Cerebral Intraventricular Hemorrhage and Subependymal Matrix Infarction in the Fetus and Premature Newborn

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THE PATHOGENESIS of cerebral intraventricular hemorrhage in the premature infant has remained a perplexing problem. At necropsy, this condition is often the most significant finding. Infants born at 22–35 weeks' gestation are frequently affected, with the greatest incidence in the group of prematures of 28 weeks' gestation; in the latter, cerebral intraventricular hemorrhage of some degree is present almost universally at necropsy.[1]

The role of trauma has been of prime concern as a direct cause of neonatal intraventricular hemorrhage. During birth, mechanical force is known to cause injury to certain structures of the nervous system, notably the tentorium, brain stem, spinal cord, and spinal nerve roots.[2,3] With reference to intraventricular hemorrhage, however, there is no substantial pathologic basis for relating processes of physical injury to this condition.[4-8]

Intracranial hemorrhage in the neonate, as suggested by Schwartz,[9] may be due to the difference between intrauterine and atmospheric pressure exerting its effects on the presenting part during delivery. This mechanism may be a contributing influence in intraventricular hemorrhage; however, certain aspects of the application of this theory have been questioned.[6,10,11]

Holland [12] suggested that excessive molding of the head during parturition may lead to kinking of the vena galen, with resulting obstruction of the deep venous drainage of the cerebrum and hemorrhage into the ventricles. Stretching and tearing of dural and venous structures occurs in association with molding of the head. However, as shown by the incidence studies of Hemsath [5] and Gröntoft,[7] and as evident in the present collection of neonatal material, the process of dural-venous distortion and injury is relatively common in full-weight, term infants; it is relatively uncommon in prematures, compared to the high incidence of intra-

ventricular hemorrhage in this neonatal group. Significantly, with reference to the theories of Schwartz and Holland, intraventricular hemorrhage is observed in breech delivery, cesarian section, and in fetuses dying before labor begins—in circumstances in which pressure differences and cranial molding have no bearing.[4,7,13–16]

Hemorrhagic diathesis, sometimes considered a significant cause of intracranial bleeding, appears infrequently in cases of intraventricular hemorrhage.[5,7,13]

Germinal matrix tissue, persisting as subependymal deposits in the cerebrum in the fetus and premature infant, has been cited as a factor in the pathogenesis of neonatal intraventricular hemorrhage; a number of investigators trace the origin of intraventricular bleeding to hemorrhagic lesions in the subependymal matrix tissue.[4–6,10,13,17,18] The matrix represents a germinal supply depot, giving rise to the spongioblasts and neuroblasts required in the formation of the cerebral cortex, basal ganglia, and other neuronal assemblies in the forebrain. In fetuses of 6–8 months the matrix accumulations are most pronounced, bulging from the cerebral wall into the ventricular cavity. As the fetus matures, the matrix deposits become attenuated. Investigators early drew attention to the relationship between the amount of germinal matrix in the cerebrum at a given gestational age and the incidence of neonatal intraventricular hemorrhage, pointing to the fact that as the fetus nears the end of gestation and as the deposits of cerebral matrix tissue become smaller and finally exhausted, the incidence of neonatal intraventricular hemorrhage declines.

The matrix tissue in the young fetus is highly cellular and friable, readily undergoing disintegration. Pathologically, the question of the nature of the destructive process—the necrotic hemorrhagic lesions in the subependyma matrix tissue—has been of basic importance.

It is the purpose of the present report (1) to call attention to precursor lesions in the cerebral subependymal matrix which ultimately give origin to hemorrhage into the ventricle, and (2) to indicate systemic mechanisms affecting the maternal-placental-fetal organization which contribute to the ocurrence of subependymal hemorrhage-producing lesions.

Materials and Methods

The cases prepared at the Warren Anatomical Museum, Harvard University Medical School, in conjunction with the national Collaborative Perinatal Project (Collaborative Study in Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood) were available for this study. They provided a broad source of clinically correlated material—over 500 neonatal brain specimens, of which a major portion were in the premature age group.

The technique of whole-brain serial histologic sectioning which we employed made possible the preservation of focal lesions and the consistent demonstration of their geographic relationship in the brain.

