mental health

Neurological and Psychological Deficits From Asphyxia Neonatorum

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IT is estimated that more than 500 articles have been published on various aspects of cerebral palsy and mental retardation and possible relationships of one or the other to anoxia or asphyxia at birth. Data have been collected and analyzed in less than one-fifth of these studies. A relationship between birth injury of some sort, including that induced by asphyxia neonatorum, and later neurological and mental disturbances has been suggested in most of the later articles. With so much written about these subjects, it is surprising that so little definitive research has been done.

Recently there has been a renewal of interest in the neurological and psychological deficits resulting from adverse factors in the perinatal period (the period from the first viability of the fetus to approximately one month after birth).

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At the end of August 1956, a Conference on Asphyxia Neonatorum, Brain Damage, and Impairment in Learning was held at the University of Puerto Rico School of Medicine for the purpose of bringing together, to plan a course of future studies in animals, investigators in several disciplines who are currently engaged in research or are planning research in this field. Among the accomplishments of the San Juan conference was a thorough review of the present status of the problem.

The number of persons in the United States afflicted by cerebral palsy or mentally retarded, or both, because of some damage to the nervous system occurring during the perinatal period is not accurately known, and the number of new cases added each year is uncertain. However estimates of a prevalence ranging from 336,000 to 550,000 and an incidence of 10,000 new victims have been quoted in lay circles. If these figures serve no other purpose, they remind us that the wastage in lives and resources is a major one deserving great effort toward correction.

How does one define cerebral palsy? There is no agreement. One group would include all organic central nervous injuries incurred during the perinatal period; others would limit the definition to neuromuscular defects. From the research standpoint, one must take the broad view and try to learn as much as possible about

all adverse factors which may operate to cripple the brain of the new individual.

Many of the methods employed in arriving at some estimation of the degree of mental deficit in cerebral palsy patients are subject to error. The frequency, degree, and kind of mental deficit as yet have not been accurately determined. Nevertheless, there is no doubt that mental retardation is more frequent among cerebral palsy patients than it is in the general population. It must be investigated along with other deficits following asphyxia neonatorum or other adverse factors in the perinatal period.

The condition which most clinical investigators consider cerebral palsy has been ascribed to almost every conceivable cause: hereditary factors, malformations or maldevelopment of the brain, disease or injury of the mother, prematurity, hemorrhage, deprivation of oxygen, mechanical injury of the brain at birth, incompatibility of Rh factor, and so forth. Anoxia or asphyxia at birth as causes of cerebral palsy have strong advocates. It has been claimed that anoxia and cerebral hemorrhage (which may result from anoxia) are the two most important causes of cerebral palsy. The role of obstetrical anesthesia as a possible causal agent in production of cerebral palsy has been debated pro and con.

A thorough search of the literature reveals not only that cerebral palsy and mental retardation are thought to have many causes, including neonatal asphyxia, but also that asphyxia at birth can have many effects. Indeed, it sometimes seems to result in no observable effect at all. One reason for the lack of visible effect may be the difficulty of determining whether or not an infant has been subjected to anoxia, which implies complete lack of oxygen, or only to hypoxia, which implies reduced amount of oxygen. In hypoxia, no permanent damage may be encountered even though the infant may display many signs of respiratory embarrassment.

Clinical Research

Clinical studies of possible interrelation of neonatal asphyxia, cerebral palsy, and mental retardation, to which I refer, are of two main types. The majority are characterized by selection of a group of patients who have cerebral palsy or are mentally retarded, or both, and attempting to review their histories in order to determine whether or not evidence exists of some type of birth injury. This retrospective research has features which make its results difficult to interpret. There is an immediate source of bias because the cases are selected on the basis of the appearance of the condition that is to be studied, for example, cerebral palsy. The old notes and measurements that were taken at birth were put in the record with no thought of future research and are nearly always inadequate and often unreliable. The retrospective type of clinical investigation is not worthless, but it can produce little more than trends which must be put to tests in other ways.

A more precise method of clinical research is characterized by letting nature select the cases while the investigator makes the measurements of the various factors and conditions that may prejudice well-being in the years to come. The patients are followed for a period of time during which measurements are repeated and the course of development and growth charted. This we call prospective research. Much of the bias and unreliability inherent in the retrospective type of investigation are eliminated. Attending prospective research, however, is the risk of losing cases in the followup. For example, if neonatal asphyxia leads to death or incarceration, only the patients with the mildest or perhaps undetectable damage will be left in the series. The followup studies must be carefully conducted to keep track of the lost cases. The prospective type of investigation requires careful planning and long-term financial support. For these reasons it has not been as popular as the retrospective type.

