1968

Prematurity and postmaturity in mental retardation

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PREMATURITY AND POSTMATURITY IN MENTAL RETARDATION

by

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A THESIS

Presented to the Faculty of

The College of Medicine in the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Medicine

Under the Supervision of Frank Menolascino, M.D.

Omaha, Nebraska

March, 1968

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The child is the father of the man. Events and circumstances occurring from the onset of labor to twenty-four hours after delivery can and do affect the physical and mental development of the child. The perinatal period is indeed an important and special time of life. For the infant it marks the transition between silent and secure, unconscious parasitism in utero to wailing dependency in early infancy. It may be the period that leads an infant to a full and productive life or it may be the period that truly "handicaps" his life before it has really begun. It is the purpose of medical study and research in this specific area to first understand the perinatal period and second to be able to prevent its possible complications.

At present, understanding the perinatal period and its adverse factors are by no means complete. There are basically two problems in understanding the perinatal period. One is the problem of the extreme mechanical and technical difficulty in monitoring and analysing the fetus in utero. Only recently have new techniques of analysis been developed. Briefly they include fetal cardiograms, analysis of amniotic fluid and fetal blood, and analysis of maternal blood and urine. The second problem in the study of the perinatal period is that of statistical data. The statistics on the implications of perinatal factors (e.g. prematurity) and mental retardation are not only voluminous, but also confusing and contradictory. Yet, on the other hand, some areas of perinatal factors (e.g. maternal anesthesia) have scarcely been mentioned in respect to mental retardation. Thus, the two problems of understanding and evaluating

the perinatal period must be resolved before the period can adequately be controlled. The goal in controlling the perinatal period is to prevent mental retardation resulting from adverse perinatal factors. Achieving this goal would also significantly reduce maternal and fetal mortality and morbidity.

What is the significance of adverse perinatal factors with respect to mental retardation? It is presently estimated that all combined adverse perinatal factors are responsible for some five percent of all the mentally retarded (1). To analyze this five per ce nt more closely, it is obvious that each individual adverse perinatal factor is responsible for much less than five percent of the retarded. From a percent point of view, adverse perinatal factors indeed seem somewhat insignificant. If, however, we consider actual numbers, this five percent represents some 450,000 retarded individuals. When we recall that mental retardation is a syndrome resulting from a variety of causes, and not a disease entity, we realize that there is no panacea for mental retardation, and that the hope for mental retardation lies in the removal of <u>all causes</u> regardless of how insignificant a cause may seem.

Perinatal factors are those circumstances and events which occur from the time of labor to the first twenty-four hours of life including actual delivery of the infant. Adverse perinatal factors specifically include prematurity, postmaturity, birth injury, anoxia, and maternal anesthesia. All of these factors are related temporarily to that period when the circulation of blood and oxygen

from the mother to the fetus is terminated, and the infant must initiate and maintain his own vital circulation. This crucial period is when further anoxia from adverse perinatal factors might tip the balance of an already compromised newborn. To imply that mental retardation due to adverse perinatal factors is the result of increased anoxia at a crucial, already anoxic period, is a gross simplification. There are undoubtedly many other contributing factors which are present. Some of these are genetic predisposition, maternal care and medications, toxins, and hypersensitivity conditions in the mother. When one takes into account all the possible adverse factors, the fetus must indeed be quite substantial to sustain them.

Adverse factors and accompanying conditions occur quite frequently even in "normal" pregnancies. The difference between the "normal" and the "abnormal" is probably the quantity and quality of the abnormal factors rather than the complete absence of abnormal factors. It is important, therefore, to fully evaluate the role of adverse factors and to determine their significance. In light of understanding adverse perinatal factors, medical attention can be focused on the mother and newborn subjected to adverse conditions. Because pregnancy and adverse factors are so frequent, the realistic and practical approach to this problem is to establish a concept of the high-risk mother. Once this is accomplished the mother who has an increased probability of delivering a retarded infant can have medical attention focused on her and her newborn. By recognizing

and treating this high-risk mother, it is hoped that mental retardation due to adverse perinatal factors can be made an etiology of the past.

Prematurity

The most commonly employed definition of a premature infant is an infant weighing less than 2500 grams (approximately 5½ pounds) at birth.(2). The average weight of all births is about 3400 grams or 7½ pounds.(2,3). Using birth weight alone for the definition of prematurity, as has been employed since 1935, is inaccurate and misleading. The word "prematurity," in itself, implies more of a degree of "ripeness" or development rather than merely weight alone. The definition using birth weight alone not only includes many small full-term infants, but it also excludes many large under-term infants. Furthermore, birth weight is of little value in estimating gestational age because half of the infants weighing less than 2500 grams have gestational ages of 280 days (4). Prematurity is more accurately defined in terms of both gestational age and birth weight. The birth weight is a parameter that is accurate and easy to obtain. This is not the case with the gestational age. The gestational age is calculated by determining the time interval between the first day of the last menstrual period (L.M.P.) and the date of delivery. The main difficulty with the calculation of gestational age is the large amount of human error in determining the date of the L.M.P. Most women do not consult their physician until they are three to four months pregnant; by this time the L.M.P. is largely determined by rough estimate. Instead of relying entirely on the menstrual

history for gestation age, it would be advantageous to determine and substantiate the gestational age by physical means. Usher and others present clinical findings in the newborn which can be used to accurately determine gestational age (4). Their clinical criteria for gestational age are found in Table I (4). Of these criteria, sole creases appear to be the most accurate and reliable in determining fetal age.

