PERINATAL FACTORS AFFECTING HUMAN DEVELOPMENT

PAN AMERICAN HEALTH ORGANIZATION

Pan American Sanitary Bureau, Regional Office of the

WORLD HEALTH ORGANIZATION

1969

PERINATAL FACTORS AFFECTING HUMAN DEVELOPMENT

Proceedings of the Special Session
held during the Eighth Meeting
of the
PAHO Advisory Committee on Medical Research
10 June 1969

Scientific Publication No. 185 October 1969

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION
525 Twenty-third Street, N.W.
Washington, D.C. 20037, U.S.A.

NOTE

At each meeting of the Pan American Health Organization Advisory Committee on Medical Research, a special session is held on a topic chosen by the Committee as being of particular interest. At the Eighth Meeting, which convened in June 1969 in Washington, D.C., the session surveyed some of the factors which may act on the fetus during pregnancy and labor interfering with its normal development or causing irreversible damage. Their influence on perinatal morbidity and mortality as well as their long-term consequences on the surviving child received special attention. The basis for early diagnosis, prevention and treatment was carefully reviewed. This volume records the papers presented and the ensuing discussions.

PAHO ADVISORY COMMITTEE ON MEDICAL RESEARCH

Special Session on

PERINATAL FACTORS AFFECTING HUMAN DEVELOPMENT

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OPENING STATEMENT

Roberto Caldeyro-Barcia, Moderator

Moderator: One of the main objectives of the health sciences today is to promote full, normal human development. This approach includes the somatic, sexual, neurological, and psychological aspects. Unfortunately, there are many factors that may interfere with this normal development. At this meeting we have a distinguished group of scientists from widely different disciplines, all of which are interested in studying the factors that may affect normal development. We shall focus on some agents that may act during pregnancy, labor, and the early stages of the infant's life.

The first series of papers will be devoted to factors affecting the intrauterine development of the fetus during pregnancy and the consequences for the newborn and adult—maternal nutrition, placental circulation, diabetes, hypertension, rapid succession of pregnancies, familial factors, weight of the mother before pregnancy and weight gained during pregnancy, and others. All of these may affect the growth of the fetus during pregnancy. Special attention will be devoted to newer methods recently developed to evaluate the condition of the fetus during pregnancy. The information supplied by these methods will be most useful for deciding the therapy to be applied in each case.

Later we shall study the more acute effects of labor on the fetus, starting with one aspect that has received little attention in recent years: the compression received by the fetal head and the possible resulting damage to the brain. Fetal electroencephalography is a very promising method for the study of this topic.

We shall then turn our attention to the more fashionable subject of intrapartum fetal asphyxia and acidosis resulting from acute failure of placental exchanges in labor, and also to the corresponding defensive reactions of the fetus. The long-term neurological consequences of fetal asphyxia will be discussed from experimental studies in primates and from clinical data.

Finally, the methods for the treatment of acute intrapartum fetal asphyxia will be discussed; both the currently accepted procedures and some recent proposals will be presented.

I should like to express the gratitude of the organizers of this meeting to the National Institutes of Health of the United States, and particularly to the National Institute of Neurological Diseases and Stroke, for their contribution and also to Dr. Heinz Berendes and Dr. John Churchill for their cooperation in shaping up the program.

EFFECTS OF PROTEIN AND ZINC NUTRITION ON BEHAVIOR IN THE RAT[1]

Donald F. Caldwell and Donald Oberleas[2]

Although many factors may account for the paucity of research dealing with the effects of malnutrition on development of the nervous system and behavior patterns, a significant one is the doctrine of "brain sparing." To a great extent, sparing is a valid phenomenon in considering the effect, or absence of effect, of some form of stress applied to the mature nervous system. However, with the discovery of "critical" periods during the process of growth and development, numerous investigators have shown the effects of malnutrition during these periods to affect brain morphology profoundly (*6, 7, 15, 16, 17, 18, 19, 20, 21, 22, 23, 31*). Of prime importance has been current research on whether various states of malnutrition when applied prenatally, perinatally, or neonatally result in impaired performance (*2, 3, 4, 5, 8, 9, 11, 12, 13, 14*).

Initially, we attempted to compare the behavioral effects in progeny from fifteen 80- to 90-day-old Harlan-Wistar rats fed either a 7.20 per cent or a 23.93 per cent protein diet administered throughout the total gestation period. We were unable to obtain a single testable offspring from the low-protein group, although maternal weight data and autopsy results confirmed that most of the subjects had conceived. The experiment was repeated beginning from the eleventh day of gestation through parturition (*8*). Our choice of this period was based mainly on observations in the first study indicating a large percentage of pregnancy terminations during the period of major organogenesis. In addition, we were interested in the interval during which the brain undergoes rapid maturation. Although pair-feeding was not instituted, daily ration weights were measured for each subject and not found to differ significantly between experimental and control groups.

Table 1 presents the biometric data from this

TABLE 1. Biometric data for protein-depleted and control diet groups

	PROTEIN-DEPLETED DIET GROUP	CONTROL DIET GROUP
Litters bred	10	10
Mean number born per litter (alive and stillborn)	11.14 (9 to 13)	9.55 (4 to 13)
Mean number stillborn per litter (3 litters eaten completely at birth)	1.43	1.11
Mean gestation days	22.89 [a] (21 to 26)	21.67 (21 to 23)
Mean weight (alive) of standardized litter at birth	4.13 g [b]	6.88 g
Mean litter size at weaning	4.67 [c]	7.50
Mean weaning weight	43.02 g [c]	51.70 g

[a] $p = 0.05$.
[b] $p < 0.001$.
[c] $0.02 < p < 0.05$.

[1] Supported by USPHS Grant AM-08142 and HD-01335-03, Detroit General Hospital Research Corporation, Veterans Administration, and Gerber Products Company.

[2] Presented by Dr. Caldwell.

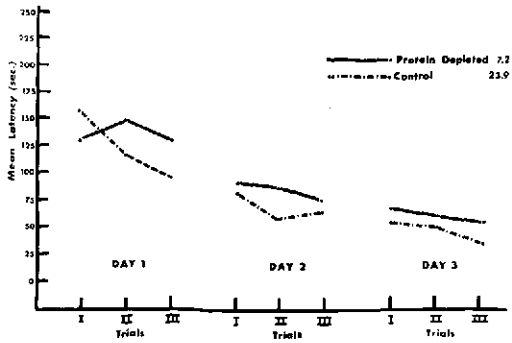

FIGURE 1. Mean latency to traverse Lashley III water maze on each of three trials for three consecutive test days. From eleventh day of gestation to parturition, subjects received either a 7.20 per cent protein diet (protein-depleted group, N = 25) or a standard laboratory chow diet containing 23.93 per cent protein (control group, N = 58). Testing began at 30 days of age. Each test trial was 10 minutes.

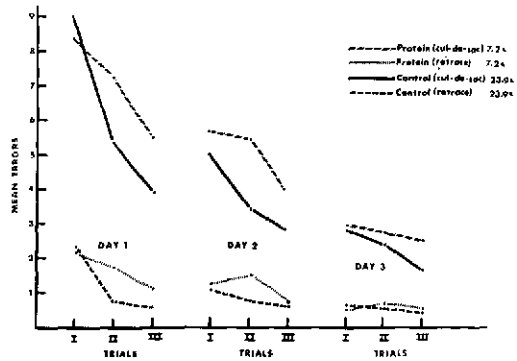

FIGURE 2. Mean number of cul-de-sac and retrace errors in Lashley III water maze for each of three daily test trials administered for three consecutive days to subjects fed from eleventh day of gestation to parturition either 7.20 per cent (N = 25) or 23.93 per cent (N = 58) protein diet. Testing began at 30 days of age. Each test trial was 10 minutes.

study for the period from birth to weaning at 21 days of age. The gestation period was significantly longer and the birth weight lower for subjects in the low-protein (7.20 per cent) treatment. Similarly, the weaning weight was lower and the preweaning mortality greater for the protein-deficient subjects—differences that may in part reflect, since cross-fostering was not applied in this study, a detrimental influence of the maternal protein deficiency on early lactation. At parturition, the subjects in the low-protein group were placed on the 23.93 per cent protein diet.

Beginning at 30 days of age, all animals were tested for learning ability with the Lashley III water maze. Three test trials were administered daily for three consecutive days, and the results for mean response latency are shown in Figure 1. The low-protein subjects took significantly longer to solve the maze, but only for the first day of testing (mean = 126.02 and 133.82 seconds for the 23.93 per cent and 7.20 per cent protein groups, respectively; $t = 1.97$, $p < 0.025$). However, the high-protein group showed, and the low-protein group did not, a significant intraday reduction in response latency for each test day (see Table 2). Figure 2 presents the graph of mean number of errors for the two groups on the maze test. Analyses for differences between treatments in rate of improvement revealed that only for combined cul-de-sac errors on day 1 of

TABLE 2. Comparison of first and third trials for each test day for mean response latency on Lashley III water maze of 23.93 and 7.20 per cent protein groups

	MEAN, TEST DAY 1		MEAN, TEST DAY 2		MEAN, TEST DAY 3	
DIET	1ST TRIAL	3RD TRIAL	1ST TRIAL	3RD TRIAL	1ST TRIAL	3RD TRIAL
23.93% protein (N = 58)	157.21 [a]	94.84	87.12 [b]	66.95	54.53 [a]	40.27
7.20% protein (N = 25)	133.64 [c]	134.00	94.76 [c]	80.76	73.16 [c]	54.84

[a] $p < .0005$.
[b] $< .025$.
[c] Not significant.

TABLE 3. Comparison of first and third trials for each test day for mean cul-de-sac and retrace errors on Lashley III water maze of 23.93 and 7.20 per cent protein groups

DIET	MEAN, TEST DAY 1		MEAN, TEST DAY 2		MEAN, TEST DAY 3	
	1ST TRIAL	3RD TRIAL	1ST TRIAL	3RD TRIAL	1ST TRIAL	3RD TRIAL
23.93% protein						
Retrace	2.22 [a]	.46	1.10 [b]	.69	.83 [b]	.41
Cul-de-sac	9.00 [a]	3.95	4.91 [a]	2.86	2.97	1.65
7.20% protein						
Retrace	2.08 [c]	1.12	1.24 [d]	.72	.52 [d]	.56
Cul-de-sac	8.32 [b]	5.48	5.72 [d]	4.00	3.04 [d]	2.60

[a] $p < .0005$.
[b] $p < .01$.
[c] $p < .05$.
[d] Not significant.

testing were the two group means significantly different (mean=5.05 and 2.84 reduction in cul-de-sac errors, for the 23.93 per cent and 7.20 per cent protein groups, respectively; $t=5.89$, $p<.0001$). However, intra-treatment comparisons showed that the high-protein group decreased significantly in both types of errors (cul-de-sac and retrace) within each test day, whereas the low-protein group showed a significant decrease only within the first day of testing (see Table 3).

Figure 3 depicts the performance of the groups on the pole-jump conditioned-avoidance test at 50 to 55 days of age. Avoidance responses were noted only for the high-protein subjects, and the over-all mean latency scores for the two groups were significantly different (mean= 5.99 and 9.19 seconds for the 23.93 per cent and 7.20 per cent protein groups, respectively; $F=4.52$, $df=1$ and 19, $p<.01$).

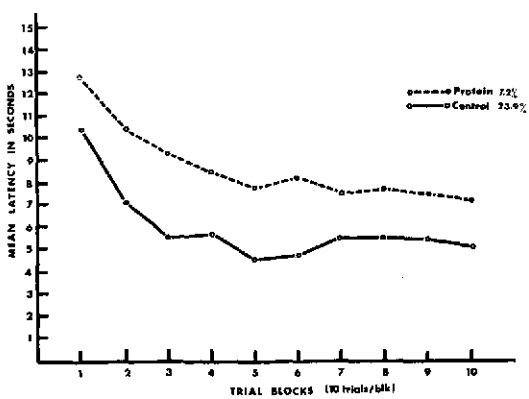

FIGURE 3. Mean response latency on pole-jump conditioned-avoidance test at 50 to 55 days of age of subjects administered either 7.20 per cent (N = 10) or 23.93 per cent (N = 58) protein diet from eleventh day of gestation to parturition. Conditioned stimulus interval was 5 seconds.

Histological examinations of a random sample of nine protein-deficient and seven control subjects at 70 to 90 days of age revealed no gross cerebral malformations, hemorrhagic demyelination, or other forms of destructive lesions. However, the brains of the protein-deficient rats were observed to have a narrower cortex, fewer large pyramidal cells, satellitosis, clumping of cytoplasmic chromatin, and neuronal shrinkage.

Currently we are conducting research on the role of zinc in the diet and its relationship with level and type of dietary protein and behavior. Our findings to date suggest a need for reappraisal of the importance accorded both quantity and quality of dietary protein *per se* in the development of the organism and its behavior.

For years, biochemists and nutritionists have cautioned us on the use of plant protein as a substitute for animal protein in the diet, using reduced growth rate as their prime evidence of the inferiority of plant protein. In 1957 O'Dell and Savage (27) discovered that zinc was less available to animals fed plant-seed protein. In

1960 they demonstrated (*28*) that phytate, a normal constituent of plant foodstuffs generally found in highest concentration in the seed portion and in some roots and tubers, decreased availability.

More recently, Oberleas and Prasad (*26*) compared the growth of weanling rats placed for 10 weeks on either a zinc-supplemented (55 mg/kg) or a nonsupplemented diet of 4, 8, 12, 16, or 20 per cent soy assay protein. Corn oil (10 per cent), minerals (5 per cent), calcium carbonate (2 per cent), vitamins and methionine, and glucose monohydrate to make up the balance were used for all diets, and phytate was equalized at 1 per cent. Figure 4 shows the mean relationship between growth (weight gain for 3 weeks) and level of dietary protein as affected by zinc. The correlation between protein level and growth for the zinc-deficient diets probably reflects, in part, the basal levels of zinc in these diets, since no attempt was made to free the soy protein of zinc in the nonsupplemented diets. When compared to the growth curves for comparable non-zinc-supplemented casein protein diets, the data indicated that soy protein supplemented with zinc is similar in quality to casein. This finding confirmed earlier observations (*25, 28, 30*).

It has been shown that zinc insufficiency results in decreased net synthesis of DNA, RNA, and protein (*29*). Concomitant with this would be decreased activity or concentration or an increased turnover of enzymes. However, the biochemical interrelationship of zinc and protein has only recently become the object of investigation and still remains unclear.

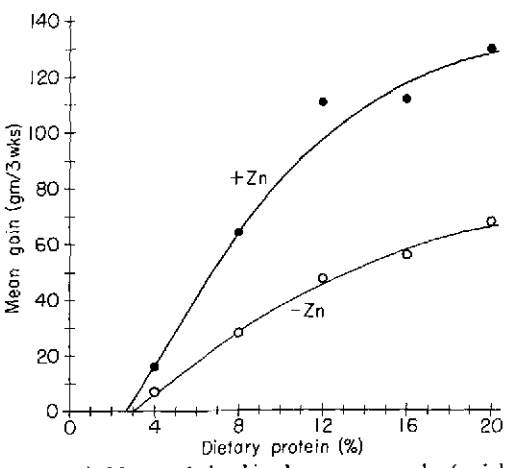

FIGURE 4. Mean relationship between growth (weight gain for three weeks) and five levels of dietary soy protein either supplemented with 55 mg/kg. zinc carbonate or nonsupplemented (basal level).

We have recently begun studies to determine the behavioral effects of varying zinc loads in the diet (*24*). Table 4 summarizes the results of an investigation designed to test the effects on the behavior of offspring of rats fed 18 per cent soy protein with or without zinc supplementation beginning ten weeks prior to breeding and throughout gestation and lactation. The supplemented diets contained 70 ppm zinc, the nonsupplemented 10 to 14 ppm, which was considered to constitute a *mild* zinc deficiency. At weaning, all offspring were placed on the zinc-supplemented 18 per cent protein regimen. Although the females on the nonsupplemented diet appeared normal throughout the duration of the study, prepartum ruptured uteri or postpartum death occurred in 56 per cent of them. Furthermore, only one litter survived to weaning at 21 days of age. An absence of typical maternal behavior (nest-building, cleaning of pups, consumption of placenta, retrieval, and so forth)

TABLE 4. Biometric data for zinc-supplemented and nonsupplemented 18 per cent soy protein diet groups

	SUPPLEMENTED DIET (70 PPM ZINC)	NON-SUPPLEMENTED DIET (10-14 PPM ZINC)
Number of gravid females	15	16
Per cent with total litter stillborn	0	32
Mean weight of liveborn at birth (g)	6.40 [a]	4.85
Mean number liveborn per litter	10.13 [b]	7.73
Per cent litters with total preweaning mortality	0	93.7

[a] $p < .0005$.
[b] $.05 < p < .02$.

was observed consistently in *all* the zinc-deficient females. A similar observation has recently been reported by Apgar (*1*).

Beginning at 45 days of age, the nine surviving progeny from the nonsupplemented treatment and a randomly selected litter of nine pups from the supplemented treatment were tested for behavior differences. Figure 5 shows the clear superiority of the subjects from zinc-supplemented mothers over the nonsupplemented animals on the Lashley III water maze. Performance on the platform avoidance-conditioning test is shown in Figure 6; statistical analyses again revealed a significant superiority for subjects in the zinc-supplemented treatment (mean=5.07 and 3.76 seconds for nonsupplemented and zinc-supplemented groups, respectively; $F=4.58$, $df=1$ and 16, $p<.05$). The results of an analysis computed to determine whether the groups differed for number of conditioned responses versus escape responses showed a significant increase in CR's for zinc-supplemented subjects ($\chi^2=17.72$, $p<.001$). Finally, after a single five-minute exposure in the open field, a significantly higher activity score was manifested by animals in the zinc-supplemented treatment, a result interpreted as indicating lower emotionality than the performance of the nonsupplemented subjects (mean=

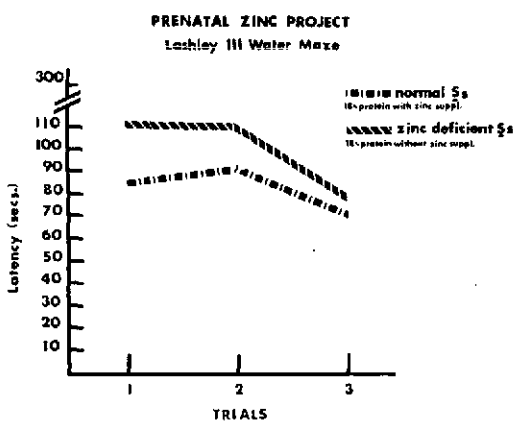

FIGURE 5. Mean latency to traverse Lashley III water maze on each of three trials for three consecutive test days of progeny of females fed 18 per cent soy protein diet supplemented with zinc (N = 9) and without supplementation (N = 9).

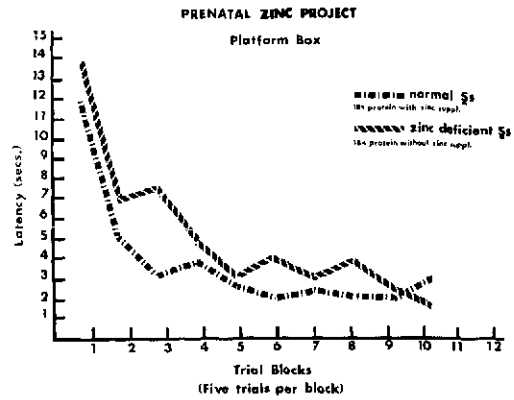

FIGURE 6. Mean response latency on one-way conditioned-avoidance test of progeny of females fed 18 per cent soy protein diet supplemented with zinc (N = 9) and without supplementation (N = 9).

195.0 and 278.0 squares traversed in one five-minute trial for nonsupplemented and zinc-supplemented subjects, respectively; $t=2.45$, $p<.05$).

We next tested the behavior of normal laboratory-reared male rats after being placed on an 18 per cent soy-protein zinc-deficient (8 ppm) diet for 48 days beginning at 30 days of age (10). Pair-fed control animals received an identical diet that contained 70 ppm zinc. The diets contained 60 per cent glucose, 10 per cent corn oil, vitamins, and minerals; dietary phytate was equalized at 1 per cent for both. Figure 7 shows the significantly greater mean response latencies by the 12 nonsupplemented subjects in the Lashley III maze (mean=161.22 and 102.72

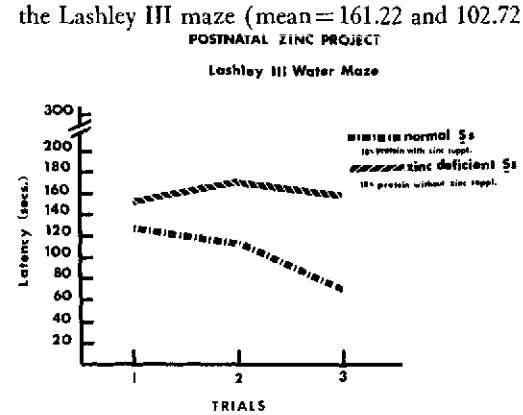

FIGURE 7. Mean latency to traverse Lashley III water maze on each of three trials for three consecutive test days. Subjects received either zinc-supplemented (N = 12) or nonsupplemented (N = 12) 18 per cent soy protein diet for 48 days commencing at time of weaning.

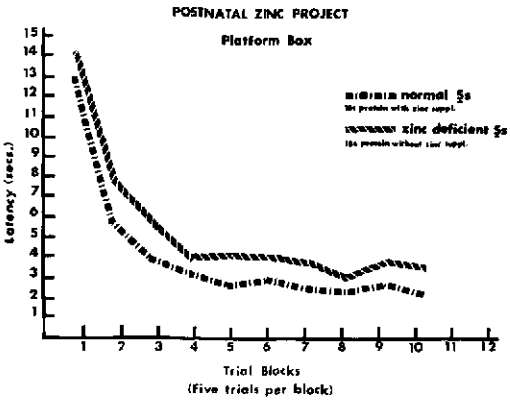

FIGURE 8. Mean response latency on one-way conditioned-avoidance test of subjects receiving either zinc-supplemented (N = 12) or nonsupplemented (N = 12) 18 per cent soy protein diet for 55 days commencing at time of weaning.

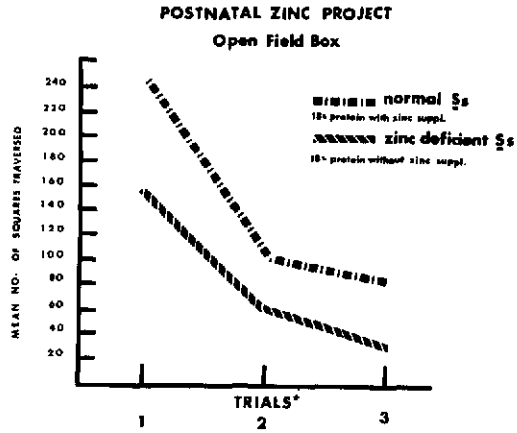

FIGURE 9. Mean number of squares traversed for each of three daily five-minute test periods on open field test for subjects receiving either zinc-supplemented (N = 12) or nonsupplemented (N = 12) soy protein diet for 55 days commencing at time of weaning.

seconds for nonsupplemented and zinc-supplemented groups, respectively; $F = 6.80$, $df = 1$ and 33, $p < .025$). The differences between the groups for performance on the conditioned-avoidance test were also statistically significant (Figure 8) and again indicate superior learning by zinc-supplemented subjects (mean = 5.19 and 4.06 seconds for nonsupplemented and zinc-supplemented groups, respectively; $F = 15.32$, $df = 1$ and 110, $p < .001$). A significantly larger proportion of conditioned responses was made by the zinc-supplemented animals ($X^2 = 21.04$, $p < .001$). Finally, reduced emotionality levels were observed for zinc-supplemented subjects for the three days of testing in the open-field maze (mean = 82.52 and 144.58 squares traversed in one five-minute trial per day for three consecutive days for nonsupplemented and zinc-supplemented groups, respectively; $F = 14.88$, $df = 1$ and 33, $p < .001$), as is seen in Figure 9.

