Mental Retardation Due to Germinal Matrix Infarction

Brain damage in the fetal-neonatal period linked to development of mental retardation.

Abraham Towbin

Introduction

In the human fetus and premature newborn, the cerebral germinal matrix deposits are frequently the site of hypoxic damage. The lesions are pathologically of infarctional origin and are located predominantly in the periventricular layers of the cerebrum (*1*) (Figs. 1 and 2). Significantly, investigators have pointed out that, in cases of mental retardation and cerebral palsy, the chronic lesions present, of encephaloclastic character, are in most cases located in the deep, periventricular structures (*2*) (Fig. 3). The similarity of the cerebral lesions in the neonatal and the mental retardation cases—the corresponding location and pathologic character of the lesions—is not a random relationship. In this study, attention is focused on the evolution of these encephaloclastic processes—the transition between the cerebral damage found in the newborn and the chronic cerebral lesions found in mental retardation.

In the past, attempts to analyze the pathogenesis of the chronic cerebral lesions in mental retardation and cerebral palsy by studies of the brain at autopsy, confronting the pathologic process in the end-stage, have not been fruitful. The cerebral lesions have their origin mainly during gestation and in the perinatal period; the key to the pathogenesis of these lesions lies in correlating patterns of cerebral damage occurring in the fetus and newborn with patterns of cerebral lesions present in mental retardation and cerebral palsy.

Traditionally, the occurrence of hypoxic damage in the neonatal brain has been minimized, the opinion being widely held that few if any consistent changes could be demonstrated. The examination of the newborn brain, soft and friable, at times diffluent, offers technical difficulties often insurmountable for the neuropathologist.

Methods developed in the present investigation permitted detailed histopathologic study of the fetal and neonatal central nervous system. The technique of whole-brain serial histologic sectioning (*3*) made possible the consistent identification of focal lesions, large and small, and the demonstration of their geographic relations in the brain (*4*). A broad source of clinically correlated case material, over 600 fetal and neonatal brain specimens, were available for study.

The occurrence of mental retardation, cerebral palsy, and other disorders of the nervous system in children born prematurely is a problem of mounting concern. Over 300,000 premature children are born annually in the United States. Manifestly, clinical skill in maintaining survival of the premature infant has surpassed the ability to preserve the organic and functional integrity of the unripe brain. Infants born extremely premature (very small prematures) who survive have a very high incidence of mental retardation. In general, the severity of the nervous system deficit is proportional to the degree of prematurity. In premature infants with birth weight under 2500 grams, the incidence of mental retardation [intelligence quotient (I.Q.) less than 70] is over 10 percent, almost twice that in infants born at term. Very small prematures—with birth weight of 1500 grams or less—who survive have I.Q. test scores about 10 to 12 points lower than in term infants. Twenty-five percent of such very small prematures who survive have an I.Q. of 80 or less (*5*). Analogously, in cerebral palsy, a history of prematurity is obtained in over 25 percent of cases (*6*).

Related to the problem of nervous system damage in premature infants is the clinical enigma of children with a history of uncomplicated, noncyanotic delivery, born at term, who develop cerebral palsy and mental retardation.

Hypoxic complications affecting the fetus and newborn may lead to death precipitously, before local organic damage can be imprinted in the brain. Or, the damage may be severe but not lethal, the lesions becoming subacute and chronic in form, ultimately resulting in mental retardation and other crippling neurologic deficits. Less extensive acute damage may occur, the effects remaining latent.

In investigating brain damage in the fetus and newborn, other pathologic processes, as well as hypoxic cerebral infarction, bear consideration. Of common occurrence neonatally is mechanical injury of the spinal cord and brain stem (*7*). Significantly, with this type of injury producing central nervous system depression, surviving infants may show secondary cerebral hypoxic damage. Injury to the cerebrum due to direct trauma appears infrequently in the premature period. Subdural hemorrhage into the posterior fossa when it occurs is usually rapidly fatal, and has no bearing on the occurrence of mental retardation. Extensive subdural hemorrhage over the cerebrum is uncommon in premature infants (*8*).

A host of other neonatal nervous system disorders—genetic anomalies, metabolic defects, infectious diseases, and neoplastic processes—make their appearance and, although rare, consume vast academic attention. In a broad view, as evident in the present study comprising more than 600 cases, the bulk of cerebral damage that occurs in the fetus and newborn is of hypoxic, infarctional origin (*1*).