To support the accuracy and usefulness of this criteria, Usher correlates these criteria with birth weight and two conditions frequently seen in premature infants. These conditions are respiratory distress syndrome and fetal malnutrition. Fetal malnutrition is most often seen in low birth weight, full-term infants (dysmature) while respiratory distress syndrome is most often seen in low birth weight, under-term infants. In Usher's series of 10,938 consecutive life births the incidence of prematurity by birth weight, less than 2500 grams, was 6.7 percent of 729 infants (4). By using his criteria for gestational age only 52 percent of these 729 infants were premature; yet, these 52 percent contained 96 percent of the cases of respiratory distress syndrome, which is seen in low birth weight, under-term infants. Of the 729 premature by weight infants, 24 percent were found to be full-term and 24 percent were found to be borderline premature by gestational age. Fetal malnutrition was significantly confined to those infants who were less than 2500 grams, but were full-term by gestational age. Usher also found that among

Table I. CLINICAL CRITERIA FOR GESTATIONAL ASSESSMENT (4)

	Gestational Age		
	To 36 weeks	37-38 weeks	39 weeks or more
Sole creases	Anterior transverse crease only	Occasional creases anterior two thirds	Sole covered with creases
Breast nodule diameter	2 mm	4 mm	7 mm
Scalp hair	Fine and Fuzzy	Fine and Fuzzy	Coarse and silky
Earlobe	Pliable - no cartilage	Some cartilage	Stiffened by thick cartilage
Testes and scrotum	Testes in lower canal Scrotum small Few rugae	Intermediate	Testes pendulous Scrotum full Extensive rugae

the 8,863 infants who weighed more than 2500 grams, 4 percent were premature and 15 percent were borderline premature by gestational age. In the 368 cases of respiratory distress syndrome, 88 of the cases weighed more than 2500 grams at birth, yet by Usher's criteria, all but three of these were found to be less than 39 weeks gestation(4). In summary, pathologic conditions in the premature newborn appear to be related to both gestational age and birth weight. In most all past studies of research correlating mental retardation with prematurity, birth weight alone is used as the criteria for prematurity. This obviously introduces another bias into the studies of mental retardation and prematurity.

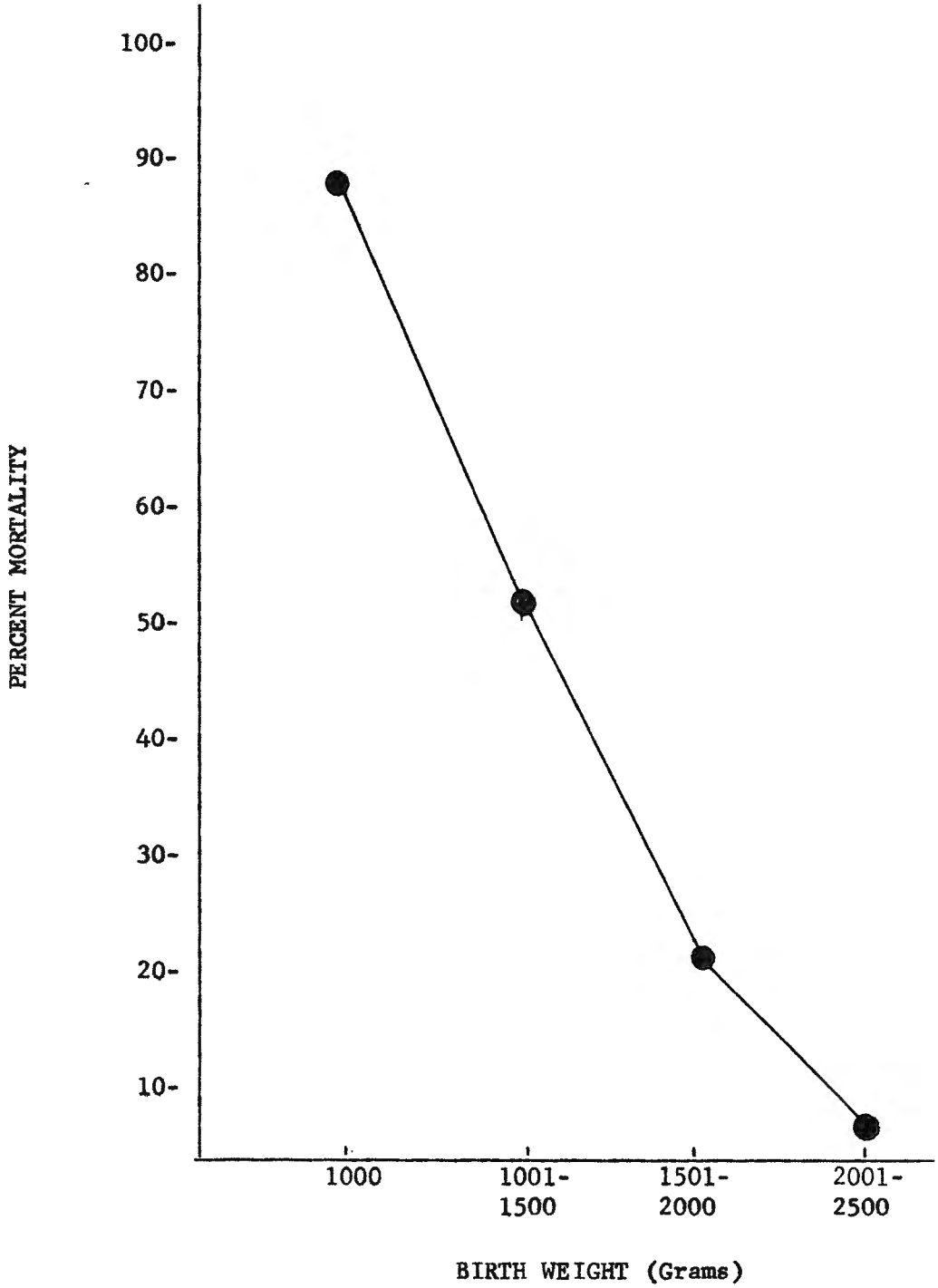
Prematurity is the most frequent recurring factor now implicated in infant death and morbidity (5). As such, it has become the largest single problem in modern obstetrics and pediatrics. Of a series of over four million live births in 1960, Malamud found the rate of prematurity to be 7.7 percent in the United States (6). In Jansson's study in 1966, he found the incidence of prematurity to be about 5 percent of all live births in Sweden (7). In Baumgartner's study of low birth rate in the United States in 1957, he found the rate of prematurity to be 7.6 percent, almost identical to that of Malamud's (3). In the United States, this rate of prematurity has stayed remarkably constant over the years at about 7 percent. The highest rate of prematurity in the world is Calcutta, India, whose rate is 34.7 percent; Holland has one of the lowest rates of prematurity at 3.5 percent (8).

