Neuropathology of Certain Forms of Mental Retardation

Experiments on monkeys illustrate probable mechanisms of brain damage in human infants.

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Mental retardation is an organic condition of arrested or limited neural development that blocks successful evolution of the capacity of the brain to function; as a result of this block, behavior and (at least in man) intellectual ability are impaired. Forms of behavioral and intellectual impairment that are related solely to socioenvironmental factors are excluded, since in these cases there is no detectable pathology. The forms of mental retardation which concern us here are related to anatomical and chemical disturbances in the nervous system during late prenatal life, at birth, or in the early postnatal period. In this article I discuss brain damage induced experimentally, mainly by interference with labor and parturition in ways that lead to asphyxiation of the fetus or postpartum depression of the offspring. The concept that mental retardation frequently is related to anoxia or asphyxia during parturition is by no means new. There have been literally hundreds of speculative commentaries written on this topic, but few controlled human studies and even fewer animal experiments have been carried out to establish the relationship, determine the extent of permanent brain damage, and set the stage for instituting methods of prevention and therapy (*1*).

I became interested in this subject at Northwestern University 25 years ago, and it was here at the outbreak of World War II that my associates and I completed basic experiments with guinea pigs, demonstrating a relation between structural changes of asphyxia neonatorum and neurological and learning defects in the offspring (*2*). These investigations lapsed for several years during and after the war. When programs were being considered for the newly created National Institute of Neurological Diseases and Blindness, at Bethesda, Maryland, our investigations were reviewed and brought to the attention of the congressional subcommittees on appropriations. Soon thereafter, large-scale support of research on neurological disorders originating in the perinatal period, including mental retardation, was given the institute. Animal experimentation was renewed at Bethesda in 1954; in 1956 the program was extended to laboratories in San Juan, Puerto Rico, where a breeding colony of mature rhesus monkeys, *Macaca mulatta,* had existed, on a small nearby island, since 1939. Later, a comprehensive multi-institutional collaborative effort to collect data from human subjects was launched by the institute.

The Old World monkey *Macaca mulatta* is an ideal animal for studying fetal-maternal relations which are comparable with those in human beings. These rhesus monkeys have menstrual cycles of about 28 to 30 days, almost identical with those of women. In captivity they breed freely in all seasons, and most of them conceive when mated on day 11 of the cycle (*3*). Placentation is similar, though not identical, to that in the human being. Gestation is a little shorter, lasting 6 lunar months on the average, and the offspring is a little more advanced in its development at birth than a human infant. Moreover, in *M. mulatta,* biochemical constants for maternal and fetal blood and other tissues are quite similar to those in the human being. Therefore, we are better able to transfer experimental results from the monkey to the human being than from the guinea pig (the animal used in our first experiments) to the human being.

Mental retardation rarely occurs spontaneously in rhesus monkeys. At least, we have not encountered it in more than 600 natural births. But we were able to produce it experimentally. Asphyxia during birth or soon afterward appears to be one of the most important causative factors in the neuropathology of mental retardation. By "asphyxia" I mean anoxia and concomitant biochemical changes. Some of the effects of asphyxia cannot be separated clearly from those of anesthetics and other drugs used in human obstetrics, but in laboratory animals we can separate the various factors and control the experiments.

One way in which we induced asphyxia in the monkey fetus near term was to perform a Cesarean section under local anesthesia of the abdominal wall (an accepted procedure in human obstetrical practice), quickly detaching the placenta and lifting out the entire uterine contents. With the fetal membranes intact, no air could enter the lungs of the offspring. We timed asphyxia from the moment of placental separation until the moment when the membranes were broken and oxygen or air was admitted to the lungs or artificial respiration was instituted (*4*).

Asphyxia Neonatorum Requiring No Resuscitation

Asphyxia lasting 5 to 20 minutes was induced. The fetuses began to make respiratory movements within the amniotic sac as hypoxia developed—first, shallow rhythmical movements, followed by apnea, then by gasps, which lasted about 10 minutes. Consequently, monkeys delivered from the fetal membranes after short periods of asphyxia did not require resuscitation. They were "breathing." They were deliberately killed by perfusion with fixing solution at various ages. The brains were removed and sectioned serially. We found no neuropathology in the monkeys

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asphyxiated for 6 minutes or less, but in monkeys which had been asphyxiated for 7 to 9 minutes but which had not required resuscitation there were some discrete lesions in the thalamus and inferior colliculus. The newborn monkeys with these small brain lesions showed no "mental retardation," but our clinical and psychological tests may not have been sufficiently refined to detect the effects of relatively minor damage limited to basal regions (*5*). At least we can say that these little monkeys were not palsied and that they behaved normally.