I have emphasized these points of difference in approach to clinical investigation in this field because of the importance of establishing projects which give the most promise of arriving at definite and positive conclusions. There is great need for research of the prospective type. To help fill the need, the National Institute of Neurological Diseases and Blindness of the Public Health Service is spon-

soring a broad program of cooperative, prospective clinical investigations.

Animal Experimentation

Clinical studies have been unable to tell us whether or not asphyxia neonatorum is the predominant cause of the brain damage which results in cerebral palsy and ultimately mental retardation or whether there are other factors of equal or greater importance causing the neurological and psychological deficits. Many investigators are convinced that no amount of clinical investigation will ever give a final answer. They believe this is clearly a case for the laboratory scientist and that it should be possible to obtain the answer from animal experiments in which anoxia at birth can be deliberately brought about—in which it does not just happen. In view of the long felt need for experimentation along these lines, it is amazing that so little animal work has been done. Only 5 teams of investigators have published results of research of this type during the past 30 years, and only 2 of these are active at present. It is only fair to add, however, that several additional groups have begun animal experiments recently, and we may expect to hear reports from them in the not too distant future.

Reports were given at San Juan by several of the investigators who had studied brain damage after neonatal anoxia or hypoxia in animals, mostly in rats, chickens, and guinea pigs. One presented a short motion picture film illustrating effects of asphyxiation and resuscitation at birth of a newborn monkey. Aside from this single experiment, I know of no studies in higher mammals.

Experiments on guinea pigs conducted in my laboratories at Northwestern University Medical School several years ago remain the most definitive series of animal experiments available. The observations form the basis for present plans to study neurological and psychological deficits related to adverse factors in the perinatal period of higher mammals.

Pregnant guinea pigs at full term were given a local anesthetic. One fetus of the litter was immediately delivered by cesarean section to serve as a control for one or more litter mates which were asphyxiated by occluding the blood vessels leading to the uterus or clamping the umbilical cords for various lengths of time, usually about 15 to 20 minutes. These asphyxiated animals had to be resuscitated. This was brought about by gently inflating their lungs rhythmically with oxygen, a process which required well over an hour in some instances—roughly proportional to the duration of the asphyxiation.

Regardless of how short a time they had been asphyxiated, all the guinea pigs which were resuscitated exhibited neurological deficits, at least transiently. The more prolonged the asphyxiation, the more marked and persistent were the neurological deficits. After respiration had been established, the animals remained in coma for a short time. Then a series of motor phenomena ensued. Convulsive twitchings of the muscles of the face and limbs, decerebrate states, and coordinated running movements appeared before the animals could right themselves. Tremors, ataxia, spastic gait, incoordination, and unresponsiveness to loud sounds or bright lights sometimes persisted for several days or even longer. Survival of the most severely palsied guinea pigs was brief. Motor recovery, when it occurred, was more rapid and complete than recovery from the sensory deficits. Occasionally, an animal displayed convulsions after it appeared to have recovered normal motor function. This may have been a more common occurrence; constant vigil was not kept. By 2 weeks after resuscitation it was usually impossible to detect neuromotor deficits in the surviving animals, but some of them appeared to be dull and unresponsive to tactile, auditory, or photic stimulation. They permitted themselves to be handled, and when placed in unusual positions they remained as though cataleptic.

The brains of most asphyxiated animals and their nonasphyxiated controls were collected for histopathological studies. They formed a series gradating from 1 hour to several months after asphyxiation. Brain pathology was found in nearly all the animals that had been asphyxiated for 8 minutes or more and in some of those which had been asphyxiated for less than 8 minutes. About 1 hour after

resuscitation, and up to 5 or 6 days, multiple small hemorrhages were found in the brains. Some neuronal changes unrelated to hemorrhages were manifested as early as 90 minutes after resuscitation. Two to six days later, certain nerve cells had lost their chromophilic substance, the phenomenon of chromatolysis culminating in destruction of isolated cells or groups of neurons. Some animals showed general neural damage with atrophy of the brain; others were affected in focal areas only. The cerebellum, hippocampus, and corpus striatum, three parts of the human adult brain considered to be easily damaged by oxygen lack, were not severly injured in the newborn guinea pig. Certain other parts of the brain, notably the lateral thalamic nuclei and geniculate bodies—way stations in the important sensory pathways to the cerebral cortex—were more frequently involved in the degenerative processes than any other parts of the brain. The cerebral cortex came next.