In the United States, prematurity ranks eighth as the cause of death written on all death certificates (9). Between 50 percent and 75 percent of all infants who die in the neonatal period are premature infants (10,11). An infant born alive and weighing 1000 to 2500 grams is sixteen times more likely to die within the neonatal period than an infant weighing more than 2500 grams at birth (12). One discouraging aspect of prematurity is the failure of the survival rates of premature infants to improve with time. In the Boston Lying-In Hospital from 1943 to 1963, the overall neonatal death rate for premature infants has remained virtually constant at about 15 percent (13). One encouraging exception, however, has been the improvement of the survival rates of infants with birth weights of less than 1000 grams. The survival rates for infants of birth weights less than 1000 grams was zero percent from 1932 to 1939 as compared to 23.5 percent from 1948 to 1955 (14). Figure I presents the overall rate of neonatal mortality with respect to birth weight in 1960 in the United States according to E.C. Dunham (10).

A five year study of prematurity by Pilor and others in 1956 revealed mortality rates for the different weight groups to be almost identical to those of Dunham (15).

The causes of prematurity are not well understood. In the past, a definite causative factor was known in less than 30 percent of all cases of prematurity. Prematurity due to unknown causes still comprises a significant portion, but presently some studies have resulted in yielding causes for over 45 percent of the cases of

Figure I. Overall Rate of Neonatal Mortality According to Birth Rate in United States (10)



prematurity (7,16). Among the well known causes of prematurity are multiple births, toxemia of pregnancy, premature rupture of the membranes, placenta previa, abruptio placenta, pelvic infections, chromic systemic infections and diseases of the mother, congenital malformations of the fetus and fetal malpresentation.

Janssen, in his study of prematurity in Sweden in 1966, was able to attribute etiology to 45 percent of his 240 cases (7). Of these 240 cases, 31 were attributed to toxemia, 27 to twin pregnancies, 16 to placental and cord implications, 15 to severe fetal malformation and 11 due to other causes (7).

Dann and others in 1958 studies 73 premature infants of birth weight less than 1000 grams. The incidence of maternal complications was high in this series...75 percent. Eleven mothers had toxemia, 20 had vaginal bleeding, five had infections and four had miscellaneous complications which could be implicated as the cause of prematurity. In addition there were eleven multiple births and eleven with premature rupture of the membranes (16).

Alm's series of 999 premature boys in 1953 showed 24 percent to be of multiple births. He confirmed the importance of placenta previa, abruptio placenta, toxemia, acute and chronic infections in the mother and cardiac diseases in the mother (17). Multiple pregnancies overall appear to be responsible for some 12 to 15 percent of all premature infants (10).

In addition to the above maternal and fetal complications which are thought to cause prematurity, there are several interesting social,

ethic and environmental factors implicated in prematurity. Negroes are more likely to deliver premature infants than are Caucasions (3,18). In 1957, of more than four million live births in the United States, 12.5 percent of the non-white and 6.8 percent of the white births were premature by birth weight of less than 2500 grams (3). Premature births are about twice as common in lower social economic classes as in upper social economic classes (19). In all countries and ethnic groups, premiparas of all ages have a higher percentage of premature infants than women of multiple parity (20). Prematurity rates, however, excede those of primiparas in grandmultiparas (21).

An interesting and intriguing aspect of prematurity in primiparas is that the premature infants tend to be of near full-term gestation (22). Grandmultiparas tend to produce premature infants of considerably less than full term (2). Prematurity is also more frequent in the younger mother, especially less than twenty years of age (23). Although all births produce more male infants, infants weighing less than 2500 grams are more often female (18,24).

Other factors associated with prematurity or implicated as a cause of prematurity are under present investigation. Smoking, heart volume, bacteruria, psychological factors, high altitudes, anemia, and folic acid are the main factors now being considered in association with prematurity. Many of the studies on these factors are conflicting and any present conclusions would be "premature."

The hazards of prematurity are not confined to the previously mentioned increase in perinatal and neonatal mortality rates. Many

of the hazards of prematurity can be illucidated by studying the causes for the increase in mortality rates.

The main causes of death in the premature infant appear to be primarily the result of labor and factors in the infant. The stormy labors that premature infants tend to undergo are well known. Premature infants tend to result from an increased number of caesarian sections (7,15,16,20). The positive association between hyaline membrane disease in the infant and caesarian sections is well known (15). The other hazards of labor in prematurity are the result of trauma to the infant during delivery. The trauma during delivery is primarily due to the immaturity of the infant, the increased frequency of breech presentation, and increased frequency in rapid birth and expulsion, which lead to intracranial and spinal hemorrhage (25).

Factors primarily related to the infant as the causes of death are respiratory diseases, infection and congenital anomalies. A series of 1300 live born premature infants at the Chicago Lying-In Hospital reported 216 perinatal and neonatal deaths (9). Of the 216 deaths, 52 were attributed to hyaline membrane disease, 38 deaths were attributed to malformations, and 18 deaths were attributed to infection and pneumonia. No cause of death could be established in 47 cases. Twenty deaths were attributed to abruptio placenta and 34 deaths were attributed to other causes including erythroblastosis (9).

Puffer and Verhoestraete found the majority of deaths in premature infants to be from congenital malformations, birth injury and infection (8).

Congenital anomalies occur quite frequently in prematurity. Some series report as high as 18 percent (7,26). It is interesting that premature infants with slow growth rates (full term) reportedly have an increased incidence of congenital anomalies when compared to premature infants with fast growth rates (less than full-term) (26). Other than congenital anomalies associated with growth rates; respiratory distress syndrome (hyaline membrane disease) is also associated with growth rate. Respiratory distress syndrome has a much higher frequency in premature infants with fast growth rates (i.e., infants weighing less than 2500 grams...born before term) (4). Van den Berg and others also found that premature infants with fast intrauterine growth rates had mortality rates twice that of premature infants with slow growth rates (26). They also found that premature infants with fast growth rates had more respiratory difficulty the first week of life, but were healthier later than the premature infants with slow intrauterine growth rates (26). From these preliminary reports, it appears that premature infants of low gestational age (i.e., fast intrauterine growth rates) owe their morbidity and mortality to the complications of labor, delivery and early infancy; once they have survived this high-risk period, they appear to have no greater complications than normal infants (4,26). On the other hand, premature infants of normal gestational age (i.e., slow intrauterine growth rates) appear to have their morbidity and mortality spread from labor and delivery into childhood (26).