In analyzing the role of hypoxic damage in the pathogenesis of mental retardation and cerebral palsy, in defining the stage-by-stage development of the cerebral lesions, it is requisite

From the Department of Neuropathology, Harvard University Medical School, Boston, Massachusetts; The Laboratory of Neuropathology, Danvers State Hospital, Hathorne, Massachusetts; and the Department of Pathology (Neonatology), St. Margaret's Hospital, Boston, Massachusetts.

that (i) the acute forms of the cerebral hypoxic damage in the fetus and newborn be identified and correlated with (ii) the intermediate, subacute stage of the encephaloclastic process in fetuses and newborn who live for a period after exposure to hypoxia; the transitional changes at this stage are to be linked ultimately with (iii) the chronic forms of the cerebral damage, with the end-picture, as demonstrated in cases of mental retardation and cerebral palsy.

Acute Cerebral Infarctional Damage

Two specific forms of acute hypoxic cerebral damage occur neonatally (*9*). The patterns of cerebral damage are determined by the gestational age, the distribution of lesions in the premature being different from that of the mature infant. (i) In the premature fetus and newborn, hypoxic damage is consistently localized in the deep, periventricular strata of the cerebrum. (ii) In the mature fetus and newborn the tissue mainly affected by hypoxic damage is the cerebral cortex.

In the premature newborn of 25 to 35 weeks' gestation, the predilection for localization of the cerebral damage in the deep tissue is influenced by specific biologic factors. (i) At this period, local organogenesis in the forebrain is most prominent in the deep structures, where elaboration of neurohistologic elements from the deposits of germinal matrix tissue is highly visible. In contrast, the rudimentary cerebral cortex appears as an inert, poorly vascularized, compact, thin ribbon. (ii) Germinal matrix tissue persists in the cerebrum of the early fetus and premature newborn, forming thick subependymal accumulations lining the lateral ventricles (Fig. 1). The deposits of germinal matrix are depots of spongioblastic anlage tissue required for the future formation of the cerebral cortex and deep neuronal assemblies. These masses of subependymal germinal tissue, highly cellular and richly vascularized, are manifestly vulnerable to hypoxia, readily undergoing disintegration. (iii) The deep venous drainage system of the cerebrum is prominently formed in the premature, the superficial cerebral veins being inconspicuous. In the deep cerebral tissue of the premature fetus and newborn, not only are the parenchymal elements being actively proliferated, but also the vascular structures, especially the veins. In whole-brain histologic sections of the premature brain, the deep cerebral veins, the Galen system, stand out strikingly.

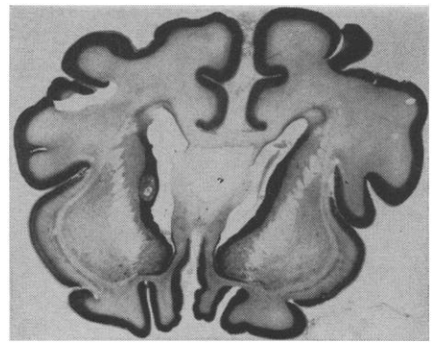

Fig. 1. Germinal matrix tissue in the human fetal brain (gestational age 32 weeks); thick, compact, deeply staining periventricular (subependymal) germinal matrix layer on the lateral walls of the cerebrum; on the left, dilatation and thrombosis of the vena terminalis with perivascular hemorrhagic patch of matrix devastation. Case No. T-3. Cresyl-violet stain (× 1.7).

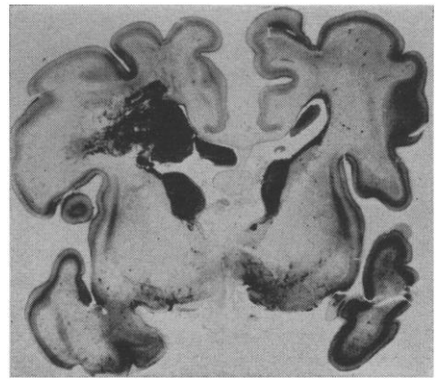

Fig. 2. Periventricular acute infarction of the cerebrum in the premature infant; on the left, the area of hemorrhagic necrosis extends from the subependymal germinal matrix deposit at the caudo-thalamic groove upward into the deep white matter on the lateral aspect of the hemispheric wall. Case No. W-59. Cresyl-violet stain (× 1.6).