Attention was focused upon 120 cases, technically suitable, in which the infants were between 22 and 35 weeks' gestation. A basic incidence evaluation is presented. Detailed incidence-localization analysis of intracranial hemorrhage in the over-all material, correlated with clinical and systemic factors, is the subject of a separate study. In the present report, of the 120 cases analyzed, illustrative examples are presented, selected to demonstrate the step-by-step evolution of intraventicular hemorrhage.

Review of Case Material

In analyzing this condition pathologically, it is necessary to bring into focus the course of events which occur systemically and locally, resulting in intraventricular hemorrhage. It is necessary to interpret the neuro-pathologic findings in the light of the obstetric history, the neonatal course, the pathologic findings in the placenta, and the findings in the general necropsy. Viewed thus, in preliminary studies of cases of neonatal intraventricular hemorrhage, a basic pattern emerged: maternal history of gestational complications; consequent fetal and neonatal hypoxia, associated with impairment of systemic function, progressive circulatory failure, and generalized bodily venous congestion; in the brain, resulting venous stasis, often with thrombosis, associated with local infarction and consequent hemorrhage.

In the maternal history, episodes of vaginal bleeding and signs of toxemia in the period prior to parturition were recorded frequently. The gestational complication was usually of placental origin, often related to premature detachment of the placenta. The effects of the intrauterine complications on the neonate were plainly evident in the delivery room; the records of the Apgar score generally showed a range of from 1 to 4. The prematurely delivered infants, limp and cyanotic during their brief survival, usually evidenced mounting hypoxia, with gradual failure of respiratory, cardiac, and other systemic activity.

The necropsy regularly revealed organic changes in the neonate associated with systemic circulatory failure—cyanosis, generalized venous congestion, peripheral edema, ascites, swelling and engorgement of the liver, spleen, and other viscera; the presence at necropsy of systemic venous congestion has been consistently reported in the past in infants with intraventricular hemorrhage.[7,11,13] The histologic findings in the lungs were of particular interest; as noted by Gröntoft[7] and others,[18] in premature infants with intraventricular hemorrhage, the bronchial and alveolar spaces often contain squames and bile pigment from aspirated amniotic fluid, indicative of the early (intrauterine) onset of the hypoxic process.

The brain characteristically was swollen, edematous, and congested. Histologically, in the whole-brain sections, the cases reviewed showed a broad range of consecutive progressive cerebral lesions, defining patho-

logically the processes leading to intraventricular hemorrhage. In the cerebrum the element affected most consistently was the germinal matrix tissue, especially the large subependymal deposits in the lateral ventricles along the caudo-thalamic groove anteriorly. The subependymal matrix showed varying areas of disintegration and hemorrhage.

In analyzing the pathogenesis of intraventricular hemorrhage, the key to the problem lay in defining early precursor lesions—related nascent changes in the subependymal deposits of matrix—lesions present prior to the time the affected tissue becomes flooded with blood.

In preliminary observations, it was evident that the primal pathologic process taking place in the subependymal matrix was that of infarction. In some instances, early lesions of this order were present alone, and at times were observed in brains which also showed more advanced destruction of matrix in other areas, with hemorrhage in the germinal tissue, often with intraventricular hemorrhage. The early infarctional lesions occurring in the subependymal matrix tissue appeared in the Nissl preparations as patches of paling, as islands of cellular devastation. Lesions of this order are illustrated in the following case.

Case 1

The infant in this case (W 73-61), of 32 weeks' gestation, weighed 3 lb. 4 oz. and lived 2 days. The placenta showed evidence of premature separation. Terminally, the infant developed respiratory complications, of both central and peripheral nature. The necropsy revealed visceral congestion and multiple thrombotic and embolic vascular occlusions; the portal vein contained a thrombus, and the entire small intestine was infarcted. Pulmonary embolism was found. Hyaline membrane disease was evident histologically. The brain weighed 240 gm.; gross examination revealed that the superficial cerebral veins were moderately congested.

In the histologic section through the frontal region shown in Fig. 1A and B, a mound of deeply staining matrix tissue on the lower lateral aspect of each ventricle is evident in the cerebrum. Within the matrix are patches of pale necrotic tissue—areas of early infarction, portions of which are hemorrhagic. Veins in the matrix are distended with conglutinated blood. At a more posterior level in the brain, the lesion appearing on the right was increased in size and showed more extensive suffusion of blood through the devitalized disintegrating tissue, and, related to this, blood was present in the adjacent ventricle.