Cerebral palsy appears to have a significant relationship to prematurity; although one cannot project incidence from retrospective studies, association can be revealed. In Eastman's study of 753 cases of cerebral palsy, he found 31.2 percent of the cases to have a background of prematurity as compared to 8.2 percent of the controls (27). Harper found spastic diplegia, a form of cerebral palsy, to be five times more frequent in infants of less than four pounds birth weight than in control normals (28). In a follow-up study of infants weighing less than 1500 grams at birth, Knobloch found 35.1 percent of 57 cases to have cerebral palsy or overt neurological damage (29). In 63 cases of premature infants less than 1500 grams at birth, Reed found 68 percent to be handicapped by central nervous system (C.N.S.) disorders, the main one of which was spastic diplegia (30). He also found 25 percent of his cases to have retrolental fibroplasia which, because of studies of prematurity, is now a handicap of the past (30). One of the main problems in studying spastic diplegia is due to the very protean nature of the disease. Spastic diplegia tends to vary greatly in severity and in fact tends to decrease in severity with age; thus many cases are asymptomatic by school age and many cases are not reported or recognized.

The association between cerebral palsy and prematurity is offered as supportive evidence for the case that prematurity can be associated with neurological damage and mental retardation in the infant. The study of the relationship between prematurity and mental retardation is no uncomplicated task. Most of the studies in this area are

retrospective and one cannot predict incidence or causation from retrospective studies. Many biases are present in studies in this area. The first bias is that of definitions. "Prematurity" and "mental retardation" in themselves are not easily defined or quantitated and are, therefore, not uniform. Another bias is that of the observer; what is recognized or evident to one observer may not be to another. The population under observation has its own biases. Most large series are conducted in clinic settings and have the biases of socioeconomic status and racial background. The very nature of the time span involved in the study of prematurity and mental retardation produces bias; mental retardation of less than severe degree is often not noted until well into childhood. Few studies have greater than 75 percent follow-up at six to eight years following the premature birth. Another bias present is that of associated conditions with prematurity, e.g. toxemia, birth trauma, placental conditions, respiratory diseases and infections in the neonate. The relationship and significance of these factors should be evaluated when assessing prematurity and mental retardation. Finally, there is the bias of the treatment afforded to infants and their mothers. Varying morbidity and mortality rates, as well as varying prematurity rates, reflect the variability of maternal care and newborn infant care.

An early study (1953) of prematurity by Alm in Sweden illustrates several biases (17). In this series only males were studied (999). They were born between 1902-1922, far before even the advent

of antibiotics. Assessment of intelligence was determined not by I.Q. but by enrollment in "special classes" for "marked mental deficiency." In his study a significant difference was noted between premature infants in "special classes" and control normal infants in "special classes." Eight times as many premature infants were enrolled in special classes as were normal control infants. In this study, to conclude that the incidence of mental retardation is significantly greater in premature infants, we must at least assume that biases present were equal in both the premature and control group. We know this is not the case, because prematurity rates are higher in lower socioeconomic classes (19). Furthermore, lower socioeconomic classes are associated with lower I.Q.s (30,31,32). Biases supporting this study are the facts that zero percent of infants less than 1000 grams survived, and without antibiotics probably only the strong, healthy premature infants of greater weight survived (14).

In 1962, Rossier studied 175 premature infants of less than 1500 grams birth weight in Paris (33). One hundred twenty-five of the cases, 71 percent, were able to be examined and tested. Thirty-one were studied by questionnaire...three had died and sixteen could not be traced. The study was restricted to evaluating motor and mental development in 156 cases. Eleven percent showed marked motor retardation; half of these, however, had retrolental fibroplasia which attributed somewhat to their motor retardation. Eleven percent of his cases had marked retardation in mental development; again, half of these patients had retrolental fibroplasia, which was believed

to have contributed adversely to mental development. The cases without blindness due to retrolental fibroplasia had signs of anoxia and repeated cyanosis at birth. Because of these associated adverse factors, Rossier concluded that prematurity itself does not cause motor deficit on mental retardation (33). The primary biases in this study are; the lack of any control group, 30 percent of the series was not examined or tested, and the overstressed importance of retrolental fibroplasia. Not to belittle the role of blindness in mental development, but it does seem that probably only the very anoxic patients received 100 percent oxygen therapy. These patients have developed mental retardation even if they did not receive oxygen sufficient to cause blindness.

In 1956 Knoblock studied 500 single born prematures and 492 controls (29). Each was examined and tested at forty weeks of age. Of the infants less than 1500 grams at birth, 17.6 percent were borderline mentally retarded. The incidence of mental retardation in controls was 1.6 percent. The overall incidence of mental retardation was 2.6 percent for the premature group, not significantly different from the controls. But if dull normal mental development is included, the overall incidence of retardation in the premature group is 5.4 percent, which is significantly greater than the controls. Furthermore, no infant whose birth weight was less than 2000 grams was considered to have a superior intellect. Although this study is well controlled and has excellent follow-up, there is much difficulty in determining mental ability at forty weeks of age.

Reed also studied infants of markedly low birth weights less than 1500 grams (30. His original series was 187 cases, 87 of which died in the neonatal period and six which died in the first 11 months of life. Of the 94 remaining, he was able to follow 63 patients. He found 40 percent of 25 cases to have I.Q.s of less than 80. Reed also introduced another parameter in evaluating prematurity. He performed electroencephalograms (E.E.G.) on all available patients and controls. It was found that 60 percent of the premature patients and six percent of the controls had abnormal E.E.G.s. Furthermore, he found 12 patients in the premature group, and none in the control group to have 6 and 14 per second spikes. This E.E.G. abnormality is frequently associated with behavioral problems.