Research has demonstrated zinc to be an indispensable trace element for proper protein utilization and consequent growth. Furthermore, for phytate-rich plant diets, zinc supplementation appears crucial. The present series of studies has shown for both prenatal and postnatal nutrition that even a mild zinc deficiency has a profound influence on behavior potential despite an apparently adequate protein level in the diet.

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DNA CONTENT OF PLACENTA AND FETAL BRAIN

Myron Winick, Elba Velasco, and Pedro Rosso[1]

Growth may be defined simply as an increase in the size of an animal or an individual organ. This increase in organ size is the result of a continuous accretion of protein and in some cases lipids. Hence the rate of net protein synthesis determines the rate of growth. When protein synthesis and protein degradation reach equilibrium, growth ceases. Since net protein synthesis is linear in all organs *in utero* and for a varying period postnatally, growth would appear to be a homogeneous process. However, this is only one aspect of growth. The protein in any organ is packaged within cells. The same total organ may be contained in numerous small cells or in a few larger cells. The constant amount of DNA within the diploid nucleus of any cell in a particular species makes possible an accurate determination of the total number of cells by chemical methods (*2*).

During normal growth, total organ DNA content or cell number increases linearly, then begins to decelerate, and finally reaches a maximum long before the organ size, as determined by net protein accretion, has reached its maximum (*16*). As a consequence of this pattern, three phases of growth can be described: proportional increase in weight, protein, and DNA content (hyperplasia); an increase in DNA slower than the increase in protein and weight (hyperplasia and concomitant hypertrophy); and finally no further increase in DNA content, with net protein and weight continuing to increase at the same rate (hypertrophy).

[1] Presented by Dr. Winick.

The growing period, then, is not a homogeneous process when viewed in cellular terms. It is possible that stimuli that retard or accelerate growth may result in different effects, depending on whether they influence the rate of cell division (DNA synthesis) or the subsequent increase in cell size.

It has been shown in rats that early malnutrition will curtail the rate of cell division if it occurs during the period of hyperplasia. In brain, this period is prior to weaning. Neonatal undernutrition not only will curtail the rate of cell division but will result in a permanent deficit in brain-cell number (*17*). Malnutrition after weaning will prevent the subsequent increase in cell size—an effect that can be reversed by later rehabilitation. During the period of rapid cellular proliferation, undernutrition will

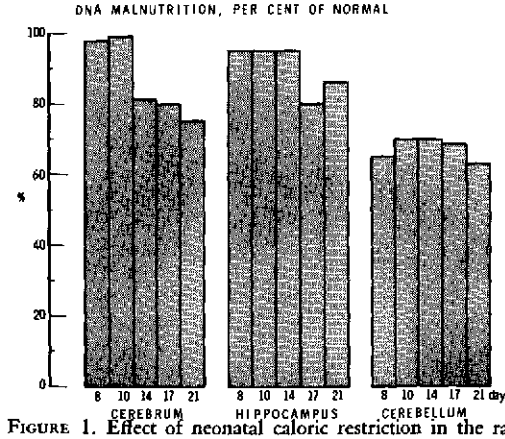

FIGURE 1. Effect of neonatal caloric restriction in the rat on total DNA content of various brain regions.

affect the rate of cell division in any brain area where cells are dividing and in any cell type in the process of division (*14*). Figure 1 demonstrates that in animals malnourished from birth, cerebellum, where cells are most rapidly dividing, is affected earliest and most severely. Figure 2 focuses on the cell types involved. In cerebral cortex, neurons are not dividing postnatally and hence are not affected by undernutrition. The number of glia, however, is reduced. In cerebellum all cell types are reduced. The areas under the lateral ventricle and under the third ventricle are other areas in which primitive neuronal division is curtailed. Thus discrete brain areas are disproportionately affected by neonatal undernutrition. The magnitude of the effect is proportional to the rate of cell division in a particular area. In contrast, if increased nutrition occurs during the proliferative phase, it will accelerate cell division and result in a permanent increase in brain-cell number (*15, 19*).

Thus, within certain limits, the number of cells ultimately present in the adult brain may be programmed during early life—during that period in postnatal life when brain cells are still dividing. Can this type of programming take place during prenatal life? Certainly all fetal organs are in the proliferative growth phase and therefore would appear susceptible to permanent cellular effects. However, the fetus

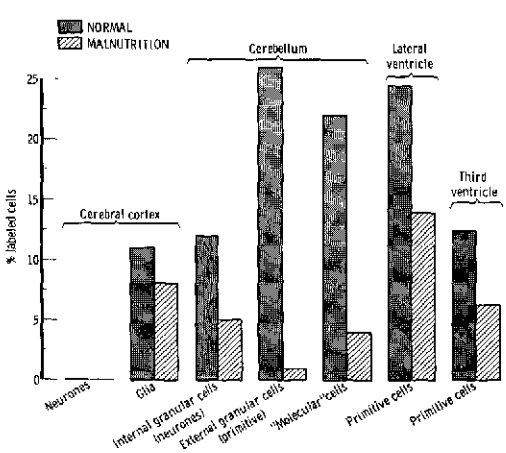

FIGURE 2. Effect of neonatal caloric restriction on various cell types in rat brain.

is protected from the environment by the mother and the placenta. It may therefore be asked, Can the mother and/or the placenta protect the growing fetus from adverse environmental stimuli such as maternal malnutrition, maternal disease, or insufficient uterine vascular supply?

In animals it is possible to monitor the effects of various maternal stresses on the cellular growth of both placenta and fetal organs. In the human the fetus is not available for organ analysis of this kind, and therefore the placenta, which is accessible after birth, is the only organ that can be examined when the fetus is born in a viable condition. Thus if changes in the pattern of cellular growth in placenta may be correlated with the cellular growth of fetal organs in animals, perhaps similar changes in human placenta will give us a clue to the effects of similar maternal stresses on the human fetus.

Normal placental growth, both in the rat and in the human, proceeds in the same way as was described above for the organs of the rat. In the rat placenta, DNA synthesis and hence cell division stop at 17 days of a 21-day gestation (*18*). In the human placenta, cell division continues until around the thirty-fourth to thirty-sixth week of gestation (*20*). In both cases net protein synthesis continues to term. Thus the same three phases of cellular growth may be described as for other organs of the rat. Stimuli imposed prior to the seventeenth day or thirty-sixth week, respectively, should lead to a permanent reduction in placental cell number, whereas stimuli that are active only after cell division has stopped should affect the size of individual cells but not their total number. Hence examination of the ultimate cellular make-up of the placenta should give us an idea of when, during the course of growth, a stimulus has been active.

With these principles in mind, let us examine the effects of a number of precisely timed experimental stimuli on placental and fetal growth in the rat. Then we shall examine the ultimate effects of naturally occurring stimuli on the human placenta. Finally we shall attempt to

determine the time during pregnancy when these stimuli are active.

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 there was a progressive decrease in cell number in all the organs studied. By term there were only about 85 per cent as many brain cells as in control animals (Table 1). These data agree with previous data of Zamenhof, which showed a similar reduction in total brain-cell number in term fetuses whose mothers were exposed to a slightly different type of nutritional deprivation (*22*). Thus the cellular changes produced by severe prenatal food restriction are reflected in placenta even earlier than in the fetus, but a retardation of cell division in all fetal organs including brain can be clearly demonstrated.

By employing radioautography after injecting the mother with tritiated thymidine, cell division can be assessed in various discrete brain regions (*1*). Differential regional sensitivity can be demonstrated in this way by the sixteenth day of gestation in the brains of fetuses of protein-restricted mothers (Figure 3). The cerebral white and gray matter are mildly affected. The area adjacent to the third ventricle and the subiculum are moderately affected, whereas the cerebellum and the area directly adjacent to the lateral ventricle are markedly affected. These

TABLE 1. Effect on fetal growth of rats caused by maternal protein restriction

	% NORMAL CONTROL			
TISSUE	WEIGHT	PROTEIN	RNA	DNA
Whole animal	87	81	83	81
Brain	91	85	82	84
Heart	84	84	79	81
Lung	82	85	85	89
Liver	82	80	85	85
Kidney	84	81	82	85

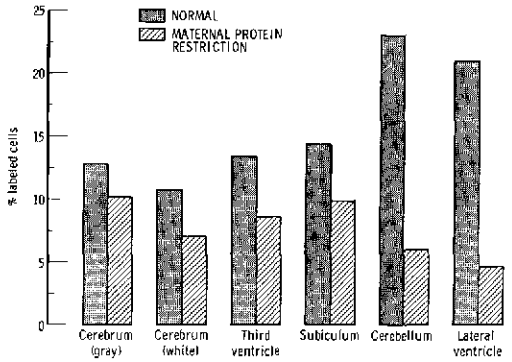

FIGURE 3. Effect of maternal protein restriction on regional DNA content of fetal brain.

data again demonstrate that the magnitude of the effect produced on cell division is directly related to the actual rate of cell division at the time the stimulus is applied. Moreover, they demonstrate that the maternal-placental barrier in the rat is not effective in protecting the fetal brain from discrete cellular effects caused by maternal food restriction.

The subsequent course of these animals born of protein-restricted mothers can be examined. Chow has reported that, even if they are raised normally on foster mothers, their ability to utilize nitrogen is permanently impaired (*3*). Data from our own laboratory demonstrate that if they are nursed on normal foster mothers in normal-sized litters, they will remain with a deficit in total brain-cell number at weaning. Thus we can again see early programming of the ultimate number of brain cells. This program, moreover, is written *in utero* in response to maternal nutrition.

These same newborn pups of protein-restricted mothers may be subjected to postnatal nutritional manipulation. If they are raised in litters of three on normal foster mothers until weaning, the deficit in total number of brain cells may be almost entirely reversed. But, although quantitatively the number of cells comes to approach normal, qualitatively the deficit at birth might very well be made up by an increase in cell number in different areas from those most affected *in utero*. Thus although it may appear that optimally nourishing pups after exposing

them to prenatal undernutrition will reverse the cellular effects, this may not actually be so in specific brain areas.

Perhaps the situation most analogous to that in humans is exposing these pups, malnourished *in utero,* to subsequent postnatal deprivation. Animals reared on foster mothers in groups of 18 show a marked reduction in brain-cell number by weaning. This effect is much more pronounced than that of either prenatal or postnatal undernutrition alone. As has been pointed out, animals subjected to prenatal malnutrition alone show a 15 per cent reduction in total brain-cell number at birth. Animals subjected only to postnatal malnutrition show a similar 15 to 20 per cent reduction in cell number at weaning. In contrast, these "doubly deprived" animals demonstrate a 60 per cent reduction in total brain cell number by weaning (Figure 4). These data demonstrate that malnutrition applied constantly throughout the entire period of brain-cell proliferation will result in a profound reduction in brain-cell number—greater than the sum of effects produced during various parts of the proliferative phase. The duration of malnutrition as well as the severity during

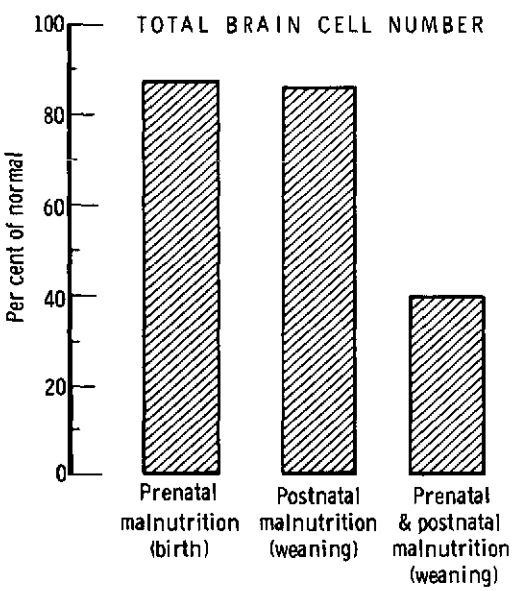

FIGURE 4. Comparison of caloric restriction after birth, protein restriction during gestation, and "combined" prenatal and postnatal restriction.

this early critical period would appear to be extremely important in determining the ultimate cellular make-up of the brain.

It has been shown in rats that clamping the uterine artery supplying one horn of the uterus will curtail fetal growth (*11*). The accompanying cellular events can be examined. Regardless of when the clamping is performed, cell division is curtailed in all fetal organs except brain (Table 2). In contrast, the DNA content of placenta is reduced only if the clamping is done before the seventeenth day; after this time the cell size (protein/DNA) is reduced. The RNA/DNA ratio in placenta increases following uterine artery ligation at any time (*13*). The exact significance of this is not known. An elevated RNA/DNA ratio has been observed under a variety of conditions involving tissue "stress," and is one of the first changes noted in cardiac hypertrophy secondary to experimental aortic ligation (*6*), in uterine hypertrophy induced by estrogen (*8*), and in muscles exposed to repeated nerve stimulation (*7*).

Organs of animals delivered on the twenty-first day from ligated horns and then foster-nursed to weaning do not attain the expected number of cells by weaning. Thus again a change produced *in utero* will persist throughout life. In these animals, however, brain was normal at birth and remained normal at weaning.

Recently Zamenhof demonstrated that artificially reducing the number of fetuses *in utero* will result in offspring with an increased number of brain cells (*10*). Certainly, then, in rats,

TABLE 2. Effect on cell division in rat fetuses of clamping artery supplying one horn of uterus

	% NORMAL CONTROL			
TISSUE	WEIGHT	PROTEIN	RNA	DNA
Whole animal	67	71	63	71
Brain	91	95	104	99
Heart	84	84	79	91
Lung	62	65	55	59
Liver	62	70	75	55
Kidney	64	61	82	75

manipulation of the maternal environment during gestation will produce permanent cellular changes in the offspring. The effects of similar naturally occurring environmental stresses during human pregnancies are more difficult to demonstrate, but certain clear changes can be noted.

Placentas from infants with "intrauterine growth failure" show fewer cells and a higher RNA/DNA ratio than controls (*12*). Fifty per cent of placentas from an indigent population in Chile showed similar findings, and placentas from a malnourished population in Guatemala had fewer cells than normal (*4*). In a single case of anorexia nervosa in which a severely emaciated mother carried to term and gave birth to a 2,500-gram infant, the placenta contained less than 50 per cent of the expected number of cells (Figure 5). Thus both vascular insufficiency and maternal malnutrition will curtail cell division in human placenta. The cellular make-up of the placenta in both of these situations strongly suggests that both stimuli have been active for some time prior to the thirty-fourth to thirty-sixth week of gestation.

The effects of these stimuli on the cellular growth of the fetus are more difficult to assess. In both situations fetal growth is retarded and birth weight reduced (*9*). Indirect evidence would suggest that cell division in the human

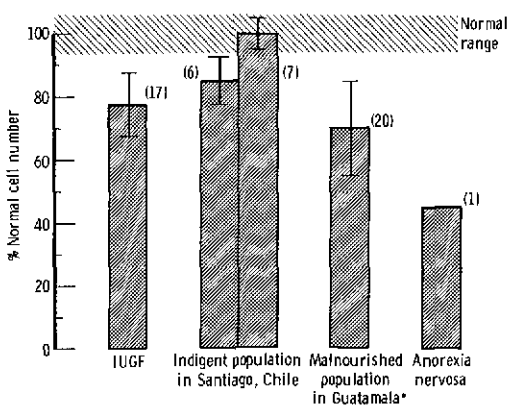

FIGURE 5. Placental cell number in various types of maternal undernutrition.

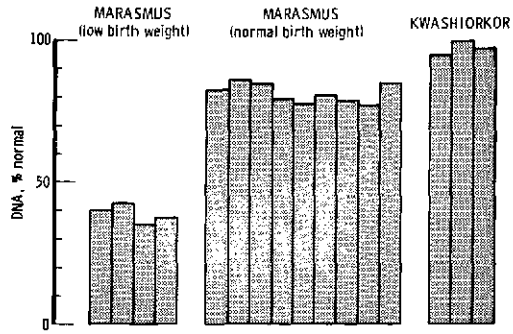

FIGURE 6. Total DNA content in brains of children who died of malnutrition.

fetus might be retarded by maternal undernutrition. If the available data on infants who died after exposure to severe postnatal malnutrition are examined, three separate patterns emerge: 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 2,000 g 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 (Figure 6) (*21*). It is possible that these children were deprived *in utero* and represent a clinical counterpart of the "doubly deprived" animal. It is also possible that these were true premature infants and that the premature is

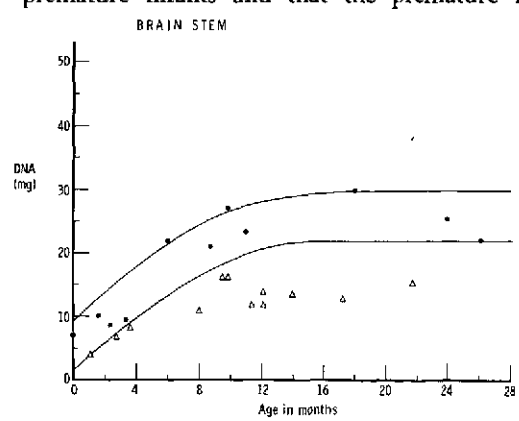

FIGURE 7. Regional growth of human brain in normal and marasmic children.

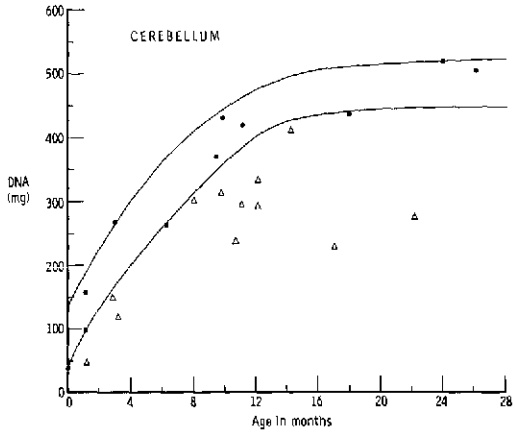

FIGURE 8. Regional growth of human brain in normal and marasmic children.

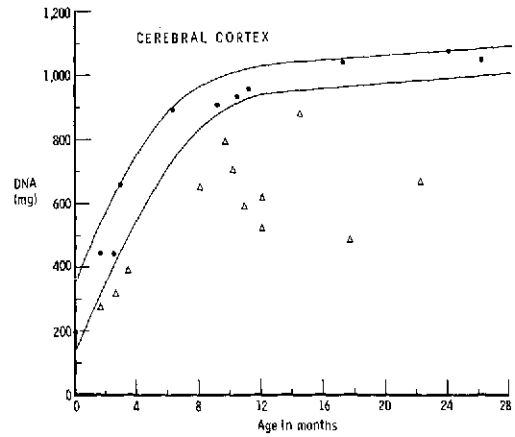

FIGURE 9. Regional growth of human brain in normal and marasmic children.

much more susceptible to postnatal malnutrition than the full-term infant.

Regional growth in the human brain is somewhat different from in the rat brain. Cell division stops at about the same time (eight to ten months) in cerebellum, cerebrum, and brain stem. Severe malnutrition during this proliferative phase retards cell division in all three of these regions (Figures 7, 8, 9). The rate of cell division is about the same in cerebrum and in cerebral cortex, and both are severely affected by malnutrition. In comparison to the rat (*5*), cell division in human cerebellum is much more rapid during postnatal growth, and human cerebrum is much more affected by postnatal malnutrition. Thus postnatal malnutrition curtails cell division in human brain as it does in rat brain. Prenatal stimuli affect human placenta in much the same way as rat placenta.

Although at this time human fetal data are still sketchy, the suggestion that cell division in fetal organs can be curtailed by maternal undernutrition appears to be valid enough to require further studies. In view of the tremendous public health implications of this possibility, and in view of the evidence in animals that these changes are permanent, it would seem to us that every effort should be made to quickly confirm or rule out the possibility that undernutrition of the mother may permanently reduce the number of brain cells in her offspring.

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RELATIONSHIPS OF MATERNAL AMINO ACID BLOOD LEVELS TO FETAL DEVELOPMENT[1]

K. S. Moghissi, J. A. Churchill, and C. Frohman[2]

Previous reports on the relationship between low birth weight and intelligence quotient suggest that maternal nutritional deficiencies may produce intrauterine stunting and impairment of fetal brain development (*1, 3, 4*). Protein deprivation in pregnant rats results in offspring with decreased birth weight and impaired learning ability that persists after maturity (*2*). Dobbing found that weanling rats given low-protein and low-calorie diets had brains different in chemical composition from those reared on normal diets.

This study was designed to investigate the effects of protein deprivation during human gestation by comparing varying maternal blood levels of free alpha-amino acids as related to infant birth weight, length, and cranial volume. Controlling and assessing the diets of pregnant women is difficult. Hence, other measures of nutrient supply were sought by determining blood protein and amino acid levels. Transfer of maternal amino acids to the fetus is known to be free and proportional (*8*).

Study groups

All the patients selected for study were admitted to the hospital. All were in Social Class V according to the Hollingshead-Redlich scale. Dietary assessments were made by a dietitian, who estimated the amounts of nutrients ingested on 24-hour recall of food eaten. Two groups were studied—those with daily protein intakes greater than 70 g and those with less than 50 g. Gravidas with medical and/or obstetric complications were excluded. Prenatal visits were bimonthly until Week 31 and weekly thereafter. All the patients were examined by one of the investigators. Fetal age was estimated from the date of the last menstrual period.

Methods

Twenty milliliters of oxalated blood was obtained between Weeks 32 and 34 and again between Weeks 34 and 36 of gestation. Folin-Wu filtrates were prepared immediately from 10 ml of each sample. The remaining 10 ml was used for measurement of proteins by paper electrophoresis. Total free alpha-amino acid determinations were performed in duplicate on half of the filtrate by the modified method of Folin (*7*). Uric acid was also measured, to avoid false values from this source. The rest of the filtrate was lyophilized and stored for future determination of specific amino acids.

Birth weights and newborn lengths were recorded. One length measurement was made from the level of the atlas to the tip of the coccyx. Occipitofrontal, biparietal, and porion measurements were made with calipers 10 times during the first 24 hours and 10 times between 36 and

[1] Supported by a grant from the Seyforth Foundation and grant PH–43–68–669 from the National Institute of Neurological Disease and Blindness, National Institutes of Health, Bethesda, Maryland, U.S.A.

[2] Presented by Dr. Moghissi.

48 hours of life. The 20 measurements of each diameter were averaged.

Using the means of the measurements, cranial volume (V) was calculated by the formula

$$V = 0.52 \times (L \times B \times H) - P$$

where L, B, and H represent occipitofrontal, biparietal, and porion diameters, respectively. P is an estimate of the volume contributed by scalp and skull thickness, which is 140 cc for neonatal males and 125 cc for females (5).

Results

The first and second maternal blood amino acid levels were averaged in each case. The mean amino acid value of a group of 88 pregnant women at term was found to be 4.18 mg/100 ml (Table 1). For analysis, patients with high amino acid levels—over 4.0 mg/100 ml (control group)—were compared with patients whose amino acid levels were less than 4.0 mg/100 ml (study group). They were matched for race, sex of their babies, and weeks of gestation at delivery. These data were subjected to pooled t tests. Infant measurements were grouped and analyzed both together and separately by sex. The babies whose mothers had blood amino acids above the group mean (4 mg %) were matched for race, sex, and weeks of gestation at birth with those whose mothers had lower levels of amino acids (Table 2).

