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Special Session on  
PERINATAL FACTORS AFFECTING HUMAN DEVELOPMENT

(Abstracts of Papers)

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Special Session on  
PERINATAL FACTORS AFFECTING HUMAN DEVELOPMENT

(Abstracts of Papers)

Table of Contents

	<u>Page</u>
1. Protein Starvation of Pregnant Rats and Learning Ability of Offspring	1
2. DNA Content of Placenta and Fetal Brain	2
3. Relationships of Maternal Amino Acid Blood Levels to Fetal Development	3
4. Physical and Mental Deficits of Twinning	4
5. Effect of Maternal Diabetes on Physical and Mental Development of Children	5
6. Maternal Factors and Mental Performance in Children	6
7. The Effect of Rapid Succession of Pregnancy on the Neuropsychological Development of the Offspring	7
8. Perinatal Factors in Mental Subnormality	8
9. The Problem of Prematurity and of Intrauterine Growth Retardation	9
10. Maternal Factors Affecting Birthweight	10
11. Familial Factors Affecting Fetal Growth	11
12. Sonographic Depiction of the Growth and Development of the Human Fetus	12
13. Utero-Placental Circulation	13
14. Test of Fetal Tolerance to Induced Uterine Contractions for the Diagnosis of Chronic Distress	14
15. Fetal Tolerance to Maternal Exercise Hypoxia	15
16. Pressure Exerted on the Fetal Head During Uterine Contractions	16

	<u>Page</u>
17. Effects of Uterine Contractions on the EEG of the Human Fetus During Labor	17
18. The Human Fetal Electroencephalogram	18
19. Influence of Rupture of Membranes on Compression of Fetal Head During Uterine Contractions	19
20. Effect of Uterine Contractions on Maternal Blood Flow through the Placenta	20
21. Disturbances in Composition of Fetal Blood During Labor	21
22. Changes in Fetal Heart Rate Associated with Intrapartum Fetal Asphyxia	22
23. The Fetal Effects of Umbilical Cord Compression	23
24. Cardiovascular Adjustment of the Fetus During Asphyxia	24
25. Subacute Asphyxia and Brain Damage in Rhesus Monkey	25
26. Apgar Scores as they Relate to Performance on the Four-Year Psychological Examination	26
27. Intrapartum Fetal Heart Rate and Neurological Development of Children	27
28. Brain Damage at Birth: Functional and Structural Modifications with Time	28
29. Administration of Glucose, Base, and Oxygen to Mother and Newborn	29
30. A New Approach to the Treatment of Acute Intrapartum Fetal Distress	30

PROTEIN STARVATION OF PREGNANT RATS AND  
LEARNING ABILITY OF OFFSPRING

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There has been a paucity of research focused on the question of behavioral effects of prenatal malnutrition. The difficulties of control and administration of such research frequently appear overwhelming to the new initiate and the experienced alike; the importance of data in this area nevertheless demands that it be carried out. The present paper reports on the first prenatal nutritional deprivation study in an otherwise long series of projects investigating the postnatal behavioral effects of prenatal treatments in infrahuman subjects conducted in the Division of Psychobiology at the Lafayette Clinic.

The effect of a protein-deficient diet administered throughout gestation on postnatal behavior was studied in 90-day-old Wistar rats. Diets containing either 7.2 per cent or 23.93 per cent protein were begun at the earliest indication of conception and fed until parturition, at which time all animals were placed on the 23.93 per cent protein diet. Behavioral testing was not done in this study owing to the failure of all females in the protein-deprived treatment to produce live births. In a second project the same diets were fed commencing on the eleventh day of gestation (the period of the fetus and one denoted by marked growth). The protein-deficient animals had a significantly longer gestation period and their progeny were lighter at birth and at time of weaning. Two measures of learning ability administered between 30 and 90 days postpartum revealed that the performance of the subjects on the 23.93 per cent protein regime was superior to that of the ones receiving the protein-deficient treatment. However, significant performance differences lasted only for the early phases of learning, which suggests that the protein deficiency resulted in subjects of slow learning ability rather than an incapacity to perform the tests. Whether this observation indicates that the protein deficiency was only moderate or that

the nervous system is more resistant to a nutritional insult during the fetal period is but one of the questions yet to be investigated.

A brief discussion will be made of current ongoing research on the behavioral effects of prenatal zinc deficiencies and the relation of this element to protein deficiencies.

DNA CONTENT OF PLACENTA AND FETAL BRAIN

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Maternal protein restriction in rats will retard both placental and fetal growth. In placenta, cell number (DNA content) was reduced by 13 days after conception, cell size (protein/DNA) remained normal, and the RNA/DNA ratio was markedly elevated. Retardation in fetal growth first became apparent at 15 days. After this, the cell number in all organs studied showed progressive reduction. Thus the cellular changes produced by severe prenatal restriction are reflected in the placenta even earlier than in the fetus.

When nursed on foster mothers in normal-sized litters (8 to 10 animals), animals from these protein-restricted mothers still showed at weaning a deficit in cell number that persisted to adulthood. In contrast, animals raised in groups of three showed nearly complete recovery by weaning. In animals raised in groups of 18, there was a marked reduction in cell number in all organs at weaning. The reduction in liver, brain, and lung DNA was 60 per cent; thymus DNA was less than 10 per cent of normal. These "doubly deprived" animals also showed an alteration in the pathway of glucose metabolism in brain.

These data demonstrate that maternal protein restriction affects the developing fetus and that these alterations persist to adulthood under normal nursing conditions. Moreover, these prenatally malnourished animals are extremely susceptible to subsequent postnatal deprivation. The data also suggest that optimal nutrition begun at birth may reverse the cellular effects of maternal protein restriction on the offspring.

Clamping the uterine artery to one horn will result in retardation of both fetal and placental growth. Regardless of when the clamping is performed, cell division is curtailed in all fetal organs except brain. In contrast, the DNA content of placenta is reduced only if the clamping is done before 17 days; after this, cell size (protein/DNA) is reduced.

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The RNA/DNA ratio in placenta increases following uterine artery ligation at either time.

These animal studies suggest that fetal malnutrition, secondary to either maternal protein deprivation or vascular insufficiency of placenta, will result in reduced cell number early and reduced cell size later.