Akessen studied 349 mentally retarded subjects in Sweden and compared them to 698 control normal patients (1). The study compared the incidence of various factors in the control group versus the same factors in the mentally retarded group. Among those factors studied were length of gestation, neonatal asphyxia, rate of caesarian sections, rate of forceps delivery, rate of prolonged labor, rate of toxemia, rate of twining, and rate of cord around the neck at delivery. Of these eight factors, a significant statistical difference was found in length of gestation, asphyxia, and twining. The significant difference in length of gestation was only evident when the low grade mentally retarded (I.Q. less than 52) were compared to the controls. The rate of asphyxia was 10.9 percent for the study group and 2.2 percent for the controls. The rate of twining

was 4.6 percent for the study group and 1.3 percent for the controls. The study of Akesson's was a retrospective study, but Harper in his prospective study found that twins and triplets of less than four pounds had lower mean I.Q.s than control single born infants (28).

In a retrospective study by Barker in 1966, the mean birth weights and length of gestation were studied in 607 cases whose I.Q.s were less than 75 (34). The mean birth weights of these cases were found to be significantly ($p < .05$) lower than the expected normal mean birth weight. The length of gestation was also significantly lower than that expected. In his series, 40.6 percent of the children were born at less than 38 weeks gestation as compared to 7.6 percent being born at less than 38 weeks gestation in the normal population (34).

Dann studied 100 children of birth weights less than 1000 grams (16,35). Siblings were used as the controls. He found a significantly lower mean I.Q. in the low birth weight group, the mean I.Q. for the study group was 94.6 versus 106.9 for the controls. Dann was unable to examine 83 other children originally in his study. By communication with social workers, these children had a very high incidence of institutionalization and mental deficiency. Another variable appeared to be significant in this study: a significantly higher proportion of the premature children with I.Q.s above 100 was found among families who had private medical care and a higher socioeconomic level. This study produced three important points in the study of prematurity and mental retardation. First, many

studies lack good controls; the use of siblings as controls removes many of the socioeconomic biases. Second, many studies lack good follow-up; Dann suggests that many of those who are not followed-up are the least successful and are more frequently mentally retarded. Third, prematurity alone should not be studied in relationship to mental retardation without considering other influencing factors, such as socioeconomic status.

Bacola rated the importance of socioeconomic factors in mental development (32). He found that a higher educational level, a better economic standing, and being white tended to go together and were definitely associated with mental development on the part of the children. Bacola studied two weight groups of premature infants: 1500 to 2500 grams and less than 1500 grams. In both groups, statistically significant lower I.Q.s were found when compared to controls. Moreover, significantly more infants were retarded and were retarded more severely in the lowest weight group (32).

Robinson and Robinson studied 135 low birth weight infants and 92 controls (36). Covariance techniques and factor analysis were utilized to hold background factors constant. They found no significant difference in mental development when the two groups were compared with respect to birth weight. In their study, they found instead that social class assumes much more importance than does birth weight in determining a child's developmental prognosis. This study is one of the first to utilize factor analysis and covariance technique to minimize the effects of background factors. To

illustrate the confusion of statistics and results in studies of prematurity and mental retardation, Weiner and others utilized the same statistical methods of analysis and concluded opposite results (37).

In Weiner's study, 500 low birth weight infants and 492 full-term infants were investigated. For their data analysis, 46 infants, including 16 retarded and 13 emotionally disturbed, were eliminated from the low birth weight group. Seventeen infants, including two retarded and eight emotionally disturbed, were eliminated from both groups so that performance and psychological factors could be measured; the retarded and emotionally disturbed could not be adequately tested in these areas. From their study, it was concluded that the premature infant is psychologically impaired when race, maternal attitudes and social class are controlled. It was also found that the severity of psychological impairment increased with decreasing birth weights. The areas of performance, perceptual-motor disturbances, flaws in comprehensive abstract reasoning, perservation trends, and impaired I.Q.s, significantly identified low birth weight children (37). To attempt to determine how two studies can conclude conflicting results, one must closely inspect the investigations.

Robinson's series was conducted at the University of North Carolina and originally contained 423 subjects (36). These 423 subjects consisted of 141 "on program" premature infants, 141 "off program" premature infants and 141 normal weight infants. The "on program" infants were premature infants cared for at the clinic.

Twenty-four of the "on program" died, sixty-two of the "off-program" died, and six of the normal weight infants died. The number of infants available for the study was 135 premature infants and 92 normal weight infants. Of the 135 premature infants, 33 weighed less than 1500 grams and 102 weighed between 1500 and 2500 grams. Wiener's series consisted of 500 low birth weight infants and 492 normal weight control infants at John Hopkin's University.(37). The infants available for the analysis were 396 premature infants and 398 normal weight infants. About one-third of the premature infants weighed less than 2000 grams. Many possible biases and differences exist between these two populations. Robinson's series was quite small. Of Robinson's initial 282 premature infants, less than half (135) were "available" for analysis. It also seems significant that "on program" and normal weight infants had less eliminations and deaths. Each group originally had 141 infants yet 62 "off program" infants died. This in itself suggests lesser mortality in normal weight infants and premature infants with closer medical care. Furthermore, with these eliminations of the less healthy, is the final sample truly a valid random collection? Wiener's series was much larger and had fewer eliminations. Furthermore, more data was available as to length of gestation, delivery and neonatal status. This information was "unavailable" in Robinson's study. Both studies had relatively similar distributions of birth weights, socioeconomic status, and racial status. Both studies obtained information on the subjects by social workers and psychologists. Both studies used the Stanford-

Binet Test and the Goodenough Draw-A-Man Test. In addition, Robinson used the Jastek Wide-Range Achievement Test and Wiener used the Bender-Gestalt and Lincoln-Oseretsky Test of Motor Development. Wiener's subjects were six to seven years of age at the time of examination, while Robinson's subjects were all about ten years of age. Both studies utilized computer factor analysis and covariance techniques. Both papers were so cluttered with complex statistical symbols and data that any physician with less than a B.S. degree in statistics could not determine if the conclusions reached were significantly valid.