With subependymal matrix infarction, the process of necrosis may extend outward from the matrix layer and overrun the neighboring white matter.[5,11,13,16] In the next case, illustrated in Fig. 2, disintegration of the matrix occurred and, as is evident on the left of the cerebrum, the areas of infarction and hemorrhage progressed to involve the adjoining white matter.

Case 2

The infant in this case (W 59-61) was born at 35 weeks' gestation, weighing 2390 gm. The mother was a controlled mild diabetic. Premature rupture of membranes

occurred and spontaneous labor developed. The infant appeared edematous at birth and was in respiratory distress; toward the end of the first day he showed sudden rapid deterioration, became unresponsive, and died 23 hr. after birth. The placenta showed the absence of one umbilical artery. Necropsy revealed acute passive congestion of the liver, spleen, and kidneys; hyaline membrane disease and bronchopneumonia were present; the pancreas showed islet hyperplasia. The brain weighed 244 gm. and showed prominent congestion of the superficial veins.

Significantly, in this case the zone of necrosis in the cerebral wall was more extensive than the area of hemorrhage, indicating that the primary nature of the lesion was infarctional, and the hemorrhagic suffusion secondary. Leakage of blood into the lateral ventricle also occurred. Within the hemorrhagic debris lining the ventricle, dilated veins with thromboses were evident.

Case 3

The infarctional process beginning in the subependymal matrix may ultimately consume most of the wall. In this case (B 265-62) thrombosis of the tributaries of the vena terminalis occurred, associated with massive infarction and hemorrhage of the subependymal matrix and adjoining white matter, extending deeply into the cerebral wall. The pregnancy terminated at 27 weeks. Prolapse of the cord and excessive bleeding occurred during labor. The infant was delivered stillborn from a compound presentation, with the left arm presenting with the vertex; the weight was 960 gm. The placenta showed evidence of recent retromembraneous and retroplacental hemorrhage. Necropsy revealed spinal injury, with laceration of the cord dura, and laceration and hemorrhage of spinal nerve roots; this was correlated with the history of the complicated compound presentation. The brain showed prominent congestion of superficial veins on gross examination. In addition to massive cerebral infarction on one side, in the other hemisphere the vena terminalis was dilated and filled with a thrombus (Fig. 3). In sections of the cerebrum at a deeper level, intraventricular hemorrhage was present. Histologic study revealed that the infarctional process affected not only the matrix and adjoining white matter of the forebrain, but also the basal ganglia.

The hemorrhagic infarcts in the matrix leading to intraventricular bleeding, as observed in the present study, were essentially of acute nature histologically. In some instances, however, the lesions were older and more advanced; with extension of the infarction into the adjoining white matter and into the basal ganglia, affected areas at times showed active gliosis, with numerous macrophages and prominent vascular proliferation. Rydberg[10] and others[9,17] have described similar patterns of histologic reaction in cerebral periventricular areas of necrosis in prematures.

The case material in the present study demonstrates 2 fundamental relationships in pathogenesis of neonatal intraventricular hemorrhage

1. The size of the matrix lesion is generally inversely proportional to the gestational age. The most extensive matrix infarction occurred in young fetuses.

2. The amount of intraventricular hemorrhage was directly propor-

tional to the size and severity of the matrix infarction. Generally only small deposits of blood appeared in the ventricles in infants with early matrix infarction, as in the case illustrated in Fig. 1 and 2. The relationship of early gestational age, large matrix infarction, and severe hemorrhage is illustrated in Fig. 3, a premature infant of 27 weeks' gestation, and in the following case, an infant of 24 weeks' gestation.

Case 4

In this case (W 61-61), the maternal history indicated there was severe vaginal bleeding at 18 weeks; bleeding recurred at 24 weeks and labor ensued. The 1-lb., 11-oz. infant, delivered by breech, was flaccid and apneic, and died after 40 hr. The placenta showed extensive decidual necrosis and retroplacental hemorrhages. At necropsy the lungs revealed evidence of aspiration of amniotic fluid and showed early pneumonia. The brain was swollen and gross examination revealed congestion of the pial veins. The brain sections showed massive infarction in the large persisting matrix deposits, with profuse intraventricular hemorrhage (Fig. 4).