Placentas from infants with "intrauterine growth failure" show fewer cells and a higher RNA/DNA ratio than controls. In an indigent population in Chile, 50 per cent of placentas showed similar findings. Placentas from a malnourished population in Guatemala had fewer cells than normal. In a single case of anorexia nervosa in which a severely emaciated mother carried to term, the placenta contained less than 50 per cent of the expected number of cells. Thus both vascular insufficiency and maternal malnutrition will affect cellular growth of human placenta. Breast-fed infants malnourished during the second year have a reduced protein/DNA ratio but a normal brain DNA content. Full-term infants who subsequently died of severe food deprivation during the first year of life had a 15 to 20 per cent reduction in total brain-cell number. Infants weighing 2000 gms or less at birth who subsequently died of severe undernutrition during the first year of life showed a 60 per cent reduction in total brain cell number. It is possible that these children were deprived in utero and represent a clinical counterpart of the "doubly deprived" animal.

These data suggest that fetal malnutrition can occur in the human, that placental cell division is curtailed, and that when the infant is exposed to postnatal malnutrition the organs show cellular growth retardation similar to that of "doubly deprived" rats.

RELATIONSHIPS OF MATERNAL AMINO ACID  
BLOOD LEVELS TO FETAL DEVELOPMENT

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Previous reports on the relationship between low birthweight and intelligence quotient suggest that maternal nutritional deficiencies may produce intrauterine stunting and impairment of fetal brain development. In this study, the relationship between maternal dietary intake, blood levels of free alpha amino acids, serum proteins, and infant birthweight, length, and cranial volume has been investigated.

Maternal blood amino acid levels during pregnancy were found to be related significantly to infant weight ( $t$  4.28 and  $P < .001$ ), cranial volume ( $t$  2.73 and  $P < 0.01$ ), spinal length ( $P < .001$ ) and crown heel length ( $P < .01$ ). No clear relationship could be established between estimated dietary intake, maternal serum albumin or globulins, pre-pregnancy weight, or weight gain during pregnancy and the status of the infant or maternal amino acid values.

These data suggest that maintenance of high maternal blood amino acid levels during pregnancy may be important in reducing the incidence of low-birthweight babies.



PHYSICAL AND MENTAL DEFICITS OF TWINNING

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Twinning is known to produce offspring of smaller birthweight and shorter pregnancy duration. Moreover, prematurity has been noted by some authors as being associated with lower developmental scores and possibly with lower intelligence quotients. The present study examines the effects of twinning on both physical and psychological development.

Two hundred and twenty-six twins were compared with 226 single births. The twin population, all fraternal twins who had a Binet IQ score at four years of age, was part of the Perinatal Collaborative Research Project of the National Institute of Neurological Diseases and Stroke of the National Institutes of Health. These twins were matched, according to race, sex, social class, and institution of birth, with single-birth children from the Project. The children were compared for birthweight, pregnancy duration, Bayley developmental scores at eight months of age, and a standard revision of the Binet IQ at four years of age. The data were subjected to a t-test for paired data. Significant differences were noted for all comparisons. There appears to be no difference with respect to race or sex.

In order to eliminate the possibility that the differences could be attributed to prematurity, the data were examined using only those twins who had a pregnancy duration equal to or greater than the control singletons. Significant differences remained when the numbers were adequate. In some subgroups, the numbers were so small that significance was not observed; however, the predicted trends remained.

The cause of the physical and psychological deficits noted in twinning is unknown. It might be hypothesized that the effects are produced by an increased nutritional demand on the mother that cannot be readily met. If this is the case, then increased dietary uptake, especially of protein, should be recommended when a multiple birth is suspected.

EFFECT OF MATERNAL DIABETES ON PHYSICAL AND MENTAL  
DEVELOPMENT OF CHILDREN

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This study is addressed to the question whether the neurologic and psychological status of children born to diabetic mothers differs from that of children of nondiabetic women. In addition, the question is posed whether an effect, if found, could be attributed to diabetes directly or to a complication of the disease, such as acidosis or prematurity. Particular attention was directed toward the occurrence of acetonuria, since previous studies have shown that perinatal mortality is exceedingly high when diabetic acidosis occurs. Other studies have indicated that perinatal mortality is similar in both latent and florid diabetic states. Therefore, the neuropsychological status of children born to mothers with mild and with severe diabetes was studied separately.

The cases for study were drawn from the Perinatal Collaborative Research Project of the National Institute of Neurological Diseases and Stroke, which covered about 50,000 pregnancies altogether. The study population included only pregnancies resulting in single, liveborn babies who had been given the Bayley mental and motor examination at eight months or the Stanford-Binet IQ test at four years of age. Each diabetic case was matched with a nondiabetic control for race, sex, hospital of birth, socioeconomic status, maternal age, and birth order.

In 237 matched pairs, maternal diabetes mellitus during gestation was found to have an adverse effect on the neuropsychological attributes of the children. Deficits were observed in the Bayley scale measured at eight months of age, in posturing factors derived from neurologic examination given at twelve months of age, and the Binet IQ at four years of age. Of singular importance was the finding that diabetes accompanied by acetonuria was associated with these adverse effects on the fetus, whereas no deficits were found in the offspring of diabetic mothers free of acetonuria, regardless of the severity of the disease.

MATERNAL FACTORS AND MENTAL PERFORMANCE IN CHILDREN

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Since January 1960, an obstetric/pediatric research group at the Princess Mary Maternity Hospital has collected simple socio-medical data on all maternities in women resident in the City of Newcastle upon Tyne (some 4,000 to 4,500 maternities each year). In previous publications the organization of the study has been described and certain preliminary results relating to perinatal mortality have been given. Interest in possible damage to the child short of perinatal death has led to a simple follow-up study of the survivors, limited to children born in the City during the three-year period 1960-1962. At that time the main emphasis was upon breech presentation and the adverse effect this form of delivery had upon the child's intelligence quotient at the age of five years (as judged by the Goodenough Draw-a-Man test). It was concluded that trauma accounted for a lowering of IQ among these children.

The effects of other factors in the mother's social and medical background upon the child's IQ (at the age of five years) are now available for presentation and for discussion. Our research group now has information about the effect on the child of such social factors as the mother's socio-economic status, her number of pregnancies, her height, and the living density of the family. Again we have information on the gestational age and the child's performance at five, and our results correlate closely with the relationship between gestational age and reading ability presented in the recently published second report of the British Perinatal Mortality Survey.

From our own material we have examined the relationship between IQ at the age of five and such common antenatal complications as essential hypertension, pre-eclamptic toxemia, antepartum hemorrhage and anemia. In most, the effect on IQ is not very marked, though there does appear to be a significant reduction of IQ in association with severe hypertension and some

varieties of antepartum hemorrhage. We are well aware of the "clustering" of several of these socio-medical influences. The number of diabetics in our community is small, and among children born to these mothers there is no apparent reduction in IQ but an obvious increase in various congenital malformations.