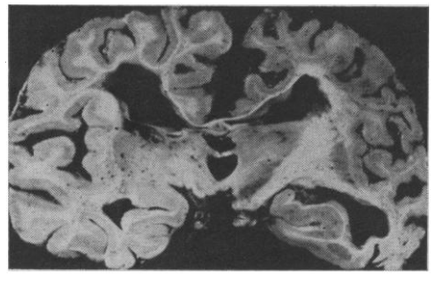

Fig. 3. Periventricular chronic lesion in 8-year-old girl with mental retardation, spasticity, and convulsive disease. The cystic necrosis and scarring on the left near the caudothalamic groove involves the subependymal portion of the basal ganglia and the thalamus and extends upward with destruction of the deep white matter lining the lateral ventricles. Case No. CSS 10762.

Infarction—localized devitalization of tissue, ultimately leading to necrosis—is the result of interference with local circulation. Infarction may be due to slowing and obstruction of arterial inflow or to venous outflow. With stasis of circulation leading to venous infarction, the lesion tends to be hemorrhagic.

In the cerebrum of the premature fetus and newborn, circulatory stasis in the vena galen is directly reflected upstream; the veins in the periventricular matrix and white matter become dilated and engorged, often undergoing thrombosis. As the process of venous congestion and thrombosis manifests its effects, the surrounding tissue undergoes necrosis, ultimately showing far-advanced infarction; in affected areas, with breakdown of engorged necrotic blood vessels, the disintegrating tissues become flooded wtih blood. Schwartz (*10*) and others (*11*) have described the occurrence of hemorrhagic necrosis of the basal ganglia and other deep cerebral structures in association with thrombosis of deep cerebral veins in prematures. From the onset, the infarctional process in the deep cerebral tissues causes damage not only to the parenchymal cells but also to stromal elements, particularly to venous structures. At an early stage, the blighted periventricular tissues may show numerous focal hemorrhages. Likewise, small focal areas of periventricular leucomalacia make their appearance (*12*); these are lesions having the character of microinfarcts, related in their genesis to the large, deeply located venous infarcts in the cerebrum of the premature (*9*).

The occurrence of cerebral venous infarction in the fetus and newborn is not a local phenomenon, but represents the endstage in a consecutive series of systemic pathologic processes which may have their origin before, during, or after birth. The development of cerebral infarction in the newborn evolves through three stages, each precipitating the next.

1) Fetal or newborn hypoxia develops. Occurring prior to birth or after, the hypoxic complication may be of maternal, placental, fetal, or neonatal origin. Prenatally, hypoxia most commonly is due to placental disorders, par-

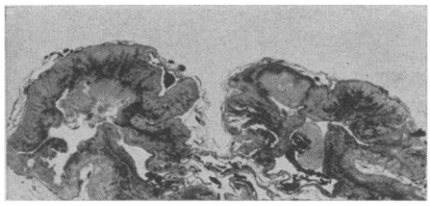

Fig. 4. Subacute stage, neonatal cerebral periventricular venous infarction; vena galen thrombosis. History of maternal illness with vaginal bleeding, requiring hospitalization 2 months before delivery; term infant, lived 18 hours. Section shows active advanced infarction, with organization and scarring of necrotic periventricular tissue. Case No. T-1. Hematoxylin and eosin stain (× 1.4).

ticularly premature detachment. Postnatally, especially in the premature, hypoxia is often of peripheral pulmonary origin, hyaline membrane disease, or pneumonia.

2) Systemic circulatory failure occurs as a consequence of prolonged hypoxia; generalized venous engorgement develops.

3) Local visceral (venous) infarctional damage becomes manifest, organs having a large blood flow volume, the brain and kidney, being especially susceptible. The most vulnerable site in the premature is the deep tissues of the cerebrum.

As the fetus nears term, the momentum of histogenesis at the core of the cerebrum declines; the subependymal germinal matrix tissue becomes depleted. On the other hand, in the cerebral cortex, architectural activity is intensified at this time. The cerebral convolutional pattern is evolved, and the cortical laminar structure is differentiated. Correspondingly, near term, the site of hypoxic cerebral infarctional damage shifts from the periventricular strata to the actively proliferating, vascularized cortex (*13*). It merits emphasis that the cortical damage in the mature newborn is analogous to the deep cerebral damage in the premature—the consequence of pathologic processes initiated by systemic disturbances.