Asphyxia Neonatorum Requiring Resuscitation

A rather constant pattern of central nervous system damage was found in all monkeys (more than 3 dozen) asphyxiated long enough to require resuscitation. The severity of the damage was roughly proportional to the duration of the asphyxia. The neuropathology constitutes a syndrome that has not been recognized generally in the human brain (*5*).

When, after separation of the placenta, the fetus can no longer obtain oxygen, and asphyxiation in the amniotic sac ensues, the central nervous system is affected by the acidosis as well as by the lack of oxygen—that is, by depletion of carbohydrate stores, with rise in carbon dioxide and decline in tissue *p*H and in arterial blood pressure. Under these conditions nerve cells are damaged and some die. Not all parts of the brain are affected equally. We do not know why this is true. One factor may be that metabolism is more active in some centers than in others. Those regions in which oxygen is being used most rapidly at the time of asphyxiation may be the ones most promptly and most severely damaged.

Structural defects invariably were found in the brains of resuscitated asphyxiated monkeys killed at 4 to 10 days of age. Lesions were present in nuclei of the thalamus and basal ganglia, throughout the brain stem, and even in the spinal cord. They were discrete and circumscribed, bilaterally symmetrical, and limited to the boundaries of a particular nucleus or a related group of nuclei. Within each affected nucleus, nerve cells were destroyed, often totally. Neuroglia cells, too, were destroyed in some nuclei, but usually they were spared and the astrocytes were hypertrophied. The organism reacted to the injury in the usual manner—that is, by phagocytosis; the lesions became filled or encircled by microglia cells (*6*). These lesions of uncomplicated asphyxia neonatorum were nonhemorrhagic.

In the brain stem, sensory systems were more severely affected than other systems. Nuclei of the central auditory pathway were damaged or destroyed in all instances. Way stations in afferent paths from the body surface to the cerebral cortex also were injured. Primary motor nuclei usually were spared. The visual system was not affected. The neocortex appeared to be undamaged, but there were defects in the hippocampus, hypothalamus (mamillary bodies), and subthalamus. With passage of time, the appearance of the lesions changed. The microglial reaction disappeared, cells proliferated from the adventitia of blood vessels, and these, with the astrocytes, contributed to the formation of scars.

Animals exhibiting these neural defects were hypoactive, hyporeactive, and sometimes ataxic; most were unemotional and awkward and lacked manual dexterity; some were aphonic (*7*). At first they could not suck, right themselves, or crawl. Feeding in the nursery (the monkey infants were not reared by their mothers) was an around-the-clock chore.

We do not know at what point in time during or after an episode of birth asphyxia the neural damage becomes irreversible. When oxygen is given in resuscitation, the return of most biochemical components to preasphyxial levels lags behind restoration of a normal oxygen content of the blood. It would seem that if the lack of oxygen per se kills the nerve cells, there is not much hope of therapy and one can only strive to avoid asphyxia during birth. But if, as is more probable, circulatory failure and acidosis, including the chemical changes that result in lowered tissue *p*H and exhaustion of carbohydrate substrate for glycolysis, are responsible for the neuropathological changes, a therapy may be devised to save the nerve cells. There are experiments now under way in our laboratory that give hope of accomplishing this. In these experiments, by administering alkali to prevent the blood *p*H from falling and, at the same time, supplying carbohydrate during and after asphyxial episodes of monkeys at birth, the circulation was maintained, glycolysis was continued, and the survival rate was significantly increased; clinical signs of mental retardation appeared as usual in nontreated infants but were lacking in the treated infants (*8*). It is too early to say whether or not development of the brain-stem lesions was prevented in the experimental animals, because the histological sections are being read under code and I do not know which are from treated animals and which are from controls.

Asphyxia Neonatorum with Postpartum Complications

Another neuropathological syndrome has been observed in the animal experiments. Some monkeys asphyxiated, usually for 15 or 16 minutes, at birth and resuscitated uneventfully with artificial respiration, later went into profound postpartum depression for reasons as yet not clear. On the second or third day of life in the incubator they tended to become dyspneic and cyanotic, and the attendant called for help. Some of the depressed animals lost the ability to swallow and had to be fed by *gavage*. Muscle fasciculations, seizures, and, occasionally, status epilepticus were seen. If the monkey survived, it later exhibited marked neurological defects and often closely resembled a human being with cerebral palsy.

The animals in this category were found to have the same bilaterally symmetrical diencephalic and brain-stem lesions that were found in other asphyxiated and resuscitated monkey infants. But more than that, there was neocortical and sometimes cerebellar damage. Here again, the lesions tended to be bilateral, although they were not always symmetrical. All the brains in which defects of this kind were found came from monkeys that had experienced stormy postpartum periods.

