specimen (49 mm — about 10 weeks) both the centra and the neural arches were laid down in cartilage and the widely divergent arches gave clear indication of the bifid condition of the spine from which all of these related malformations take a part of their names. In the 160-mm embryo the configuration of the vertebrae is clearly established with their ossification centers standing out as conspicuous landmarks in the laterally displaced neural arches (fig. 9).

Rabbit term fetus. A rabbit term fetus sent in by Doctor Sawin furnished the material for the 4th stage in our developmental series. This specimen was from an inbred strain being used to study the genetic influences on sex ratio (Sawin and Gadbois, '47). It was promptly and well fixed so its tis-

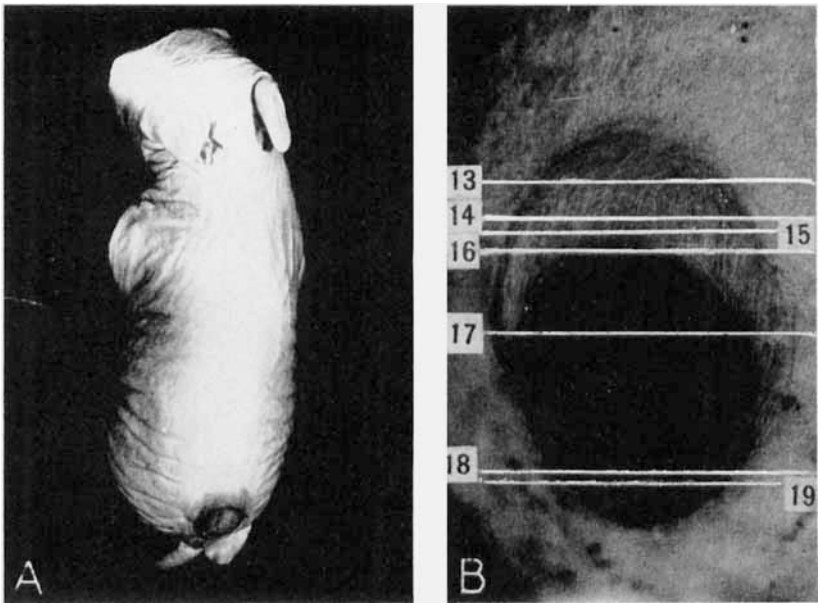

Fig. 11 (A) Rabbit fetus, at term, showing spina bifida with myeloschisis. The specimen was sent in by Dr. Paul B. Sawin from one of his inbred strains. In terms of relative development it constitutes a 4th stage in that it is more advanced than the human embryos covered by figures 2, 4, and 8.

(B) Enlarged view of defect. The dark oval is the area where the neural tube is open and degenerated. Its darkness is due to underlying extravasated blood (see fig. 17). The lighter crescent above is where the fluid of the meningocele has caused the skin to become elevated from the underlying structures. The numbered lines indicate the level of the sections photographed for figures 13–19.

sues were in excellent condition for study. Most important of all, perhaps, was the fact that the region involved in the rabbit was small enuogh to make it feasible to section it as a complete series. Figure 11 A shows the size and location of the region involved. Figure 11 B is an enlargement of the area of the defect with the numbered white lines indicating the levels of the sections photographed for figures 13 to 19.

As the region of the defect is approached the most striking histological changes in the sections are in the skin. Before there is any other recognizable departure from the normal picture the epidermis becomes noticeably thinner. The hair follicles and sebaceous glands become progressively less well developed as the lesion is approached. At the zone of transition from skin to open neural plate there are only curious peg-like rudiments representing these structures (fig. 20). In the dermis there are many engorged blood vessels and accumulations of considerable amounts of interstitial fluid. This condition of the skin extends entirely around the lesion as a sort of marginal zone. Not only are the blood vessels numerous and engorged, as emphasized by von Recklinghausen (1886) in his classical description of spina bifida in newborn infants, but also they appear to be sending out new vascular sprouts (fig. 21, Spr).

Underneath the crescentic, elevated area at the cephalic part of the malformation (fig. 11 A) the skin has been undermined and distended by the accumulation of fluid. Open communication of this superficial sac with the subarachnoid space (see arrows in fig. 13) does not appear in the sections until they have been cut beyond the marginal zone and well into the crescent. In other words, the meningocele has expanded subcutaneously far cephalic to the region of its direct continuity with the subarachnoid space. (Note the level of line numbered 13 in figure 11 B). Where the communication first becomes direct, the spinal cord is still at about its normal dorsoventral level within the open neural arches. There is a slight indication of loss of clean-cut organization in the dorsal part of the cord but it is still relatively little altered from its normal configuration.