Intracerebral hemorrhagic damage in the premature reaches its highest incidence at 28 weeks' gestation, being observed almost universally in this age group at autopsy. In the present material, of 140 technically suitable cases available between gestational age of 22 and 35 weeks, severe infarctional lesions were present in 26 cases; matrix lesions of moderate severity were present in 41; in the remaining 73 cases, cerebral congestion with small hemorrhages were present. In 110 term or near-term newborn brain specimens, severe cortical damage was evident in five cases. The occurrence in prematures of extensive, deep cerebral hypoxic lesions is over ten times greater than the incidence of term cases with cortical devastation.

Cerebral hypoxic damage, sometimes far advanced, occurs during intrauterine life. The development of infarctional lesions in the cerebrum of the fetus has been demonstrated before and was evident in this investigation. In premature infants, stillborn, cerebral periventricular infarctional lesions are commonly present (*1*, *8*); in term stillborn, less often, infarctional lesions are evident in the cortex (*13*, *14*). Pertinently, cerebral infarctional damage is present at times in cases in which fetal death is known clinically to have occurred prior to labor. With hypoxic complications occurring early in the last trimester, and if gestation terminates directly with fetal or neonatal death, cerebral lesions present in the periventricular tissues at autopsy are correspondingly fresh. However, if pregnancy is maintained after a damaging hypoxic event, or if premature delivery occurs and the newborn survives for a period of weeks or months, subacute and chronic cerebral lesions are elaborated.

Subacute Cerebral Hypoxic Damage

Cases of subacute cerebral infarctional damage in the newborn offer an important link pathologically in relating the processes of neonatal cerebral damage to the chronic cerebral lesions found in mental retardation.

Subacute infarctional damage of the cerebrum in the newborn, as with acute, is found most frequently in the deep, periventricular tissue. Cortical cerebral infarction in the newborn is comparatively rare; such damage, present in mature infants, generally is the result of hyaline membrane disease or other hypoxia-producing complications after birth.

Subacute infarctional damage in the deep cerebral tissues, as indicated, may develop (i) in the premature fetus, early in the last trimester, or (ii) in the premature newborn infant, born at 25 to 35 weeks' gestation, who survives for a period of weeks or months. Infants born at term may thus present subacute

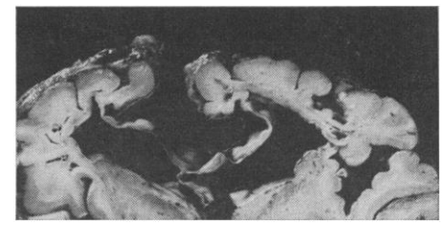

Fig. 5. Chronic periventricular necrosis; characteristic pattern of cerebral damage in organic mental retardation and cerebral palsy. Seven-year-old spastic quadriplegic with mental retardation. Case. No. CSS 5064.

infarctional lesions in the deep cerebral tissues, the consequence of hypoxic gestational complications occurring weeks or months before, the gestation having been maintained despite the cerebral damage suffered by the fetus.

The subacute infarctional lesions in the deep cerebral tissues vary from small, latent periventricular foci of necrosis and scarring, to massive deep areas of destruction consuming the core of the hemispheric wall. The smaller lesions, visible microscopically, consisting of focal areas of necrosis undergoing organization and gliosis, are marked by clusters of hemosiderin-containing phagocytes. These smaller lesions are most frequent in the subependymal tissues at the caudo-thalamic groove, the previous site of thick deposits of germinal matrix tissue. Larger lesions, evident grossly as areas of tan softening, sometimes cystic, likewise occur near the caudo-thalamic groove, involving the periventricular white and gray matter. The devastation may penetrate deeply into the basal ganglia, at times eroding the entire core of the cerebral hemispheres.

The following case is an example of extensive subacute periventricular cerebral infarction (Fig. 4). The mother became acutely ill 2 months before delivery with a respiratory infection and vaginal bleeding, and required hospitalization. The pregnancy was maintained. The infant, delivered at term and weighing 2770 grams, lived 18 hours. Externally the infant appeared well formed; the head was of proportionate size. The brain was very small, weighing 130 grams (average 360 grams). The miniature cerebrum showed well-defined convolutions, giving the specimen the appearance of a collapsed loaf of braided bread. The histologic sections indicated clearly the mechanism of the damage; the vena galen and its deep cerebral tributaries contained well-

established thromboses; the periventricular layers of the cerebrum were destroyed by multiple confluent infarcts undergoing organization and scarring. The cerebrum appeared reamed out by the infarction, leaving the hemispheres as irregular thin-walled sacs covered with distorted cortical tissue.