The mean birth weight of the infants in the control group was 3.26 kg (Table 2). The mothers in the study group had babies with a mean birth weight of 2.86 kg ($t=4.28$; $p \leq .001$). The mean atlateal-coccygeal length of infants whose mothers had high amino acid levels was 208 mm, compared with 196 mm in those whose mothers had low levels ($t=3.65$; $p<.001$). Conventional crown-heel length was likewise significantly different in the two groups: 483 mm for the control babies and 460 mm for the study infants ($t=2.70$; $p<.01$). The mean cranial volume associated with high amino acid levels was 453 cc, whereas the cranial volume of the low amino acid group was 421 cc ($t=2.73$; $p<.01$).

The birth weight, cranial volume, and fetal length were not significantly related to the estimated dietary intake of protein or to blood albumin levels. However, the dietary diaries showed a trend toward a relationship between the amounts of ingested amino acids and birth weight. Mothers with high blood amino acids

TABLE 1. Relationship of blood alpha-amino acid levels to material factors

	MEAN				
	CONTROL	STUDY	NO.	t	p
Alpha-amino acid (mg % blood) [a]	4.42	3.59	44	—	—
Maternal dietary protein (g/day)	57.7	52.9	44	1.03	[b]
Maternal albumin (mg % blood)	3.47	3.48	44	0.19	[b]
Maternal globulin (mg % blood)	3.39	3.36	44	0.83	[b]
Maternal ht. (cm)	162	159	44	2.36	< 0.05
Pregnancy wt. (kg)	65.7	60.4	44	1.65	[b]
Maternal wt. gain (kg)	11.8	8.6	44	0.43	[b]

[a] Mothers with high amino-acid levels (above 4 mg % blood) in the last trimester of pregnancy were matched to those with low amino acids (below 4 mg % blood) for race, sex, and week of gestation at delivery. Maternal factors were then compared in the two groups.

[b] Not significant.

TABLE 2. Maternal blood amino acid level and developmental measures of offspring

	MEAN				
	CONTROL	STUDY	NO.	t	p
Alpha amino acid (mg % blood) [a]	4.42	3.95	44	—	—
Birth wt. (kg)	3.26	2.86	44	4.28	$\leqslant .001$
Spinal length, atlas to coccyx (mm)	208	196	42	3.6	$< .001$
Cranial capacity (cc)	453	421	43	2.73	$< .01$
Crown-heel length (mm)	483	460	42	2.70	$< .01$

[a] Babies born of mothers with high amino acid levels (above 4 mg % blood) in the last trimester were paired with those whose mothers had lower levels (below 4 mg % blood). They were matched for race, sex, and weeks of gestation at birth.

ingested an average of 57.7 g protein daily, compared to 52.9 for those with low levels.

Comparison of blood amino acid levels with plasma albumin content revealed no significant relationship. The mean albumin was 3.47 and 3.48 g/100 ml blood, respectively, for patients with high and low amino acid levels.

The maternal weight gain in pregnancy and the prepregnancy weight of the mothers were not significantly related to the babies' birth weight, length, or cranial volume. However, the maternal height exhibited a significant relationship to these factors: the mean height of the control group was 162 cm, and that of the study group 159 cm ($t=2.36$; $p<0.05$).

Discussion

A striking relationship between maternal blood alpha-amino acid concentration and birth weight, length, and cranial volume was observed. Mothers with blood amino acid levels below 4 mg/100 ml had lighter and shorter babies with smaller cranial volumes than those whose amino acid levels exceeded 4 mg/100 ml. This study suggests that fetal development is stunted when amino acids available to the fetus are diminished. No significant relationship was found between maternal blood albumin levels and these infant measurements. If hydration were related to fetal size, one would expect to find decreases not only in amino acids, but also in blood albumin concentrations. On the basis of previous work relating low intelligence quotient to low birth weight (*3*), it may be conjectured that when mothers have low amino acid blood levels, their babies may have lowered intelligence quotients.

No clear relationship between what these patients said they ate and their blood amino acid levels was observed; nor was maternal dietary asessment, pregnancy weight gain, or pregestational weight of the mothers related significantly to fetal size at birth. The extent to which blood amino acid levels reflect the quantity and quality of ingested proteins must be resolved. Fetal development and prognosis may be more closely related to maternal blood amino acid levels than to information derived from patient dietary records.

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

Summary

In this study the relationship between the maternal dietary intake, blood levels of free alpha-amino acids, serum proteins, and infant birth weight, length, and cranial volume has been investigated.

The maternal blood amino acid levels during pregnancy were found to be related significantly to infant weight, length, and cranial volume. No clear relationship could be established be-

tween estimated dietary intake and the status of the infant or maternal amino acid values.

The possible relationship between maternal blood amino acid levels during pregnancy with birth weight, fetal cranial volume, and intelligence quotients is discussed.

Acknowledgment

The authors wish to acknowledge the generous support of the Lafayette Clinic and the Department of Laboratories of Hutzel Hospital, and the diligent efforts of Miss Ingrid Engstrom and Mrs. Nancy Anderson.

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DISCUSSION

Stephen Zamenhof: Studies of Some Factors Influencing Cell Number in Prenatal Brain

This report will be concerned with the nutritional effects on one parameter only: the number of cerebral neurons. This number is final in rats at birth and in humans between the fifth and seventh month of gestation. In our study, therefore, we were interested in the prenatal nutritional effects. Our techniques [1, 2] are based on the determination of total amount of DNA per brain (cerebral hemispheres), from which total brain-cell number can be easily calculated because for all practical purposes the amount of DNA per brain cell is constant. Thus, whenever I refer to the amount of DNA, I shall mean cell number.

The amount of cerebral DNA in rat at birth reaches a plateau [3] and therefore is convenient to measure; the cells at that time are reported to be predominantly neurons or neuroblasts. This brain-cell number is one of the most constant parameters; [4] it cannot be changed by many of the nutritional treatments that can easily change brain weight, which we do not consider to be a very meaningful parameter. For example, we found that on a protein-adequate pellet diet the brain weight of rats is considerably lower than on a 27 per cent protein diet but the brain DNA remains the same. We also found that daily intravenous injections of 20 per cent glucose result in a temporary hyperglycemia of the pregnant rat and the fetuses and a considerable increase in newborn brain weight, but again brain DNA remains practically the same. The increase in body weight is also considerable, which may remind you of the increased body weight of the fetuses of diabetic mothers, but in humans this occurs after six and a half months of gestation, at which time the number of neurons becomes final. Conversely, 2-deoxyglucose, which is an antimetabolite, produces hypoglycemia and a significant decrease in brain weight, but brain DNA still remained the same.

Another example is related to placental development, which is of course part of the problem of prenatal nutrition. The rabbit, unlike the rat, sometimes shows a nice correlation between the placental weight (including placental blood volume) and neonatal body weight or brain weight. Some such correlation may also be true for humans. But again we found no correlation between brain weight and brain DNA.

It appears that this important parameter, brain DNA or brain-cell number, is subject to strict regulation, perhaps by an efficient system of interlocking checks such as availability of specific enzymes and specific substrates at specific times. The regulatory mechanism itself may be very complex and involve cell differentiation

[1] Zamenhof, S., H. Bursztyn, K. Rich, and P. J. Zamenhof. The determination of deoxyribonucleic acid (DNA) and of cell number in brain. *J. Neurochem.* 11: 505–509, 1964.

[2] Margolis, F. L. DNA and DNA-polymerase activity in chicken brain regions during ontogeny. *J. Neurochem.* 16:447–456, 1969.

[3] Zamenhof, S., E. Van Marthens, and H. Bursztyn. The effect of hormones on DNA synthesis and cell number in the developing chick and rat brain. Conference on Hormones in Development, Nottingham University, England, 1968. National Foundation. In press.

[4] *Ibid.*

and migration and the control (e.g., by hormones and by gene derepression) of specific enzymes necessary for nutrient utilization, for permeability, and for synthesis of DNA, RNA, protein, and other cell constituents. The flow of nutrients as such to the fetus will depend on the maternal nutrient supply and the mobilization of maternal nutrient storage, placental transfer (placental development, concentration gradients, active transports), and intrauterine competition between fetuses.

After having examined to date something like 1,500 neonatal rats and 2,500 newly hatched chicks, we find that the final result is *not* foolproof. In one out of 500 cases, a newborn rat will have its brain DNA and cell number far above the range for the same litter. A similar situation is found in chicks.[5] What causes this rare deviation? We do not know. What we do know is that normally it is very difficult to change this value (neonatal brain DNA and cell number), and when we do see a change we know we have it. In the remaining part of my lecture I shall discuss two procedures by which this number can be experimentally changed.

One is maternal malnutrition.[6] Our experimental group of rats was maintained on a low (8 per cent) protein diet and our control group on an adequate (27 per cent) diet, one month prior to mating and throughout pregnancy. The experimental animals had enough calories, however, because they received more starch. This restriction is such as to still permit full-term gestation and normal number of offspring. The offspring in the experimental group had considerably lower body and brain weight. The reduction in brain DNA and brain-cell number was less, but still highly significant. Since presumably the brain cells at birth are predominantly neurons, and their number is final, these rats had to go through life with a neuron deficiency. The amount of protein per brain cell was also 10 per cent lower.

The behavior and the learning ability of offspring of mothers undernourished during pregnancy have been investigated in various laboratories and found to be considerably impaired. But is it because of deficiency in number of neurons, deficiency of protein per neuron, or some other alteration? At present no one knows. We therefore extended our study to the second generation. The undernourished mothers and their offspring were put on a normal diet right after delivery, the offspring were mated on maturity and kept on a normal diet, and the second generation was investigated. At birth, as expected, the body weight and brain weight were normal, but, unexpectedly, brain DNA and brain cell number were still 13 per cent lower. The learning ability of these animals in a water maze was tested in our Department of Psychology in collaboration with Dr. Gaylord D. Ellison and found to be significantly impaired.

Needless to say, such long-lasting effects may be of interest for studying the situation of infants in underdeveloped areas. The changes are, of course, not genetic. At least six phenomena could explain our findings, but I shall not have time to discuss them.

As to future projects in this area, we also plan to investigate whether restriction of a single *essential* amino acid during pregnancy will result in a neonatal brain cell deficiency.

Now, how about increase in number of neurons by *prenatal* improvement of feeding, to parallel Dr. Winick's finding on glia by *postnatal* improvement? This subject lies in the area of intrauterine competition, which is also of concern to humans: the individual birth weight of quadruplets is less than that of triplets; this is less than that of twins; and so on.[7] But these differences appear only after the sixth month of gestation, at which time the number of neurons becomes final. We have investigated brain DNA and cell numbers in newborn rats and found that the number is constant, regard-

[5] *Ibid.*

[6] Zamenhof, S., E. Van Marthens, and F. L. Margolis. DNA (cell number) and protein in neonatal brain: alteration by maternal dietary protein restriction. *Science* 160:322–323, 1968.

[7] McKeown, T., and R. G. Record. Observations on foetal growth in multiple pregnancy in man. *J. Endocrinol.* 8:386–401, 1952.

less of how many were in the litter.[8] Thus, during the evolution, an efficient controlling mechanism has been developed to achieve constancy of this important parameter. However, Miss van Marthens, in our laboratory, succeeded in fooling the mechanism by tying one of the two uterine horns prior to mating, so that only half of the normal number of fetuses developed. Each of the newborns in this experimental group had significantly more DNA and brain cells [8]—presumably because the controlling mechanism was set to support the growth of, say, sixteen fetuses and only eight developed, so each had more nutrients.

I have no time to speculate on the nature of this controlling mechanism or to mention our preliminary studies in the area of placental insufficiency, though this is also in the field of prenatal nutrition. I shall end by simply mentioning our future projects: Will experimental reduction from, say, sixteen fetuses to one or two only give more striking results? Can an increase in the number of neurons be achieved by some special prenatal nutrition *per se* or mobilization of maternal nutrient storage? Finally, will the animals with more neurons have better learning ability?

General Discussion

Halsted: It seems to me that when we talk about protein nutrition we need to emphasize the type of protein more than is usually done. I think Dr. Caldwell's paper is extremely important in bringing out the effect of phytate in plant protein, with the resulting zinc deficiency, as one very important aspect.

Gruenwald: It is not quite clear to me—and this refers particularly to Dr. Zamenhof's presentation—why the cells at birth, as derived from DNA determinations, should be predominantly neurons, because DNA doesn't distinguish between the cells of neurons and glia; if cell multiplication stops shortly thereafter, then the full number of glia cells should also have been reached by that time.

Zamenhof: I am referring to the work of Brizee, who determined the neuron/glia ratio in newborn rat brains and found it to be on the order of 4. Of course, both glia and neurons are affected at birth, but glia cells still have time to develop later, whereas neurons have a shorter time and therefore may be more affected, or at least as much so.

Winick: Dr. Gruenwald reminds me of a point that I think is important, and I should like to introduce a word of caution here. When we talk about neurons and glia, we perhaps tend to think of the neuron as the more important cell. This may not be so. The glia have been shown by Hyden and others to be very important in the function of the total cellular complex within the brain. Secondly, the oligodendroglia is the cell in which myelinates and myelin have been shown to be severely reduced both in animals and in the human during severe malnutrition. It may well be the reduction in myelin, not the reduction in the number of cells, that is functionally important. It may therefore turn out that glia are more important than neurons.

We just don't know, and I think we should keep an open mind about the cell types involved and their functional importance.

Churchill: Maybe I can help sort out the DNA, neuron ontogeny, and glia problem. Most neurons have already divided, of course, by the time the mammal is born. However, one class of neurons, the microneurons, may go on proliferating for finite periods of time after birth.

Possibly one reason why changes dated to postnatal time were found by Winick in cerebellum is that the cerebellum is loaded with microneurons as granular cells. The glia, of course, always maintain the ability to react and to divide; they can multiply at any time, given the proper stimulus.

Moderator: I gather that there is some lack of agreement between Dr. Winick's and Dr.

[8] Van Marthens, E., and S. Zamenhof. Deoxyribonucleic acid of neonatal rat cerebrum increased by operative restriction of litter size. *Exper. Neurol.* 23:214–219, 1969.

Zamenhof's data on the time at which reproduction of neurons stops.

Winick: I do not think there is any disagreement. I think that again we have to be careful of the specific terminology we use. Dr. Zamenhof is talking about DNA in cerebral cortex; we were talking about DNA in whole brain. I simply do not know, from our data, when *neuronal* division stops in the cerebral cortex either in the rat or in the human. There are data suggesting that neuronal division stops in the rat at around birth, and there are data suggesting that neuronal division in the human cerebral cortex stops considerably before birth.

I think, however, that with newer techniques available, especially in the rat, where tritiated thymadine can be injected, a re-evaluation of this whole situation is probably in order.

Zamenhof: I am in perfect agreement with Dr. Winick. What he stresses, and rightly so, is the problem of the relative importance of reduction in the number of neurons versus reduction in the number of glia cells and their further development. It will eventually be solved by experimentation, but at present we just do not know which is more harmful.

Moderator: Dr. Moghissi, you found no significant correlation with the dietary intake of the mothers. What is your explanation for the difference in blood level of amino acids, which have such a striking relation to the birth weight and other conditions of the newborn?

Moghissi: As you know, Dr. Caldeyro-Barcia, it is very hard to analyze the diet of people. Our dietitian has gone to considerable lengths to do so. However, when a patient says, for example, that she ate two ounces of meat, there is no way to determine whether she actually did—she may have eaten only one ounce.

The second problem is how much of this is absorbed and used. What was the nutritional state of the mothers before they became pregnant? The nutritional deficiencies may be the result of a long period of protein deprivation that may be shown only partially by measurements of amino acid. Dr. Caldwell brought up the very pertinent question of the type of protein ingested and the little-known area of trace elements. We have just begun to scratch the surface, and there is much more to be done before we know what relationship the dietary intake of these elements bears to protein utilization and transfer to the infant.

Now, in this instance we are completely ignoring the role of the placenta. How much of the nutritional material is transported through the placenta? Is there any way to determine the role of the placenta in nutritional deficiencies? These are all unanswered questions, and until we find some answer I do not think we can answer your question completely.

The point, however, is this: By measuring the amino acids we have, I think, for the first time, something we can put our finger on; we can say that here is a mother who is destined to bear a child who will be smaller and perhaps will not become as intelligent as its counterpart.

Waterlow: I should like to challenge your concept, Dr. Moghissi. I see no reason to suppose that amino acid levels are equivalent to amino acid supply. I might suggest that you examine the situation in Africa. On the whole the babies there are normal in birth weight but the amino acid pattern in the blood is extremely distorted compared to what is considered to be normal in this country. That would provide you with a great deal more material, I think.

Moghissi: Actually, I do not know of any data reported in the literature on anything similar to what we have done, comparing two groups of people in the same population. You obviously cannot take an African population or a South American population and compare it to an American or English or any other population. I think the study is only valid if it is done within the same population, taking into consideration variables that are so important in every segment of the population under study.

Therefore, I would have to say simply that this may be true in Africa, but it does not seem to be quite true in Detroit, Michigan.

PHYSICAL AND MENTAL DEFICITS OF TWINNING[1]

W. L. Holley and J. A. Churchill[2]

In humans, multiple birth presents stresses for the mother and the fetus. Many retrospective studies, reviewed by Anastasi, (*2*) have shown that twins differ from singletons physically and mentally. In 1955, Allen and Kallman reported that twins constituted 3.1 per cent of all admissions to institutions for the mentally retarded in New York State, as compared to the expected 2 per cent (*1*). Several other investigators have shown an increased percentage of twins among the mentally retarded (*12*).

In 1952, Russell pointed out an increase in the incidence of maternal complications and infant morbidity and mortality (*13*). Koch reported in 1966 on the low birth weight of twins with subsequent failure to "catch up" with controls by four years of age (*10*).

This presentation on prospectively collected data re-examines the findings of previous investigators in regard to the physical and mental deficits of twinning. It is also designed to evaluate the effect of birth weight on intelligence quotient independent of gestational age. Churchill has pointed out the relationship in previous studies (*6, 14*).

[1] A report from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood, which is supported by the National Institute of Neurological Diseases and Stroke of the National Institutes of Health, Bethesda, Maryland, U.S.A. These papers must be regarded as preliminary explorations of Collaborative Study data. Possibilities remain that differences observed in the offspring, if indeed they are proven to be of practical significance, may reflect differences in maternal characteristics other than those variables under study here. Such critical factors, if present, should be disclosed in the course of the comprehensive analysis of the data, which has begun.

[2] Presented by Dr. Holley.

Methodology

Subjects and controls were drawn from the cohort of the Perinatal Research Branch of the National Institute of Neurological Diseases and Stroke (*5*)with 14 collaborating medical centers.[3] Approximately 56,000 women registered in the study, and detailed obstetrical records were obtained. The offspring were examined periodically for an evaluation of mental and physical development; a speech, language, and hearing assessment; and a review of childhood illness and injuries. At eight months of age, each infant was evaluated by a psychologist using a standardized modification of the Bayley Scale of Infant Development; (*3*) at four years, the Revised Stanford-Binet Form L-M test was administered.

All fraternal twins, proved by blood typing, who had a Binet IQ score reported at four years of age were included. The controls were chosen from all single births who had a Binet IQ available. Excluded were mongoloids and children of mothers with diabetes and acetonuria, with heavy albuminuria, or who registered in the study during labor. The controls were matched with subjects for race, sex, institution of birth, and social class (*11*). An approximate match was made for maternal age.

The twins were compared with singletons on the following items: birth weight in grams, gestation length in weeks completed, Bayley scores of mental and motor development at eight

[3] Boston Lying-in Hospital, Brown University, Charity Hospital, Children's Hospital of Buffalo, Children's Medical Center in Boston, Columbia University, The Johns Hopkins University, Medical College of Virginia, New York Medical College, Pennsylvania Hospital, Children's Hospital of Philadelphia, University of Minnesota, University of Oregon, and University of Tennessee.

TABLE 1. Results of evaluation of all fraternal twins

	BIRTH WEIGHT (G)		PREGNANCY DURATION (WEEKS)		BAYLEY (8 MONTHS) MENTAL		BAYLEY (8 MONTHS) MOTOR		IQ (4 YEARS)	
	C	T	C	T	C	T	C	T	C	T
All twins										
N	226		226		196		196		226	
X	3158	2503	39.2	37.2	79.7	74.7	32.7	28.9	97.7	87.7
t	14.2468		7.74236		5.0204		6.35107		7.88985	
p	≪.001		≪.001		≪.001		≪.001		≪.001	
All whites										
N	88		88		85		85		88	
X	3300	2678	39.7	38.0	80.2	76.6	32.4	29.1	106.9	96.1
t	7.97178		4.56513		3.3380		3.66023		5.50445	
p	≪.001		<.001		<.005		<.001		≪.001	
All Negroes										
N	138		138		111		111		138	
X	3068	2392	38.9	36.7	79.3	73.2	33.0	28.8	91.8	82.3
t	11.9292		6.26891		4.95966		5.21629		5.7135	
p	≪.001		≪.001		≪.001		≪.001		≪.001	
All males										
N	111		111		98		98		111	
X	3263	2571	39.3	37.2	80.2	74.3	32.8	28.4	96.4	86.3
t	9.80334		5.78415		5.18718		5.55888		5.52474	
p	≪.001		≪.001		<.001		≪.001		≪.001	
All females										
N	115		115		98		98		115	
X	3121	2486	39.2	37.2	79.2	75.1	32.7	29.5	98.9	88.9
t	9.64287		5.21782		3.32496		3.20408		5.60808	
p	≪.001		≪.001		<.005		<.005		≪.001	
White males										
N	44		44		43		43		44	
X	3461	2725	39.9	38.0	80.8	76.3	33.1	29.1	105.1	94.2
t	6.0137		3.91447		3.18535		3.35838		4.07479	
p	≪.001		<.001		<.005		<.005		<.001	
White females										
N	44		44		42		42		44	
X	3307	2756	39.5	38.1	79.5	77.0	31.7	29.2	108.8	97.9
t	4.51918		2.60225		1.61174		1.8833		3.69502	
p	≪.001		<.02		N.S.		N.S.		<.001	
Negro males										
N	67		67		55		55		67	
X	3132	2469	38.8	36.8	79.7	72.7	32.5	27.9	90.7	81.2
t	7.75203		4.30601		4.12928		4.41816		3.8621	
p	≪.001		≪.001		<.001		≪.001		<.001	
Negro females										
N	71		71		56		56		71	
X	3007	2319	39.0	36.6	79.0	73.7	33.4	29.7	92.8	83.4
t	9.11439		4.54606		2.92443		3.06355		4.1964	
p	≪.001		≪.001		<.005		<.005		≪.001	

Note: C = controls; T = twins.

months of age, and the Stanford Binet IQ at four years of age. The results were analyzed using a t test for correlated samples. A p value of less than .05 for a two-tailed analysis is considered significant.

Results

There were a total of 226 fraternal twins matched with 226 singletons. These twins include all who had an IQ score reported, among them broken pairs where one twin may have died. Of these 226 pairs, 88 (38.9 per cent) were white and 138 (61.1 per cent) were Negro. There was a nearly equal sex ratio—111 (49.1 per cent) male and 115 (50.9 per cent) female. The data indicate that twins differ from singletons according to all the measures examined. In both races and in both sexes they have lower birth weight, shorter gestational age, lower Bayley scores, and lower IQ. Table 1 shows the means and p values.