THE EFFECT OF RAPID SUCCESSION OF PREGNANCY ON THE  
NEUROPSYCHOLOGICAL DEVELOPMENT OF THE OFFSPRING

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Previous investigation has demonstrated the intellectual and scholastic superiority of first-born children over their siblings. A corollary finding suggests that this difference is accentuated among pairs with short inter-sib intervals. On intelligence tests, children born less than two years after their siblings obtained significantly lower mean scores than those for whom the interval was greater.

These studies suggest that close spacing has an effect on the intellectual performance of school-age children independent of birth order. The purpose of the present study is to examine the effects of rapid succession of pregnancy on neonatal and infant development as well as preschool intelligence.

Offspring born within one year of a previous full-term pregnancy were matched with children born after an interval of two to five years. These two groups were matched for race, sex, hospital of birth, socioeconomic status, maternal age, and parity.

The results from 251 matched pairs from the Perinatal Collaborative Research Project, National Institute of Neurological Diseases and Stroke, indicated that children born within the one-year interval had significantly lower birthweight, lower scores on the COLR Revision of the Bayley Scales of Mental and Motor Development at eight months of age, and lower scores on the Revised Stanford-Binet Form L-M at four years of age. In addition, this group showed a greater incidence of suspicious or abnormal neurological examinations at one year of age.

One interpretation of the data is that rapid succession of pregnancy may exert an effect on the fetus in utero. Perhaps the mother has had

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insufficient time between pregnancies to restore supplies of critical nutrients. She may then have insufficient supplies of nutrients required for optimum fetal body development and brain ontogeny.

PERINATAL FACTORS IN MENTAL SUBNORMALITY

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These data on a total population derive from a collaborative study of the relation of obstetrical and perinatal factors to mental subnormality conducted in Aberdeen, Scotland. All mentally subnormal children in special and in regular school placement who were born in the years 1952 to 1954 were studied when between eight and ten years of age and their perinatal course was compared with that of all other children born in the community during those years.

The data support the view that mental subnormality is significantly associated with complications of pregnancy and the perinatal period. This association is real and not merely an artifact of the common elevation of prevalence rates in particular social groupings for both mental subnormality and obstetrical complications. Elevated prevalences for moderate and severe pre-eclamptic toxemia, early and late bleeding, abnormalities in presentation and delivery, gestational age, low birthweight, and poor condition as a newborn were found in the mentally subnormal children. When social and clinical sub-segments of the mentally subnormal population were compared with appropriately controlled social class groupings in the normal population, the differences remained even when such explicit maternal factors as parity and maternal age are equated.

Complications of the perinatal period were most frequently present when intellectual impairment was severe and when associated clinical findings of central nervous system damage were present. However, low birthweight and exceptional shortness in the mothers were overrepresented even in cases in which no independent evidence of such damage was obtained. The latter findings suggest that certain women, who in the main come from the lowest social classes, may well provide an inadequate intrauterine environment, with negative consequences for the child, in the absence of defined obstetrical complications. The association of poor fetal growth with suboptimal postnatal social, nutritional, and environmental circumstances appears to contribute to the defective development of intellect.

THE PROBLEM OF PREMATURITY AND OF INTRAUTERINE  
GROWTH RETARDATION

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It has only been in the last 10 years that investigators realized what should long have been clear: that fetuses may be small not only because of short gestation, but also as a result of inadequate growth. Improper use of the term prematurity (that is, by birthweight only) is largely responsible for failure to appreciate this long ago, and in 1961 the WHO suggested to replace the term by infant of low birthweight. It has now been suggested that the term prematurity be avoided entirely, since it has been misused for so long, and contrast pre-term birth (at less than 38 weeks after the last menstrual period) with fetal growth retardation. There are obviously transition and combination forms.

Maturation is much less affected by unfavorable conditions in utero than growth is. Compared with a pre-term infant of the same weight, the growth-retarded one is more mature; on the other hand, it bears the marks of chronic deprivation.

Little is known about the causes of fetal deprivation. Here again, an inappropriately chosen term threatens to interfere with progress: placental insufficiency has been invoked indiscriminately, and the implication is that little is to be learned and nothing to be done about it since the placenta in situ is so well protected from interference. Actually, there is growing evidence that the maternal organism is more often at fault than the placenta, and the sooner we realize this, the sooner we can plan to study the mother and perhaps affect her ability to provide properly for her fetus. Maternal factors may be manifested acutely during the pregnancy under consideration or may be chronic and insidious, including the circumstances under which the mother developed years ago. Here is a new and difficult field of patho-physiologic investigation.



MATERNAL FACTORS AFFECTING BIRTHWEIGHT

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The identification of the many maternal factors that influence a baby's birthweight, and the measurement of the degree to which they do this, are extremely difficult. The wide variety of these factors, and their complex interrelationships, are real hazards to meaningful investigation.

Researchers of the Perinatal Collaborative Research Project have used a mathematical approach, multivariate regression analysis, to obtain leads for investigations in depth. Separately for Negroes and whites with one or more prior pregnancies, they have identified 20 out of 32 factors that, taken together, are demonstrably associated with birthweight, and have estimated their individual impacts. The multiple correlation coefficients, based on some 11,000 Negro and 8,300 white cases, are .54 and .58 respectively.

Two of the variables with the greatest influence on birthweight are the prepregnancy weight of the mother and her maternal weight gain.

A series of studies of the association of these two factors with birthweight was undertaken. The most recent included 2,500 women who had been enrolled in the Collaborative Project at least twice and had had at least two uncomplicated term pregnancies; of these, half had babies of the same sex. For each woman, the differences in prepregnancy weight, in maternal weight gain, and in the birthweight of the babies were measured. Since the measurements were taken from two pregnancies of the same women, to a great extent these differences should be unrelated to other characteristics of the women. From one pregnancy to the next, where both babies are of the same sex, there is a small increase in birthweight, a small increase in prepregnancy weight, and a slightly diminished weight gain.

There exists a strong, linear, inverse association between change in prepregnancy weight and maternal weight gain change. As maternal weight

gain increases, there is a strong, linear increase in birthweight. If the women are divided into subgroups by the change in their prepregnancy weights, the resulting family of maternal weight gain/birthweight lines is parallel. A 5 lb. increase in maternal weight gain is associated with an 80 gm increase in birthweight, while the expected increase in birthweight for a 5 lb. increase in prepregnancy weight is 57 gms.

FAMILIAL FACTORS AFFECTING FETAL GROWTH

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A study has been made of the factors affecting the rate of growth of the human fetus. Growth-retarded and growth-accelerated infants were ascertained at birth by setting their birthweight, for length of gestation, against a sex-mixed grid. The criterion used was that each infant should be two standard deviations or more above or below the mean. The two series were compared with each other and with controls.