Just a little farther caudal in the series the dorsal part of the cord becomes obviously distorted (figs. 14, 22) and a few sections thereafter shreds of completely disorganized nervous tissue can be seen to stream out toward the surface (fig. 15). At the same time the communication of the pia-arachnoid

spaces with the subcutaneous spaces of the meningocele open out broadly (cf. figs. 13 and 14 and 15).

Where the tissue of the spinal cord first reaches the surface it is overlaid by clotted blood (fig. 16), and throughout the entire central part of the malformed area the subarachnoid space has become clot-filled (fig. 17). The absence of any sign of organization indicates that the extravasation did not occur long before death. The presence of this mass of freshly clotted blood is obviously the reason that the central part of the lesion appeared so dark in photographs of its external appearance (fig. 11).

Perhaps the most significant condition in the central part of the lesion is the nearly complete disintegration of the neural plate tissue (fig. 17). Since this will be considered at some length in the discussion it is sufficient here to call attention to the extent of the degenerative changes which have occurred.

As the section series is followed toward the caudal part of the malformed area, changes similar to those noted in approaching the defective area tend to repeat themselves in reverse order. There is one striking difference. The lesion is located so far back in the body that the spinal cord tailwards from it is very slender. One would expect at this level to be encountering the filum terminale and the pulled out nerves of the cauda equina. Although there is a clearly recognizable reduced terminal portion of the spinal cord representing the filum terminale (fig. 23), the many cut nerves which would normally be associated with it are absent. It seems probable that the broad attachments of the wide open neural plate to surrounding structures may have interfered with the cephalic displacement of the spinal cord with reference to the spinal column which is normally involved in the formation of the cauda equina (Streeter, '19).

DISCUSSION

In connection with the 8-mm human embryo, mention was made of the large amount of neural plate tissue present at the level of the myeloschisis in the developing spinal cord.

The open region may conveniently be characterized as exhibiting a local overgrowth of neural plate tissue. The primary basis for such a characterization was the fact that there was obviously more neural plate tissue present in the open region than there was in the adjacent normal cord. Furthermore, the extent of the neural plate tissue appeared greater than normal in relation to other surrounding structures. To

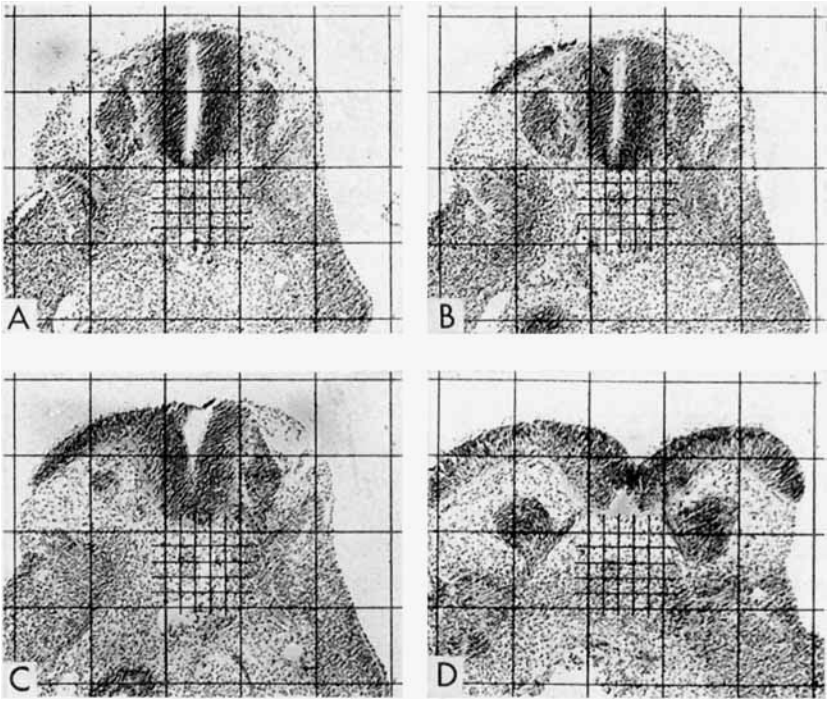

Fig. 12 Four sections of the 8-mm human embryo (EH 260) photographed at the same scale, through a grid, to facilitate size comparisons. A, essentially normal spinal cord just cephalic to the defect. B and C, neural plate tissue starting to spread out on the surface. The fact that it appears at first only on the left indicates merely that the plane of sectioning is slightly diagonal with reference to the defect. Note that the spinal cord proper still exhibits essentially the same size and configuration as in A, with the neural plate tissue flaring out to the side clearly constituting an excess. D, section through the center of the defect. Notice, by using the squares of the grid to aid comparison, that there is enough neural plate tissue in the wide open area to make at least two spinal cords of the normal size just above the defect (cf. D and A of this figure).