It is evident that neonatal leucoencephaloclastic damage of this degree, advancing from the subacute stage of infarction to the chronic form in infants who survive, may ultimately result in the formation of multiple cavities and scarring in the deep cerebral white matter (Fig. 5); in extreme cases it may terminate with hydranencephaly and with small cerebral hemispheres of thin leather-like character covered with remnants of cortical tissue associated with profound mental deficiency and other severe nervous system deficits during life.

Chronic Lesions in Mental Retardation

In early neuropathologic studies of mental retardation and cerebral palsy, in analyzing the chronic lesions in the brain, two basic forms of cerebral damage were described—deep and cortical. The two patterns of damage, stemming from hypoxic lesions present neonatally, were defined in past investigations by Malamud (*2*) and have been recognized by others (*15*). Deep cerebral damage is far more frequent in mental retardation and cerebral palsy than cortical scarring. Significantly, the frequency of deep cerebral damage evident in cases of mental retardation is analogous to the high incidence of deep cerebral damage observed in the neonatal case material. The deep lesions in the forebrain in mental retardation and cerebral palsy involve the periventricular white matter, the basal ganglia, and the thalamus. The distribution of the deep chronic lesions reflects an origin related to the deep venous drainage system (*2, 10*).

Pathologically, the chronic lesions are characterized by decimation of parenchymal elements with resulting scarring and cystic necrosis. Characteristic of old hemorrhagic infarctional damage, the areas of destruction at times have a tan discoloration grossly and show hemosiderin phagocytosis microscopically.

The pathologic pattern of the chronic lesions, their extent and severity, depends on the intensity and duration of the original hypoxic insult. Scholz (*16*) has pointed out that if the hypoxic exposure is mild, cellular elements may be lost, but often such depopulation is not discernible microscopically; with more severe hypoxia, local destruction of parenchymal elements and gliosis result; with extreme hypoxia, total necrosis occurs with the formation of scars and cystic lesions.

The common basic patterns of chronic brain damage in mental retardation and cerebral palsy (*2, 15*) have not become widely known medically. For the most part, the cerebral lesions occurring in these disorders are pathologically of the same mold—encephaloclastic processes presenting with local parenchymal loss, scarring, and cystic destruction. The clinical manifestations of the damage depend essentially on the location of the lesions. Destruction in the precentral region is associated with spastic cerebral palsy; if the process of devastation sweeps over the cerebrum frontally, defects in mentation appear; if the occipital lobe is damaged, blindness follows; if the deep neuronal assemblies of the forebrain are affected, athetosis or other forms of dyskinesia may appear. In the course of hypoxic injury, if an epileptogenic scar is imprinted in the cerebrum, the common clinical triad of mental retardation, cerebral palsy, and epilepsy is rendered complete.

The relation between deep chronic cerebral lesions and previous exposure to hypoxia during fetal life is indicated in the reports by Neuberger (*17*) and Hallervorden (*18*). In the cases described, the fetus was subjected to hypoxia months before birth during maternal attempts at suicide by asphyxia. Clinically, evidence of severe mental retardation and motor disturbances was present in the infants; postmortem examination showed extensive cerebral destruction, with scarring and cyst formation in the white matter and basal ganglia.

Thrombosis of the deep cerebral veins causing periventricular cerebral damage in the newborn and the association of this process with the development of deep cerebral lesions in mental retardation and cerebral palsy has been indicated by Schwartz (*10*), Malamud (*2*), and others (*19*). The infarctional nature of status marmoratus, the process having origin neonatally, and the association of the lesion with chronic cystic damage and scarring, often with evidence of old hemorrhage, has been pointed out in the past; the distribution of lesions in status marmoratus in the basal ganglia and thalamus indicate a relation to the deep cerebral venous drainage system (*2*).

The frequent small periventricular cerebral lesions in the neonatal case material are precursors of analogous lesions in the adult. In routine sections of the adult cerebrum, the occurrence of small subependymal scars, often prominent near the caudo-thalamic groove, generally dismissed as incidental, may in some instances represent sequels of periventricular infarctional damage dating from the fetal and neonatal period. The significance of such latent lesions merits careful consideration. Scholz (*16*) has emphasized that such depletion of cellular elements in the brain, diffusely distributed although inauspicious anatomically, may be associated with serious crippling of neurologic function.