General maternal health and socioeconomic factors were the same for all three series. There was an excess of heavy smokers and hypertensive women in the growth retarded series. When biological factors were compared, no significant differences were found between the mothers of growth-retarded infants and the controls. The mothers of growth-accelerated infants were older, of greater parity, taller, and heavier than controls.

The mean birthweights of previous liveborn siblings were as follows: controls, 7.25 lbs. (3,288 g); growth-retarded, 5.9 lbs. (2,676 g); growth-accelerated, 8.68 lbs. (3,937 g). This indicated that the regulation of the intrauterine growth rate of her young is fairly constant in any given woman; but ascertainment bias through last-born is stressed.

The mean birthweights of the mothers were as follows: controls 7.11 lbs. (3,226 g); growth-retarded 6.44 lbs. (2,921 g); growth-accelerated 8.04 lbs. (3,647 g). This suggested that the degree of constraint imposed on the conceptus is related to the degree of constraint experienced by the mother when she herself was a fetus.

Data on the birthweights of 1,783 distaff kin and fathers, ascertained through growth-retarded and growth-accelerated probands, have been analyzed and are presented. The findings support the hypothesis that maternal constraint of fetal growth is prepotent and is related to the intrauterine experience of the mother. When such constraint is relaxed, as in the

growth-accelerated series, several additive factors, both maternal and familial, appear to influence the rate of fetal growth.

Since ascertainment was made on a mixed grid, and boys grow faster than girls in utero, to enter the growth-retarded series boys must be more constrained than girls. This point was illustrated by analysis of the pedigree data according to the sex of the proband. In the growth-retarded series, each class of distaff relative was of lower mean birth-weight when ascertainment was made through boys than when it was made through girls.

SONOGRAPHIC DEPICTION OF THE  
GROWTH AND DEVELOPMENT OF THE HUMAN FETUS

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Ultrasonic techniques have progressed to a point where the rate of growth of the human fetus can be measured from the fifth week of pregnancy to term. Early in pregnancy the gestational sac can be visualized and measured. This structure disappears about the tenth week of gestation and the biparietal diameter of the fetal head appears and is measurable from the twelfth week onward. Uterine size can also be measured throughout the first 20 weeks of gestation.

Regression lines with estimates of error correlating the several measurements with the length of pregnancy can be constructed. There appears to be a linear rate of growth of all of these structures throughout pregnancy. Significant deviations of these growth rates indicate abnormal development. These are especially evident and interesting during early pregnancy.

## UTERO-PLACENTAL CIRCULATION

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Evidence has been presented that in late pregnancy the uterus occludes the inferior vena cava (IVC) and obstructs and displaces the aorta when the woman is in a supine position. In these conditions, how is the placenta supplied and drained so as to meet the growing metabolic needs of the fetus? Vascular adjustments to pregnancy have been studied in 100 women by serial angiography, with 30 nonpregnant controls.

Uterine arteries dilated (three times) were joined by widened ovarian arteries in 70 per cent of the angiograms, and by canalized round ligament arteries in 40 per cent. Thus a virtual arterial circle surrounding the placenta was formed. Arcuate and spiral arteries increased progressively in width (10 and 30 times) and became more tortuous as they approached the placenta. Extraplacental vessels remained straight and narrow.

Preferential perfusion of placenta was found, with the placenta acting as a center of uterine circulation. Inversely to findings in arteriograms from nonpregnant women, dye cleared twice as quickly through uterine arteries toward the placenta as through gluteal or femoral arteries. The latter circuits are blocked because their drainage through IVC is occluded. Grafted in parallel to these obstructed parietal circuits, placental circulation offers less resistance to blood flow because its vascular bed is dilated and because it finds an alternative pathway of venous return through the ovarian veins, bypassing the retrouterine vena cava occlusion.

To test this hypothesis, venous drainage conditions have been studied. In seven women contrast medium injected by transparietal puncture into the intervillous space cleared predominantly through ovarian plexuses, not through uterine veins, tributaries of the occluded pelvic veins.

The effect of IVC occlusion on blood distribution and pressure has been studied in 31 ilio-cavograms with concomitant aortography. In 23 women IVC

was found completely occluded: 12 were normotensive; 11 presented preferential placental perfusion, as did 3 of the 4 hypertensive patients. Only 7 patients presented supine hypotension, those with markedly distended pelvic venous reservoirs and, in 5, with poor placental perfusion. Of the 8 women with unobstructed IVC return, as many as 7 presented hypertension, with poor placental perfusion in 4.

Occlusion of IVC seems to improve placental circulation by diverting blood flow from parietal circuits. Preferential perfusion of placenta provides for adequate venous return, uniform blood distribution, and normal blood pressure. Circulatory homeostasis fails in hypotensive disorders, as a result of sequestration of circulating blood mass in pelvic venous reservoirs, and in hypertensive disorders of pregnancy, when blood escapes through patent IVC towards the arterial capacitor.

TEST OF FETAL TOLERANCE TO INDUCED UTERINE CONTRACTIONS  
FOR THE DIAGNOSIS OF CHRONIC DISTRESS

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Each uterine contraction of labor produces a transient reduction in fetal  $pO_2$ . When it falls below a critical level (18-20 mm Hg), vagal stimulation occurs and a dip II is produced. (A "dip II" is a transient fall in the fetal heart rate (FHR) occurring immediately after a uterine contraction; Hon's term "late deceleration" is a synonym). In normal conditions the baseline  $pO_2$  in the fetus is about 24 mm Hg, and during transient falls produced by uterine contractions the fetal  $pO_2$  does not reach the critical level; dips II are not produced. But when the baseline fetal  $pO_2$  is lower than normal, a transient reduction (of an amplitude similar to that produced by the contractions of normal labor) will drive it below the critical level and a dip II will occur.

The high perinatal mortality observed when the mother suffers from toxemia of pregnancy, chronic arterial hypertension, or perhaps very severe diabetes mellitus can be explained, at least partially, by a chronic insufficiency of feto-maternal exchanges. It is therefore logical to assume that the fetal  $pO_2$  values may be lower than normal. In these conditions, if uterine contractions similar in amplitude to those of normal labor are artificially induced, they will cause dips II.

This study was conducted in 20 pregnant women between the 30th and 40th week of gestation, all suffering from toxemia, chronic arterial hypertension, or diabetes mellitus. In each of these patients the amniotic fluid pressure and fetal heart rate were simultaneously recorded. FHR was inscribed with an external method based on the Doppler effect with ultrasonic waves. Continuous intravenous infusion of oxytocin (4 to 8 mU/min) was administered in order to produce a few uterine contractions similar to those of normal labor. The induced uterine contractility was maintained for about 30 minutes. However, if dips II appeared, the infusion was immediately discontinued. The test was

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considered negative when contractions with a peak pressure of 30 mm Hg or more did not cause dips II, and positive when they did. In all the patients the indications for the time and procedure of delivery were decided by the attending physician according to clinical considerations, regardless of the result of the test.