assess this situation more accurately, 4 photomicrographs were made at the same magnification, through a ruled ocular. The first one of these was taken through the normal neural tube adjacent to the defect (fig. 12 A). The next two were made as the sections began to involve the abnormal area of the neural tube (fig. 12 B, C). The 4th photograph was through the center of the open area (fig. 12 D). The extent to which the neural plate suddenly flares out laterally is most striking. As one follows the series from the normal cord into the defect, abruptly there appears enough neural plate tissue to make at least two neural tubes of the size seen in the adjacent unaffected region. That there has been marked local overgrowth is unmistakably clear. Concerning the underlying factors precipitating such an overgrowth there is as yet no real evidence. Certain recent observations on non-human embryos are suggestive of one possibility. Fowler ('53) [2] has mechanically induced myeloschisis in chicks by slitting open the roof-plate of the developing neural tube. He found a considerable subsequent increase in the volume of spinal cord tissue where the tube had been laid open. It is conceivable that in human embryos such as that shown in figure 2 the overgrowth was a sequel to an early failure of the neural folds to fuse. If a failure to close did precede the disturbance in growth, there still remains the problem as to whether the overgrowth was the result of some sort of local stimulation, or due to the absence of some restraining factor.

As far as any evidence now available is concerned, it would be equally logical to take the standpoint that the local overgrowth was the primary departure from the normal course of events, and had started sufficiently early to interfere with the normal closure of the neural tube. There are a number of instances of different types in which overgrowth of neural tissue is encountered without there having been any previous cutting open of the developing neural tube as in the experiments of Fowler. One example that might be cited is from the

[2] At the time this was written Fowler's paper was available to me only in the form of an advanced abstract.

work of Snell and his collaborators ('34, '35, '41). They found marked overgrowth of brain tissue occurring in a considerable number of the offspring of a strain of mice which they were breeding in an effort to follow the results of gene translocation following x-ray exposure of male parents. The way similar defects are carried on genetically has been further studied by Bonnevie ('36). Her illustrations contain a number of interesting photomicrographs showing abnormal growth in various parts of the central nervous system. Even more striking is the extensive overgrowth of the walls of the neural tube in the brain occasionally encountered in young human embryos that may appear essentially normal in external configuration (Patten, '52). In the more extreme of these cases the redundant neural epithelium is thrown into bizarre festoon-like folds that sometimes fill the whole cranial cavity.

There are a number of reasons for being especially interested in this matter of local overgrowth. It represents a type of abnormal development which contrasts sharply with the much more familiar disturbances in which a growth process seems to have been retarded in some manner. In seeking the underlying causes of defects of the so-called developmental arrest type, we have been likely to think in such negative terms as inadequate nutrition, or deficient oxygen supply, or damaged or missing genes. The recognition of local overgrowth as a quite different type of abnormal development forces us to scrutinize possible causative factors from other categories, closer to phenomena such as those which must be involved in the overactive growth of specific tissues as seen in neoplasms. Interesting in this connection is the tumor-like mass reported by Bergel ('28) growing into the central canal of the neural tube of a 16½-mm embryo, and also the curious dorsoventral doubling of the cord accompanied by considerable overgrowth which was reported by Fischel ('07). Still more pertinent are the disturbances in brain growth reported by Sinclair ('51) as a result of the transplacental effect of urethane, and the neoplasms of brain tissue induced by Roentgen irradiation of rat embryos (Wilson, Brent, and Jordan, '52). Some

of their illustrations show conditions almost exactly like those I have seen in cases of brain overgrowth in human embryos.

Another, quite different, point of interest in connection with this group of embryos involves the relationship between the defect of the spinal cord and the coexisting unclosed neural arches of the vertebrae. The 8-mm embryo with myeloschisis is so young that, as yet, there are not even mesenchymal concentrations foreshadowing the neural processes of the vertebrae. This means that the spina bifida that would undoubtedly have developed if this particular embryo had lived another month would have been secondary to a primary disturbance in the formation of the neural tube. It should be emphasized that this carries no implication that spina bifida always so arises. The fact that there may be spina bifida occulta with an apparently normal spinal cord (fig. 1 A) is sufficient evidence on this point.