Discussion

The processes of gestation and birth expose the fetus to many hazardous complications. The maternal-placental-fetal organization is delicately balanced; the placenta has a narrow margin of safety; pathologic changes such as premature detachment and infarction of the placenta, contravening oxygen exchange, may cause fetal death or render the fetus hypoxic for prolonged periods. During gestation and delivery, the fetus is subjected to rapid, often turbulent alterations in its environment and is required to make complicated changes in circulation, respiration, and other system functions. Particularly the premature, unready and fragile, born through a physiologically unprepared, unrelaxed birth canal, is highly vulnerable to hypoxic and mechanical damage.

The fetal and neonatal period has a death rate greater than any other time of life. The frequency of sublethal damage—the organic attrition suffered by the fetus and newborn—often escapes consideration. The broad, varied spectrum of diseases which affect the fetus includes most of the organic disorders which occur in the adult. Many latent pathologic processes in the nervous system and other organs initiate their damage in the fetus and manifest their effects in the adult.

Although all organs of the fetus and newborn are vulnerable to hypoxia, the

most sensitive register of such damage proves to be the brain. For the fetus, during its marginal existence *in utero* and as it is pistoned down the birth canal and separated, some degree of hypoxic and mechanical damage to the nervous system is inescapable. Gestation and birth form an inexorable leveling mechanism; with the brain blighted at birth, the potential of mentation may be reduced from that of a genius to that of a plain child, or less. The damage may be slight, imperceptible clinically; or, it may spell the difference between brothers, one a dexterous athlete, the other "an awkward child." Substantially, it is said, all of us have a touch of cerebral palsy and mental retardation, some more, some less—the endowment pathologically of gestation and birth.

Manifestly, fetal and neonatal hypoxic cerebral damage results not only in the reduction but also in distortion of nervous system function. The child with cerebral palsy exhibits spastic paralysis and often the abnormal motor activity of athetosis. Clinically, in addition to the three generally recognized sequels of neonatal hypoxic cerebral damage—cerebral palsy, epilepsy, and mental retardation—attention is being increasingly directed to a fourth category, reflecting the high incidence of behavioral disorders in children with history of complicated birth and prematurity (*20*).

Clinically, it is indicated that 3 percent of the general population, having an I.Q. of less than 70, are to be classified as mentally retarded. Biologically, two categories of mental retardation are defined: (i) Mental retardation as a manifestation of genetic, environmental, and other nonorganic influences; this type is generally of moderate severity, occurs mainly in the lower social levels, and is estimated to comprise five-sixths of all mentally retarded. (ii) Mental retardation of organic, encephaloclastic origin, the consequence of gestational and parturitional cerebral damage; commonly this form is of severe degree, is nonfamilial, occurs in all social levels, and is estimated to comprise one-sixth of all mentally retarded (0.5 percent of the general population). The present study concerns itself with this latter form.

The high incidence of mental retardation, cerebral palsy, and other neuropsychiatric disorders in children born prematurely has been broadly considered clinically; the posture of this matter is indicated by the variety of gestational and parturitional factors suspected, including defective nutrition, mechanical trauma, maternal drug intoxication, hematological disorders, and infectious agents. Prior to the national Collaborative Perinatal Project, facilities for the comprehensive pursuit of this problem in the pathology laboratory were not available.

The initial findings emerging from the neuropathologic investigations in the project focused attention on the occurrence of germinal matrix damage; the pathogenesis of these lesions was clarified (*1*). Interest was centered on the large destructive hemorrhagic infarctional lesions in the subependymal cerebral matrix tissue, commonly leading to intraventricular hemorrhage and death of the fetus or premature newborn.

Small diffuse sublethal lesions are observed in the cerebral germinal matrix tissue almost universally in prematures examined (Fig. 1); involutional forms of such minimal lesions, glial-hemosiderin scars, appear commonly in infants who live for a short period after birth. These small infarctional lesions in the matrix tissue may have profound effects clinically in infants who survive. The untimely loss of this anlage tissue, occurring in the fetus and premature newborn, may not be recovered; the precocious depletion of this cellular building material required in the growth and differentiation of the cortex and other cerebral structures may be reflected in the high incidence of mental retardation and other nervous system disorders in children born prematurely (*21*).

The intrauterine occurrence of cerebral matrix infarction merits broad clinical attention. Parenthetically, paradoxically, it is said that the premature is born too early and too late.

The findings in the present study have a bearing not only on the sequels of prematurity, but on the whole problem of organic mental retardation. The underlying pathologic processes affect both premature and term infants. From observations in this study, a formula emerges for interpreting the time of occurrence and pathologic mechanism responsible for cerebral lesions in mental retardation. The high incidence of deep cerebral damage, much greater than cortical damage, in both the neonatal and chronic case material, indicates that in a large proportion of cases of organic mental retardation, the cerebral lesions are imprinted early in the last trimester of pregnancy, rather than at delivery or postnatally. This concept offers a solution, on an organic basis, to the problem of the common occurrence of cerebral palsy and mental retardation in children with a history of uncomplicated term delivery.