After delivery the test result was correlated with the condition of the newborn as evaluated by the Apgar score at the fifth minute of life. In all 12 patients in whom the test had been negative, the newborns were vigorous (Apgar score 7-10). In 6 of the 8 who had one or more positive tests, the newborns were depressed (Apgar score 6 or less). The correlation was highly significant ( $p < 0.001$ ).

The test is simple and harmless. A positive result indicates that the fetus will not be able to tolerate the stress produced by the uterine contractions of labor and that a cesarean section is the best procedure to terminate pregnancy; it would also indicate that the fetal oxygen reserve is lower than normal, as part of a more general metabolic disturbance of the fetus caused by a chronic insufficiency of feto-maternal exchanges. If this interpretation is correct, the test would be very helpful to select the most appropriate timing for interrupting pregnancy.

FETAL TOLERANCE TO MATERNAL EXERCISE HYPOXIA

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This paper describes an attempt to work out a diagnostic method whereby it would be possible to detect states in which the fetus does not suffer openly from hypoxia but there is an enhanced possibility that it may develop in the last weeks of a pathologic pregnancy (late toxemia, postmaturity). Starting with the assumption that utero-feto-placental transport was unfavorably affected by those pathologic conditions first of all, we tried to make the transport temporarily worse by means of an acute, short-lasting load. We presumed that the greater the distress of the fetus as a consequence of the pathologic pregnancy, the more it would respond to experimentally caused hypoxia.

Exercise load was provoked either by pedaling on a bicycle in a lying position or by a three minute step test. The heart action of the fetus was recorded in the form of a phonocardiogram on the Galileo polygraph and the frequency of the heart sounds was evaluated at five second intervals, two minutes before and two minutes after the exercise load. A special scoring system to evaluate the heart sounds was established. The absolute frequency and its balancing both before and after the load were evaluated. The test was repeated at intervals of two or three days up to the onset of labor.

The results in 109 pregnant women with pathologic pregnancy showed that higher test scores were closely connected not only with more frequent occurrence of meconium staining and dips II during labor but also with more frequent occurrence of depressed newborns and more frequent necessity for operative termination of pregnancy because of fetal distress. This test therefore makes it possible, toward the end of a pathologic pregnancy, to determine with 80 per cent reliability which fetuses are more distressed and require either special attention during labor, induction of labor, or even primary Cesarian section, not only to avert perinatal death (only 1 fetus out of 109 pathologic pregnancies died perinatally) but also to prevent serious hypoxia that could have an unfavorable influence on the newborn's subsequent life.

PRESSURE EXERTED ON THE FETAL HEAD  
DURING UTERINE CONTRACTIONS

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The pressure exerted by uterine contractions on the fetal head was recorded during labor by means of flat pressure receptors introduced between the uterine wall and the fetal head, outside the membranes. Simultaneous records of amniotic pressure and fetal heart rate were obtained.

Each contraction produces a compression of the fetal head, which, depending on the obstetrical conditions, is equal to or greater than the rise of pressure in the amniotic cavity. For each period of labor, and for a given receptor, there is a direct linear relationship between the pressure recorded by that receptor and the amniotic pressure. Receptors placed near the equator of the fetal head record higher pressures than those placed further away - up to 2.5 times higher than the amniotic pressure in the former, as against equal pressure in the latter.

The stronger compression exerted by uterine contractions on the equatorial zone causes a deformation of the fetal head. This molding is usually characterized by bulging of the parietal bone because it receives less pressure than the occipital and frontal bones, which are at the equatorial zone. During each contraction the intracerebral pressure increases and the cerebral blood flow is consequently reduced.

The transient cerebral ischemia stimulates vagal tone and causes a temporary fall in fetal heart (dip I) simultaneous with the uterine contraction. Rupture of the ovular membranes increases the compression at the equatorial zone, diminishes the counterpressure at the parietal bone, facilitates molding of fetal head, and increases the production of type I dips. The possible damage to the fetal brain resulting from ischemia and deformation deserves further investigation.

EFFECTS OF UTERINE CONTRACTIONS ON THE  
EEG OF THE HUMAN FETUS DURING LABOR

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Fetal electroencephalograms were recorded during advanced labor by means of electrodes inserted in the fetal scalp. They were introduced via the vagina and cervix after rupture of the membranes; the cervical dilatation was greater than 4 cm and the fetal head was beyond station 0. A Grass electroencephalograph was used.

Uterine contractions were inscribed by recording the intrauterine pressure. Fetal and maternal heart rate and, in some instances, maternal arterial pressure were also recorded. Periodic determinations were made, in both maternal and fetal blood, of hemoglobin saturation with oxygen,  $pO_2$ ,  $pCO_2$ , pH and base deficit.

The background EEG activity (recorded between uterine contractions) had a frequency of two to three cycles a second and an amplitude of 20 to 50 microvolts. Slight variations in the patterns were observed as labor progressed.

Uterine contractions of weak or medium intensity (pressure less than 40 mm Hg) did not cause EEG changes. Those above 50 mm Hg provoked consistent changes. The most frequently observed variation in the EEG pattern was the appearance of irregular, high-amplitude slow waves of 50 to 100 microvolts and 0.5 to 1 cycles a second. These changes were present in all the fetuses studied and usually coincided with transient falls in fetal heart rate (dips I), which were also synchronic with the peak of the uterine contractions.

Some fetuses evidenced random and/or rhythmic epileptic activity. These electroencephalographic changes coincided also with the strong uterine contractions. In these cases the newborn EEGs also demonstrated epileptic activity. This finding indicates that fetal epileptic activity observed during labor was caused by abnormal brain conditions that persisted in the newborn.

The changes caused in the fetal EEG by strong uterine contractions may be explained by a transient episode of ischemia of the fetal brain due to cranial hypertension or deformation (molding) of the fetal head. This interpretation is in agreement with the coincidence of EEG changes with dips I in fetal heart rate. It is also supported by the obstetrical conditions present (ruptured membranes, advanced cervical dilatation, head deeply engaged in the pelvis), all favoring strong compression of the equatorial zone of the fetal head by the uterine contractions.

THE HUMAN FETAL ELECTROENCEPHALOGRAM

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The electrical energy derived from the human brain is a sensitive indicator of metabolic alterations within that organ. While interest in the human fetal electroencephalogram has existed for many years, a successful technique for continuously monitoring it has not been available. This procedure requires an electrode monitoring system that incorporates the following principles: the electrode must be harmless and easily applied early in labor; it must be totally isolated from the conductive vernix and amniotic fluid that surrounds and coats the fetal skin; it must eliminate artifacts produced by uterine contractions, maternal pulse, respirations, and movements; and it must not record the fetal heart beat.