Certain implications of the timing of the developmental processes involved in the establishing of these frequently associated defects seem quite clear. A spina bifida which coexists with a myeloschisis should be regarded as secondary to it. It must have had its abnormal pattern established in advance of its own development by the disturbed configuration of the territory in which it was to grow. A spina bifida occulta, in contrast, must arise independently much later in development. Its abnormal shape is a primary malformation of the skeletal system resulting from factors involving the regulation of the growth of the vertebrae themselves. The meningoceles and the myelomeningoceles probably stand in an intermediate situation between these two conditions. A meningocele with little involvement of the cord (fig. 1 B) may well be a sequel to a primary spina bifida in which the unclosed neural arches invited the herniation of fluid-dilated meninges. A myelomeningocele could quite logically involve the combination of delayed or incomplete separation of the spinal cord from the superficial ectoderm with defective development of the neural arches. These latter suggestions must be regarded as tentative for, although this group of embryos gives us the

best series of developmental stages we have had up to the present time, it is still far from adequate. There must be a much more complete series before any final conclusions are reached.

The histological picture of the neural tissue in the open cord of the term fetus of the rabbit (fig. 17) shows interesting differences in comparison with the conditions seen in the human embryo of 18 weeks (fig. 9). The conspicuous clot in the subarachnoid spaces in the rabbit can probably be dismissed as of no great significance from the developmental standpoint. It seems quite clearly to be the result of recent bleeding into the distended subarachnoid spaces which in the human embryo were filled with nonsanguineous fluid. It should, I believe, be regarded as merely an accidental condition in this particular specimen, and not as a regular part of the picture in malformations of this type.

In both specimens the extreme vascularity of the zone adjacent to the fluid-filled subarachnoid spaces is a conspicuous feature. The functional significance of this zone is of considerable importance clinically. The possibility of hydrocephalus occurring after the surgical repair of a spina bifida is well known. There is, however, considerable difference of opinion among neurosurgeons as to the causal relationships in such occurrences. One of the points at issue is whether the highly vascular marginal zone is to be interpreted as a maze of venous channels overloaded in carrying off an excess of fluid arriving in the area by way of the cerebrospinal pathways, or whether it should be looked upon as the source of additional fluid compensating for the fluid loss by seepage through the open defect. Only experimental work with living material can satisfactorily solve such problems. It is, however, of interest that the presence of numerous vascular sprouts (fig. 21, Spr) shows that, at term, the richness of this vascular zone is still being increased. Whatever may be going on in the blood vessels, the loosely-woven and fluid-distended connective tissue of this marginal zone and the poor quality of its epithelial structures clearly indicate the underlying reasons for its complete ex-

cision, which is the well recognized surgical practice in making any repairs of such malformations.

In any defects in this general category, the fate of the nervous tissue of the open spinal cord is of the greatest significance. In the 18-week human embryo the topography of the neural plate was clearly recognizable (fig. 9). Although there was some evidence of degenerative changes, in the presence of blood clots and loss of clearness of histological detail, it was still possible to recognize the general limits of white and gray matter and such characteristic elements as the large ventral horn, motor cell bodies (fig. 10, MNC). In the term fetus of the rabbit there has been almost complete deterioration of the nervous tissue in the region of the myeloschisis. The excellent preservation of the specimen as a whole clearly indicates that this is not the result of poor fixation. This secondary degeneration must have been a relatively late occurrence, for the well-formed ventral nerve roots (fig. 17) could never have been established unless the malformed cord had for a considerable time possessed active neuroblasts capable of producing the robust bundle of nerve fibers so clearly representing the ventral nerve roots. The obvious inference is that the malformation as seen in the rabbit at term must have passed through a stage similar to that exhibited by the 18-week human fetus. The broken line superimposed on the photomicrograph of a section through the center of a malformed area suggests the probable extent of the neural plate before its degeneration (cf. figs. 9 and 17). Whether or not all individuals in which myeloschisis is established at the very early period shown in this series of specimens will exhibit such extensive nervous tissue destruction as shown at term by this last specimen can be determined only by the recovery and microscopic study of additional cases. Certainly it would seem quite clear that with a defect as radical and as early established as the type represented in the three human embryos here reported there is every probability of profound neurological damage and a correspondingly discouraging outlook for any surgical intervention.

SUMMARY

Three recently acquired human embryos in the University of Michigan Collection show progressive stages in the development of myeloschisis with spina bifida. The youngest of these (8-mm, early 6th week) exhibits a broad opening of the neural tube in the lumbo-sacral region. Measurements of sections through the malformed area show that the bulk of the neural plate tissue is much greater in the region of the defect than it is in the adjacent normal areas of the cord. Another point of interest shown by this embryo is the fact that the neural tube defect is established prior to the spina bifida, for the myeloschisis is already definite when there are only suggestions of mesenchymal concentrations about the notochord representing the primordia of the centra of the vertebrae, and no indication whatever of the primordia of the neural arches.