Applied in a broader sense, the findings in the present study indicate that infarction of germinal matrix, producing residues of chronic cerebral damage, is a basic mechanism of pathogenesis in mental retardation and other related infantile brain disorders.

Summary

Mental retardation is known to occur as the consequence of hypoxic complications during gestation and birth. The underlying pathogenesis has not been clear. The present study describes the transition between acute cerebral infarctional damage in the newborn and chronic encephaloclastic lesions in mental retardation. Available for this investigation were over 600 fetal-neonatal cases, clinically correlated; the technique of whole-brain serial histologic sectioning permitted detailed pathologic analysis of the central nervous system.

The findings indicate that in the fetus and newborn most hypoxic cerebral lesions are of infarctional origin. The cerebral infarcts are the end stage in a consecutive series of systemic pathologic processes stemming from hypoxia-producing disorders in the maternal-placental-fetal-neonatal organization.

The most frequent form of neonatal cerebral hypoxic damage, characteristic of the fetus and premature, results in the destruction of periventricular tissues, especially the subependymal germinal matrix. Of direct significance, investigators in past studies of the brain in mental retardation and cerebral palsy found, correspondingly, that the chronic hypoxic encephaloclastic lesions present were in most cases located in the cerebral periventricular structures. Hypoxic damage of the cerebral cortex is relatively infrequent, in both the acute neonatal and chronic case material. The similarity in the organic nature, location, and frequency of the deep form of cerebral damage in the neonatal and chronic case material reflects a common pathogenesis. This is substantiated by the occurrence of subacute forms of cerebral infarctional damage linking the acute fetal-neonatal lesions with the chronic lesions of mental retardation.

The high incidence of mental retardation, cerebral palsy, and related nervous system disorders in infants born prematurely is of mounting concern. The present study focuses attention on the process of germinal matrix infarction as the basic causal mechanism in the premature. This considered, the present day clinical methods of management in premature delivery bear reconsideration.

Correlating the acute and chronic neuropathologic case material, with reference to the occurrence of deep and cortical cerebral damage, a formula emerges for interpreting the time of incurrence and pathologic mechanism in cerebral palsy, mental retardation, and related nervous system disorders. The deeply rooted concept attributing organic mental retardation and cerebral palsy to "birth injury" may be in error to a significant degree; it is apparent that in a major portion of cases the hypoxic brain damage, located deeply in the cerebrum, affecting the germinal matrix tissue and surrounding structures, is imprinted weeks or months prior to delivery. This accounts for the frequent occurrence of organic mental retardation and cerebral palsy in children with a history of uncomplicated delivery.

Affecting infants born at term and prematurely, the precocious destruction of cerebral germinal matrix tissue, antecedent to mental retardation and cerebral palsy, is a phenomenon which has generally escaped consideration clinically and in the pathology laboratory.