The experiments with asphyxia neonatorum in monkeys have resulted in a concept of the neuropathology rather different from the neuropathology we have been accustomed to expect in human subjects. Few studies of uncomplicated asphyxia neonatorum in human beings have been made. However, findings analogous to the nonhemorrhagic brain-stem lesions of uncomplicated asphyxia in the monkey recently have been reported in human tissue by neuropathologists who made

an effort to examine appropriate regions (*5*). For the neocortical lesions of the asphyxiated and resuscitated monkey infants that had experienced postpartum complications, recognizable counterparts have been found in the human brain. However, we have been led to expect a rather high incidence of hemorrhages associated with asphyxia neonatorum in the human being; this is not the case in the rhesus monkey. I discuss this a little later.

Cerebral Cortical Pathology without Asphyxial Lesions

Mental retardation results from conditions other than asphyxia neonatorum, conditions in which a different type of neuropathology is found. I can illustrate by describing some other experiments with monkeys. Efforts were made to induce labor by administering oxytocin near the end of gestation. Strong uterine contractions occurred, and the intrauterine pressure rose. This artificial labor was prolonged in some of the monkeys for many hours, and the fetus died before delivery, or the offspring survived less than a day. Bilateral hemorrhages were found in the globus pallidus of one of the offspring. Others of the newborn monkeys were depressed at birth and during the postpartum period but lived until we deliberately terminated the experiment. A survey of the histological sections of the brain of one of these clinically retarded monkeys revealed none of the lesions in the thalamus and brain stem that are characteristic of asphyxia neonatorum. Nevertheless, marked bilateral atrophy of the postcentral gyri of the cerebrum had occurred. This was similar to the neocortical lesions in the brains of monkeys that had experienced asphyxia neonatorum and postpartum complications. Apparently asphyxia during birth was not complete in the oxytocin experiments but some other adverse factor came into play in the postpartum period (*9*).

Cerebral Hemorrhage in the Newborn

We do not know to what extent cerebral hemorrhages at birth are responsible for mental retardation in human infants. Few infants with tentorial tears and other trauma survive. Traumatic hemorrhages may be more prevalent in human babies than in newborn monkeys. At birth, the head of the human baby is much larger than that of the monkey infant. Nevertheless, we have encountered one traumatic breech delivery in which the monkey's head was retained and hemorrhages were produced when it was extracted. In another breech presentation manual delivery and resuscitation were required. There could have been petechial hemorrhages at birth, but when the monkey was killed more than 2 years later, no evidence of them remained. The animal had showed severe mental retardation.

Petechial hemorrhages in brain tissue of newborn human babies have been thought to be caused by asphyxia at birth. They are said to be more prevalent in premature than in full-term infants. We have been unable to confirm either of these beliefs in our findings with experimental subjects. I doubt that hemorrhages are often present in surviving human infants who suffered uncomplicated asphyxia during birth. Let us examine the evidence. The type of petechial hemorrhage in question is found at autopsy—that is, the infant died, and when it died its blood pressure declined and a considerable amount of blood shifted from the arteries to the capillaries and veins. Had the capillary walls been weakened by preceding events, including asphyxia during birth, ruptures might have occurred with this agonal shift.

No cerebral hemorrhages have been found in animal fetuses asphyxiated until they died. In animal infants severely asphyxiated, successfully resuscitated, and killed deliberately sometime later by perfusion with fixing solution, no cerebral hemorrhages have been seen. None has been seen in premature infant monkeys. Nevertheless, we did find petechial hemorrhages in the brains of monkeys that had been resuscitated and had been about to die after postpartum depression, sometimes in status epilepticus, when we killed them by the perfusion-fixation technique. And, of course, petechial hemorrhages were present after traumatic delivery. I am inclined to believe that leakage of blood into the cerebral tissues is related usually to some kind of trauma or is a terminal agonal artifact. The fact that nontraumatic hemorrhages are seen in human brains at autopsy does not mean that they are present in the brains of the infants who survived asphyxial episodes (*10*).

Hyperbilirubinemia and Kernicterus

Another cause of mental retardation has been thought to be kernicterus, which is a selective bile-salt impregnation of certain neural tissues associated with hyperbilirubinemia and erythroblastosis fetalis. It has been impossible to arrive at a clear picture of this condition in human infants; in many cases in which a clinical diagnosis of kernicterus has been made and in some infants who show the neuropathology there have been other complications, such as asphyxia neonatorum or trauma during birth. In animals, a condition resembling kernicterus has been found in the Gunn rat, but it is doubtful that this condition is the same as kernicterus in human beings. Monkeys have physiological jaundice at birth. Kernicterus was produced in newborn monkeys in our laboratory for the first time in January. Experimental elevation of the blood level of bilirubin (to 20–35 mg/100 g) for 2 to 3 days after birth, by injecting solutions of indirectly reacting bilirubin (2 mg/100 g) intravenously every 6 hours, produced hyperbilirubinemia but not kernicterus. However, in the presence of hyperbilirubinemia, the imposition of an asphyxial episode led to passage of the pigment from the blood into the brain tissues, including neuroglia cells and neurons, in a selective pattern similar to that observed in human infants (*11*). The kernicteric monkeys were unquestionably retarded.