Similarly in the second embryo (49-mm, late in 10th week), there is marked overgrowth of neural tissue at the site of the defect with the additional factor of local cord duplication toward the cephalic end of the malformed area. In this specimen the neural arches are well formed in cartilage, and can be seen to flare out laterally on either side of the enlarged, open spinal cord.

The third specimen (160-mm, 18 weeks) is beginning to show degenerative changes in the open cord and clubbing of the feet. The ossification centers of the vertebrae are clearly marked and the characteristic bony configuration of a spina bifida is unmistakably established.

The acquisition, through the generosity of Dr. Paul B. Sawin, of the term fetus of a rabbit showing the same type of defect as that exhibited by the three human embryos here described furnished an interesting 4th stage in the series. At the same time, because of its excellent preservation, it offered an unusual opportunity for studying the details of the histological changes characteristic of malformations of this type. The cutaneous changes in the marginal zone around the defect involved thinning of the epidermis, loss of hair follicles and sebaceous glands, edema of the connective tissue, and a

tremendous increase in vascularity. In the regions where the neural tube was open to the surface there had been almost complete disintegration of the nervous tissue.

Conditions presented by this series of specimens strongly suggest that the open neural tube is cases of myeloschisis may be the result of local overgrowth which interfered with its closure, rather than the result of a "developmental arrest" which left the tube unclosed because of too little growth of the neural folds. The importance of this possibility lies in its implications as to causation. Because of the emphasis which has been placed on the developmental arrest concept, search for causes of congenital defects has been largely directed toward conditions which might inhibit growth. If anomalies can be caused, also, by local overgrowth we must scrutinize causative factors of quite different types.

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PLATE 1

EXPLANATION OF FIGURES

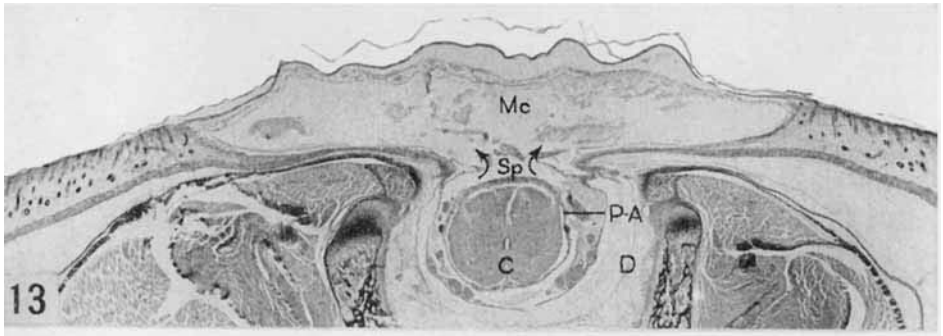
The level of each section is indicated by the white line on figure 11 B which bears the number corresponding with that of the figure on this plate.

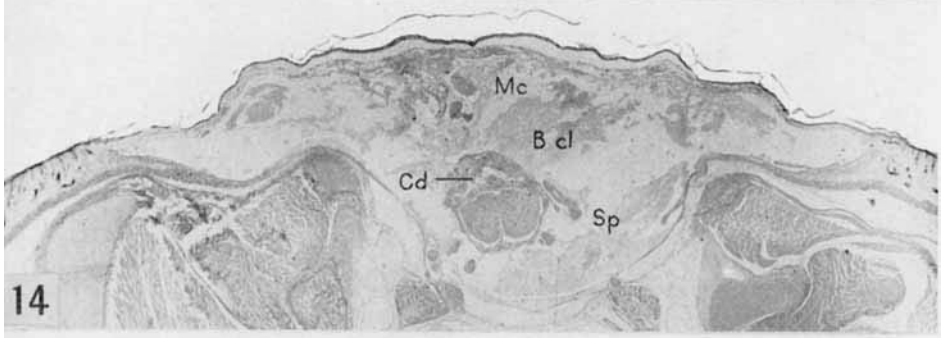
13 Spinal cord (C), still essentially normal. Subarachnoid space (Sp) around cord shows beginning of communication (see arrows) with the meningocele (Mc). Other abbreviations: D, dura mater; P-A, pia-arachnoid.