The predisposition for the hemorrhagic process in the premature brain to be periventricular and intraventricular is attributable in a significant measure to the architectural bearing of the terminal vein and its tributaries. These vessels, lying along the floor and lateral aspects of the ventricles and covered by a thin layer of matrix and ependyma, are highly vulnerable. The process of infarction leads to dissolution of parenchymal matrix cells and, as the process mounts in severity, conspicuous necrosis of distended large caliber veins in the matrix under the ependyma occurs, leading to direct exsanguination into the ventricle. This process is illustrated in sections of the brain in the next case.

Case 5

In this case (W 111-62), spontaneous rupture of membranes occurred at approximately 23 weeks; at 25 weeks, the mother was admitted in labor and a 500 gm. infant was delivered. The infant was weak and cyanotic, with the Apgar score 1 at 1 min. and 1 at 15 min., and died after 3 days. The placenta showed extensive inflammation. The brain weighed 106 gm.; pial veins were congested. The ventral surface of the brain presented a layer of blood, up to 3 mm. thick, in the subarachnoid space of the interpeduncular fossa and around the pons and medulla. Histologic sections of the brain revealed that the source of the blood in the subarachnoid space about the brain stem was from gaping dilated veins in the hemorrhagic infarction of the cerebral subependymal matrix tissue (Fig. 5).

Figure 6, from an adjoining saggital section of the same brain, illustrates the extension of the hemorrhage from the ventricular system into the subarachnoid space about the brain stem.

In the present study, in considering the pathogenesis of neonatal intraventricular hemorrhage, the basic pattern of incidence encountered is of significance. Of the 120 premature infants included in this study, there were infarctional lesions of extensive degree in 23 cases; all in this group

showed prominent congestion of the deep venous system of the cerebrum, often with thrombosis of veins and extensive intraventricular hemorrhage. In a second group of 34 cases, matrix lesions of moderate extent were present, accompanied by cerebral venous congestion and intraventricular hemorrhage which varied in extent. In the remaining 63 cases, cerebral congestion was generally pronounced, often with petechiae present and, in some instances, associated with slight intraventricular hemorrhage. The small and medium size lesions generally were distributed through the matrix in both cerebral hemispheres, reflecting the diffuse nature of the venous stasis. However, in the cases having large infarcts the lesions were often asymmetric; at times a massive infarction occupied one side of the cerebrum (Fig. 3).

The choroid plexus has been considered an important source of intraventricular hemorrhage.[19] Others believe this to be infrequent.[5,7,10] In the present material, the choroidal structures did not appear to be a significant source of bleeding.

Discussion

The pathogenesis of neonatal intraventricular hemorrhage, as indicated in the present study, evolves through 3 consecutive stages, each precipitating the next (Text-fig. 1).

1. The Hypoxic Onset

Frequently the hypoxic process is activated by gestational complications having onset late in intrauterine life and extending postnatally. Placental disorders and other hypoxia-producing intrauterine accidents may precipitate death in the fetus or in the neonate soon after delivery; advanced hypoxic brain damage may be present at necropsy, and, at times in the young premature, massive intraventricular hemorrhage.[7,11-14,16,20,21] If the hypoxic gestational condition is severe, but not lethal, it may imprint crippling organic damage, especially to the developing nervous system.

The most important placental cause of fetal hypoxia is premature separation, with antepartum retroplacental hematoma formation.[7] The influence of premature separation is evident in the cases illustrated in Fig. 1, 3, and 4. The placental detachment may be partial and gradual, concealed and symptomless, progressing over a period of weeks with the fetus subjected to increasing severity of hypoxia and suffering increasing debility.[12]

Gröntoft,[7] in 22 cases of neonatal cerebral intraventricular hemorrhage, found significant pathologic changes in the placenta in 13, including 8 instances of partial separation. Ross and Dimmette,[13] in a study of 30

1. HYPOXIC ONSET

In the fetus: Hypoxic intrauterine complications: premature placental detachment, placenta previa, umbilical cord compression, and other conditions disrupting maternal-placental-fetal organization

In the premature newborn: Hypoxia due to central respiratory failure (spinal cord and brain stem injury at birth) or due to peripheral pulmonary disorders (hyaline membrane disease; pneumonia)

2. SYSTEMIC CIRCULATORY FAILURE

Generalized bodily venous congestion in fetus or premature newborn

3. LOCAL VISCERAL (INTRACEREBRAL) SEQUELAE

Stasis-thrombosis of veins in affected viscera
Stasis-thrombosis of deep cerebral veins

Infarction (hemorrhagic) of subependymal matrix

Extension of hemorrhagic infarction into perivascular white matter
Involvement of basal ganglia and other deep structures
Penetration of hemorrhagic infarction through the ependyma, leading to cerebral intraventricular hemorrhage

Extension of hemorrhage into the third and fourth ventricles and out into subarachnoid space about brain stem, into posterior fossa; consequent lethal brain stem compression

TEXT-FIG. 1. Pathogenesis of cerebral intraventricular hemorrhage in the premature newborn.

cases of intraventricular hemorrhage, reported the occurrence of episodes of vaginal bleeding in 13 cases and abnormalities of the placenta in 16.