In summary, what is the relationship between prematurity and mental retardation? Both prematurity and mental retardation are syndromes resulting from a variety of causes. Seldom is one syndrome implicated as the cause of another; if such an implication is made, the net result is usually one of vague generalities and confusion. I believe this has been much the case with prematurity and mental retardation. The evidence at this time is strongly in favor of an association between prematurity and mental retardation; this is the vague generality. What is the association? Is it significant? Is the association a causal one? Does prematurity per se cause mental retardation? These are at present still unanswered and the evidence remains inconclusive. The foundation and the floor plans in this area have been developed. What remains is the design of the final structure.

In the last two years, two studies have more intensely begun to define the role of prematurity and mental retardation (36,37). They have utilized more elaborate statistical methods and better controls in their investigations of the many variables in prematurity and mental retardation. The final answers will undoubtedly be discovered in light of these many variables. It is probably not prematurity per se that leads to mental retardation but rather a combination of supporting conditions with or without prematurity that can lead to mental retardation. A complex, but not unusual, example would be an infant born at 32 weeks gestation, weighing 1800 grams, displaying cyanosis and respiratory distress at birth, and whose mother is a short, young, unmarried, seventeen year old negro female from a low socioeconomic class. With so many variables and many of them most difficult to quantitate, it is no wonder that consistent answers in the area of prematurity and mental retardation are most difficult to derive.

To further analyze and perhaps confuse the issue of prematurity and mental retardation, one more intriguing concept can be noted. Instead of prematurity, with or without adverse factors, leading to mental retardation, perhaps the converse is true. Perhaps primary factors that can by themselves produce mental retardation (e.g. genetic factor) can predispose to prematurity and all the complications thereof. We know this seems to be the case with congenital malformations. This aspect should be known and kept in mind in the complete evaluation of prematurity and mental retardation.

In conclusion in comparison with infants weighing more than 2500 grams at birth: (1) low birth weight infants are more likely to be born with a mental and/or physical handicap due to an increased frequency of congenital anomalies; (2) low birth weight infants are more likely to develop mental handicaps as a result of complications of labor and the neonatal period; (3) low birth weight infants per se without complications have not been shown to be more susceptible to mental or physical handicaps; (4) low birth weight infants are more frequently associated with a lower socioeconomic background, which in itself is associated with lower mental and performance developmental expectations; (5) the degree of prematurity is associated with mental development and probably reflects more severe prenatal factors in the more premature, infants with birth weights of less than 1500 grams have a definite excess of gross mental and physical defects.

Postmaturity

The belief that pregnancy might be prolonged far beyond the usual period was held even in early times. After consulting with his physicians and wise men, the Roman Emperor, Hadrian (A.D. 76-138) decreed that in cases in which the woman was of chaste manner and irreproachable conduct the child born eleven months after the death of the husband was legitimate (38). The Supreme Court of Friedland in 1634 decided that a child born 333 days after the death of the husband was legitimate (38). In the United States and England, there is no law with respect to the duration of pregnancy; individual cases are decided on their own merit.

The usual definition of postmaturity is a pregnancy of greater than 294 days or 42 weeks gestation. A more complete definition is that given by Trolle in 1959: "A pregnancy that is more than 14 days past term (term equals 280 days after the first day of the last menstrual period) provided the menstrual cycle is regular, 25 to 35 days, and the time of quickening accords with the calculations." (39).

This is a reliable and practical definition but it is used too infrequently in statistical studies. Too often the estimated due date is made by history alone without the confirmation of "quickening" or without an adequate past menstrual history of the mother. One of the biggest problems therefore in this definition of postmaturity is a certain inherent error in the calculation of the length of gestation. This error in the calculation of the due date is probably one of the most frequent causes of so-called postmaturity.

Prolonged pregnancy and post-term pregnancy are two frequently used synonyms; in view of the definition, these terms would be more accurate. Postmaturity or hypermaturity imply more of a biological development state than the chronological length of gestation. Postmaturity is presently the preferred term and is used in reference to the development of the infant and in reference to the length of gestation.

The incidence of postmaturity varies considerably from one study to another, ranging from 3.5 percent of all pregnancies to as high as 10.6 percent of all pregnancies (5,40). These studies define

postmaturity as a pregnancy of greater than 42 weeks gestation. Many authors feel the figures of the incidence of postmaturity are too high because of errors in the calculation of the due date. Unlike that of prematurity the incidence of postmaturity appears to reflect little race prediction (40). The age alone of the mother or father does not appear to affect the rate of postmaturity but parity does (41,42). Nulliparous women over 35 years of age appear to have an increased number of postmature pregnancies (4,39,42). There appears to be no geographic or ethic influence on postmaturity and infants born of postmature pregnancies show no unequal sex distribution (39).

Studies of postmaturity are not nearly as extensive as those of prematurity and the causes of postmaturity are more obscure than those of prematurity. Until more is known about the mechanisms which determine the length of gestation and which initiate and sustain labor, the causes of prematurity and postmaturity will largely remain those of speculation and association.

A postmature pregnancy may or may not be abnormal. The length of gestation for a given pregnancy is an individual matter to that mother. In large populations the average length of all pregnancies is 280 days with a standard deviation of seven days (11). Thus, by normal distribution we could expect 2.5 percent of all pregnancies to be of greater than 294 days duration. One cause then of postmaturity is normal individual variance, probably genetically determined.

Many explanations for the abnormal postmature pregnancies have been given. One recent theory is that of "placental insufficiency" or "placental dysfunction." In late gestation, placental growth is slower than that of the fetus and placental blood flow progressively decreases (43,44,45). Walker and Turnbull in 1953 and MacKay in 1957 presented data describing a significant and progressive decline in fetal oxygenation and a compensitory rise in fetal hemoglobin as pregnancy passed 41 weeks duration (46,47). This relative hypoxic state would presumably tend to lengthen the pregnancy or delay the onset of labor. More recent studies have shown no significant change in fetal oxygenation or hemoglobin concentration in post-mature pregnancies (48,49,50,51). There is little doubt that placental insufficiency does exist in some cases, but its overall role in postmaturity presently is not known. Other authors feel postmaturity occurs as the result of a relatively late fetal maturation and the fetus therefore has a longer stay in-utero (52,53).