To see whether the differences observed were due to prematurity, all pairs were eliminated where the subject had a shorter gestation than the control. Table 2 shows that there is still a significantly lower birth weight and lower IQ. In fact, the mean differences in the Binet IQ scores are found to have widened from 10 to 13 points. The Bayley motor score differences disappear, probably because this measure is sen-

TABLE 2. Results of evaluation of all fraternal twins where pregnancy duration is equal to or greater than control

	Birth weight (g)		Pregnancy duration (weeks)		Bayley (8 months) Mental		Bayley (8 months) Motor		IQ (4 years)	
	C	T	C	T	C	T	C	T	C	T
All twins										
N	72		72		60		60		72	
X	3029	2730	37.5	39.5	79.2	76.1	32.2	30.5	98.9	85.9
t	3.60984		—7.7272		2.64771		1.74241		5.99202	
p	<.001		≪.001		<.02		N.S.		≪.001	
All whites										
N	31		31		30		30		31	
X	3115	2881	38.3	40.1	79.3	76.6	31.6	30.3	106.7	92.5
t	1.77064		—4.75601		1.53364		0.86031		4.26809	
p	N.S.		<.001		N.S.		N.S.		<.001	
All Negroes										
N	41		41		30		30		41	
X	2964	2616	36.9	39.1	79.1	75.5	32.8	30.7	93.0	80.9
t	3.27198		—6.07754		2.19641		1.65851		4.18568	
p	<.005		≪.001		<.05		N.S.		<.001	
All males										
N	33		33		27		27		33	
X	3080	2815	37.8	39.9	80.0	75.0	31.9	29.8	93.9	82.9
t	1.96382		—6.3996		2.62415		1.50226		3.55262	
p	N.S.		≪.001		<.02		N.S.		<.005	
All females										
N	39		39		33		33		39	
X	2986	2658	37.2	39.2	78.5	76.9	32.4	31.0	103.1	88.4
t	3.17795		—4.929		1.10325		0.99295		4.8333	
p	<.001		<.001		N.S.		N.S.		≪.001	

Note: C = controls; T = twins.

sitive to gestational age. The Bayley mental scores still remain significantly different, though the difference is somewhat less.

Approximately a quarter of the fraternal twins were of the same sex (DZSS). This proportion is uneven because many of the same-sex twins have undetermined zygosity to date. Both the DZSS and the mixed-sex twins (DZOS) show the same differences observed in all fraternal twins (Tables 3 and 4). When the DZSS are subdivided into various subgroups, it is found that statistical significance is lost in some groups because of the small number of cases. The mean difference continues to be in the predicted direction.

Discussion

This study confirms previous retrospective studies by means of prospectively collected data of the COLR. Interpretation of the findings is speculative. What mechanism is at work to cause physical and mental deficits in twins compared with singeletons?

One is tempted to incriminate prematurity as the basic factor involved. Certainly, several articles have demonstrated delayed physical and mental development among prematurely born infants (*7, 8, 9*). However, even if prematurity is accepted as the underlying cause, there are still certain factors that need further illumina-

TABLE 3. Results of evaluation of same-sex fraternal twins (DZSS)

	BIRTH WEIGHT (G)		PREGNANCY DURATION (WEEKS)		BAYLEY (8 MONTHS) MENTAL		BAYLEY (8 MONTHS) MOTOR		IQ (4 YEARS)	
	C	T	C	T	C	T	C	T	C	T
All cases										
N	49		49		44		44		49	
X	3110	2396	39.4	36.3	79.8	74.4	32.7	29.2	98.1	89.9
t	6.3087		5.2649		5.3636		2.6562		3.0314	
p	≪.001		≪.001		<.001		<.02		<.005	
All whites										
N	20		20		20		20		20	
X	3232	2571	39.4	37.0	79.6	75.8	36.7	29.9	105.9	93.9
t	3.2227		2.8642		1.5848		1.37602		3.0903	
p	<.005		<.01		N.S.		N.S.		<.01	
All Negroes										
N	29		29		24		24		29	
X	3026	2276	39.4	35.8	79.9	73.3	32.8	28.5	92.6	87.1
t	5.70728		4.4263		2.5501		2.31131		1.5202	
p	≪.001		<.001		<.05		<.05		N.S.	
All males										
N	23		23		22		22		23	
X	3305	2459	39.4	36.4	80.6	70.1	33.9	26.1	97.2	87.8
t	4.9627		3.9333		3.5223		4.4289		2.94465	
p	<.001		<.001		<.005		<.001		<.01	
All females										
N	26		26		22		22		26	
X	2937	2341	39.4	36.2	79.0	78.7	31.5	32.2	98.9	91.7
t	3.9706		3.54875		0.1743		—0.3957		1.67186	
p	<.001		<.005		N.S.		N.S.		N.S.	

Note: C = controls; T = twins.

TABLE 4. Results of evaluation of mixed-sex fraternal twins (DZOS)

	BIRTH WEIGHT (G)		PREGNANCY DURATION (WEEKS)		BAYLEY (8 MONTHS) MENTAL		BAYLEY (8 MONTHS) MOTOR		IQ (4 YEARS)	
	C	T	C	T	C	T	C	T	C	T
All cases										
N	177		177		152		152		177	
X	3172	2522	39.2	37.5	79.7	74.8	32.8	28.9	97.6	87.0
t	12.9979		5.9899		4.92105		3.86184		7.30834	
p	$\ll .001$		$\ll .001$		$< .001$		$< .001$		$\ll .001$	
All whites										
N	68		68		65		65		68	
X	3320	2695	39.8	38.3	80.3	76.9	32.3	28.9	107.3	96.7
t	7.56369		3.6031		2.92191		3.43077		4.58253	
p	$\ll .001$		$< .001$		$< .005$		$< .005$		$< .001$	
All Negroes										
N	109		109		87		87		109	
X	3079	2414	38.8	36.9	79.2	73.1	33.1	28.9	91.6	81.0
t	10.565		4.7951		4.24577		4.18391		5.66919	
p	$\ll .001$		$< .001$		$< .001$		$< .001$		$< .001$	
All males										
N	88		88		76		76		88	
X	3252	2589	39.2	37.5	80.1	75.5	32.4	29.1	96.2	86.0
t	8.60564		4.50765		3.95806		3.40789		4.76795	
p	$\ll .001$		$< .001$		$< .001$		$< .005$		$< .001$	
All females										
N	89		89		76		76		89	
X	3092	2457	39.2	37.4	79.3	74.0	33.0	28.7	98.9	88.1
t	9.90692		3.98713		3.42415		4.19241		5.59048	
p	$\ll .001$		$< .001$		$< .001$		$< .001$		$\ll .001$	

Note: C = controls; T = twins.

tion: (1) What causes an increased incidence of prematurity among multiple births? (2) What constitutes prematurity? Should one consider only birth weight, or only gestational age, or some combination of the two?

Another possible explanation of the differences in Bayley scores and Binet IQ is the effect of postnatal experience. Twins tend to communicate with each other and with playmates of their own age more frequently than singletons do; singletons seek more communication with adults (2). Thus, perhaps the twins are depriving themselves of the environmental enrichment available from adult contact. The postnatal environment will influence, at least to some degree, the mental development of a child. However, the decreased birth weight and shorter gestation among twins are still unexplained. The relationship of environmental influence upon the early developmental measures is also unclear.

One might speculate that many intrauterine factors are at work, either alone or in combination. The uterus may not be able to expand sufficiently to meet the space requirements of the growing infants. Perhaps the placenta is unable to supply sufficient vascularization to provide oxygen or adequate exchange of waste products. Another possible explanation is that of an intrauterine nutritional deprivation. Previ-

ous animal studies have shown that dietary deficiencies in the gravid animal produce low-birth-weight animals, increased mortality, and decreased learning abilities (*4, 13*). Winick has demonstrated the importance of antenatal and early postnatal nutrition on the cellular growth of the brain both in animals and in humans (*15*). It would seem reasonable that multiple births produce an increased nutritional demand on the mother. These nutrient demands may be difficult to meet, thus producing body stunting, impaired brain development, and the physical and mental deficits noted.

We may conclude that twinning does cause mental and physical deficits. The causes are unclear, but it seems reasonable to assume that nutritional deprivation is at least a partial factor.

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INTELLIGENCE OF CHILDREN WHOSE MOTHERS HAD ACETONURIA DURING PREGNANCY[1]

John A. Churchill and Heinz W. Berendes[2]

This presentation deals firstly with the neurological and psychological effects of maternal diabetes on offspring and secondly with acetonuria of nondiabetic origin occurring in pregnancy. Complications of diabetes, such as prematurity, vascular disease, keto-acidosis, and therapy, have also been considered. Mild as well as severe diabetes has been implicated in poor outcomes of pregnancy: in high rates of fetal loss, neonatal deaths, and congenital malformations (*2, 4–8, 10–15, 17, 19–22, 28–31, 35*).

The cases for study were drawn from the Collaborative Study of Cerebral Palsy, National Institute of Neurological Diseases and Stroke, which involves a total of about 55,000 pregnancies. The study population included only pregnancies resulting in single, liveborn babies who had been given an IQ test at four years of age.

Effects of maternal diabetes on offspring

Method of procedure

Mothers were considered diabetic if their glucose-tolerance curves during the current pregnancy met the criteria set forth by Szmogyi-Nelson or, in lieu of glucose-tolerance curves, if the patient was clearly known as a diabetic and was treated with more than 20 units of insulin daily (*27*). Diabetics were classified in accordance with the system of White (*34*). Mothers who had Class A diabetes, including cases with abnormal glucose-tolerance curve and gestational diabetes, were grouped separately from those who had diabetes of Classes B, C, D, E, and F (referred to hereafter as Class B+).

In addition to keto-acidosis of a degree considered to be clinically significant, the presence of acetonuria alone was noted. Urine tests for acetone (and for diacetic acid) were performed in the clinical laboratories of the participating institutions in accordance with routine methods (*18*). Cases were assigned to the acetone-positive group if any urine test done in the last trimester of pregnancy, but earlier than 24 hours before birth, was recorded 1+ or more positive for acetone. No test for acetone had been done in 15 cases. Since the patients were tested for acetone at irregular intervals, the possibility exists that any patient found negative on one day could have been positive the next or that any patient positive for acetone could have been positive on only that occasion.

The types and amounts of medication given during pregnancy were noted.

Each of the 122 diabetic cases was matched for hospital of birth, race, and sex with a single nondiabetic acetonuria-free case. "Controls" were matched also for the same or next-lower socioeconomic index value, the same or

[1] A report from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood, which is supported by the National Institute of Neurological Diseases and Stroke of the National Institutes of Health, Bethesda, Maryland, U.S.A. These papers must be regarded as preliminary explorations of Collaborative Study data. Possibilities remain that differences observed in the offspring, if indeed they are proven to be of practical significance, may reflect differences in maternal characteristics other than those variables under study here. Such critical factors, if present, should be disclosed in the course of the comprehensive analysis of the data, which has begun.

[2] Presented by Dr. Churchill.

TABLE 1. Comparison of offspring of all diabetics (D) with matched nondiabetics (C)

	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	D	C	D	C	D	C	D	C	D
Means	39.6	38.1	3.26	3.41	80.9	78.9	33.8	32.5	102.7	95.8
N	122		122		116		116		122	
t	5.1		—2.3		2.0		2.2		4.1	
p	<.001		<.05		<.01		<.05		≪.001	

greater maternal age, and the same or nearest birth order (*23*). If multiple cases met all matching criteria, the control case was determined by the identification number closest to that of the diabetic subject. Cases weighing less than 2.0 kg at birth were not included in analysis of the data.

The dependent variables studied were (1) duration of pregnancy in completed weeks of gestation; (2) birth weight; (3) Bayley mental and motor scales given to babies at eight months of age; (4) IQ determined at four years of age; (5) factors in neurological examination performed at twelve months of age. The means of dependent variables were compared by t tests for correlated samples except for neurological factors, which were reported by frequency.

Results

As Table 1 shows, the offspring of diabetic mothers differed significantly from matched nondiabetics in Bayley mental and motor scores given at eight months and IQ administered at four years of age. The duration of pregnancy was significantly shorter in the diabetics than in the controls, yet the birth weight of the diabetics was somewhat greater. The frequency of neurological abnormalities was approximately equal in the diabetic and the control groups, except for postural control, which was poorer in diabetic than in control offspring.

Table 2 shows that the acetone-positive diabetic cases showed significantly greater developmental deficits than their matched controls. Again, the duration of pregnancy was signifi-

TABLE 2. Comparison of offspring of acetone-positive and acetone-negative diabetics (D) with matched nondiabetics (C)[a]

	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	D	C	D	C	D	C	D	C	D
Acetone-positive diabetics and controls										
Means	39.3	37.8	3.26	3.32	80.7	78.3	33.3	31.3	102.3	93.1
N	62		62		60		60		62	
t	3.9		—0.6		2.9		2.5		4.0	
p	<.001		N.S.		<.01		<.05		<.001	
Acetone-negative diabetics and controls										
Means	40.1	38.7	3.27	3.58	81.0	81.5	34.0	35.6	101.3	100.3
N	45		45		42		42		45	
t	2.7		—3.0		—0.6		—2.1		0.4	
p	<.05		<.005		N.S.		<.05		N.S.	

[a] 15 cases untested for acetone.

TABLE 3. Comparison of offspring of Class A diabetic groups (D) with matched nondiabetics (C)

	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	D	C	D	C	D	C	D	C	D
Acetone-positive Class A diabetics and controls										
Means	39.1	38.3	3.28	3.21	80.8	77.6	33.1	31.3	101.5	91.6
N	29		29		28		28		29	
t	1.4		0.5		2.4		1.6		2.9	
p	N.S.		N.S.		<.05		N.S.		<.01	
Acetone-negative Class A diabetics and controls										
Means	40.4	39.1	3.28	3.56	81.1	82.1	34.2	36.1	100.0	98.1
N	37		37		37		37		37	
t	2.2		—2.3		—1.3		—2.5		0.5	
p	<.05		<.05		N.S.		<.05		N.S.	

cantly shorter for the diabetics, although the birth weight was slightly, but not significantly, greater.

The acetone-negative diabetic cases did not differ from their controls in the psychological tests. The duration of pregnancy was shorter than for the controls, as with the acetonuric diabetics, but the birth weight was considerably greater than that of the controls. The differences seen between the acetonuric and the nonacetonuric diabetics might be explained by a high prevalence of severe diabetics in the former subgroup and a very low prevalence in the latter. However, as can be seen in Table 3, the effect on IQ remained the same when mild (Class A) diabetics were examined independently of severe (Class B+) cases.

The question whether prematurity accounted for depressed neuropsychological functioning was investigated by examining the outcome for diabetic and acetonuric mothers whose pregnancies were as long as or longer than those of their matched controls (Table 4). This drastic treatment of the data reduced the number of cases to 20, but the IQ still showed significantly lower values for children born to acetonuric diabetic mothers.

Discussion

Maternal diabetes mellitus was found to have an adverse effect on the neuropsychological attributes of children. Of special interest was the fact that, while diabetes accompanied by acetonuria was associated with the adverse effects, no such deficits were found in the offspring of

TABLE 4. Comparison of offspring of acetone-positive diabetics (D) with matched nondiabetics whose pregnancies were of the same or shorter duration (C)

	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	D	C	D	C	D	C	D	C	D
Means	37.5	39.5	3.05	3.36	79.7	78.5	32.1	31.4	104.6	95.1
N	20		20		20		20		20	
t	— 6.1		—1.8		0.8		0.6		3.0	
p	—		—		N.S.		N.S.		<.01	

mothers without acetonuria. The effects of acetonuria were demonstrated in mild as well as in severer classes of diabetes. The appearance of an association between the severity of diabetes and greater developmental deficits in the offspring was accounted for by a higher frequency of acetonuria in severe grades of disease.

Insulin reactions, reported previously, did not appear to be associated with impairments in the mentality of the offspring (*3*).

The diabetic mothers had significantly shorter pregnancies than the nondiabetic ones. But whereas this was true of both acetone-positive and -negative groups of diabetics, the neuropsychological deficits were confined to the acetonuric groups. Furthermore, the differences between offspring of diabetic and nondiabetic mothers were shown to be independent of prematurity. Vascular disease attending diabetes could hardly account for the deficits observed in the offspring, since vessel changes must be trivial in Class A diabetics (*1, 9, 16, 24–26, 32, 33*). The presence of acetonuria appeared to be an important indicator of impaired fetal development.

Acetonuria in nondiabetics

The question was then posed whether acetonuria occurring in nondiabetic gravidas would also be associated with neuropsychological deficits in the offspring. Most instances of acetonuria result from fasting when energy stored in the form of fat is drawn upon. Episodes of acetonuria may signal inadequate dietary intake of carbohydrate and protein.

Method of procedure

The method employed to study the problem of acetonuria in nondiabetics was similar to that used for the study of diabetes. Most tests for acetone were carried out routinely as part of the prenatal visit urinalyses, with no medical indication determining the selection of cases tested. However, some acetone testing was performed because of hyperemesis gravidarum.

To some extent, the test intervals were determined by frequency and regularity of attendance at prenatal clinics. Cases untested for acetone or with trace amounts of acetone were not included in the study. The subjects included in the study were those whose mothers had had at least one positive test for acetone of Grade 1+ or more during any trimester of pregnancy. The trimesters when tests for acetone were done were noted. Cases with urinalyses negative for acetone on all occasions were used as controls.

Results

There were 111 subjects whose mothers had acetonuria in the third trimester of pregnancy. Table 5 shows that they did not differ significantly from the controls in duration of pregnancy or in birth weight. The groups differed slightly in Bayley mental scores, but the difference was not statistically significant; the motor scores were slightly lower in the acetonuric group than in the controls. The acetonurics had significantly lower IQs at four years of age than the controls, the means being 89.0 and 97.6, respectively ($p < .001$).

TABLE 5. Comparison of matched offspring of nonacetonuric mothers (C) and those acetone-positive in last trimester of pregnancy (A)

	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	A	C	A	C	A	C	A	C	A
Means	39.2	39.3	3.18	3.11	82.1	80.7	34.6	33.2	97.6	89.0
N	111		111		99		99		111	
t	−.22		1.06		1.35		2.17		5.05	
p	N.S.		N.S.		N.S.		<.05		≪.001	

This difference remained when whites and nonwhites were considered separately. Negro gravidas comprised 78 per cent of all acetonuric cases, but about 50 per cent of the entire Study population.

The mothers of 99 of the subjects had acetonuria in the first or second trimester but not in the third. As can be seen from Table 6, the only statistically significant difference between the acetonurics and the controls was found in IQ; on this measure, the acetonurics were somewhat depressed ($p<.05$).

Discussion

The results suggest that acetonuria occurring during pregnancy, whether as a complication of diabetes or not, is associated with lower IQ of the offspring. One interpretation of these results is that acetonuria operates upon the fetus in such a way as to impair the higher cerebral functions. Given this interpretation, the finding could be explained, on the one hand, by a direct toxic effect of acetone or keto-acids or by a disturbance in acid-base balances induced by the presence of keto-acids. On the other hand, it may be that the acetone in the urine merely signifies an episode during which the nutrient supply of the mother has been reduced to levels insufficient for the needs of the fetus. In diabetes, acetonuria may signify episodes when glucose cannot be utilized because of insulin lack; in fasting, dietary insufficiency causes acetonuria.

The observation that the IQ of the offspring is more affected by acetonuria occurring during the last trimester of pregnancy than by its appearance earlier in gestation is consistent with a theory of nutritional impoverishment. As the mass of the fetus increases, the demand for larger quantities of nutrients may also be expected to increase. A shortage of nutrients late in pregnancy would be expected to have greater impact than early shortages, when the fetal needs could be met by relatively small amounts of critical substances.

Possibly other explanations can be offered, since the groups we have compared could differ by other characteristics that might also explain the observed IQ difference; but we have been unable to identify any. Finally, the question of bias should be considered, since there are differences in the frequency of testing for acetonuria in our population and we do not know how this problem affects our findings. However, examination of other pregnancy and postnatal variables of this group does not suggest an obvious effect on this relationship.

Perhaps, in clinical practice, closer attention should be paid to ketonuria as an indicator of suboptimum fetal environment.

TABLE 6. Comparison of matched offspring of nonacetonuric mothers (C) and those acetone-positive before third trimester of pregnancy (A)

	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	A	C	A	C	A	C	A	C	A
Means	39.0	38.5	3.14	3.00	81.6	81.7	33.8	33.7	96.1	92.8
N	99		99		90		90		99	
t	0.95		1.79		−0.15		.01		2.09	
p	N.S.		<0.1		N.S.		N.S.		<.05	

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MATERNAL FACTORS AND MENTAL PERFORMANCE IN CHILDREN

J. K. Russell and D. G. Millar [1]

A previous communication (*4*) has described the organization of a community maternity and pediatric study based on the City of Newcastle upon Tyne in northeastern England (Figure 1). Our original study, begun on 1 January 1960, was designed to identify the social and medical factors that contributed to the relatively high perinatal mortality rate in our City. A team of obstetricians and pediatricians established simple social and medical information for all maternities beyond 28 weeks among women normally resident in the City, and for the first three years of the study in 88 per cent of the babies who were stillborn or died within seven days of birth, a postmortem examination was carried out by a neonatal pathologist. Information about these deaths has already been presented (*1*). Interest in possible damage to the child short of perinatal death led us to a simple follow-up study of the survivors in collaboration with the local health and educational authorities. This part of the study has been under the direction of Dr. G. A. Neligan. In a contribution to the conference of the National Institutes of Health in Nebraska in October 1968 (*3*), I described our findings on the part played in our community by trauma in perinatal death and in the impairment of the child's mental development in certain types of delivery, especially breech delivery. Further analyses linking events in pregnancy to the outcome for the child have been made and are presented here.

[1] Presented by Dr. Russell.

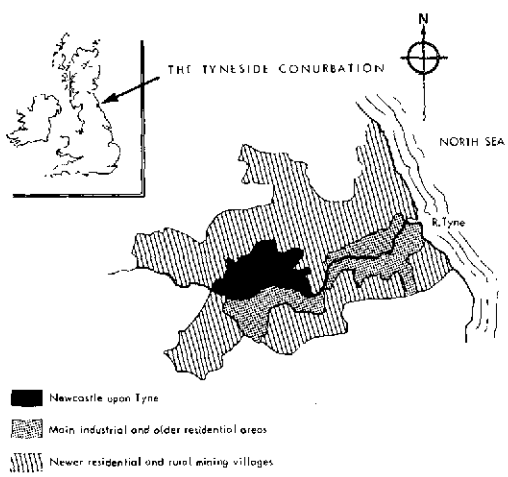

FIGURE 1. City of Newcastle upon Tyne, England

But first I should like to describe again, briefly, the methodology of our study. Each year, in our city, some 4,000 babies are born (beyond 28-week gestation) to mothers normally resident in Newcastle upon Tyne. On a standard form we collected, from all but a few of these women, simple social and medical information about her, the pregnancy, the labor, and the baby. We have such data as the mother's age, details of the menstrual history and her last period, the occupation of her husband, her past obstetric history, her height, a record of significant complications antenatally or during labor, the duration of labor, and the method of delivery, together with an assessment of the baby's condition at birth and

its weight. For the most part, this information has been collected by nurse-midwives (who have received special instruction in data collection) but where there has been a significant complication, a medical member of the research team has personally investigated and corroborated the details. Making use of the statutory records of the Local Authority Health Visitors, the usual important milestones in the child's development have been recorded for the first two years of life and any important malformation or illness has been noted. In association with the educational authorities, children born during the first three years of the study have had, on entering school at the age of five years, a standard series of tests designed to measure coordination, hand dominance and IQ. The first two tests were prepared by Dr. Herbert Birch. For the measurement of IQ, Dr. Neligan and his colleagues have used the Goodenough Draw-a-Man test. We are aware that this simple test has not been fully validated in a population of this age group, and our interpretations must therefore remain tentative until its value is confirmed by more sophisticated measurement at a later age. Such evidence as we have, however, does suggest that the Goodenough test is of acceptable accuracy and it correlates well with other measures of intelligence in a smaller group of children who have been subjected to more detailed examination. The test does have the theoretical advantage that it can be applied at an early age, close to the events of pregnancy and birth in which we are interested and at a time when environmental factors, such as schooling, have had less effect than at later ages. One possible disadvantage is that girls aged five may be able to draw better than boys of that age, whose interests may lie elsewhere.