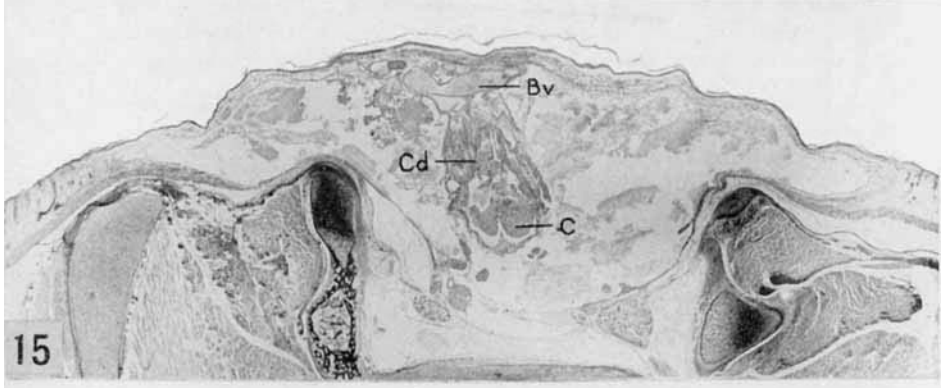
14 Dorsal portion of spinal cord beginning to show degeneration (C d). Greatly enlarged subarachnoid space (Sp) broadly continuous with meningocele (Mc). There is some clotted blood (B cl) mixed with the fluid of the meningocele but not as much as appears farther caudally (cf. fig. 17).

15 At this level there is very marked disintegration of dorsal part of spinal cord (Cd). Engorged blood vessels (B v) are conspicuous.

16 The completely disorganized nervous tissue (N d) of the spinal cord extends to the surface. Considerable recently extravasated, clotted blood (B cl) is present in the meningocele (Mc).