Abnormal fetus may affect the length of pregnancy as reflected by the increased incidence of postmaturity in anencephalus and hydrocephalus (54). Some past favorite theories of postmaturity include deficient estrogen (55,56), excess progresterone (57,58), delayed implantation (59,60), and fetal size (61). Recently Hawker and Klemm have found below normal concentration of oxttocic substance in prolonged labor in the early first stage of labor (62). Presumably the lower concentration of oxytocic substance would inhibit

uterine contractions and prolong, if not delay, normal labor thus leading to a prolonged pregnancy. At present the cause or causes of postmaturity are not known and will not be understood until further insight has been gained into the mechanism of labor.

The classical appearance of a postmature infant is that of premature senecense with a wrinkled, dry and macerated outward appearance. The normally present protective vernix caseosa is scanting or lacking in postmature infants. The loss of protection leads to maceration that is particularly evident on the skin of the scrotum, labia, soles of the feet and palms of the hands (42). Because of the absence of vernix and presence of meconium, the skin may also show a yellow tinge particularly around the nails and unbilicus. In postmaturity the amniotic fluid volume is frequently diminished giving the infant a dry, wrinkled, dehydrated appearance (52,63,64). At birth these infants also appear to have long thin arms and legs and frequently have their eyes open wide. Some of these signs of postmaturity appear to reflect the prognosis of the infant. Clifford staged the postmaturity syndrome into three stages (63).

Stage I included infants with decreased vernix, macerated and wrinkled skin, no yellow stain and no meconium in the amniotic fluid.

Stage II included all the findings in Stage I except with meconium in the amniotic fluid.

Stage III included all the findings in Stages I and II except with yellow-green staining of the skin, nails and unbilical cord.

Clifford found no infant deaths in his Stage I, but Stages II and III had infant mortality rates of 40 percent and 15 percent respectively; furthermore he found an increase in serious illness in Stages II and III. His reason for the lower mortality rate in Stage III was that Stage III included primarily those healthier infants who were strong enough to survive Stage II.

The average size of infants born from postmature pregnancies does not appear to be greater than that of full term infants (23, 41). However, it appears that infants weighing greater than 4000 grams at birth are twice as frequent in the postmature pregnancies (41). This somewhat correlates with the observation that there are twice as many cases proportionately of dystocia in post-term pregnancies versus term pregnancies (41).

Not all infants born postmature display the classical appearance of postmaturity. In the series of Holtorff and Schmidt in 1966, they found an overall incidence of postmaturity of 10.5 percent on 661 infants (52). Of these 661, however, only 10.3 percent or 68 infants displayed the classical postmaturity syndrome. In Strands study of postmaturity, she found the classical signs of postmaturity in 40 percent of all prolonged pregnancies (42). Most of the studies of the complications and the perinatal mortality of postmaturity fail to differentiate between those infants with the signs of postmaturity and those infants born postmature without signs of postmaturity. This in itself is one source of bias and would tend to lessen the significance of the postmaturity syndrome.

Are postmature infants in a high-risk group? There are two opposite views in regard to this question. Some authors have found no statistically significant difference between the perinatal mortality rates of term infants and postmature infants (48,53,65,66). Their perinatal mortality rates for both groups range from 1.8 percent to 2.5 percent. Other authors feel there is a significant statistical difference in perinatal infant mortality rates (5,41,52). Their perinatal mortality rates range from .7 percent for full term infants to 3.7 percent for postmature infants (41,52). Further studies of the perinatal infant mortality rates clarify these conflicting results by subdivision of the postmature group. Clifford, Hesselsjo and Lindgren feel that only postmaturity in primiparas has significantly greater mortality rates (40,67,68). Their highest figure for the incidence of infant mortality in postmature multiparae and in full term infants was 1.8 percent while the highest incidence of perinatal mortality in postmature primiparas was 6 percent (67,68). Holtorff subdivided the postmaturity group into those displaying the postmaturity syndrome and those not found to be clinically postmature (52). He found the perinatal mortality rate to be 10.3 percent for those with the postmaturity syndrome and 2.6 percent for those without the classical postmaturity syndrome. Most perinatal mortality statistics do not include stillborns. Clifford states 85 percent of all postmature babies die in utero, are stillborn, and are not included in perinatal mortality (67). Lindgren studied 13,322 deliveries in Sweden and included stillborns