2. Systemic Circulatory Failure in the Fetus and Newborn: Generalized Venous Congestion

Whether occurring in the fetus in association with a placental accident, or occurring in the newborn infant with pulmonary complications, the pathologic responses of the body to sustained hypoxia are essentially the same—cardiovascular failure with consequent generalized venous stasis.[11,15,18] Clifford,[15] Potter,[8] Magregor,[16] and others have emphasized that these effects may occur in the fetus; under conditions of intrauterine hypoxia, mounting circulatory failure takes place within the fetus, evident in the stillborn as venous engorgement throughout the body. Gröntoft[7] and others[11,13] have pointed out the consistency with which generalized visceral congestion is present at necropsy in premature infants with subependymal and intraventricular hemorrhage, as well as in other forms of neonatal brain damage.

3. Local Visceral (Intracerebral) Sequelae: Subependymal Matrix Infarction and Intraventricular Hemorrhage

The basic nature of the hemorrhage-producing lesions in the periventricular tissue has not been clearly evident in the past. Separate facets of the process were emphasized. Thus it was recognized in the past that infants with neonatal intraventricular hemorrhage died in circulatory failure, showing visceral venous congestion. In the brain, engorgement of the deep venous drainage system, often with thromboses, was reported in studies of intraventricular hemorrhage.[9,13,17,18,22] Observers described the occurrence of large areas of periventricular necrosis associated with intraventricular hemorrhage.[5,9–11,13] In the present investigation, in studying the whole-brain histologic sections, the relationship pathologically of these separate facets was evident. In the histologic sections 2 basic features—(1) cerebral venous stasis-thrombosis, and (2) necrosis of cerebral periventricular matrix—appeared together with consistency in the cases of intraventricular hemorrhage. It was conclusive histologically that the subependymal lesions giving rise to the intraventricular bleeding were infarcts.

Although it is not generally realized, infarctional lesions of the brain, of varied character and location and often massive, occur with some frequency in the neonatal period.[9,16,23,24] The processes of neonatal cerebral infarction may begin prenatally; areas of encephalomalacia with a well established histologic pattern of recent infarction have been observed in

premature and term stillborn infants.[5,9,10,14,20] Infarctional hemorrhagic
lesions have also been described in slightly mascerated fetuses, in in-
stances in which intrauterine death was known to have occurred before
labor.[7,16] Likewise, the process may develop in the neonate after birth;
fresh cerebral infarcts have been observed in premature and term infants
who live for a period of days. These infarctional lesions in the cerebrum,
occurring postnatally, prove in most instances to be the consequence of
venous stasis and thrombosis.[16,25-28]

In reviewing the present material, it was not uncommon to find cases
showing lesions in the matrix and adjoining cerebral tissue with the his-
tologic pattern of infarction and with engorgement of veins—but with-
out the characteristic laminated organizing thrombi. In the interpreta-
tion of such lesions, the absence of thrombi did not preclude the diagnosis
of infarction. Thromboses when present were of supportive significance
in identifying infarcts. However, the ultimate diagnosis of infarction was
made on the basis of the pattern of the local necrotic lesion, in correlation
with evidence of local circulatory stasis.

Intraventricular extravasation of blood in the fetus and premature in-
fant has been attributed to weakness of the small blood vessels in the
cerebral tissue[1,6,7] and to an unusual vulnerability of these vessels to
hypoxia.[6,8,15,18] In the fine vasculature hypoxic endothelial damage may
lead to the formation of punctate hemorrhages. The present study and
the studies reported in the past, however, indicate that these minute le-
sions do not foster the development of extensive hemorrhage. Thus
Hemsath[5] analyzed the occurrence in prematures of petechiae of the
thymus, visceral pericardium, and visceral pleura, and compared the
incidence of these punctate "asphyxial hemorrhages" with the occurrence
of intraventricular hemorrhage. He stated that no parallelism was evident:
Of the 250 neonatal deaths studied, out of 19 showing intraventricular
hemorrhage 3 showed visceral asphyxial petechiae.