Summary

In presenting the neuropathology of asphyxia neonatorum and some related conditions, as illustrated in experiments with monkeys (*12*), I have tried to make six principal points. (i) Newborn monkeys need not be asphyxiated to the point of terminal apnea to suffer structural brain damage. Mental retardation has not been proved, but neither has it been excluded, in these monkeys. (ii) Asphyxia neonatorum requiring resuscitation of the offspring, which otherwise would die, is associated with a remarkably constant syndrome of bilaterally symmetrical, nonhemorrhagic lesions in thalamic and brain-stem nuclei, mainly those of afferent systems. The individuals in this category clearly are retarded. (iii) Asphyxia neonatorum of this second degree may be associated with postpartum

complications leading to neocortical atrophy, often of considerable magnitude. The individuals are markedly retarded, often palsied, epileptic, and in a few instances even comatose. (iv) Increased intrauterine pressure in the monkey during prolonged labor leads to fetal and postpartum depression, in connection with which cerebral cortical injury occurs in the absence of typical asphyxial lesions. (v) The relationship of cerebral hemorrhages to mental retardation is not clear, but their presence at autopsy probably signifies trauma during birth, or is an agonal artifact associated with death after postpartum depression. (vi) Finally, kernicterus, a condition in which bile pigment escapes into the brain tissues from the blood when the bilirubin level is high and when there is, in combination with it, some depressing factor such as asphyxia, has been produced in the newborn monkey. It, too, is associated with mental retardation.

References and Notes

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12. I wish to acknowledge the untiring efforts of the staff of the Laboratory of Perinatal Physiology in carrying out these experiments. The findings reported here were made by many investigators, including visiting scientists from several other institutions, American and foreign, working as teams.

Chemical Strengthening of Glass

After more than 70 years of research, glasses can now be made strong enough to be bent sharply.

Joseph S. Olcott

Glass is one of the oldest engineering materials known to mankind. Samples exist today which archeologists date back to many thousands of years before the birth of Christ. Through the years glass has been particularly noted for its transparency, refractoriness, and chemical durability. Unfortunately, because of its fragility, the use of glass has been limited wherever even modest forces might be applied to it. During the past few years, however, steps have been taken by glass scientists to reduce the vulnerability of glass to fracture.

Prince Rupert Drops

It seems strange that even though man has known for many centuries that glass can be strong, very little has been done until recently to make strong, useful articles.

Specimens of glass, now known as Prince Rupert drops, were reported in the mid-17th century as being extremely strong. These were named after Prince Rupert of Bavaria, who presented them to his uncle, King James I of England, in the early 17th century. A Prince Rupert drop is made by allowing a drop of molten glass to be quenched in a cold water bath. The glass generally assumes a teardrop configuration with a long, curled tail (Fig. 1). The thick part of the drop is so strong that it can be hit very hard with a hammer and still remain intact, and it is even said to withstand scratching by diamond. However, if the tail of the drop is flexed sufficiently to cause it to break, the great internal stresses are released suddenly with such violence that the glass shatters, frequently with a loud report, and the whole drop disintegrates into a fine powder. Figure 2 shows the powder that was produced when the Prince Rupert drop in Fig. 1 was broken in this manner. Samuel Pepys commented on these drops in his diary (13 January 1662): "Mr. Peter did show us the experiment of the chymicall glasses, which break all to dust by breaking off a little small end; which is a great mystery to me."

Indeed this must have been a great mystery to the 17th-century mind and although we understand the phenomenon of Prince Rupert drops today, we cannot, for a number of reasons, equal their strength in other forms of bulk glass.

Research by technologists who are attempting to increase the mechanical strength of glass has depended upon which end of the Prince Rupert drop they focused their attention. In the early days of glass manufacture, the main efforts were concentrated on the tail. People thought that the cataclysmic disintegration of glass was something to be carefully avoided. It was. Hence the art of annealing glass was developed.

Annealing is a process whereby the non-uniform stresses in a piece of glass are replaced by a controlled, very low stress level. It is accomplished by heating a formed object to a temperature where it can flow and relieve the internal stresses produced during formation. Then, by cooling it slowly and uniformly, the minimum amount of new strain is introduced. In a sense, one might say that annealing strengthens

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