With these principles in mind an electrode monitoring system will be presented for the continuous recording of the human fetal EEG. This system makes it possible to record from the fetus in labor with as much facility and clarity as from the newborn infant. The steps taken to prove that this material is EEG, a proposal for a program to evaluate this method of fetal study, and suggestions as to its place in the already applied parameters in fetal monitoring will be presented.

INFLUENCE OF RUPTURE OF MEMBRANES ON COMPRESSION  
OF FETAL HEAD DURING UTERINE CONTRACTIONS

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Dips I are transient falls of fetal heart rate occurring simultaneously with uterine contractions. Much evidence indicates that they are due to a strong compression and deformation of the fetal head resulting in vagal stimulation. This stimulation may result either from the cephalic deformation or from cerebral ischemia due to intracranial hypertension produced by cephalic compression. The association of dips I with EEG alterations agrees with the latter hypothesis. It is not known whether permanent brain damage may be produced by this mechanism.

The incidence of dips I in a given period of labor is expressed as a percentage of the uterine contractions that caused them. In a group of 26 parturient women it was significantly greater after the rupture of membranes (33 per cent) than when these were intact (4 per cent). The rupture of membranes facilitated the compression and deformation of the fetal head by uterine contractions. The incidence rose markedly as cervical dilatation increased and the station of the fetal head progressed. In advanced labor (cervical dilatation greater than 6 cm, fetal head beyond station 0, and ruptured membranes) it was about 50 per cent, as against about 2 per cent in early labor (intact membranes, cervical dilatation smaller than 4 cm, and fetal head above -3 station).

In this study the membranes were ruptured when cervical dilatation was between 4 and 6 cm, as has become accepted practice. It would be highly interesting to make a similar study in a group of patients in whom the membranes could remain intact until the second stage of labor.

EFFECT OF UTERINE CONTRACTIONS ON  
MATERNAL BLOOD FLOW THROUGH THE PLACENTA

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Insufficient feto-maternal exchanges may be produced by several factors. Uterine contractions are the most important cause of the reduction of blood flow through the intervillous space of the placenta (IVS) because (1) they are always present during labor; (2) they may per se produce fetal distress; (3) they act through different mechanisms that potentiate each other; (4) they are often iatrogenically augmented by the administration of oxytocic drugs.

Uterine contractions reduce the maternal blood flow through the placenta by the following mechanisms:

1. The compression of intramyometrial vessels. When the uterus contracts, even in normal conditions, the intramyometrial pressure exceeds the mean arterial pressure. The muscular fibers of the uterus act like sphincters. This effect has been demonstrated as follows: (a) uterine hypercontractility markedly prolonged the time of clearance of  $^{131}\text{I}$  injected in the IVS; (b) angiographic studies showed that during uterine contractions the IVS blood flow was arrested and only restarted when the uterus relaxed; (c) uterine blood flow diminishes when the uterus contracts and varies inversely with the intensity, frequency, and duration of the contractions.

2. The compression of the main abdominopelvic vessels. During labor, when the mother is in supine position, the contracting uterus may compress the aorta or the iliac artery against the spine, reducing or suppressing arterial circulation. This effect appears in 30 per cent of the cases in our series. The compression of the great abdominopelvic vessels by the contracting uterus has been demonstrated by hemodynamic studies and by angiographic studies. In simultaneous recording of aortic and femoral pressures, we have observed that in the dorsal recumbent position (in 30 per cent of our cases) each uterine contraction produced a marked fall in the systolic pressure



and a slighter one in the diastolic pressure of the femoral artery, whereas no hypotension was observed in the aortic recording. In the angiographic studies, it was found that the contraction displaces the aorta and completely occludes the flow of one of the common iliacs and its corresponding branches. This effect disappeared when the patient changed to the lateral position.

DISTURBANCES IN COMPOSITION OF FETAL BLOOD DURING LABOR

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The discussion will be concerned with the identification of several components that interfere with fetal homeostasis during labor and delivery. Attention will be paid to the acid-base state of the mother and to the circulatory changes that occur with posture, with the administration of systemic or locally acting analgesic agents, and with alteration in intervillous space perfusion resulting from uterine contractions. Data from clinical studies and from observations on lower species, notably the Rhesus monkey, will be presented with respect to the concentration of acid-base components, oxygen tension and oxygen content, and glucose and red cell concentration in blood. On the basis of this evidence it will be proposed that under ideal circumstances labor and delivery result in only minor modification in the composition of fetal blood and that the commonly observed progressive acidosis of the fetus during parturition is preventable to a considerable extent.

CHANGES IN FETAL HEART RATE ASSOCIATED WITH  
INTRAPARTUM FETAL ASPHYXIA

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It is very important to recognize acute intrapartum fetal distress (AIFD) as soon as possible, before the fetus is irreversibly damaged. Early diagnosis followed by immediate appropriate treatment may prevent fetal lesions that otherwise would handicap the individual for the rest of his life.

The different patterns of the changes in fetal heart rate (FHR) during AIFD combine two main components: sustained and prolonged tachycardia of the baseline and dips II (i.e., transient falls of FHR that occur after each uterine contraction).

The appearance of these two signs has been studied in relation to the changes in fetal blood composition and to the condition of the newborn (evaluated by the Apgar score at the first minute of life). Tachycardia of the baseline (tentative limit over 155 beats/min) is usually associated with fetal acidosis and the delivery of a depressed newborn (Apgar score 1 to 6). Dips II are usually associated with fetal hypoxia, acidosis, and hypercapnia and the delivery of a depressed newborn; they are virtually absent in normal labor. When more than 20 were recorded during labor, the newborn was usually depressed at birth. The amplitude of dips II seems to bear no relationship to the condition of the newborn.

The presence of dips II seems thus to be a reliable sign for assessing fetal condition. On the basis of these results, a clinical test making possible an early diagnosis of AIFD was developed. A maximum of 20 uterine contractions is surveyed, and the proportion causing dips II is evaluated. If this is less than 10 per cent, the fetus is assumed to be in excellent condition and will have an Apgar score of 7 to 10 if delivered immediately. If it is 11 to 31 per cent, there is some degree of fetal distress and the newborn will be moderately depressed at birth (Apgar score 4 to 6) if delivered immediately. Above 32 per cent, the fetus is in severe distress

and may die very soon or will be extremely depressed at birth if delivered immediately.