Mc
Sp
P-A
C
D
13


Mc
B cl
Cd
Sp
14


Bv
Cd
C
15

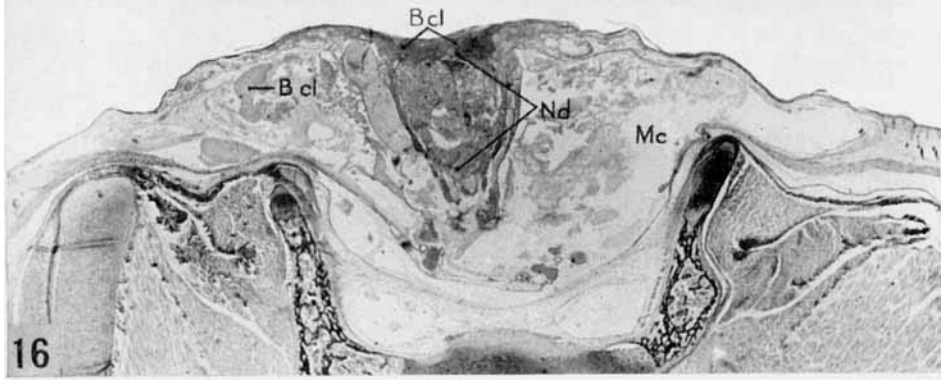

Bcl
B cl
Nd
Mc
16

PLATE 2

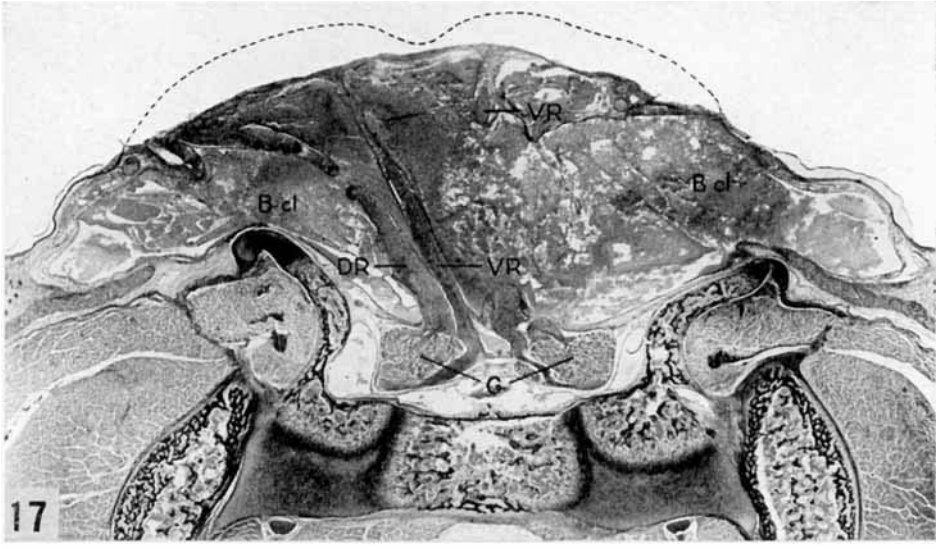
EXPLANATION OF FIGURES

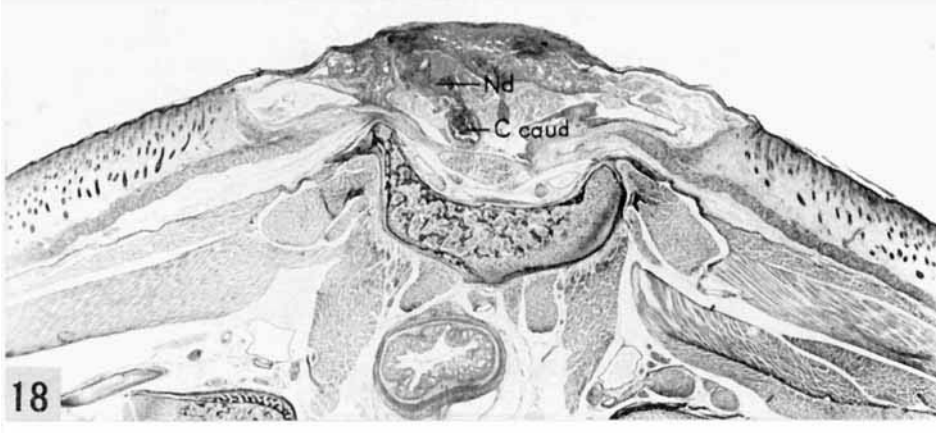
The level of each section here illustrated is indicated by the correspondingly numbered white line on figure 11 B.

17 Section through the center of the defect. Before the open neural plate disintegrated it presumably extended to the broken line, occupying much the same relative position as that shown for the neural plate in figure 9. Abbreviations: B cl, extravasated blood coagulated in the meningocele; D R, dorsal root of spinal nerve; G, dorsal root ganglion; V R, ventral root of spinal nerve.

18 Photomicrograph of section near the caudal end of the defect. Degenerated nervous tissue (N d) can be seen extending from the rudimentary caudal portion of the spinal cord (C caud) to the surface.

19 Photomicrograph showing only a few small strands of degenerated nervous tissue between the rudimentary caudal portion of the spinal cord (C caud) and the surface of the meningocele.


VR
B cl
B cl
DR
VR
G
17


Nd
C caud
18

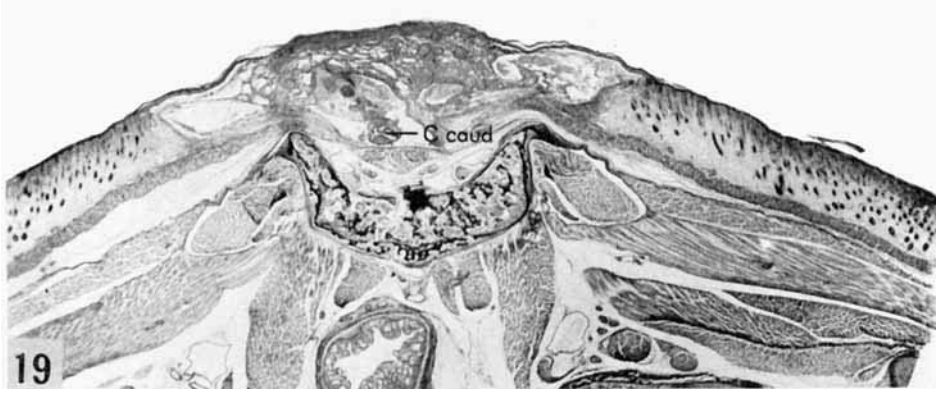

C caud
19

PLATE 3

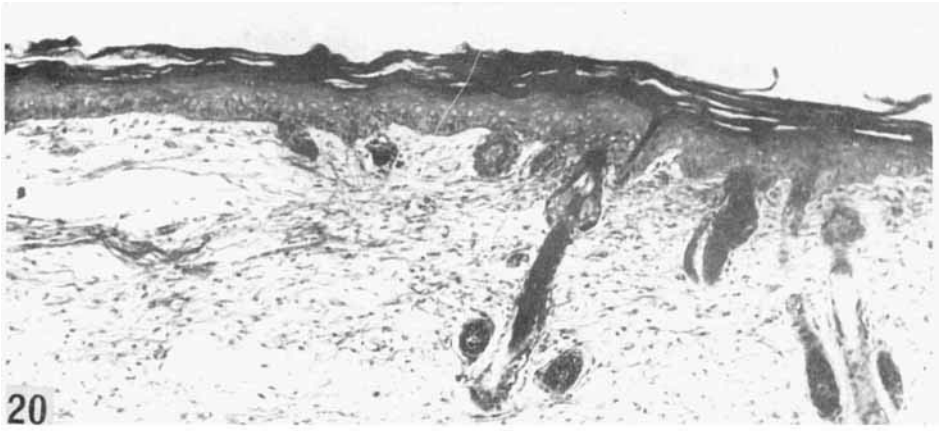
EXPLANATION OF FIGURES

20 Photomicrograph showing cutaneous changes adjacent to the lesion. The section was selected from the series just cephalic to the grossly obvious area of the malformation. The mid-line is approximately at the left-hand margin of the illustration. Note the diminution in the size of the hair follicles, and the enlarged interstitial spaces in the connective tissue on the side toward the defect.