It must be emphasized that the processes leading to neonatal intraven-
tricular hemorrhage may begin before, during, or after parturition. With
reference to postnatal onset, fresh subependymal hemorrhagic lesions
appear in premature infants who survive for periods of days.[7] More im-
portant, however, is the fact that cerebral matrix infarction and intra-
ventricular hemorrhage may often begin during fetal life. At times onset
occurs before the beginning of labor, as evidenced by the presence of
intraventricular hemorrhage in slightly macerated stillborn fetuses.[7,14,16]

Although the infarctional lesion in the cerebral matrix may form be-
fore birth, rupture of the hemorrhagic lesion into the ventricle may be
delayed for hours or days. The escape of blood from the matrix lesion

may be slow and oozing, or massive. Correlating the pathologic process with the clinical events, the hypoxic neonate, showing mounting evidence of circulatory failure, may suddenly become unresponsive and die—the agonal episode reflecting the eruption of a hemorrhagic subependymal infarct, with sudden massive intraventricular hemorrhage. This pattern was evident in the case illustrated in Fig. 2 of this study.

The morbidity and mortality associated with neonatal cerebral intra-ventricular hemorrhage lays emphasis on the importance of this condition. Arey and Anderson[3] have estimated that intraventricular hemorrhage is responsible for approximately 10% of all neonatal deaths. Ostensibly the ultimate significance of intraventricular hemorrhage varies. Uni-formly these infants are hypoxic and death is often imminently due to mounting circulatory failure. However, in infants with lesions such as those illustrated in Fig. 3, 4, and 5 of this study, and with massive hemor-rhagic cerebral infarction and intraventricular bleeding, the conclusion that the cerebral process represents a final lethal mechanism is inescap-able.

Of concern is the consideration that premature infants who survive perinatal hypoxic episodes often do not escape damage to the brain. In-voluting subependymal matrix infarctions with hemorrhage are at times observed at necropsy in premature infants who live for a period, dying of other causes. The incidence of central nervous system disorders is signifi-cantly increased in infants of premature birth.[29] The subependymal ma-trix is highly important from the standpoint of future brain growth and development.[4] Devastation of this germinal tissue in premature infants who survive may ultimately be reflected clinically as mental retardation, cerebral palsy, or as other infantile neurologic disorders.

Summary

Cerebral intraventricular hemorrhage is one of the most important processes contributing to death in the neonatal age group. The nature of this pathologic process has been obscure. Mechanical trauma and local intracranial circulatory mechanisms have been cited as the cause in the past. The present study indicates that neonatal intraventricular hemor-rhage is the final stage in the following series of pathologic events af-fecting the maternal-placental-fetal organization.

1. An hypoxic complication affecting the fetus or premature newborn initiates the succession of pathologic responses. The gestational complica-tion is commonly of placental origin, often premature detachment of the placenta.

2. Systemic circulatory failure with generalized bodily venous conges-
tion occurs in the fetus and newborn in the wake of hypoxia.

3. Local visceral effects become manifest, most pronounced in the
brain. Stasis-thrombosis of deep cerebral veins leads to the development
of hemorrhagic lesions in the persisting deposits of germinal matrix tissue
in the subependymal zones of the cerebral hemispheres. As defined in the
present investigation, the hemorrhage-producing lesions in the sub-
ependymal matrix tissue, pathologically, are venous infarcts.

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Illustrations are by Mr. Leo Goodman, Boston, Mass.


[*Illustrations follow*]

Legends for Figures

Fig. 1. Case 1. A. Infarction of cerebral subependymal matrix. Frontal section of brain at level of anterior limb of internal capsule. Section of brain shows thick, deeply staining deposit of subependymal matrix at lower lateral aspects of ventricle, with irregular pale areas of infarctional devastation. Thrombosis of veins in matrix. Nissl. $\times$ 2.0. B. Higher magnification of periventricular area. $\times$ 6.0.