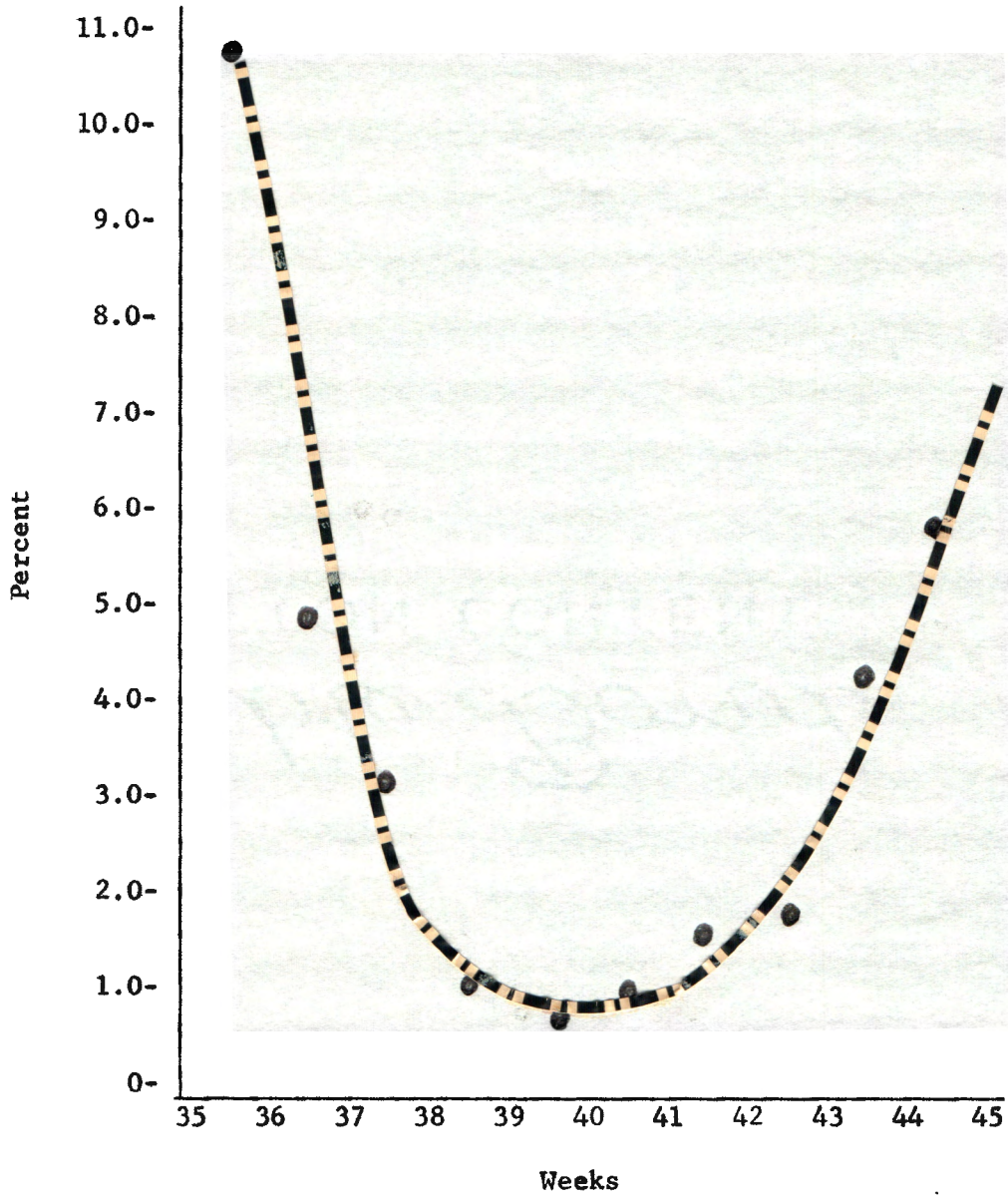
in his results. His overall perinatal mortality rate was 2.2 percent; the perinatal mortality rate for different lengths of pregnancy are presented in Figure II (40).

In view of the present data, it appears that postmaturity has an increased perinatal mortality rate primarily in infants born of primiparas and in infants with the classical signs of postmaturity.

The mortality in postmaturity, aside from stillbirths, is primarily the result of the complications of labor especially in primiparas. Labor in postmaturity appears to be significantly prolonged (40,41,52,62,65,67,68). The most frequent cause of death from prolonged labor is primarily from birth trauma and includes cerebral hemorrhage (40,69). The factors that tend to prolong labor include malpresentation, cepbalo-pelvic disproportion and uterine inertia (52). Perinatal mortality in postmaturity is also reflected by fetal distress which is more frequent in postmaturity than in term infants (53). Hesselsjo and Anberg studied 21,824 live births from 1946 to 1955. Their perinatal mortality rate for postmature infants was 3.3 percent (68). Of these 3.3 percent, half died during labor; 25 percent died antepartum and 25 percent died postpartum.

The apparent increase in perinatal mortality in infants born of postmature pregnancies has posed many problems for clinicians around the world. Many physicians do not believe that postmaturity is, in itself, a problem with which to be concerned. They feel any increase in perinatal mortality rate is primarily due to the management

Figure II. Fetal Mortality for Different Lengths of Pregnancy (28)



of postmaturity, namely induction and/or caesarian section. These physicians support expectant delivery as the management of post-mature pregnancies (41,48,53,66). Other physicians, primarily European, believe postmaturity is a definite problem with a real increase in perinatal mortality. These physicians believe that induction and/or caesarian section is indicated in all pregnancies of greater than 42 weeks gestation (5, 42,67,69).

In the final analysis, no blanket management program is presently available for the treatment of postmaturity. Each case deserves individual attention. If conditions such as pre-eclampsia, malpresentation, an elderly primipara (greater than 35 years of age), or fetal distress are present, induction should be considered. In postmaturity the attending physician should be prepared for possible caesarian section if fetal distress, cephalopelvic disproportion, or prolonged labor appear; in delivery if the liquor amnion is scanty, thick, and stained with meconium, caesarian section should be performed (64). All physicians who manage pregnancy and delivery should be prepared for the complications of postmaturity.

A review of the literature concerning mental retardation as a complication of postmaturity is essentially non-existent. The mental developement of infants born of postmature pregnancies has not been studied to any extent. Mental intelligence correlates with postmaturity have mainly been mentioned in passing in studies of prematurity and mental retardation. In fact, only one reference made definite mention of postmaturity and intelligence. Barker in

his study of intelligence and length of gestation concluded that high birth weight and prolonged gestation seemed not to be associated with an increased risk of mental subnormality (34).

In the area of postmaturity and mental retardation, no conclusions can be made on the basis of information available. If we learn from the experience of studies in prematurity and mental retardation, we should not undertake that nebulous sojourn of attempting to implicate syndromes as the cause of syndromes. Studies in the area of postmaturity (or prematurity) and mental development must be more specific to be meaningful. Even specificity itself will not irreproachably reveal the answers without a clearer understanding of the nature of mental development and gestation.

Like prematurity, it is almost certain that it is not postmaturity per se that could lead to an unfavorable mental or physical outcome in the newborn. It is undoubtedly the associated complicating factors which are most important. These complicating factors specifically are slow growth rates, chronic anoxia, congenital anomalies, toxemia, prolonged labor, birth injury, and uterine inertia (26,40, 41,52,54,63,65). All of these adverse factors identify postmaturity and must be evaluated specifically and quantitatively in relationship to mental development. Only when this is accomplished will "mental retardation due to adverse perinatal factors" become a "syndrome" of the past.

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