A sequential analysis of the presence or absence of dips II in consecutive uterine contractions may provide a very practical approach for routine clinical practice. An additional advantage of this test is that the number of consecutive contractions to be studied decreases according to the severity of fetal distress. For instance, the diagnosis of extremely severe fetal distress can be confirmed if seven consecutive contractions cause dips II.

## THE FETAL EFFECTS OF UMBILICAL CORD COMPRESSION

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In clinical obstetrics, umbilical cord complications appear to be important causes of perinatal morbidity and mortality. It is important, therefore, to be able to recognize them as early as possible. Unfortunately, this is difficult to do with intermittent stethoscopic sampling of the fetal heart rate (FHR). With the development of techniques for continuous monitoring of the FHR, it has become possible to identify definite FHR patterns in the human fetus that are similar to those described in fetal animals by Barcroft, Barron, Reynolds, Paul, Dawes, and co-workers.

The similarity in FHR patterns in the human and animal fetuses during cord compression has been confirmed by observing the pattern where there has been prolapse of the cord or by direct compression of the umbilical cord at elective Cesarean section. In addition to specific FHR changes caused by umbilical cord compression, there are also alterations in the configuration of the fetal electrocardiogram with sinus depression sometimes to the point of arrest.

The introduction of fetal scalp blood sampling by Saling has permitted an examination of the acid-base changes associated with umbilical cord compression. The combined biophysical and biochemical studies indicate that mild and moderate compression are associated with an acute respiratory acidosis. If the compression is prolonged, a metabolic component is added. Preliminary studies of auditory-evoked potentials obtained from the fetal scalp during the course of labor indicate that there are alterations in wave form and latency during episodes of umbilical cord compression.

CARDIOVASCULAR ADJUSTMENT OF THE FETUS DURING ASPHYXIA

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In fetal lambs the effect of raising and lowering arterial  $pO_2$  (by varying the oxygen content of maternal inspired gas mixture) was studied in order to determine whether the systemic arterial chemoreceptors regulated the circulation. From 0.7 of term, relative hypoxemia (reducing carotid  $pO_2$  from 40 to 20 mm Hg) caused a rise in arterial pressure and femoral vasoconstriction, unaffected or increased by section of the carotid nerves but abolished by section of the vagi or aortic nerves. It was concluded that the circulation was under reflex control by the aortic chemoreceptors during the last third of gestation in this species. The effect of varying the  $P_aCO_2$  will be discussed, together with the wider implications of these results.

FETAL ASPHYCTIC COMPROMISE AND PERINATAL BRAIN DAMAGE

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Fetal asphyctic compromise in utero is characterized by hypoxia, hypercarbia, and a metabolic and respiratory acidosis. It may be due to impairment in utero-placental exchange or in blood flow on one or the other side of the placenta. In laboratory studies, fetuses have been subjected to compromise by producing maternal arterial hypotension, by increasing uterine irritability and contractility through the use of oxytocic agents, or by inducing maternal hypoxia. In such studies, despite severe and progressive fetal deterioration, the fetal blood pressure and heart rate remain relatively stable and within normal limits. Suddenly and relatively dramatically, a deterioration occurs in the vital signs. Efforts at resuscitation at this time prove fruitless.

When rhesus monkey fetuses are subjected to a period of compromise lasting for two hours or more, a variety of changes may occur in the brain, depending upon the severity and the length of partial asphyxiation. With lesser degrees of compromise over shorter periods, the brain may give evidence only of swelling. With more severe asphyxiation, patterns of hemispherical necrosis may occur, sometimes focal and restricted in distribution and sometimes widespread over much of the hemispheres bilaterally. When the necrosis is focal, it may either be bilateral and symmetrical or may affect only one hemisphere. The areas of hemispherical necrosis may be hemorrhagic or nonhemorrhagic. Importantly, the process of tissue necrosis may extend to involve the basal ganglia. Studies on cerebral vascular perfusion have indicated severe restriction of blood flow occurring concomitantly with the development of these patterns of involvement.

When the animals are permitted to survive beyond three months, they may exhibit patterns of brain pathology grossly resembling those found in perinatally damaged, cerebral-palsied humans. Specifically, their brains may exhibit atrophic cortical sclerosis with ulegyria. This process, like the focal hemispherical necrosis of the acute period, is frequently symmetrically distributed in the two hemispheres. Associated with the atrophic

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cortical sclerosis is a sclerosis of the underlying white matter. Status marmoratus of the basal ganglia may also be seen as part of the process. The associated clinical states of these animals resemble cerebral-palsied states in the human, with spastic quadriplegia, signs of sensory loss, and so on.

The similarity between the clinical and pathological changes in this monkey experimental model and those in humans with perinatal brain damage and cerebral palsy suggests that human perinatal brain damage may also be a consequence of fetal asphyctic compromise. The etiology may vary, including circulatory or respiratory disease in the mother; impairment in utero-placental exchange, as by partial placental abruption or placental disease; or impairment in umbilical circulation as by umbilical cord compression. The circumstance of fetal asphyctic compromise involving prolonged partial asphyxia must be distinguished from total asphyxia which, with survival, results in an entirely different clinical and pathological outcome.



APGAR SCORES AS THEY RELATE TO PERFORMANCE ON THE  
FOUR-YEAR PSYCHOLOGICAL EXAMINATION

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This study evaluates the relationship between Apgar scores recorded at five minutes after birth and performance on a battery of psychological tests at four years of age. The Apgar score evaluates five signs: heart rate, respiratory effort, muscle tone, reflex irritability, and color. A score of 10 is optimum, and low scores represent infants in poor condition.

Previous studies have shown that there is a strong association between low five-minute scores and increased neonatal mortality during the first two days of life, and also that low five-minute scores are associated with neurological morbidity at one year - an association that remains when birthweight is controlled.

This study is an attempt to extend these observations to the psychological tests given to Perinatal Collaborative Research Project children at four years of age. Psychological performance at age four is assessed by the Binet IQ, Graham Block Sort test, tests for fine motor development and gross motor development, a behavior profile, and an over-all clinical impression of the child. Controls for the study have been birthweight above and below 2,500 grams, education level of the mother, race, and sex of the child.

INTRAPARTUM FETAL HEART RATE AND NEUROLOGICAL  
DEVELOPMENT OF CHILDREN

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Clinical fetal heart observations during labor, as obtained on the population of pregnant women from the Collaborative Perinatal Research Project during the first and second stages of labor, were used to study the relationship of intrapartum fetal heart rate differences to the neurological development of children. The problem was approached by retrospective and prospective analyses.

No significant differences in mental and motor development during the first year of life, or in intelligence as measured by the Stanford-Binet test at four years, were found between groups of children with low fetal heart rates during the first and second stages of labor and those with normal fetal heart rate patterns.