1A
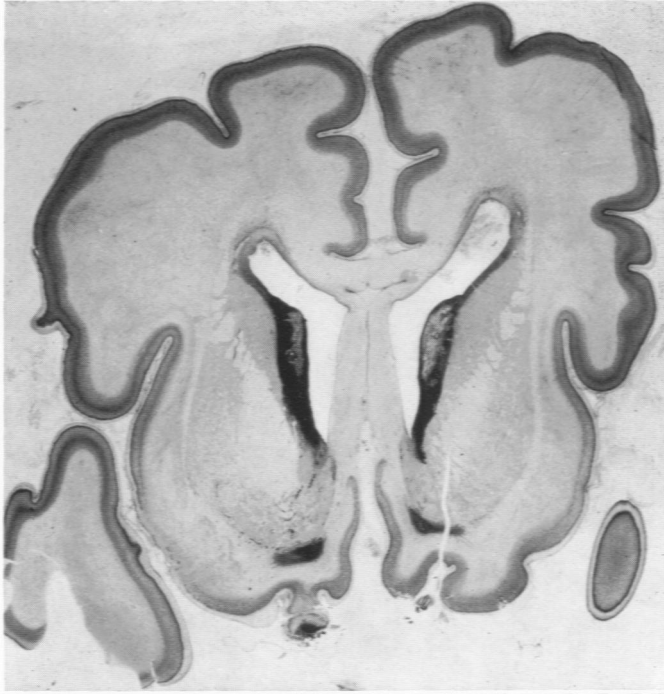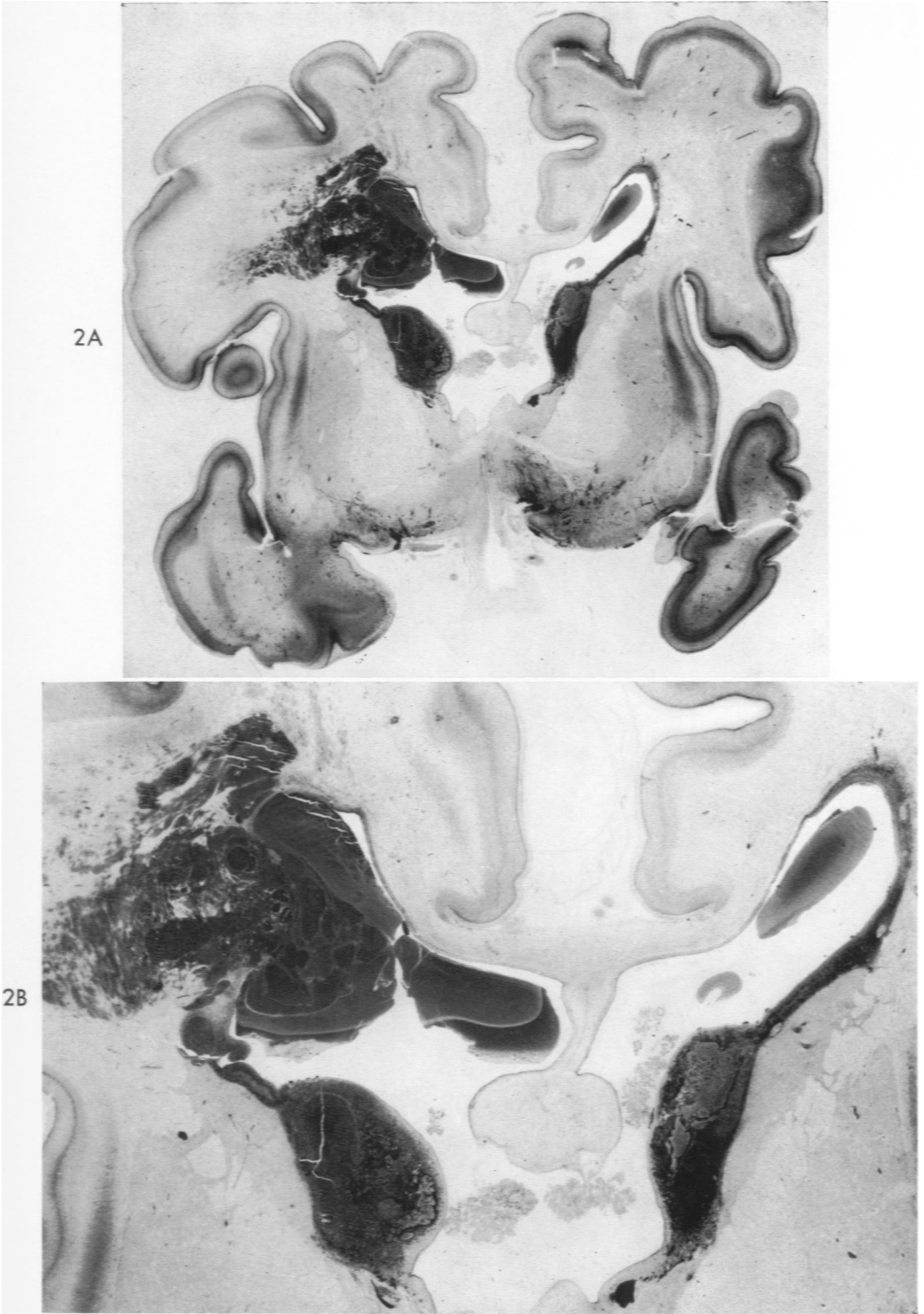
1B