21 Photomicrograph showing the characteristic histology of the margins of the meningocele. The dropping out of hair follicles as the defective area is approached is again a conspicuous feature. In the edematous connective tissue note especially the endothelial sprouts (Spr) indicative of continued increase in the already rich vascularity of the marginal zone.

22 More highly magnified photomicrograph of section of the spinal cord at the level shown in figure 14. Note the contrast between the fairly normal appearing ventral part of the spinal cord and its disorganized dorsal portion (C d).

23 More highly magnified photomicrograph of the rudimentary caudal portion of the spinal cord (C caud) at the level shown in figure 19. Although there are some strands of disorganized nervous tissue (N d) dorsal to it, there is a striking absence of the transversely cut nerves which would normally lie beside it to constitute the cauda equina.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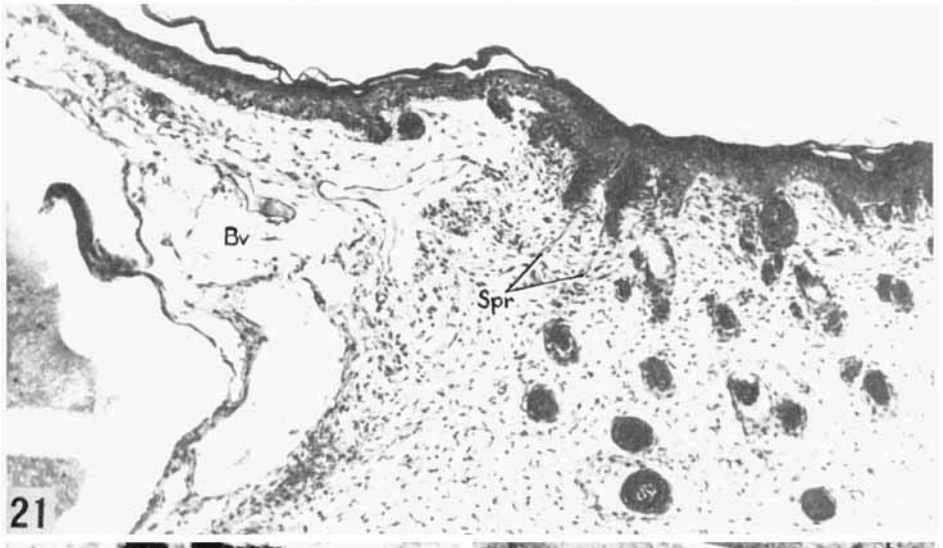
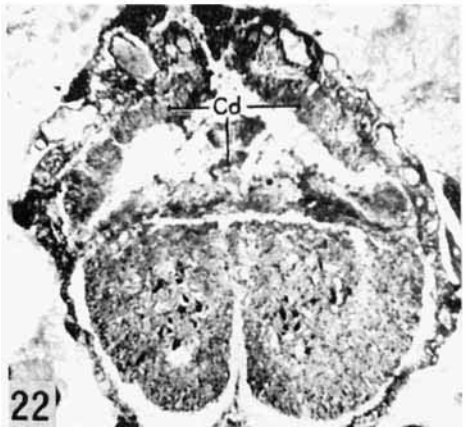
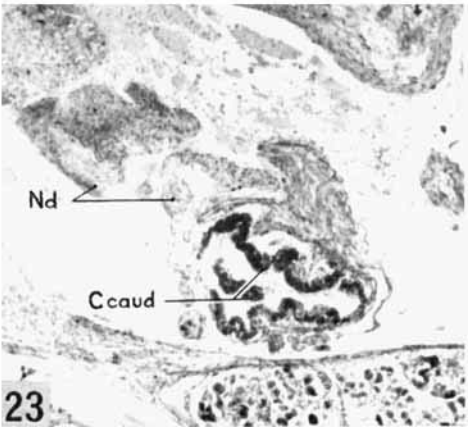

Bv
Spr
21


Cd
22


Nd
Ccaud
23