A retrospective analysis of children with cerebral palsy matched to a group of controls did not disclose significant differences related to fetal heart rate observations.

There was a small but significant increase in certain other neurological manifestations in children with low fetal heart rate observations during the first stage of labor as compared to controls.

The findings are preliminary, since they are based on an incomplete data file and the neurological findings were taken from an assessment of neurological status of one-year-old children.

BRAIN DAMAGE AT BIRTH:  
FUNCTIONAL AND STRUCTURAL MODIFICATIONS WITH TIME

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Birth in the United States is attended by more hazards than in many other countries. Perinatal morbidity from certain conditions also is high: a shocking number of year-old infants present neurologic abnormalities. Asphyxia neonatorum has long been considered one of the main causes of brain injury, but adequate clinical and experimental studies have been lacking. The monkey, Macaca mulata, serves as an experimental model for exploring factors relative to production of mental retardation, cerebral palsy, and other neurologic disorders of infancy. A number of conclusions from monkey experiments challenge common beliefs about the human fetus and neonate and suggest that asphyxia has much more serious effects than is usually thought.

Physicians are little concerned that many human infants in the neonatal period show definite neurologic abnormalities (1.5 per cent at the end of one year) because by four years of age most of the signs have disappeared. The same is true of the monkey infant at comparable stages. Nevertheless, brain lesions occur in all neonates asphyxiated longer than six or eight minutes, even if no resuscitation was necessary. The damage is found in afferent pathways, has little or no effect on the EEG, and is not permanently detectable clinically.

Asphyxia neonatorum of longer duration (12-17 minutes) produces monkey infants with disorders resembling cerebral palsy. The brain-stem pathology is more extensive. When postnatal respiratory distress develops, the cerebral cortex becomes involved. Motor and visual systems are largely unaffected. Lesions of the brain stem are mainly confined to nuclei in pathways concerned with sensory input from the body surface and the organs of hearing, notably in the ventrolateral thalamic and inferior collicular nuclei. These are focal lesions, bilaterally symmetrical, nonhemorrhagic, and sharply circumscribed by adjacent normal nervous tissue. They leave permanent scars or even cavities in the brain that are clearly visible years later.

Regardless of the extent of brain damage or the severity of the neurologic deficits, all asphyxiated monkeys permitted to live for several years have undergone marked clinical improvement. Some monkeys helpless as infants became quite normal in appearance within three or four years. After ten years, the only visible deficits are hypoactivity and impairment of manual dexterity. They are dull, quiet, and unreactive and do not voluntarily engage in normal monkey activities. Psychological tests distinctly reveal deficits in memory. They are "mentally retarded" monkeys. Their brains show remarkable structural changes. The regions to which the destroyed afferent nuclei normally project undergo atrophy and lose many of their nerve cells. Thus, the postcentral gyri of the cerebrum become thin, the reticular formation of the brain stem is denuded, and even the dorsal spinal gray matter is affected.

Clearly one should not be complacent about a child with low Apgar score at birth who weathers a distressful infancy and escapes the overt signs of cerebral palsy. The experiments in monkeys demonstrate that marked brain damage may be quite undetectable clinically, although appropriate tests will reveal mental retardation. Clearly, too, it is time to become alarmed when approximately half a million minimally brain-damaged infants are born in the United States every year.

ADMINISTRATION OF GLUCOSE, BASE, AND OXYGEN  
TO MOTHER AND NEWBORN

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The principles of glucose transport and oxygen and hydrogen ion exchange across the placenta will be discussed. These will be related to normal and pathological clinical situations.

Indications for and techniques of administering alkali to the newborn for the rapid correction of pH will be presented. Complications arising as a result of umbilical catheterization will be summarized.

A NEW APPROACH TO THE TREATMENT OF ACUTE INTRAPARTUM  
FETAL DISTRESS

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Acute intrapartum fetal distress (AIFD) is a condition produced by an acute reduction of the metabolic exchanges between the fetus and mother. Its main cause is the uterine contractions of labor, which reduce the flow of maternal blood through the intervillous space by compressing the supplying maternal vessels. In some instances the contractions may also compress the umbilical vessels and reduce the flow of fetal blood through the chorionic villi. Both mechanisms lead to reduced feto-maternal exchanges and result in fetal hypoxia, hypercapnia, acidosis, and other homeostatic disturbances. The measurement of pH,  $pO_2$  and base deficit in fetal blood microsamples (Saling's method) makes an early diagnosis of AIFD possible. This diagnosis can also be made by monitoring the appearance of typical changes in fetal heart rate.

Once the diagnosis of AIFD is made, the usual approach is to administer oxygen and glucose to the mother and, if no improvement occurs, to deliver the fetus as soon as possible, either by cesarean section or by the vaginal route. The results are not always good: many of the newborns are depressed and some, despite treatment, show irreversible damage.

A new approach to the treatment of AIFD is to inhibit uterine contractions, as soon as the diagnosis is made, by administering to the mother a continuous intravenous infusion of drugs that stimulate Beta adrenergic receptors such as orciprenaline (Alupent<sup>R</sup>) in doses of 20 to 30 micrograms a minute. A marked reduction of the uterine activity is obtained within 5 minutes. The dips II usually disappear as soon as the contractions become too weak to hinder maternal blood flow through the placenta. The baseline FHR usually takes longer to recover normal levels. The composition of fetal blood gradually returns to the normal range, indicating that a sufficient feto-maternal metabolic exchange has been restored. Even in cases with very severe fetal acidosis (pH = 7.03), normal values (pH = 7.30) have been recovered within about 40

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minutes. After fetal homeostasis has been restored, the fetus is delivered, usually by cesarean section.

In the two cases of severe AIFD treated by this method the results have been highly encouraging: the newborns had high Apgar scores, were in excellent condition, and are now developing without detectably abnormal signs. Further research is needed before the method can be recommended for clinical use.

Some of the main advantages of the new therapeutic approach are the following: (1) It suppresses the main cause of acute fetal distress - the uterine contractions. (2) The placenta is used for restoring fetal homeostasis to normal, whereas the classic method of reanimation of the newborn uses the lungs. Pulmonary ventilation is only able to restore normal  $O_2$  and  $CO_2$  but has no influence on other homeostatic disturbances related to glucose level, metabolic acidosis, and so forth. (3) It prevents cooling of the fetus, a complication that may occur during reanimation of a depressed newborn and has known adverse effects. (4) It needs no tracheal intubation or intravenous injections of bicarbonate, glucose, or tromethamine to the newborn.

The method presented in this paper may be associated with all other therapies, such as administration of glucose and of oxygen to the mother and restoration of a normal maternal circulation.