At 6 to 8 weeks of age, many of the guinea pigs were given learning tests in a simple alternation maze. Most of the asphyxiated animals were found to be inferior to their controls in terms of the number of errors made in the maze and repetition of errors. The differences were significant at or beyond the 1 percent level. All the animals used for the learning tests were subsequently sacrificed for histopathological study. Anatomical changes attributable to asphyxiation were encountered in the brain tissue of 65 percent of the asphyxiated animals. Most of these animals had been inferior to their controls in the maze, and not one of them had been superior to its control. Neuronal loss, sensory pathway damage, and cortical atrophy were found in the brains and may have been the causal factors in the animals' learning deficits.

The main point gained from these experiments is that guinea pigs asphyxiated and resuscitated at birth, showing transient neurological deficits, grew to maturity as overtly normal animals. Nevertheless, the majority of them had brain damage and, correlated with it, impaired learning ability. Although they cannot be likened to palsied human beings (most palsied animals died very young), one is tempted to draw a comparison with mentally retarded humans.

Except for the one isolated monkey experiment, mentioned earlier, no studies have been made in primates. In order to approach human conditions more closely than has hitherto been possible, additional experiments such as those in the guinea pigs are now being planned in primates. The rhesus monkey lends itself particularly well to studies of this type. It is a much more suitable animal for neurological examination than are other common laboratory species. For example, it is easier to get an electroencephalogram from a monkey than it is from a rat. The female has a regular 28-day menstrual cycle, like the human being. It usually gives birth to a single baby, rarely to twins. Pregnancy lasts 168 days, but viable infants have been born as early as the 150th day. The infant monkey can be removed from its mother's breast at birth, and, after an initial period of round-the-clock care lasting about 4 weeks, it can live quite independently. This infant is capable of solving certain problems within the first 5 days after birth. It is possible to test it at that time for deficits in learning ability caused by adverse factors which were deliberately induced during the prenatal period.

In view of these considerations, a group of scientists at the Laboratory of Neuroanatomical Sciences, Public Health Service, has begun investigating neurological and psychological deficits caused by adverse factors during the perinatal period of the rhesus monkey. The Institute of Neurological Diseases and Blindness has established a laboratory of perinatal physiology in San Juan as one component of a cooperative project involving, in addition, some of the medical faculty of the University of Puerto Rico. The free-range colony of rhesus monkeys on Santiago Island has been acquired, and animals from this colony will ultimately be used for these studies. In addition, the laboratory in San Juan has a caged colony of rhesus monkeys for controlled matings.

One of the most important results of the recent conference was a decision to try to encourage others to make greater use of primates, and a resolution to this effect was placed

in the minutes. As one of the investigators expressed it: "Problems in the brain of the human newborn infant and the human fetus are insolvable without experimental animals. The rhesus monkey seems to be the laboratory primate of choice for research of this type. It is therefore recommended that this animal be established as the standard laboratory animal for research in the area covered by this conference." With what has been learned in lower animals, with that which will be learned in laboratory primates, and with the information being obtained on human beings through adequately supported and well-controlled prospective clinical investigations, some of the answers to the question of cause and prevention of brain damage at birth should eventually be obtained.

Grants for Training in Epidemiology and Biometry

The Public Health Service has awarded 21 grants totaling $702,494 to 5 schools of medicine and 9 approved schools of public health in the United States to encourage graduate training in epidemiology and biometry.

Specifically, the purpose of the awards is to foster more extensive use of statistics in the life sciences through the special techniques of biometry and more epidemiological study of the characteristics and distribution of health problems in population groups.

The grants include 97 training stipends: 69 in biometry and 28 in epidemiology. Also included are funds for payment of salaries for additional teaching staff in the training institutions.

Additional grant applications totaling $548,528 are awaiting review at the next meeting of the Advisory Committee on Epidemiology and Biometry. The committee, made up of 17 leaders in these fields of study, was appointed by the Surgeon General to guide the program and review research grant applications. The list of grants follows.

Biometry

University of California School of Public Health, Berkeley	$24,550
University of California School of Public Health, Los Angeles	16,661
Columbia University School of Public Health and Administrative Medicine	29,921
Harvard University School of Public Health	20,000
Johns Hopkins University School of Hygiene and Public Health	17,973
University of Michigan School of Public Health	18,792
University of Minnesota School of Public Health	28,640
New York State University College of Medicine, Brooklyn	14,984
University of North Carolina School of Public Health	22,464
University of Oklahoma School of Medicine	35,466
University of Pittsburgh School of Public Health	19,980
Tulane University School of Medicine	22,454
Vanderbilt University School of Medicine	13,255
Yale University School of Medicine	20,432

Epidemiology

University of California School of Public Health, Berkeley	$22,250
Columbia University School of Public Health and Administrative Medicine	52,746
Harvard University School of Public Health	63,936
University of Michigan School of Public Health	71,520
University of Pittsburgh School of Public Health	48,784
Tulane University School of Medicine	58,447
Yale University School of Medicine	79,239