For the most part, the follow-up material presented in this paper relates to children born during 1961—of the 4,208 single live births, 2,872 infants (69 per cent) were tested at the age of 5 years. For a variety of reasons, chiefly migration from the area, more children were lost to follow-up among the upper social group.

TABLE I. Births in 1961, Newcastle upon Tyne: Mean IQ by social class

SOCIAL CLASS	I.Q.
I	118.1
II	118.9
III (non-manual)	118.1
III (manual)	113.3
IV	111.5
V	107.9

The percentage tested at five years in each social class was as follows:

I	40
II	59
III A	61
III M	70.4
IV	77.7
V	80.1

First I shall deal with certain social indices and the relationship they bear to the child's IQ at five years. Table 1 shows the mean IQ by social class and the findings are not unexpected. From the results, we decided that it might be more helpful, so far as numbers are concerned, to divide our population into three groups—non-manual, skilled manual, and unskilled manual. Parity, which is closely related to social class, is related in our material to perinatal mortality and to IQ, and this is shown in Figure 2. Perinatal mortality is lowest with the second child and rises rapidly in the sixth and subsequent pregnancy. We find that IQ at the age of five is

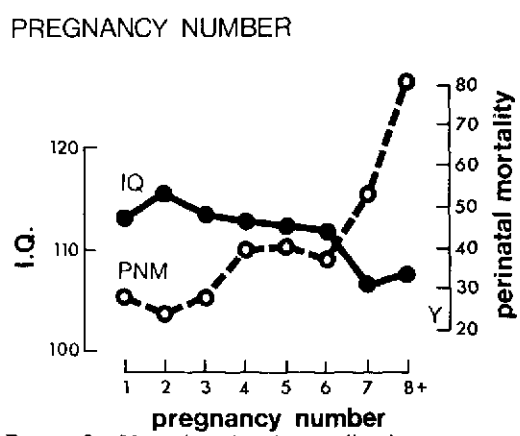

FIGURE 2. IQ and perinatal mortality by pregnancy number, Newcastle upon Tyne, 1961

virtually the mirror image of this—highest in children born in second pregnancy, then falling slowly but more rapidly after the sixth. In part, the rise in perinatal mortality after the sixth pregnancy and the fall in the IQ of the survivors could be due to the effect of social class. The relationship between IQ, social class, and pregnancy number is shown in Table 2. For the most part, the IQ of the child in the three social groups is slightly higher in pregnancies 2, 3, and 4, then falls in later pregnancies. In IQ by social class and pregnancy number, the differences in pregnancy number are highly significant ($p<0.01$) when social class is discounted. In all parities there is a fall of 8 or 9 points in IQ between non-manual and unskilled manual groups. It is possible that women in the non-manual group who have five or more children (mean IQ 115.2) are, in medical and social terms, more like women in the lower social groups—with respect to the age at which they marry and have their first child, the rapidity with which they have children, their height and general health; in fact, their whole way of life. But it is possible that, at least in part, the lower IQ of their children beyond the fifth is explained by the fact that some of these women have a sequence of abortion before they achieve a successful pregnancy; this seems to us to be an interesting possibility for further study. The relationship between social class, maternal height, and mean IQ is shown in Table 3. Even when allowance is made for social class, the difference in IQ in the various height groups is highly significant

TABLE 2. Births in 1961, Newcastle upon Tyne: Mean IQ by social class and pregnancy number

	PRIMI-GRAVIDA	PREG. 2, 3, 4	PREG. 5 +
Non-manual	118.5	119.0	115.2
	(148)	(347)	(69)
Skilled manual	112.7	114.5	110.3
	(367)	(811)	(233)
Unskilled manual	110.5	109.9	107.1
	(145)	(405)	(195)

TABLE 3. Births in 1961, Newcastle upon Tyne: Mean IQ by social class and maternal height

	SMALL	MEDIUM	TALL
Non-manual	114.5	118.5	119.0
	(64)	(241)	(223)
Skilled manual	112.4	112.3	115.4
	(253)	(590)	(483)
Unskilled manual	108.8	108.6	110.2
	(150)	(354)	(199)

($p<0.01$). Analysis of variance with unequal numbers in the subclasses using Kendall's method has been done and is significant. The converse is also true: the differences in IQ for social class and for height are independent.

Mean IQ by maternal age is shown in Table 4. Here relatively small numbers may explain the low IQ's in the youngest and oldest age groups, but these results may be due in part to the fact that women who are pregnant under the age of 20 and over 40 are drawn to a considerable extent from lower social classes. Another index of social class—living density—is examined in relation to the child's IQ at the age of five in Table 5. Higher IQ's are associated with low-density living and vice versa; here is a good measure of the environment in which the child grows up.

The various socioeconomic factors may influence the child's mental development in a variety of ways: for example, the genetic pool from which the child is created, the intrauterine environment, the chance of premature birth, and the risk of trauma and anoxia associated with birth. Again, there is a close relationship between social class and the environment in which the child grows up. These influences cluster,

TABLE 4. Births in 1961, Newcastle upon Tyne: Mean IQ by maternal age

AGE	MEAN IQ
<20	110.5 ± 1.43
20–29	112.7 ± 0.43
30–39	114.8 ± 0.64
40 and over	111.8 ± 1.69

TABLE 5. Births in 1961, Newcastle upon Tyne: Mean IQ by living density

PERSONS/ROOM	MEAN I.Q.	PROPORTION
Less than 0.5	118.3 ± 1.76	3.5%
0.5—	117.2 ± 0.64	23.8%
1.0—	113.7 ± 0.56	36.4%
1.5—	110.7 ± 0.89	15.3%
2.0	108.1 ± 0.81	18.8%

and it is difficult to agree on their relative importance.

From our own studies (and from the work of others) we are aware that perinatal mortality is closely related to gestational age. In our community 16 per cent of the mothers are unsure of the first day of their last menstrual period to within plus or minus five days; these women have been excluded from our calculations. We now find that the child's IQ at five years also bears a relationship to the gestational age at birth (Figure 3). Mean IQs for the various gestational ages are shown along with 95 per cent confidence limits (these results refer to normal pregnancies with no antenatal complications). This graph is the mirror image of that for perinatal mortality. Figure 4 gives IQ by sex by gestational age—female children are higher at all gestational ages. The importance of taking sex into account in any analysis of IQ in children aged five years is self-evident.

In the second report of the British Perinatal Mortality Survey (2) a similar sort of relationship was found between gestational age and reading ability (Figure 5). Whether gestational age by itself is of etiological significance or whether other associated factors may explain these findings is a matter for conjecture. But it is known that when the effects of social class are discounted there remains a significantly increased proportion of poor readers among children delivered pre- or post-term. It is obvious that obstetric factors such as trauma and anoxia (not infrequent complications of pre- and post-term deliveries) and environmental factors in the home during the early years of life may affect mental development.

We next examined the relationship between a variety of antenatal complications and the child's

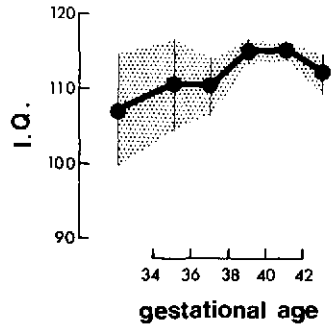

FIGURE 3. IQ by gestation, mean and 95 per cent confidence limits, Newcastle upon Tyne, 1961

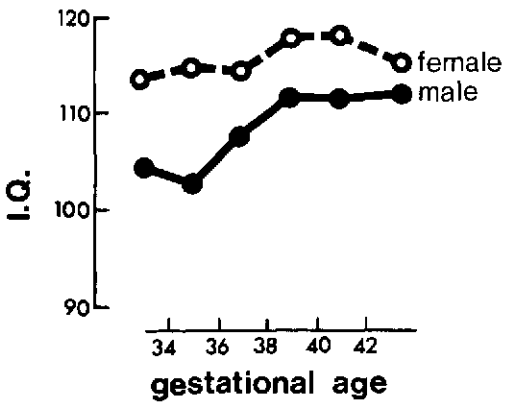

FIGURE 4. IQ by gestational age in both sexes, Newcastle upon Tyne, 1961

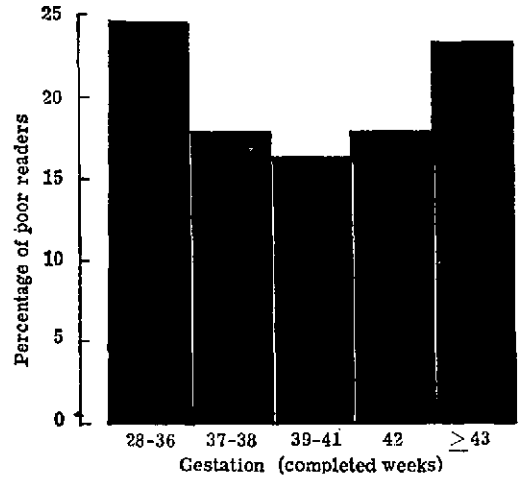

FIGURE 5. Percentage of poor readers by weeks of gestation

TABLE 6. Mean IQ associated with antenatal complications, Newcastle upon Tyne (1960–1962)

Anemia	421	111.4 [a]
Mild Pre-eclampsia	130	115.6
Mod. Pre-eclampsia	114	111.7
Severe Pre-eclampsia	25	112.2
Placenta Previa	48	108.2 [a]
Abruptio Placentae	50	111.3
Other A. P. H.	176	111.7

[a] Significantly different from normal pregnancies ($p < 0.05$).

IQ at 5 years. The results are set forth in Table 5. Those marked by an asterisk are significantly different from normal pregnancies ($p<0.05$). Figure 6 shows IQ levels at various gestational ages for placenta previa and abruptio placentae against the IQ in "uncomplicated" cases as already given in Figure 3. For placenta previa the difference as a whole (48 cases) is significant but the individual differences at the various gestational ages are not significant, presumably because of the small numbers. But it does not seem to us that the lower IQ associated with placenta previa is due to short gestational age. Nor have we been able to correlate the amount of bleeding, the time of the first bleed, the amount of blood transfused, or the grade of placenta previa with lowered IQ in these 48 cases. On the evidence we have at this stage we can only conclude that there is some biological failure in cases of low implantation of the placenta. Although the female/male sex ratio is a little higher in these cases (117 : 100) this does not, in our opinion, differ sufficiently from the normal ratio to account wholly for the lowered IQ in cases of placenta previa. The pattern is rather different in cases of abruptio placentae and is difficult to understand. With its higher perinatal mortality rate and greater risk of anoxia, we expected a lower IQ in these cases.

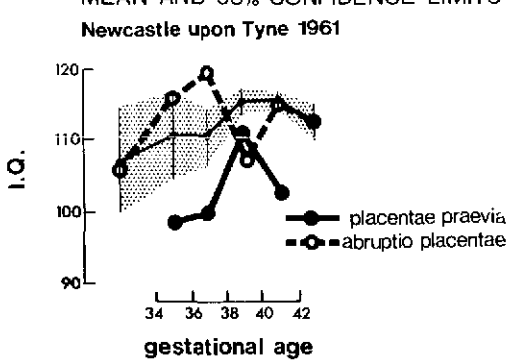

FIGURE 6. IQ of placenta previa and abruptio placentae cases, mean and 95 per cent confidence limits, Newcastle upon Tyne, 1961

My colleagues and I are conscious of the need for reservation in the interpretation of these results, especially in regard to the predictive value of events in pregnancy and in labor. But this area of investigation should help in selective screening for handicap among children and in identifying possible etiological factors. We appreciate that an association between lowered IQ and obstetric antecedent dose not necessarily mean that the two are causally related. It seems unlikely, in the light of what we know, that lowering of the IQ at the age of five is due very often to one specific antenatal or intranatal factor. A more likely explanation is that the sort of sociomedical factors we have studied, either alone or in combination, render the child more susceptible to handicap, but a great deal depends upon the ability of the individual fetus or baby to withstand various adverse medical influences associated with pregnancy and birth. And finally, we are well aware of the effect that an adverse social environment may have upon a child's mental development. We have made a very simple beginning to what is a most complicated area of research.

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EFFECT OF RAPID SUCCESSION OF PREGNANCY[1]

W. L. Holley, A. L. Rosenbaum, and J. A. Churchill[2]

Previous investigation has demonstrated the intellectual and scholastic superiority of first-born children over their siblings. A corollary finding suggests that this difference between siblings is accentuated among pairs close in age (*3*). On intelligence tests, children with intersib intervals of less than two years obtained significantly lower mean scores than those for whom it was greater. Moreover, with long intersib intervals the scores approximated those of only children, while the scores of the short-interval group approached those of twins (*9*).

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.

Methodology

The Perinatal Research Branch of the National Institute of Neurological Diseases and Stroke collaborated with 14 medical centers[3] in gathering the data (*2*). Detailed obstetrical records were obtained for approximately 58,000 women. The children were periodically subjected to neurological and psychological examinations; speech, language and hearing evaluations; and assessment of growth, development, and childhood injuries or illness by family interviews. At eight months of age, each infant was evaluated by a psychologist using a standardized modification of the Bayley Scale of Infant Development (*1*), and at age four the Stanford-Binet IQ test was administered. At one year of age, a neurological examination was administered by a physician. The study population was limited to white and Negro offspring for whom an adequate four-year IQ score was recorded. Multiple births, mongoloids, and infants with a maternal history of 3+ or greater albuminuria (*8*) or acetonuria (*4, 5*) were excluded.

All subjects who were conceived within three months and born within one year of a previous gestation equal to or greater than 36 weeks were selected and matched with controls born within two to five years after a previous gestation equal to or greater than 36 weeks. The variables used for matching were hospital of birth, sex, race, and socioeconomic index (*7;* a numerical index

[1] A report from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood, which is supported by the National Institute of Neurological Diseases and Stroke of the National Institutes of Health, Bethesda, Maryland, U.S.A. These papers must be regarded as preliminary explorations of Collaborative Study data. Possibilities remain that differences observed in the offspring, if indeed they are proven to be of practical significance, may reflect differences in maternal characteristics other than those variables under study here. Such critical factors, if present, should be disclosed in the course of the comprehensive analysis of the data, which has begun.

[2] Presented by Dr. Rosenbaum.

[3] Boston Lying-in Hospital, Brown University, Charity Hospital, Children's Hospital of Buffalo, Children's Medical Center in Boston, Columbia University, The Johns Hopkins University, Medical College of Virginia, New York Medical College, Pennsylvania Hospital, Children's Hospital of Philadelphia, University of Minnesota, University of Oregon, and University of Tennessee.

based on education, occupation, and family income, using the techniques developed by the U.S. Bureau of the Census). If two or more controls met these criteria, the closest maternal age, the closest birth order, and the closest identification number were used, in that order, to break the tie.

Two hundred and fifty-one pairs were selected, and the outcome variables studied were as follows:

1. Birth weight
2. Gestational age (calculated from last menstrual period to date of birth)
3. Bayley mental and motor scores
4. Stanford Binet IQ
5. Abnormal or suspicious neurological examination at one year of age

All data except the one-year neurological results were subjected to two-tailed t test for correlated samples.

Results

Children born within one year of a previous full-term pregnancy were found to have lower birth weights, lower scores on the COLR revision of the Bayley scales at eight months of age, and lower scores on the Revised Stanford-Binet Form L-M at four years of age than matched offspring born two to five years after a previous full-term offspring (Table 1). No significant difference in gestational ages between the two groups was found.

The question whether lower birth weight accounted for the depressed neuropsychological functioning was investigated by examining the outcome of only those rapid-succession cases whose birth weight was equal to or greater than that of their matched controls. As Table 2 shows, this resulted in the disappearance of any significant difference between the groups on the Bayley mental and motor scores. But despite the elimination of statistical differences, the trend persisted, with lower mean IQ scores among the rapid-succession cases.

Table 3 shows that twice as many rapid-succession cases as controls were found to be neurologically abnormal or suspicious at one year of age. This was due to a greater incidence of

TABLE 1. Developmental measures in offspring born within one year of previous full-term pregnancy (R) and matched offspring born two to five years after previous full-term pregnancy (C)

CASE PAIRS	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	R	C	R	C	R	C	R	C	R
White										
Means	40.1	40.2	3.45	3.28	81.0	79.6	33.2	31.7	105.4	99.4
N	92		93		84		84		93	
t	0.54		2.21		1.70		1.99		2.95	
p	N.S.		<.05		N.S.		<.05		<.005	
Negro										
Means	39.5	39.1	3.25	3.08	79.1	77.6	33.9	31.4	93.7	89.3
N	152		158		112		111		158	
t	0.94		3.27		2.20		4.02		3.12	
p	N.S.		<.005		<.05		<.001		<.005	
All										
Means	39.7	39.5	3.32	3.15	79.9	78.5	33.6	31.5	98.0	93.0
N	244		251		196		195		251	
t	1.04		3.86		2.74		4.27		4.33	
p	N.S.		<.001		<.01		<.001		<.001	

Note: C = controls; R = rapid-succession cases.

TABLE 2. Developmental measures in cases where offspring born within one year of previous full-term pregnancy (R) had birthweight equal to or greater than matched offspring born two to five years after previous full-term pregnancy (C)

CASE PAIRS	PREGNANCY (WEEKS)		BIRTH WEIGHT (KG)		BAYLEY MENTAL SCALE		BAYLEY MOTOR SCALE		BINET IQ	
	C	R	C	R	C	R	C	R	C	R
White										
Mean	40.1	40.8	3.20	3.60	81.0	81.2	32.0	32.6	105.8	102.0
N	41		42		33		33		42	
t	1.75		5.17		0.18		0.57		1.28	
p	N.S.		<.001		N.S.		N.S.		N.S.	
Negro										
Means	39.2	39.1	2.89	3.38	78.5	77.3	32.6	31.6	93.0	90.3
N	70		70		42		42		70	
t	0.16		9.11		0.92		0.89		1.28	
p	N.S.		<.001		N.S.		N.S.		N.S.	
All										
Means	39.5	39.7	3.01	3.46	79.6	79.0	32.3	32.1	97.8	94.7
N	111		112		75		75		112	
t	0.46		10.29		0.65		0.35		1.81	
p	N.S.		<.001		N.S.		N.S.		N.S.	

delayed or impaired motor development and small head size in the rapid-succession group.

In an attempt to characterize the maternal populations of both groups, a number of variables were examined. When the mothers with short conception intervals were found to be of higher parity and to have registered into the Collaborative Study later in the course of gestation than their matched controls, it was felt that this might have created a bias. However, in a selection of only those case pairs in which the rapid-succession mothers had less parity and registered earlier than the controls, the birth weight, Bayley scores, and Binet IQ scores for the former remained significantly lower.

TABLE 3. Suspicious or abnormal one-year neurological examinations in offspring born within one year of previous full-term pregnancy (R) and offspring born two to five years after previous full-term pregnancy (C)

	R	C
Total number suspicious or abnormal	34	17
Specific findings		
Delayed or impaired motor development	16	6
Small head size	5	0
Hyperreflexia	3	1
Miscellaneous	10	11

Discussion

Our results confirm what previous investigators have shown—that children with shorter intersib intervals score lower on intelligence scales than those with longer intervals. In addition, the present work also shows a difference in birth weight, in eight-month development scores, and on the neurological examination at one year of age.

The differences observed may be related to an effect of social experience unique to children with close intersib intervals. It has been postulated that sibling pairs close in age tend to receive more stimulation from each other than from their parents (*6*). Lack of adult contact may lead to poorer language development and consequently to lower IQ performance.

Postnatal health and experiential factors, such as increased incidence of infection or poorer diet, might also be cited as influencing the observed results. But while these might have something to do with the differences reflected by the Binet IQ test, they should have little influence on the Bayley developmental scale at eight months of age and, certainly, none on birth weight.

Thus, rapid succession of pregnancy may exert an effect on the fetus *in utero*. Perhaps the mother has had insufficient time between pregnancies to restore supplies of critical nutrients. She may then have deficits in nutrients required for optimum fetal body development and brain ontogeny.

The depression in birth weight seen in the rapid-succession cases cannot be attributed to prematurity. Instead, the group shows stunting, which might be expected in conditions producing intrauterine impoverishment.

Finally, rapid succession of pregnancy tends to be characteristic of large families from lower socioeconomic levels. However, since social class was controlled for in the design of the study, its effect should be minimal.

Summary

Two hundred and fifty-one children with close sibling intervals (less than 12 months) were matched according to race, sex, social class, and other factors with children with longer sibling intervals (24–60 months). The children with short intersib intervals had lower birth weight, lower Bayley developmental scores at eight months of age, lower Binet IQ scores at four years of age, and a greater incidence of neurologically suspicious or abnormal outcome at one year of age.

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PERINATAL FACTORS IN MENTAL SUBNORMALITY[1]

Herbert G. Birch

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 birth weight, and poor condition as a newborn were found in the mentally subnormal children. When social and clinical subsegments 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 were 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 birth weight 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.

[1] Abstract. The complete paper had not been received at the time of going to press.

DISCUSSION

John A. Churchill: Summary of Maternal Factors Affecting the Offspring—Theory of Intrauterine Improverishment

The reports just presented have revealed the relationships of several different maternal conditions to impairments in the offspring. Though different in kind, the conditions discussed could, as a group, affect the offspring through a common pathogenic mode. These conditions, which will be recapitulated, could each contribute to intrauterine impoverishment of critical nutrients required by the fetus for optimum prenatal growth and brain development.

These reports, concerning factors which may represent deficits in endogenous nutrient supply, therefore bear relevance to the preceding series of reports on exogenous nutrient supply of gravida and fetus.

1. Twins were shown to differ from singletons in birth weight, infant developmental scales, and IQ measured at four years of age. The effect was demonstrated to be independent of gestational age. The human gravida of twin pregnancy may fail to supply sufficient amounts of critical nutrients to permit the optimum growth of twins.

2. Studies have shown that children born soon after their preceding siblings are handicapped in achievement compared with those born after an interval of a few years. Previous authors have explained the findings in terms of psychological and social experiences unique to closely spaced latter-born siblings. Evidence confirming the findings has just been presented, but because additional facts have come to light a different interpretation is offered: the mother pregnant again soon after giving birth may not have been able to replenish stores of critical nutrients to be called upon so soon for the new pregnancy.

3. Diabetes is a metabolic disease in which glucose cannot be used as a source of energy. The gravid diabetic women must thus metabolize fats (and perhaps some amino acids) to meet her energy requirements. There may be episodes during which the supplies of some of the essential amino acids (or fatty acids) to the fetus are constrained. The presence of acetonuria appears to signal episodes in which energy is being extracted from materials other than glucose.

4. Acetonuria occurring in nondiabetic gravidas, usually as a consequence of fasting, was also found to be associated with deficits in the IQ of their children when tested at age four.

5. Babies of teen-age mothers under 16 have lower birth weights than babies of mature mothers.[1] McGanity suggests that the immature, still growing gravida may not supply sufficient nutrients to the fetus, since much is required for her own growth.[2] Young mothers and their babies are being studied from this point of view.