Fig. 2. Case 2. **A.** Infarction of cerebral subependymal matrix and periventricular white matter. Frontal section of brain shows hemorrhagic suffusion into infarcted cerebral substance, thrombosis of periventricular veins, intraventricular hemorrhage. Nissl. × 2.6. **B.** Higher magnification of periventricular area. × 5.8.
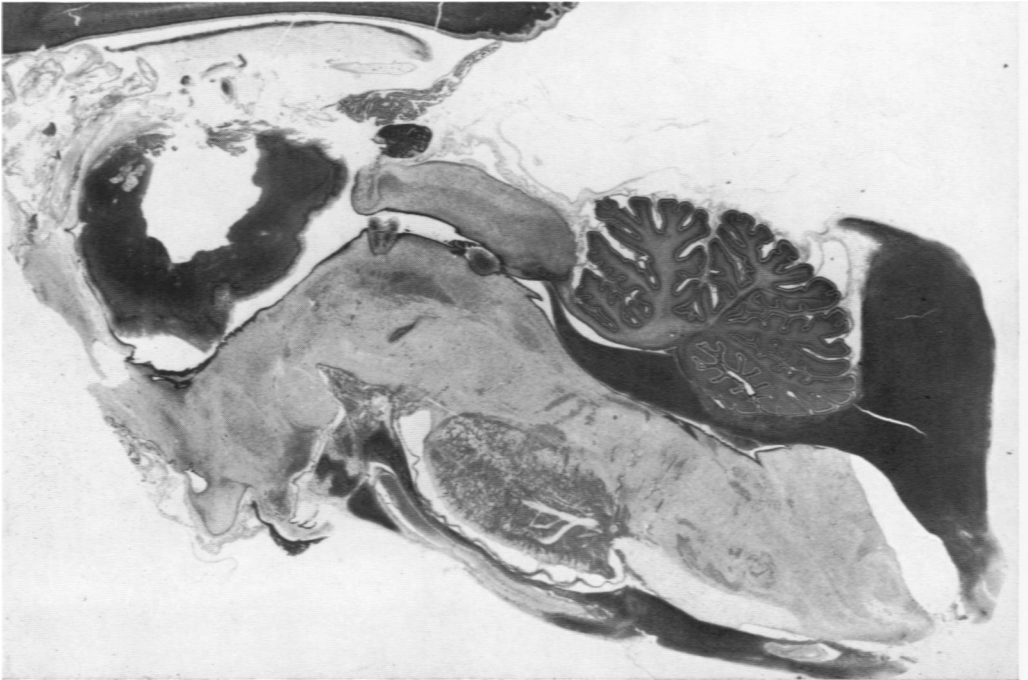
Fig. 3. Case 3. Massive infarction of cerebral wall with hemorrhage extending into peri-
ventricular matrix and white matter. On right, vena terminalis, located on lateral aspect
of ventricle, is dilated and occluded by thrombus. Horizontal section. Nissl. × 2.2.   **Fig.
4.** Case 4. Massive subependymal matrix infarction with intraventricular hemorrhage. Sagittal
section. Nissl. × 2.8.

Fig. 5. Case 5. Subependymal matrix infarction; intraventricular hemorrhage issuing from dilated disrupted venous channel in infarcted matrix. Periventricular infarction of white matter at upper aspect of ventricle. Sagittal section. Nissl. × 7.0.

Fig. 6. Case 5. Brain stem showing extension of ventricular hemorrhage into subarachnoid space. Brain appeared intact externally but showed accumulation of blood in subarachnoid space about stem. Midsagittal section. Nissl. × 4.4.