References and Notes

1. A. Towbin, *Amer. J. Pathol.* **52**, 121 (1968).
2. N. Malamud, in *Mental Retardation*, H. A. Stevens and R. F. Heber, Eds. (Univ. of Chicago Press, Chicago, 1964), p. 429.
3. Developed by P. I. Yakovlev.
4. The study was conducted in conjunction with the national Collaborative Perinatal Project (Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood).
5. H. Berendes, *Med. Tribune* **9**, 29 (1968).
6. A. M. Lilienfeld and E. Parkhurst, *Amer. J. Hyg.* **53**, 262 (1951).
7. A. Towbin, *Arch. Pathol.* **77**, 620 (1964).
8. O. Gröntoft, *Acta Obstet. Gynecol. Scand.* **3**, 308 (1953).
9. A. Towbin, *Arch. Neurol.* **20**, 35 (1969).
10. P. Schwartz, *Birth Injuries of the Newborn* (Karger, Basel, 1961), pp. 42–75.
11. E. Rydberg, *Acta Pathol. Microbiol. Scand. Suppl.* **10**, 8 (1932); H. Ehlers and C. B. Courville, *J. Pediat.* **8**, 600 (1936); J. C. Larroche, *Biol. Neonatorum* **7**, 25 (1964); R. M. Kalbag and A. L. Woolf, *Cerebral Venous Thrombosis* (Oxford Univ. Press, New York, 1967), pp. 69–73.
12. B. Q. Banker, *J. Neuropathol. Exp. Neurol.* **20**, 127 (1961).
13. A. Towbin, *Excerpta Med. Int. Congr. Ser.* **100**, 724 (1965).
14. A. Manterola, A. Towbin, P. I. Yakovlev, *J. Neuropathol. Exp. Neurol.* **25**, 479 (1966).
15. J. Hallervorden and J. E. Meyer, in *Handbuch der speziellen pathologischen Anatomie und Histologie; Nervensystem*, F. Henke, O. Lubarsh, R. Rössle, Eds. (Springer, Berlin, 1956), vol. 13, pt. 4, pp. 194–282; A. Towbin, *The Pathology of Cerebral Palsy* (Thomas, Springfield, Ill., 1960), pp. 23–171.
16. W. Scholz, in *Handbuch der speziellen pathologischen Anatomie und Histologie; Nervensystem*, F. Henke, O. Lubarsh, R. Rössle, Eds. (Springer, Berlin, 1956), vol. 13, pt. 1, pp. 1284–1325.
17. F. Neuberger, *Beitr. Gerichtl. Med.* **13**, 85 (1935).
18. J. Hallervorden, *Allg. Z. Psychiat.* **124**, 289 (1949).
19. O. Marburg and L. Cassamajor, *Arch. Neurol. Psychiat.* **52**, 170 (1944).
20. E. Denhoff and I. P. Robinault, *Cerebral Palsy and Related Disorders* (McGraw-Hill, New York, 1960), pp. 57–112.
21. A. Towbin, *Multidisciplinary Conference on the Etiology of Mental Retardation, 4th* (Kellogg Center, Univ. of Nebraska, 1968).

22. Supported by PHS grant NB 03190. This study of infantile brain disease was begun in the Department of Pathology (Neuropathology), Ohio State University in 1952, and continued in 1957 at the Deutsche Forschungsanstalt für Psychiatrie, Max-Planck Institut, Munich, Germany. The current studies were undertaken in 1961 during my tenure as pathologist in the collaborative perinatal project at Harvard University Medical School, and then as neuropathologist at Danvers State Hospital and at St. Margaret's Hospital, Department of Pathology (Neonatology). Photographs by Leo Goodman, Boston, Mass.

NEWS AND COMMENT

Campus Unrest: Riots Bring Danger of Punitive Backlash

The nation's universities, already buffeted by waves of student unrest, are now facing another danger—the possibility that irate lawmakers will encroach on traditional academic autonomy with a spate of punitive legislation. Roughly a score of state legislatures are considering bills to cope with campus disorders, and a few states have already passed such legislation. Educators in some states fear that the backlash against student unrest may result in "repressive" legislation or deep cuts in state appropriations for higher education. At the national level, sentiment against student rioters is running strong in the U.S. Congress, and the Nixon administration has adopted a tougher line toward student rioters than did the preceding Johnson administration.

Campus unrest has clearly become one of the hottest political issues of the day, largely because it is a subject which seems to stir violent feelings in the public. Opinion polls taken at the national and state levels show strong support for a crackdown on campus disrupters but little concern over what might happen to the universities in the process. In a recent California poll, for example, 72 percent of 1073 persons interviewed "agreed strongly" that "students who challenge and defy university and college authorities should be kicked out to make room for those willing to obey the rules." Only 23 percent agreed strongly that "professors in state-supported institutions should have freedom to speak and teach the truth as they see it."

There is no question that the public and the politicians are attempting to cope with a real problem, for the level of campus violence has soared alarmingly in recent months. In the state of California alone, according to testimony presented last month to a subcommittee of the U.S. House of Representatives, a partial listing of violent episodes would include the shooting and killing of two black activists at UCLA; the maiming of a secretary at Pomona College, Claremont, Calif., who lost two fingers when she opened a package containing a bomb that exploded; the disfigurement of a San Francisco State College student who lost fingers and vision when a bomb that he is charged with planting apparently exploded prematurely; and the detainment, allegedly at knife-point, of 34 administrators and faculty members at San Fernando Valley State College by militants.

Almost all campus administrators seem to agree that such violence and vandalism cannot be tolerated. Indeed, college administrators in some states are openly pleased with recent legislation giving them greater power to cope with campus disruptions. But there is a growing concern among some educators that overzealous lawmakers, in their eagerness to retaliate