[1] Hulka, J. F., and J. T. Schaaf. Obstetrics in adolescents: A controlled study of deliveries by mothers 15 years of age and under. *Obst. & Gynec.* 23:678–685, 1964.

[2] McGanity, William J., Professor and Chairman, Department of Obstetrics, University of Texas at Galveston. Personal communication.

6. The factor of maternal hypertension in the ultimate mentality of offspring was reported by Dr. Russell. It might be proposed, but only by putting the theory of intrauterine impoverishment on a long reach, that the vascular constriction and thickening of vessels that occur in hypertensive disease interfere with nutrient supply. A more direct question to explore would be whether albuminuria resulting from renal hypertensive damage leads to deficits in protein supplies to the fetus. Could the effects of toxemia on offspring presented by Russell and Birch be interpreted similarly? Rosenbaum *et al.* did find deficits in the offspring of normotensive mothers with heavy proteinuria.

7. The relationship of short stature of mothers to low birth weight and depressed IQ poses an interesting problem. Dr. Birch spoke of the association between short stature of mothers and lowered IQ of their offspring, social class being another parameter of the corollaries. It should be recalled that, as reported by Dr. Moghissi, mothers with low amino acid levels during pregnancy were shorter than those with high levels. A few studies of rats suggest that females reared on restricted diets have less well developed offspring than those reared on adequate diets.[3] Bacon-Chow claims that protein malnutrition during early development in both man and rat results in inefficient utilization of protein throughout life.[4] Depressed socioeconomic status, operating by way of malnutrition during development; could account for shortened stature in the Aberdeen study mothers described by Birch. Even excluding dietary inadequacies from the current pregnancies of these mothers, the impact of a woman's own early deprivation might, he suggests, affect her offspring.

8. Another much-discussed factor, but one not mentioned here, is maternal infection. Enteric infection from bacteria, protozoa, and helminths, particularly, could disturb the absorption of nutrients and lead to inadequate nutrient supply to the fetus.[5]

In summary, the eight factors listed here—multiple pregnancy, rapid succession of pregnancy, diabetes, fasting acetonuria, immature gravida, albuminuria with or without hypertension, early maternal nutrient deprivation, and maternal infection—could all produce deficits in the offspring by means of inadequate nutrient supply to the fetus. Together with exogenous dietary inadequacy, these endogenous factors can be grouped to compose a general theory whereby intrauterine nutrient impoverishment may stunt the prenatal development, including brain ontogeny, of the fetus. They can be tested by experiments in laboratory animals (we were shown a workable model for such studies earlier) and can also be studied by observations in humans. We have heard here something about how critical nutrients in the mothers' blood can be measured and related to outcomes in babies. The theory of intrauterine nutrient impoverishment can be subjected to test.

General Discussion

Hellman: I should like to see if it is possible to reach a common denominator from this morning's discussion. First I want to discuss the papers of Drs. Churchill and Birch. I should like to suggest that the common denominator is low gestational age. The other factors enunciated may be associated with the difficulties discussed but probably have little cause-and-effect relation.

Let me first take Dr. Churchill. He had 237 diabetics in 58,000 deliveries. These numbers may not be accurate, but the incidence is approximately half the accepted incidence of diabetes in pregnancy. The answer to this discrepancy may be that the less-severe diabetics have been eliminated. Readily identifiable diabetics are

[3] Cowley, J., and R. Griesel. The development of second generation low protein rats. *J. Genet. Psychol.* 103: 233, 1963.

[4] Chow, B., and C. Lee. Effect of dietary restriction of pregnant rats on body weight gain of the offspring. *J. Nutr.* 82:10, 1964.

[5] Scrimshaw, N., C. Taylor, and J. Gordon. Interactions of nutrition and infection. *Am. J. Med. Sci.* 237: 367, 1959.

generally delivered three to four weeks early, and the factor of prematurity, or at least low gestational age, would be increased. This skewing of the sample may be the causative factor in the poor infant results and not the diabetes *per se*.

Now let me take Dr. Birch. I am perfectly sure that Dr. Birch has thought of all the objections I may raise. There are two factors that stand out in his study: breech presentation and severe toxemia. Breech delivery decreases as maturity increases. In other words, low gestational age will have a much higher incidence of breech presentation. Similarly, severe toxemia tends to determine a premature delivery. I therefore suggest that low gestational age may in fact be the common denominator for these difficulties and that the other factors are associations but not the cause.

Churchill: I feel I should apologize to Dr. Hellman, and perhaps the rest of you too, for contributing to some confusion. The diabetic sample was drawn from the entire Perinatal Research Study population, but one of the stipulations was that we sampled the portion of the population that had been given IQ tests at age four. At that time only about half of the patients had reached age four and were tested. Thus, you see, the incidence of diabetes would appear to be low by a factor of two.

Secondly, Dr. Hellman perhaps did not grasp the meaning of one of the slides showing a procedure we carried out in each of the studies we have presented here. In the analysis of the data of some of the studies—the diabetic study, for example—gestational age was shorter in subjects than in controls. But we then analyzed just those pairs of cases in which the diabetic (subject) mother was of equal or even of longer gestational age than the control. Now, this is very drastic treatment of the data, deliberately biasing the results against the possibility that the effect could have been due to prematurity alone.

We were thus able to demonstrate the independence of the pregnancy factor effect from that of prematurity. I hope I have set this matter straight, because it involves an important point common to several of the presentations.

Birch: I think it important to point out that there is a certain kind of necessary preliminary exercise that one goes through in analyzing any complex body of data. This exercise is first to consider the single variables in and of themselves. If we were to take such variables as pre-eclamptic toxemia, multiple births, short gestational age, low birth weight, incidence of bleeding, threatened abortion, and things of this sort and consider them as single variables independent of one another, we would very shortly end up with a population every single member of which was at risk, and we would then have to find more cases to fit some of these risk conditions. This, of course, is not so. Such things as twinning, low birth weight, pre-eclamptic toxemia, short gestational age, and so on go together. Risk conditions occur in constellations and combinations, not singly, as a rule. Usually when they occur singly they tend to be trivial in their influence unless they have been of extreme degree and have indeed directly damaged the fetus itself.

For this reason—and I did not present this today—we made a careful clinical obstetrical examination of all associated conditions in every one of the cases of the mentally subnormal children we have studied and, as a consequence, emerged with a picture of a combination of factors that are differentially distributed among different social-class groupings. For example, in the lowest social-class groupings a variety of factors ranging from high pregnancy number to short maternal stature to short gestational period to poor intrauterine growth with elevated frequency of bleeding during the pregnancy itself tend to go together as a constellation of factors that are strongly associated with the presence of mild degrees of mental subnormality in later periods. Earlier pregnancy number, particularly pregnancy numbers one and two, with an elevated frequency of pre-eclamptic toxemia and a shortened gestational period in relation to that, tend to be a pattern more frequently found in the nonmanual group and to be associated with a higher frequency of more severe mental subnormality.

A real understanding of these factors requires

a definition of patterns and constellations rather than a consideration of single variables all the way through.

Gruenwald: I should like to make one very brief comment concerning twins. It has been found by a number of investigators, and I have confirmed it, that twins have a relatively larger placenta than singletons. Since we know of no abnormality that would account for the increased weight, it is probable that we are dealing with maternal rather than placental restriction in the growth retardation of twins.

With regard to diabetics, it is very striking that their infants have a very small brain—small in relation to gestational age, not just in relation to the oversized body that some of them have. I think it would be very important to examine these small brains by studying DNA content to see what it is that makes them so strikingly small for gestational age. The amazing thing is that, if we assume that surviving infants have the same change to some extent, the instance of subnormality is not much greater than it is.

Neel: Dr. Birch has drawn attention to a phenomenon long recognized by the geneticist—that, in general, the parents of severe mental defectives are drawn from all classes of society and are mentally normal, whereas the parents of mild mental defectives are often themselves on the dull side and found in the so-called lower social strata. The genetic interpretation has been that, to the extent that this is a genetic phenomenon, the severe defectives often owe their defect to homozygosity for single recessive genes, which are carried by all manner of persons, whereas the mild defectives, to the extent this is genetic, owe their defect to multifactorial inheritance, the genes concerned being dominant or semidominant.

Dr. Birch has put a somewhat different interpretation on the data concerning the mild defectives—that environmentally damaged parents are transmitting to their children the residue of their damage, in a nongenetic fashion. I submit that the truth lies somewhere in between, that in fact there are often genetic factors involved that lead to a predisposition to environmental damage. We are seeing a very complex situation between genetic and nongenetic factors that it will take us a few years to unravel.

Waterlow: I should like to ask the NIH group whether their data were analyzed in relation to social class, particularly in view of what Dr. Rosenbaum said about the effect of rapid succession of births. I have the impression that people who have children more quickly tend to be of lower social class. This is very important in interpreting his data. He suggested that the effect of the rapid succession might indicate a nutritional deficiency or inadequacy, but it might have a completely different meaning. Similarly, his data show a very large difference between Negroes and whites that presumably is related to social class.

Dr. Rosenbaum: I am sorry I did not get that point across. All the Perinatal Research Branch studies were matched for social class on the basis of a socioeconomic index derived from a modification of the U.S. Bureau of the Census index. It is a numerical index based on occupation, income, and education. In my particular study I presented a control group and a rapid-succession group. Each rapidly conceived case was paired with a control case that was matched on a number of variables. Among them was social class. So that in each instance the socioeconomic index of the rapid-succession case was equal to or higher than that of the control. In almost every instance they were matched exactly for social class.

Now, they were also matched for race, so that a Negro was matched with a Negro, a white was matched with a white, and each case was matched exactly on the basis of social class.

Moderator: At yesterday's symposium on iron deficiency [1] it was reported that rapid succession of pregnancies produced exhaustion of the mother's iron reserves. This perhaps is one example that other nutrients are also depleted by rapid succession of pregnancies.

Zamenhof: Perhaps I can contribute to an answer to Dr. Gruenwald's question on DNA and brain cell number in fetuses of diabetic

[1] PAHO Scientific Publication No. 184.

mothers. We produced experimental hyperglycemia in pregnant rats. In milder cases we obtained, of course, higher body weight and higher brain weight of neonatal animals; in more severe cases the body weight was higher but the brain weight was lower in neonatal animals. But brain weight and brain size do not mean much. The DNA in all cases was identical with that of the control.

Birch: It is possible to match for individuals in terms of occupation and similar factors and still avoid a serious consideration of the differences in ecology that may exist within given social classes themselves. We therefore took one out of five of all the families in the 8,500-odd families we were studying in the population in Aberdeen and studied very carefully the nature of the social conditions in the home, how the families lived, the degree to which they were intact, and so on. We might have some lower-class families who were functioning at non-manual levels of family and home organization and others in a chaos of disorganization and social disadvantage. It was fascinating for us to find that it was this latter group in particular—this group that ecologically was in social class "Manual Unskilled" and was the most disorganized segment of this class in a social and biological sense—that was contributing the excess of mentally subnormal children in the population we were studying and to see that they differed in their contribution from the regularly employed intact families within the lower-social-class grouping as a whole.

I think the same thing has also been found, to a certain extent, in Newcastle.

Now, of course, this leads us directly to the genetics-environment controversy, which certainly, as Dr. Neel points out, is totally insoluble at the present stage of our knowledge. The single-gene hypothesis must be rejected for severe mental abnormality. Single-gene effects contribute a very small fraction of the cases in severe mental subnormality. I would submit that trauma, illness, the kinds of things we have been talking about earlier, make their contribution as well.

In cases of mild mental subnormality, it always amuses me to try to figure out just what genes are involved in a polygenic distribution and how these may be identified statistically as contributing factors, particularly under conditions of inequality of environment. I think, really, that we can only identify the polygenic or multigenetic contributions that may be being made to the production of mental subnormality in a population by improving the general environmental circumstances under which people are in fact reproducing. As Dubjonski put it, in considering such a problem at a meeting of the American Association for the Advancement of Science a year or two ago, the most important thing for geneticists is to optimize environmental circumstances so that after several generations we can begin to look at what in fact are genetic influences of a more complex type. And I think Dr. Neel agrees with that.

THE PROBLEM OF PREMATURITY AND OF INTRAUTERINE GROWTH RETARDATION

Peter Gruenwald

It is a well-established fact that infants who are small at birth have a higher morbidity and mortality than those of normal size. Until recently it was not clear that there are several causes of small size at birth; these infants were therefore called *premature,* with a cut-off point at 2,500 grams. This practice caused most investigators to believe that all such infants really are premature and thus constitute a basically uniform group differing only in the degree of prematurity. It will be remembered that until recently most of the work on the handicaps of "prematures," acute or chronic, was based on otherwise unselected infants characterized only by their birth weight.

During the past decade the importance of fetal growth retardation as a frequent cause of small size at birth has been recognized. In 1961 the World Health Organization suggested that the group of infants characterized only by a birth weight of 2,500 grams or less be called *infants of low birth weight* rather than premature (*9*). The term *premature* should be abandoned, because after so much misuse it can no longer be used with any clarity of meaning. The term *infant of low birth weight* has itself recently been misused to indicate growth-retarded, "small-for-dates" infants; the American Academy of Pediatrics (*1*) has therefore suggested, for the characterization by weight, the use of the actual limits of any group. As to gestational age, the words pre-term, full-term, and post-term are suggested, with cut-off points at 38 and 42 weeks from the last menstrual period.

The growth and maturation of the fetus are not equally affected by unfavorable circumstances. While deprivation may cause a substantial deficit in growth, leading to a weight at term less than half of normal, maturation is little affected and a severely growth-retarded neonate is likely to be nearly as mature as a normally grown one of the same gestational age. The available criteria of functional or structural maturity are not sufficiently precise to indicate the exact degree of maturation reached by these infants. Maturity determines to a great extent the functional behavior of an infant and its ability to cope with extrauterine life, and basically is thus the more important parameter; however, growth as shown by size achieved at birth is the more sensitive indicator of deprivation and also is more readily ascertained.

Adequacy of growth must be studied in relation to time; in the fetus this is gestational age derived from the mother's history. Objective criteria of maturity are now being developed, and in the future these will no doubt make it possible to verify the dates from the mother's history, at least within broad limits. Standards based on birth weights in large numbers of deliveries have been developed by several investigators. (*2, 4, 7,* and others) From these, arbitrary limits of significant growth retardation are derived, usually either at the tenth

percentile or at mean minus 2 standard deviations. The former includes three to four times as many cases as the latter.

Birth weight subnormal by any arbitrary standards does not necessarily indicate intrauterine deprivation. Certain groups of fetuses have an abnormally low growth potential and remain small even when normally supplied. These include cases of chronic infection, for instance, with rubella or cytomegalic inclusion body disease, and those with malformation. Experimental teratology has consistently demonstrated that retarded fetal growth is part of maldevelopment, and the same is frequently found in man (*3*).

Only chronic fetal distress (*3*) produces a weight deficit of sufficient magnitude to be recognized by the standards mentioned above. In subacute fetal distress, when the fetus had grown normally until several days or at most a few weeks before birth, wasting may be conspicuous if birth occurs near term, but the weight deficit does not shift a previously normal fetus into the arbitrary group of growth retardation.

Differences in birth weight for gestational age between populations are of considerable significance (*5, 6*). When proper corrections are applied to data for the early part of the third trimester (*4, 8*), birth-weight curves for that period are remarkably similar in all populations studied (*4*). However, during the last month before term, differences appear and at a specific time the curve of each population departs from the common, straight-line course, owing to a slowing of growth. The hypothesis has been proposed that the straight-line curve (which means a steadily declining growth rate) characterizes uninhibited growth according to the growth potential of the fetus. During all this time the fetus grows more rapidly than its growth support, derived from the mother via the placenta, can increase. There comes a time in each population when the supply line is no longer adequate to support the full realization of the growth potential, and this is followed by a departure of the birth-weight curve from the straight course. In populations with a better average ability to support fetal growth this occurs later than in those with a poorer ability. Obviously, the earlier it occurs, the lower the mean weight at term.

These observations raise the question what the factors are that influence growth support of the fetus. When the idea was abandoned that a neonate must be premature if he is small, another slogan appeared that may be detrimental to progress. This is *placental insufficiency* as used indiscriminately to suggest the cause of all fetal deprivation. Actually, there is mounting evidence that maternal rather than placental factors are responsible for limitation of the fetal supply line in most instances. There is, to be sure, true placental insufficiency, but it may well turn out to be limited to gross and very extensive pathologic lesions such as infarcts, hemangiomas, areas of old separation, and the like. Except in these cases, we have at the moment no evidence that the normal transfer function of the placenta approaches the maximal capacity and may therefore occasionally fall below normal with regard to any essential nutrient or waste product. Until such evidence appears, and it should certainly be sought for, we should consider very seriously that the great majority of instances of chronic fetal deprivation are maternal in origin.

The placenta is a fetal organ. A small placenta in a growth-retarded fetus is not necessarily the cause of the fetal deprivation; it may be, but equally the placenta could be small merely as an organ of a small fetus. Maternal circulation through the intervillous space of the placenta is subject to maternal regulation or limitation and should therefore be regarded as a maternal factor, in contrast to true placental factors such as permeability or transfer function. The practice of indiscriminately designating all fetal deprivation as placental insufficiency tends to create the impression that it is not amenable to investigation, treatment, or prevention in a given pregnancy. Recognition of the possibility of maternal factors focuses attention on the mother.

Maternal causes of limitation of fetal growth support are very likely involved in the differences between populations. It is probable if not certain that this includes not only the status of the mother at the time of the pregnancy under consideration, but also the effects of earlier influences, perhaps as early as in her own fetal life, on her development. There is some suggestive evidence of circulatory factors limiting maternal blood supply to the intervillous space of the placenta. Our knowledge of specific chemical deficiencies in the human mother causing deprivation is very limited. The effects of general or protein malnutrition, so far as crucial specific substances are concerned, are poorly understood. However, it may be anticipated that with recognition of the important role of maternal factors significant advances will be made. This raises the hope that chronic fetal deprivation can be treated or prevented by making the mother able to better support fetal growth and development.

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MATERNAL FACTORS AFFECTING BIRTH WEIGHT[1]

William Weiss and Esther C. Jackson[2]

It is well known that the small liveborn baby faces a relatively high risk of early death, along with an increased hazard of neurological damage, frequently with concomitant mental retardation.

The investigation of the problem of low birth weight is complicated by the very large number of factors suspected of having an effect on birth weight, as, for example, genetic and environmental characteristics, maternal conditions, or events occurring during pregnancy.

Along with Berendes and others, we undertook a statistical evaluation to determine the extent to which certain factors were associated with birth weight. From among the hundreds of items of information collected prospectively during the course of the Collaborative Study, we selected 32 that we believed likely to be so associated.

Our study involved 8,300 white and 10,700 Negro gravidas, with separate evaluations by race. The cases were restricted to those in which there had been at least one prior pregnancy, so as to permit use of prior pregnancy data.

We did a multiple regression analysis of the 32 factors with birth weight as the predictive variable. Our objects were to estimate the total effect of these factors on birth weight, and to identify those that, in the presence of all of the others, still had an impact on it.

Table 1 gives the list of variables in the regression equation. The partial correlation coefficients[3] are given for whites and for Negroes. The coefficients of 19 of these factors were statistically significant for both Negroes and whites. For 6 of the factors statistical significance was demonstrated for one race only, and for 7 there was no demonstration of statistical significance in the data of either race.

In total these factors accounted for approximately a third of the variability in birth weight. Collectively they are important, but most of the variability is still unaccounted for. It is possible that they may be more important than we give them credit for, since the statistical methodology leaves much to be desired. It may well be, for example, that we have used an oversimplified mathematical model. We are investigating this problem. It is very likely, nevertheless, that the method is relatively accurate in separating the factors that are important in their associations with birth weight from those that are not.

[1] A report from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood, which is supported by the National Institute of Neurological Diseases and Stroke with the participation of the Boston Lying-In Hospital; Brown University; Charity Hospital, New Orleans; Children's Hospital of Buffalo; Children's Hospital of Philadelphia; Children's Medical Center, Boston; Columbia University; Johns Hopkins University; University of Minnesota; University of Oregon; and University of Tennessee.

[2] Presented by Dr. Weiss.

[3] The square of the partial correlation coefficient for a particular factor gives the percentage of variability in birth weight that was left unexplained after measurement of the effect of the other 31 factors and is now explained by this factor.

TABLE 1. Partial correlation coefficients from multiple regression analysis

FACTOR	WHITE	NEGRO
Age of gravida	—.01	.02
No. of prior pregnancies	.05 [a]	.06 [a]
Yearly income	.02 [b]	.03 [c]
Per cent of prior pregnancies		
Ending in abortion	—.07 [a]	—.04 [a]
Ending in stillbirth	—.03 [c]	—.03 [a]
Weighing ≤ 2,500 gm	—.06 [a]	—.11 [a]
Birth weight last prior pregnancy	.23 [a]	.20 [a]
Prepregnancy weight	.23 [a]	.20 [a]
Height of gravida	.01	.00
Interval between last pregnancy and study pregnancy	.01	.01
Diabetes	.00	.02 [b]
Organic heart disease	—.02	—.01
No. cigarettes smoked per day	—.17 [a]	—.11 [a]
Asthma	—.02	—.02
History of hypertensive disease	—.01	—.03 [c]
No. specific diseases	—.03 [c]	—.03 [c]
Toxemia	—.01	—.07 [a]
KUB infection	.00	—.01
2nd trimester bleeding	—.11 [a]	—.05 [a]
Premature separation	—.09 [a]	—.12 [a]
Marginal sinus rupture	—.10 [a]	—.05 [a]
Placenta previa	—.06 [a]	—.07 [a]
Hydramnios	.02	.05 [a]
Leiomyoma	.01	—.02
Coombs test	—.05 [a]	—.01
Weight change	.24 [a]	.26 [a]
Incompetent cervix	—.09 [a]	—.07 [a]
Toxoplasmosis	.00	—.02 [b]
Type of presentation	—.15 [a]	—.13 [a]
Sex of child	—.13 [a]	—.11 [a]
Congenital malformation	—.07 [a]	—.05 [a]
Interval between rupture and onset of labor	.05 [a]	.06 [a]
Multiple correlation	.577	.543
F	129.06	139.28
Number of cases	8,326	10,723

[a] S @ .001.
[b] S @ .05.
[c] S @ .01.

We note, for example, that the weight of the mother in her prepregnant state, and her maternal weight gain, are the two most important variables in this hierarchy. The recognition that these two factors are importantly associated with birth weight, and that they are manipulable, has made them the focus of a series of intensive studies by researchers associated with the program (*1, 2 ,3*).

More recently Weiss *et al.* (*4*) measured the influence of maternal weight gain and prepregnancy weight on birth weight in successive pregnancies of the same woman. We were able to do this because the Collaborative Study included 1,266 women who were enrolled at least twice and had at least two uncomplicated term pregnancies in which both babies were of the same sex.

The women were selected from the Collaborative Study according to certain standards. Both pregnancies were single live births of the same sex, with durations of pregnancy ranging from 39 to 42 weeks or, if the difference between the two did not exceed two weeks, from 37 to 42 weeks. Of the cases accepted, 78 per cent had both pregnancies in the interval 39–42 weeks. Pregnancies were excluded if the mother had diabetes, chronic hypertension, toxemia, placenta previa, abruptio placentae, prolapsed cord, asthma during pregnancy, pneumonia during pregnancy, organic heart disease, tuberculosis during pregnancy, hyperemesis gravidarum, hydramnios, drug addiction, or alcoholism. Cesarean section cases not in labor were also excluded.

These exclusions were made in order to provide a group of term pregnancies that were free of overt serious complications. For each case accepted, we used the first two Study pregnancies that met all the requirements listed above; 92 per cent were consecutive Study pregnancies.

Results

The distribution of differences in the birth weights of babies of the same sex in the two pregnancies of the 1,206 white and Negro women was obtained (Table 2). From the earlier to the later of each pair of pregnancies, there is an increase in mean birth weights of approximately one ounce (30.7 g) for whites and two ounces (52.9 g) for Negroes. Comparable distributions were obtained for changes in prepregnancy weight: white mothers showed a

TABLE 2. Distribution of changes in birth weight, prepregnancy weight, and weight gain, by race

CHANGE IN BIRTH WEIGHT (G)	WHITE		NEGRO	
	NO.	%	NO.	%
—600 and under	47	6.5	33	6.8
—500 to —599	32	4.5	18	3.7
—400 to —499	28	3.9	12	2.5
—300 to —399	54	7.5	31	6.4
—200 to —299	54	7.5	31	6.4
—100 to —199	75	10.4	45	9.2
—001 to —099	48	6.7	42	8.6
0	13	1.8	19	3.9
001 to 099	59	8.2	49	10.0
100 to 199	74	10.3	52	10.7
200 to 299	45	6.3	25	5.1
300 to 399	56	7.8	32	6.6
400 to 499	32	4.5	23	4.7
500 to 599	31	4.3	31	6.4
600 and over	70	9.7	45	9.2
Total	718	100.0	488	

CHANGE IN PREPREGNANCY WEIGHT (LBS)	WHITE		NEGRO	
	NO.	%	NO.	%
—30 and under	2	0.3	1	0.2
—20 to —29	6	0.8	4	0.8
—15 to —19	12	1.7	14	2.9
—10 to —14	31	4.3	25	5.1
—5 to —9	65	9.1	36	7.4
—1 to —4	72	10.0	45	9.2
0	132	18.4	78	16.0
1 to 4	141	19.6	93	19.1
5 to 9	118	16.4	72	14.8
10 to 14	73	10.2	57	11.7
15 to 19	30	4.2	26	5.3
20 to 29	23	3.2	21	4.3
30 and over	13	1.8	16	3.3
	718	100.0	488	100.0

CHANGE IN WEIGHT GAIN (LBS)	WHITE		NEGRO	
	NO.	%	NO.	%
—20 and under	33	4.6	25	5.1
—15 to —19	26	3.6	22	4.5
—11 to —14	41	5.7	36	7.4
— 7 to —10	91	12.7	48	9.8
— 3 to — 6	133	18.5	65	13.3
0	176	24.5	106	21.7
3 to 6	110	15.3	73	15.0
7 to 10	48	6.7	48	9.8
11 to 14	27	3.8	31	6.4
15 to 19	23	3.2	15	3.1
20 and over	10	1.4	19	3.9
	718	100.0	488	100.0

mean increase of 3.0 pounds and Negroes of 3.8 pounds from one pregnancy to the next. On the average, white mothers showed a slight diminution, 1.9 pounds, in weight gain in their subsequent pregnancy; the comparable figure for Negro mothers was a drop of 0.7 pounds.

The average increase in the prepregnancy weight of the women in this study, and the average decrease in their maternal weight gains from one pregnancy to the next, reflect a close relationship between these two characteristics. Figure 1 shows that a change in a woman's prepregnancy weight strongly influences her maternal weight gain. This association is demonstrably linear. It suggests that a change in prepregnancy weight is accompanied, on the average, by a compensating change in the maternal weight gain; that is, if prepregnancy weight increases, the maternal weight gain will be less, on the average, by a significant proportion of the prepregnancy weight increase.

A similar picture obtains if the reverse is true. If prepregnancy weight is less, maternal weight gain will be more, on the average, by a significant amount. For example, white mothers whose prepregnancy weight increased by 20–29 pounds showed, on the average, a diminished maternal weight gain of 18.3 pounds; mothers whose prepregnancy weight was less than before by 20–29 pounds, had, on the average, an increased weight gain of 19.0 pounds as compared to that in the previous pregnancy.

Maternal weight gain appears strongly to influence the baby's birth weight (Figure 2). If a woman's maternal weight gain increases she can expect, on the average, an increased birth weight in her baby. Conversely, if her weight gain is lower she can expect a baby whose birth weight is less than that of the

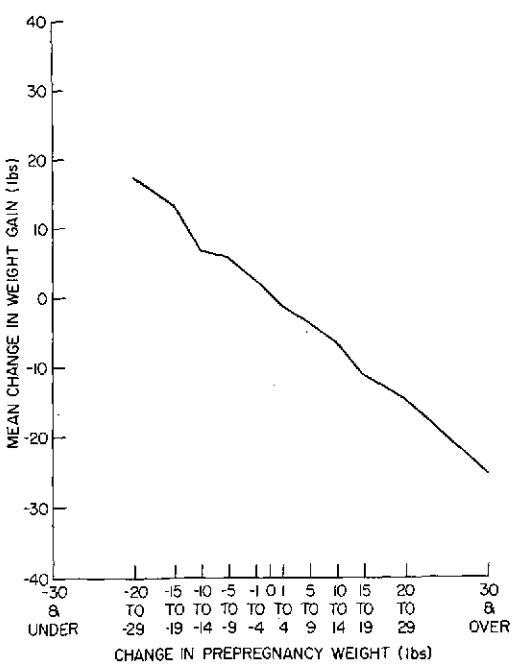

FIGURE 1. Mean change in weight gain by change in prepregnancy weight.

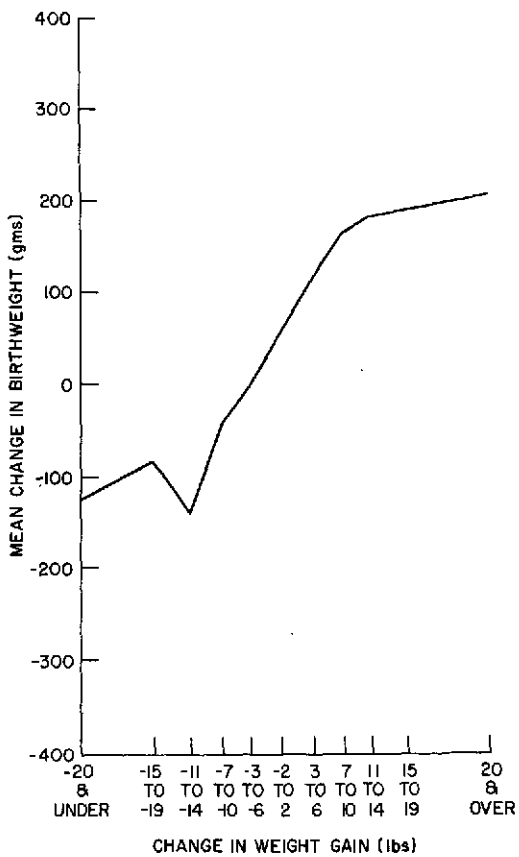

FIGURE 2. Mean change in birth weight by change in weight gain.

earlier child. The association of maternal weight gain and birth weight is linear.

We examined these two relationships by subgroups of the women by race, by age of gravida, and by number of prior viable pregnancies. In each case the lines for each subgroup were superimposed.

Additional insight into the relationship between weight gain and birth weight is provided if the women are classified by the change in their prepregnancy weights (Figure 3). The association of weight gain and birth weight for each prepregnancy-weight-change subgroup, except for the one less than or equal to minus 15 pounds, is demonstrable and linear; the calculated lines of best fit are parallel (Figure 4).

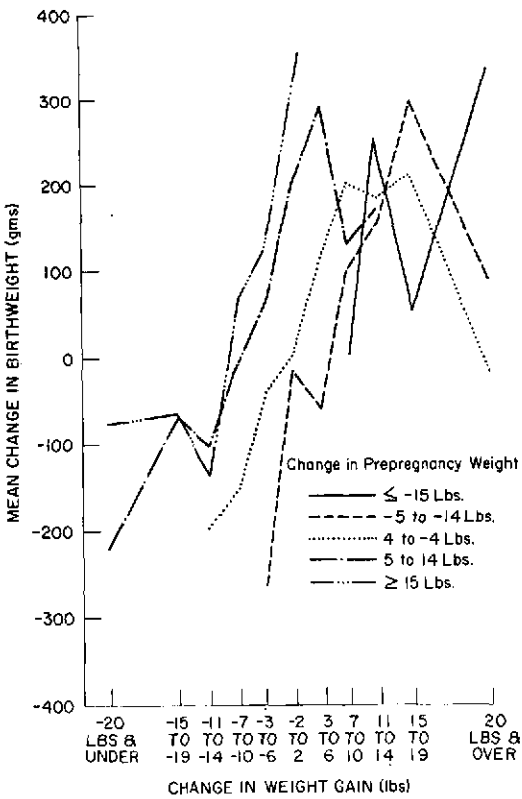

FIGURE 3. Mean change in birth weight by change in weight gain by change in prepregnancy weight.

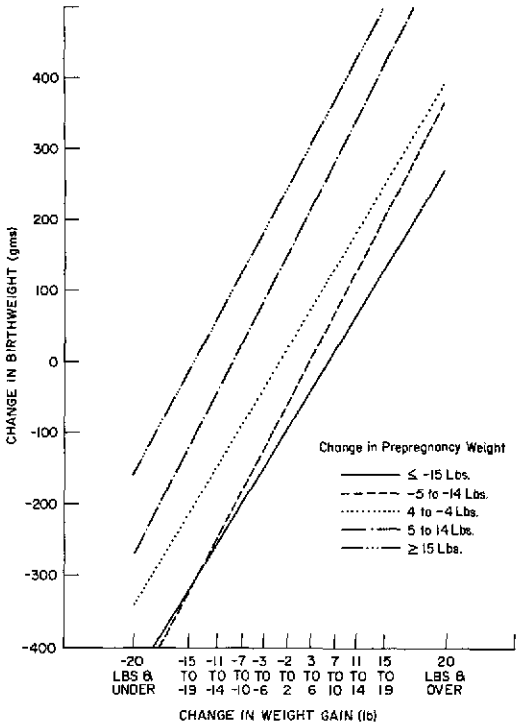

FIGURE 4. Regression lines for change in birth weight by change in weight gain by change prepregnancy weight.

The equation that best describes this family of lines is given as

Birth weight change (g) $= 21.7 + 15.97 \times$ change in weight gain $+ 11.38 \times$ change in prepregnancy weight

From the equation, we can compute that women whose prepregnancy weight and whose weight gain remain constant (zero change in each) can expect no demonstrable change in the birth weights of their babies ($+21.7$ g).

The impact of weight gain on birth weight is greater than that of prepregnancy weight by a factor of 1.4:1; a 5-pound increase in maternal weight gain is associated with a 79.9-g increase in birth weight, while the expected increase in birth weight for a 5-pound increase in prepregnancy weight is 56.9 g. A 5-pound increase in both prepregnancy weight and maternal weight gain is associated with an expected increase in birth weight of 136.8 g.

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FAMILIAL FACTORS AFFECTING FETAL GROWTH

Margaret Ounsted

In 1947 McBurney (*10*) pleaded that the "undernourished full term infant," whose low birth weight was due to slow growth *in utero,* should be distinguished from the infant whose low birth weight was due to short gestation. Since that time, many studies have been made on factors relating to intrauterine growth retardation. The criteria taken for inclusion in each study have varied, but in most of them infants have been selected by two fixed criteria of birth weight and length of gestation (*6, 11, 15*). Such a method of selection (as shown in Figure 1) produces a mixed population of infants some of whom are growth-retarded while others are near to the mean for growth rate. Another method of selection is by a clinical diagnosis: infants may be examined at birth and categorized, as a result of the findings, as having suffered from fetal malnutrition (*23*). Most of these studies have been concerned to discover pathological factors that reduce the rate of intrauterine growth.

At the other end of the scale, many studies have been made on the growth-accelerated fetus (*9, 12, 21*). In all of these the criteria for selection rested on absolute birth weight, and the minimum taken has ranged from nine to ten pounds.

The findings with regard to maternal factors and the incidence of growth retardation and growth acceleration have varied according to the criteria and to the different types of population concerned.

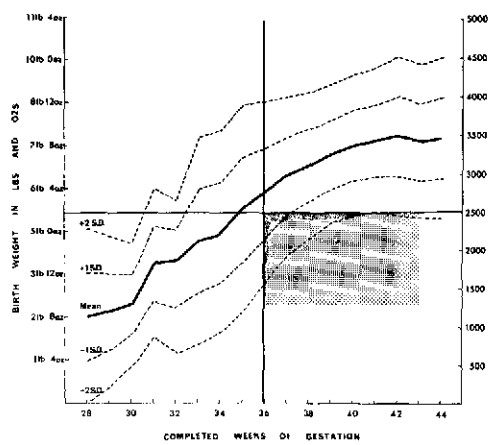

FIGURE 1. Low-birth-weight series selected by two fixed criteria.

Material and method

The present study was made in Oxford, England, where "it is fairly certain that the level of health and physique of the young women is well above the national average" (*8*). Proband infants were ascertained by a strictly statistical criterion. The growth-retarded series were two standard deviations or more *below,* and the growth-accelerated series two standard deviations or more *above,* the mean birth weight for the length of gestation. Thus we are dealing with the most growth-retarded (2.5 per cent) and most growth-accelerated (2.5 per cent) infants born in the care of our service, and the two extreme series are the mirror opposite of each other.

The grid used to define the distribution of growth rate was that made from the British Perinatal Mortality Survey of 1958 (*1*). When this study was first in progress, separate curves had not been made for males and females. Thus both sexes have been set against the same curve. Ascertainment bias through last-born is also stressed.

The two series at the extremes of growth rate were compared with a control series from the same hospital population. This consisted of a group of 225 pregnant women who were interviewed at random in the antenatal clinic and followed up to delivery. The mothers in all the series were interviewed personally and their babies were examined. The series were closed for the purpose of analysis in September 1967, but proband collection continues.

Maternal factors

The mothers in all three series were comparatively healthy, and no significant differences were found in the incidence of anemia or of urinary and other intercurrent infections during pregnancy when either extreme series was compared with controls.

There was an excess of heavy smokers and hypertensive women in the growth-retarded series. These factors were reduced in the growth-accelerated series. A slight deficiency of Social Class I and II mothers was also noted in the growth-retarded series, but this proved wholly explicable by a class difference in smoking habits (*18*); in Britain mothers of Social Classes IV and V more often smoke during pregnancy than those of the higher social classes (*1, 3*).

When biological factors were compared, no significant differences were found between the mothers of growth-retarded infants and the controls, but the mothers of growth-accelerated infants were markedly older, of greater parity, taller, and heavier than the controls (M. Ounsted, in press).

The previous obstetric history of all the mothers was investigated. The stillbirth rates were low in all three series. The previous abortion rate was the same in the growth-retarded series as in the controls, but a significantly lower previous abortion rate was found in the growth-accelerated series.

Previous liveborn siblings

The length of gestation of previous liveborn infants of the mothers did not differ, but their mean birth weights differed significantly. The respective means were for controls 7.25 pounds (3,290 g), for the growth-retarded series 5.8 pounds (2,630 g), and for the growth-accelerated series 8.75 pounds (3,970 g). When these liveborn siblings were classified in standard deviations above or below the mean birth weight for their length of gestation a striking mirror-image effect was produced (Figure 2). The scarcity of fast-grown infants born to the mothers of our growth-retarded probands was matched by an equivalent paucity of slow-grown infants among the siblings of the growth-accelerated probands. The mothers in the growth-retarded series appeared regularly to constrain the intrauterine growth of all their young. When such constraint was relaxed, as in the growth-accelerated series, it seemed regularly to remain so.

Other studies

The notion that the constraint or acceleration of intrauterine growth is determined by a maternal regulator stems from the classical studies on the horse reported on by Walton and Hammond in 1938 (*26*). These showed that foals born to Shetland dams of Shire sires were similar in birth weight to pure Shetland foals. Foals of Shire dams by Shetland sires were nearly as large at birth as pure Shire foals. There was no significant difference in length of gestation in the two groups. Thus maternal regulation in the horse was prepotent in determining the velocity of intrauterine growth.

Joubert and Hammond (*7*) did similar cross-breeding experiments with large and small breeds of cattle. The mean birth weight of the pure strain was 100.3 pounds for the large breed and 52.3 pounds for the small breed. For

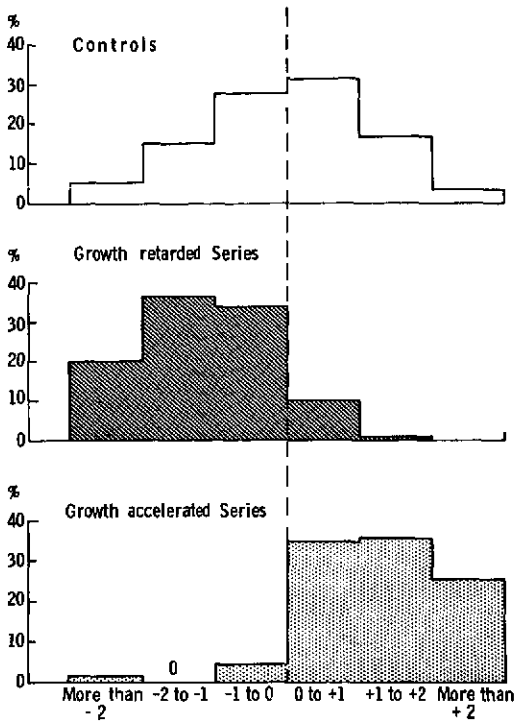

FIGURE 2. Liveborn siblings classified in standard deviations above or below mean birth weight for length of gestation.

the cross-bred fetus it was 73.4 pounds when the mother was large and 59.1 pounds when the mother was small. In this series the length of gestation was different in the two groups. The large dams carried their (smaller) cross-bred calves 3.3 days longer, and the small dams produced their (larger) cross-bred calves 9.2 days earlier, than the "normal" period for the maternal breed.

Comparable maternal effects have also been demonstrated in sheep (*5*) and rabbits (*25*). These were based both on normal breeding experiments and on the transplantation of fertilized ova from large breeds to small and vice versa.

Studies on the quantitative likeness in human birth weight in different classes of relative also throw some light on the subject. Robson (*22*) showed that the correlation between the birth weights of maternal first cousins was positive, whereas the correlation in birth weight between paternal and mixed first cousins was very small and did not depart significantly from zero. Morton (*14*) studied the quantitative likeness in birth weight of different classes of siblings. The intra-class correlation between maternal half-siblings (0.581) was higher even than that for full siblings adjacent in the birth rank (0.523); the intra-class correlation between paternal half-siblings was very low (0.102).

These findings confirm the importance of the maternal factor in the regulation of fetal growth.

Maternal birth weights

An analysis of data on the birth weights of mothers in our three series showed that the mean values were 7.11 pounds (3,220 g) for the controls, 6.26 pounds (2,840 g) for the growth-retarded series, and 8.07 pounds (3,660 g) for the growth-accelerated series. Figure 3 illustrates that there was a shift downward of about one standard deviation when the probands were growth-retarded, and a comparable shift upward of about one standard deviation when the probands were growth-accelerated.

Theory

In a series of communications (*16, 17, 18, 19, 20*) the following theoretical proposals were put forward:

1. Slow intrauterine growth is due in part to constraint exercised by a maternal system.
2. The quantitative set of the hypothetical regulator is constant within limits for any given woman.
3. The level at which the regulator is set does not depend wholly on the mother's genotype. Its limits may in part be determined by the degree of constraint imposed on the mother when she herself was a fetus.

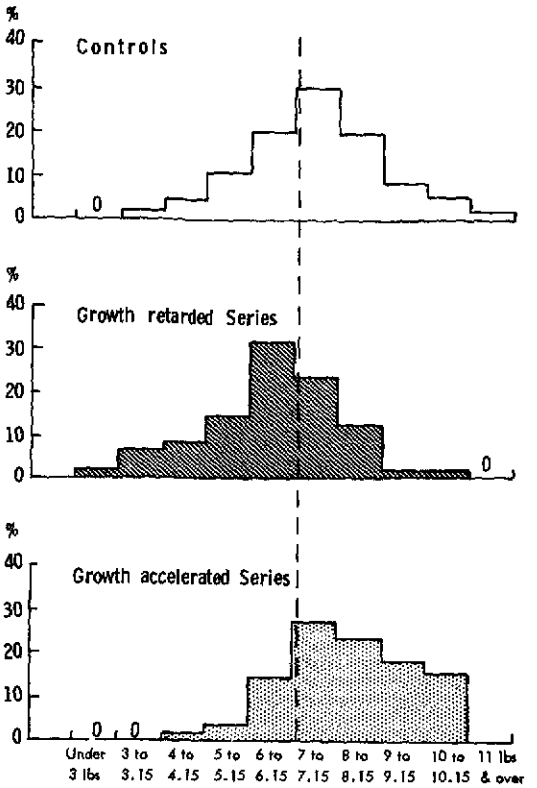

FIGURE 3. Maternal birth weights.

4. A second class of mechanisms may be involved. Antigenic interaction between the conceptus and maternal mechanisms was suggested as a factor contributing to the variance in fetal growth rate.

In order to test some of these notions, data were collected on the birth weights of relatives of our growth-retarded and growth-accelerated probands.

Pedigree data

Preliminary analyses were made of the birth weights of 1,144 kin (*20*). The findings are illustrated in Figures 4 and 5.

A clear sequence is seen from an inspection of the growth-retarded pedigrees. The mean values ascend, on the distaff side, from a mean of 5.806 pounds for liveborn siblings and 6.27 pounds for the mothers to a mean of 7.454 pounds for first cousins through maternal uncles. The latter did not differ from the general population mean. There was a highly significant difference of 0.691 pounds (314 g) between the offspring of maternal aunts and maternal uncles. These findings support the notion that constraint is transmitted through mothers only.

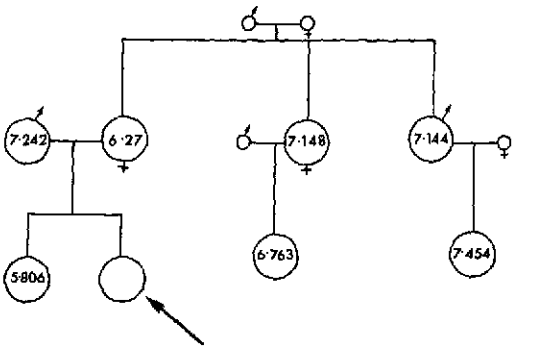

FIGURE 4. Pedigrees of growth-retarded probands: mean birth weight of relatives.

Inspection of the growth-accelerated pedigrees shows a more complex pattern. The mean birth weight of each class of relative was above that for the general population, but the difference between relatives was small. There was only 0.94 pounds (425 g) between the largest (liveborn siblings) and the smallest (first cousins through maternal aunts). The birth weights of the two classes of maternal first cousins did not differ.

The mean birth weight of the fathers of growth-retarded infants did not differ from that of the general population. The mean birth

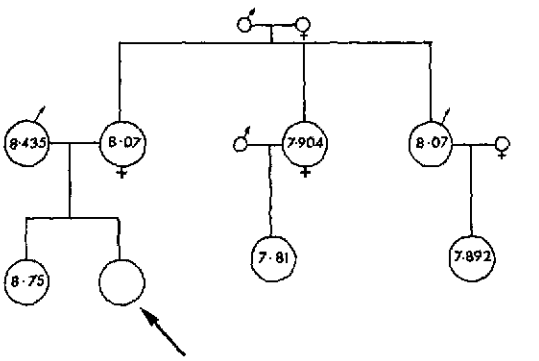

FIGURE 5. Pedigrees of growth-accelerated probands: mean birth weight of relatives.

weight of the fathers of growth-accelerated infants was 8.435 pounds (3,829 g), higher even than that of the mothers in this series.

Data collection continues, and analysis has now been made of the birth weights of 1,783 relatives of growth-retarded and growth-accelerated probands. In Table 1 each class of relative is compared in the two series. With the exception of first cousins through maternal uncles, where there is no significant difference, all the group values for a specific relationship are different to a highly significant degree: $p < .001$. These findings, which are illustrated in the histogram (Figure 6), confirm the former ones on little over half the number of relatives. The sequential order of mean birth weights in the growth-retarded series remains the same.

Sex of the proband

Boys grow faster than girls *in utero* (*1, 24*). Our theories suggest that a greater degree of constraint is needed for boys to satisfy the criterion than for girls.

From this, seven predictions arise. When growth-retarded pedigrees are ascertained through males, then siblings, mothers, children of maternal aunts, and maternal aunts and uncles should be of lower mean birth weight than the same classes of relative ascertained through females. No such differences should be found in the mean birth weights of fathers or children of maternal uncles. Figure 7 shows that these predictions are fulfilled.

In the growth-accelerated series no such march is seen.

TABLE 1. Birth weights of relatives ascertained through growth-retarded and growth-accelerated probands

	GROWTH-RETARDED SERIES (POUNDS)			GROWTH-ACCELERATED SERIES (POUNDS)		
	MEAN	S.D.	N.	MEAN	S.D.	N.
Liveborn siblings	5.9	1.18	198	8.68	1.183	242
Mothers	6.4	1.5	148	8.04	1.44	126
1st cousins through maternal aunts	6.76	1.25	123	7.86	1.25	144
Maternal aunts	7.12	1.55	114	7.93	1.32	110
Maternal uncles	7.2	1.38	96	8.0	1.37	118
1st cousins through maternal uncles	7.44	0.81	67	7.57	0.97	131
Fathers	7.35	1.32	71	8.39	1.42	96

Discussion

Our proband infants were ascertained by a mirror criterion. The velocities of intrauterine growth of liveborn siblings showed precise mirroring. Similar mirroring was found when mothers' birth weights were analyzed. It is tempting to infer that a single maternal parameter is operating at each extreme, respectively to enhance and to constrain fetal growth rate. But this does not fit all the facts. The only notable biological differences between mothers of slow-grown infants and controls were con-

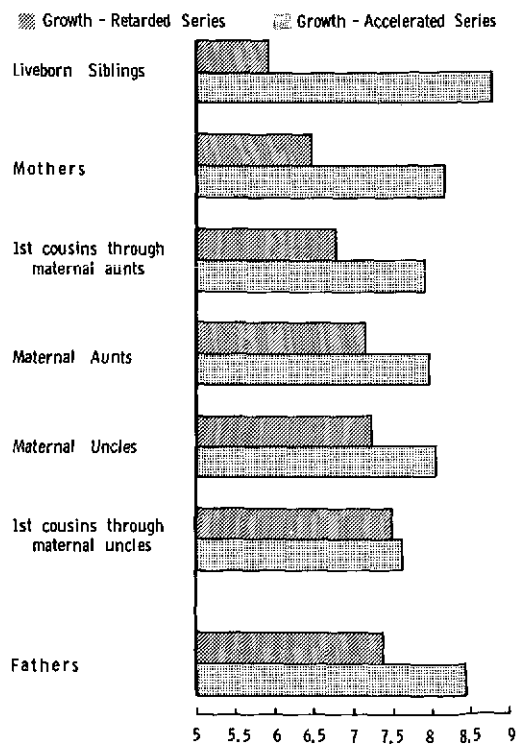

FIGURE 6. Mean birth weights of relatives.

straint of growth of all their young and constraint of their own growth as fetuses. When the same analyses were applied to the growth-accelerated series, many maternal factors of large effect emerged. These mothers were older, of greater parity, taller, and heavier than the controls. Thus it appears that when maternal constraint is relaxed, other factors enter and take up some of the variance. Here also the fathers may play a role. The mean birth weight of the fathers in the growth-retarded series was only a little below the average for the general population. The fathers of growth-accelerated infants had a mean birth weight larger even than the mothers in these pedigrees.

We have suggested (*20*) that it is degree of constraint rather than velocity of growth that is transmitted on the distaff side. This idea is supported by the finding in the growth-retarded series that the birth weights of first cousins through maternal aunts converge on the proband

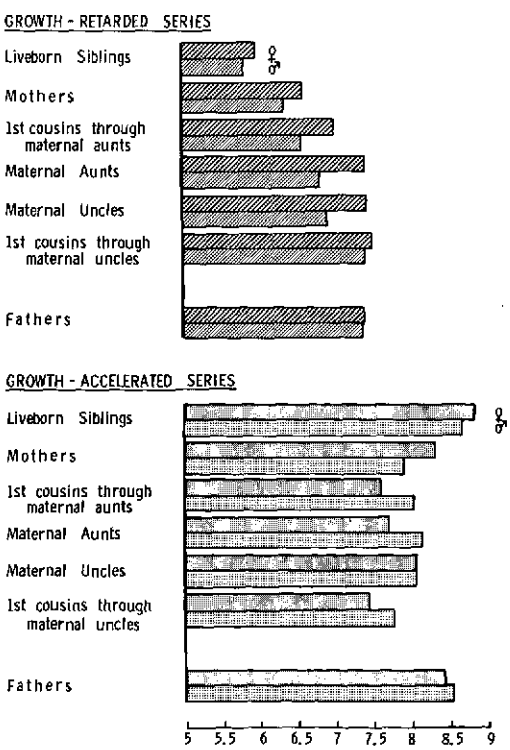

FIGURE 7. Mean birth weights of relatives analyzed according to sex of proband.

(Figure 4). These infants were of lower mean birth weight than their own mothers.

The sex of the proband proved to be a delicate probe of the growth-retarded-pedigree data. There was a shift downward throughout the distaff pedigree when the probands were males, except for the children of maternal uncles.

The maternal constraint imposed upon the growth rate of the fetus appears to be familial. This need not mean that transmission is wholly genetic. We have suggested that the maternal regulator is quantitatively set by the degree of constraint imposed upon the mother when she herself was a fetus. We realize that such an unusual theory requires biological justification.

Let us consider an analogy. Certain birds show the phenomenon of "imprinting" shortly after hatching. They have to learn afresh in each generation how to recognize the species to which they belong. One may ask why such a fundamental aspect of behavior should be transmitted in this dangerously nongenetic way. The answer may be found in species undergoing rapid gerontomorphic evolutionary change. If recognition were written into the genome, then for every assimilated gerontomorphic mutation a corresponding mutant in the genes for recognition would be required.[1]

The velocity of intrauterine growth is basic to the fitness (measured by reproductive achievement) of any population. If poor Indian peasants, living on a meager carbohydrate diet, bore young weighing 12 pounds, the parasitic conceptuses would kill them. Slow intrauterine

[1] Mutant genes are manifest at different points in ontogeny. Walter Garstang introduced the notion of the pedomorphic mutant: a mutant, that is to say, whose effect is manifest early in development. Sir Gavin de Beer supplied the corollary: a gerontomorphic mutant is one manifest only in the adult form (*2*). These distinctions are vital to evolutionary theory. Gerontomorphic mutations bring about gradual evolutionary phenotypic change adapting the adult form ever more closely to an ecological niche. Pedomorphic mutants, provided they are coupled with neoteny—that is, the accelerated capacity for reproduction—produce large evolutionary jumps in step-function form. They provide the genetic basis for dispersion in new ecological settings. When Garstang laughed away Haeckel's dictum in 1921 he put the matter in a nutshell: "Ontogeny does not recapitulate Phylogeny; it creates it."

growth under these conditions is favored, and our growth-retarded probands would be at an advantage. It was shown in Figure 4 that their distaff first cousins through maternal aunts do in practice converge on them, their mean weight being reduced by nearly one pound. The pedigree data display, as it were, the evolutionary model in progress.

Optimal birth weight is operationally defined as that weight at which perinatal mortality is lowest. In all populations so far studied, the mean birth weight is less than the optimal birth weight (*4*). Thus there is selection at work in favor of larger infants. The model proposed would allow for rapid shifts in the mean velocity of fetal growth as change occurs in the conditions under which populations live.

Antigenic dissimilarity between mother and conceptus has been suggested as a factor enhancing fetal growth (*19*). Thus under conditions of exogamy more rapid mean intrauterine growth would be found—an example of the well-known but little-understood phenomenon of heterosis or hybrid vigor. How could such an arrangement be adaptive to a population? This question would seem significant, particularly in countries that contain diverse ethnic groups (*13*). Where large quantitative physiological differences exist in the mode of intrauterine growth, studies of this natural variation are a necessary basis against which to set information about differing pathologies.

Acknowledgment

I should like to thank Professor J. Stallworthy, Mr. M. P. Embrey, Mr. E. A. Williams, Mr. E. Cope, Mr. D. Ellis, Dr. H. Ellis, and Dr. B. Bower for permission to study their patients; my husband Dr. C. Ounsted for his continued help and inspiration; Mr. M. Oakes for statistical analysis of the data; and my assistant Mrs. S. Marsh for her patience and care throughout this study.

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DISCUSSION

Russell: I am intrigued to know how Dr. Ounsted got the mothers' weights. For example, I have no idea what my mother's birth weight was and I am certain my wife does not know hers either.

Ounsted: The mothers in our series were, I think, a little younger than both Dr. Russell and I, and mostly their parents were still alive. Where the maternal granny was not alive we could not get the information. But this was all a personal series; whenever I saw a mother I made a plan of her family tree, wrote it all down carefully, and then asked her to take it home and consult granny and her brothers and sisters and other relatives on the required birth weights. I have pedigree data on about 150 growth-retarded probands and 150 growth-accelerated probands out of 200 of each.

Zamenhof: I should like to comment on the important subject of placental insufficiency mentioned by Dr. Gruenwald.

In our studies with rats, within a plus or minus 1 standard deviation from the mean placental weight, there is absolutely no correlation between neonatal body weight, brain weight, cerebral hemispheres, and placental weight, or rather placental blood volume, which we consider more important than placental weight but which fortunately is proportional to placental weight. The situation is different when placental weight is below two standard deviations from the mean. Such animals have everything low: neonatal body weight, brain weight, and brain DNA. On the other hand, animals whose placental weight is more than one standard deviation higher will also occasionally have higher brain weight, body weight, brain weight, and brain DNA.

Unfortunately, that does not answer the very challenging idea of Dr. Gruenwald's that the low placental weight is the effect rather than the cause of low neonatal body weight.

Moghissi: I should like to suggest that the reason Dr. Weiss found an inverse correlation between the weight gain in pregnancy and the prepregnancy weight of the mothers is that most obstetricians tell the obese pregnant woman to restrict her diet. This is still a common practice.

Weiss: Are you trying to evaluate the possibility that in this country the possible control of weight gain during pregnancy is, or may be, associated with a low birth weight of the child and not an observed measurable increase in toxemia? But we have dealt here with changes in prepregnancy weight and changes in weight gain, and we have seen that the association between these two factors is inverse. I think that the possibility does exist that if a woman has increased her prepregnancy weight from one pregnancy to the next, either she or the obstetrician may restrict the weight gain in the later pregnancy.

Winick: I might mention some chemical changes that have been described in placenta both in experimentally produced intrauterine growth failure—in rats, by malnutrition and by clamping the uterine artery—and in the placental insufficiency that occurs in the human. One is a marked increase in the RNA-DNA ratio. This kind of change is nonspecific, as far as we can tell, and as been described in tissues under a number of stress-type situations. It can be produced by clamping the aorta or by giving estrogen and allowing the uterus to hypertrophy.

The point is that there may be other biochemical measurements as well as this one by which so-called placental insufficiency can be identified. So I do not think the problem is necessarily insoluble.

Gruenwald: I want to make it clear that I have not said, or intended to say, that there is no such thing as placental insufficiency. There is in some instances. But if we call all fetal

growth retardation "placental insufficiency" we forget to look at the mothers; in effect, we are saying that there is nothing we can do about it. The important thing is not to let this happen. We should study the mother very carefully, because there may be something we can do.

Dawes: Dr. Gruenwald's characteristic challenge must not go unmet. He suggested, you remember, that the placenta was part of the fetus and that the clear relationship in growth and weight between the two might not be causal. But the evidence from mating experiments on mice makes it much more likely that there *is* causality. James and Kirby have produced good evidence to suggest that there is an immunological change at implantation such that outbreeding produces large placentas with which large fetuses are associated, while inbreeding does the reverse; artificial induction of tolerance in outbreeding mating prevents this.

The most obvious explanation of the relationship between placental and fetal weight is a causal one.

Adamsons: As additional evidence, the work of Whigglesworth and also, more recently, of Dr. Blanc and associates indicates that there is a striking reduction in blood supply to the placenta when the blood supply is impaired. It is interesting to note further that the fetal blood supply is more affected than the placental blood supplies.

I have taken the liberty of refreshing my memory on the figures he presented to our meeting a year ago. The fetuses of the ligated horn had a body mass that was 67 per cent that of the controls, whereas the placental weight was 84 per cent. There was also a difference in the RNA and DNA proportions. The RNA content in the placenta was not as much reduced as in the whole animal. These studies certainly seem to indicate that impairment of the uterine blood supply may lead to an underdevelopment of placenta and to an even more pronounced underdevelopment of the fetus.

Gruenwald: I do not regard maternal blood supply to the placenta as a placental factor. I am talking about the tissues of the placenta. If the placenta is not so far behind in growth as the total body, the same thing could be said of the brain, for instance. I am not sure this is a pertinent argument. I have never denied a causal relationship. However, it is hard to tell which way it works.

THE SONOGRAPHIC DEPICTION OF THE GROWTH AND DEVELOPMENT OF THE HUMAN FETUS

Louis M. Hellman, Mitsunao Kobayashi, Lewis Fillisti, and Ellen Cromb [1]

Attempts to ascertain fetal growth and development *in utero* as an indicator of fetal health have occupied an increasing number of investigators over the past two decades. Definition of the state of health of the fetus is, in itself, a worthy scientific objective. At a clinical level this information is at least of prognostic value, and some detectable deficits may even now be ameliorated either by early delivery or by such other measures as intrauterine transfusion.

The problem of fetal growth has been approached along several different pathways. Clinically, crude estimations of fetal size and changes in maternal weight have been thought indicative, but are of course grossly inaccurate. More precise estimates of fetal growth have been obtained by X-ray (*3, 7*) and sonography (*2, 4, 10*).

The purpose of this paper is to review briefly the significant contributions of ultrasonic techniques to the ascertainment of fetal size and growth. These techniques have been applied to the problem by Donald and his co-workers in Glasgow, Thompson and the group at Denver, Hellman and his co-workers in New York, and other workers (*1, 2, 4, 5, 10*).[2]

[1] Presented by Dr. Hellman.

[2] The principal groups of workers in this field referred to are as follows: in Denver: J. H. Holmes, E. S. Taylor, K. R. Gottsfeld, and H. E. Thompson; in Glasgow: I. Donald, J. Willocks, J. MacVicar, U. Abdulla, T. C. Duggan, and N. Day; in New York: L. M. Hellman, M. Kobayashi, L. Fillisti, M. Lavenhar, and E. Cromb. Because the senior authors vary with their publications they will occasionally be referred to by their respective geographic designations.

In order that the reader may have a more complete understanding of this subject, a brief description of the equipment, safety, and general techniques follows.

Equipment

The equipment used to produce the two-dimensional sonograms in this section has the following basic specifications:

Type: Contact coupled scanner (manually controlled scan motion)

Frequency: 2.0 megaherz

Transducer: focused, lead zirconate, ½ in. diameter

Oscilloscope: Tektronix Storage Oscilloscope (screen size 8 x 10 cm, displaying 24 x 30 cm scanned area)

Camera: Tektronix, Type C-27 (using Polaroid Type 107 film)

Manufacturer: Picker Electronics, Longmont, Colorado

The experience of over 4,000 examinations with this equipment has proved the basic design well suited to the field of obstetrics and gynecology. The scanning equipment is shown in Figure 1; a separate unit is used for all A-mode measurements and is shown in Figure 2.

The unit was originally built with two oscilloscopes, one with a cathode-ray tube having a P-11 phosphor and the other with a Tektronix storage tube, so that we could ascertain which produced the best sonograms. It was found that slightly better resolution can be achieved with a non-store oscilloscope, but in clinical use the convenience of seeing the image on the screen before photographing it far outweighs the minor loss of definition.

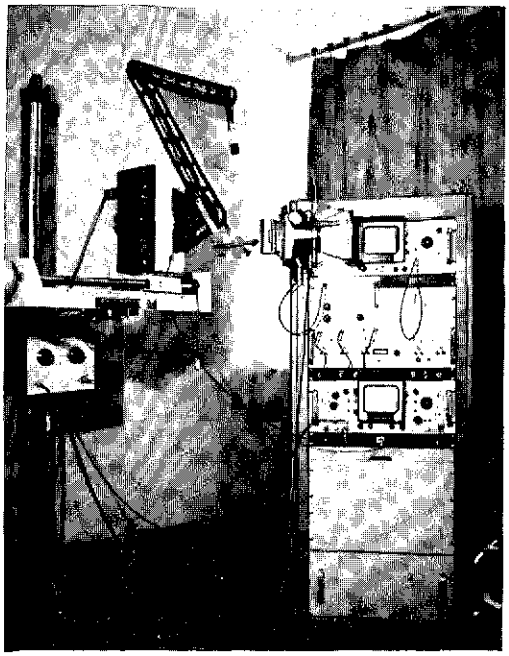

FIGURE 1. B-Scope.

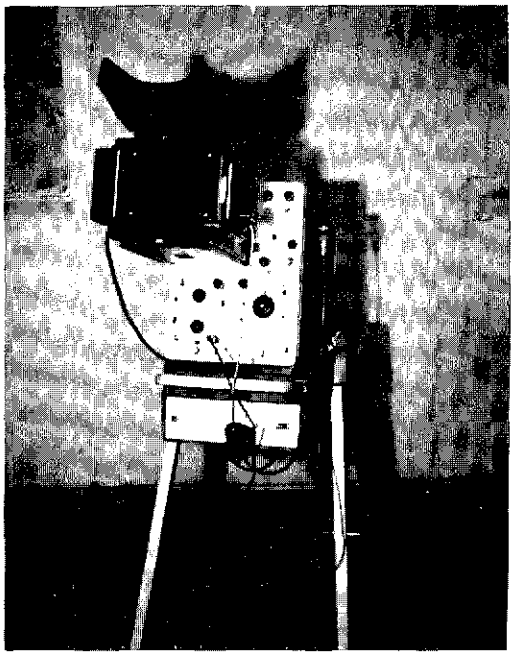

FIGURE 2. A-Scope.

A frequency of 2.0 megaherz has been used for all clinical work and, with the receiver gain available, has produced adequate penetration. The transducers are lead zirconate units supplied by the manufacturer and have been modified with the addition of a lens to focus the ultrasound beam. The current lenses are made up of concave lucite lenses in which the concavities are filled with a soft epoxy. Thus the surface in contact with the patient is flat, which facilitates coupling through a thin film of mineral oil. The focusing of the beam is apparent in improved lateral resolution. Work is in progress on the development of a higher-frequency transducer. Perhaps 3.0 megaherz may prove useful, in early pregnancy and gynecological cases, in providing slightly better resolution where greater penetration is not needed.

The over-all sensitivity of the system is controlled by a switched attenuator box placed in series with the transducer. The receiver gain control is set so that the receiver noise is just below the level needed to show on the oscilloscope screen. With this method, both the transmitted signal and the received signal are attenuated, and maximum sensitivity is at 0 decibels, with lower sensitivity expressed as a larger negative number.

It is very important to have some means of moving the patient or the scanning arm in a controlled manner, so that, when successive scans are being taken in the same plane, sections of ½ to 1 cm can be achieved. The entire scanning head of our present unit is mounted on a table fitted with a motor-driven screw; the head can be advanced any desired amount or the motor run continuously at a slow speed while scans are made and erased from the oscilloscope to scout the entire abdomen.

Safety

Although ultrasound can produce permanent damage to tissue directly at high energies and reversible damage at somewhat lower energies, the danger is significantly reduced in diagnostic ultrasound by employing energy levels one to two hundred times lower than those commonly used in therapeutic applications. Sundén (*9*) has reviewed the literature on the safety of

ultrasound and has carried out a series of careful experiments on pregnant and nonpregnant rats; with intensities similar to those employed in our equipment, he could neither damage maternal tissue nor provoke abortion or damage the newborn rat. Similarly, safety was confirmed in both rats and mice by Smyth (*8*).

The amount of ultrasonic energy derived from currently employed diagnostic machines is extremely small—about 10–20 milliwatts per square centimeter at the skin surface—and if measurable at the site of the human fetus may be lower than 100 microwatts per square centimeter. Increasing numbers of human fetuses have been exposed to these energy levels both in the United States and abroad without evidence of abnormalities. Currently a cooperative survey is being undertaken to survey systematically a very large group of infants exposed to ultrasound *in utero*. Preliminary review of the records fails to reveal any increase in the incidence of malformations.

After exposing tissue cultures of human trophoblast cells for periods of two hours to 800 times the maximum amount of ultrasonic energy yielded by our apparatus at the skin surface, we have been unable to note any morphologic changes in these cells or in their rate of propagation. In similar experiments, the Glasgow workers have found no chromosomal abnormalities in the exposed cells.

Procedures and techniques

Most obstetrical and gynecological examinations require two-dimensional ultrasonography. The A-mode is employed principally for cephalometry, and may also serve as an adjunct to scanning of cystic structures. It yields supplemental and often valuable information. The mensuration is slightly more accurate than with the two-dimensional techniques.

For sonography, the patient lies supine on an easily movable table or stretcher with the lower abdomen exposed. The Glasgow workers (*6*) have shown that in early pregnancy, in gynecological examinations, and in cases of placenta previa, sonograms of the uterus are immeasurably enhanced by a full bladder. The distended bladder not only displaces the intestines but provides a uniform fluid medium through which ultrasonic waves are easily propagated. Mineral oil is liberally applied to the lower abdomen in order to provide adequate coupling between the abdominal wall and the transducer.

Originally, compound sector scanning was carried out by moving the probe across the abdomen with a simultaneous rocking motion. This technique often produced inferior sonograms because of the refraction of the sound waves passing through the abdominal wall. Rocking of the probe has now been virtually eliminated. The scanning is nearly linear with one important modification: as the probe is passed across the abdomen its angle is constantly changed so that the beam is centered on the area of maximum interest. Most examinations consist of a series of longitudinal and transverse scans. The longitudinal scan is in a plane parallel to the long axis of the patient, and the transverse scan is at right angles to this. Occasionally an oblique scan, at an angle to these planes, is advantageous, especially in the diagnosis of multiple pregnancy and fetal presentation.

As Figure 3 shows, the scanning location is measured from the midline in the longitudinal scan and according to the distance above or below the umbilicus in the transverse scan. For example:

L + 4 = longitudinal scan at 4 cm to the right of the midline
L — 4 = longitudinal scan at 4 cm to the left of the midline
T + 5 = transverse scan at 5 cm above the umbilicus
T — 5 = transverse scan at 5 cm below the umbilicus

To change from a longitudinal to a transverse scan, the stretcher on which the patient lies is turned to 90°. The transducer is tilted from the vertical in order to maintain contact with the curved abdominal wall or to obtain a better view of the area being examined.

Tilt is described in degrees and is designated either right or left in longitudinal scans, or caudad or cephalad in transverse scans, accord-

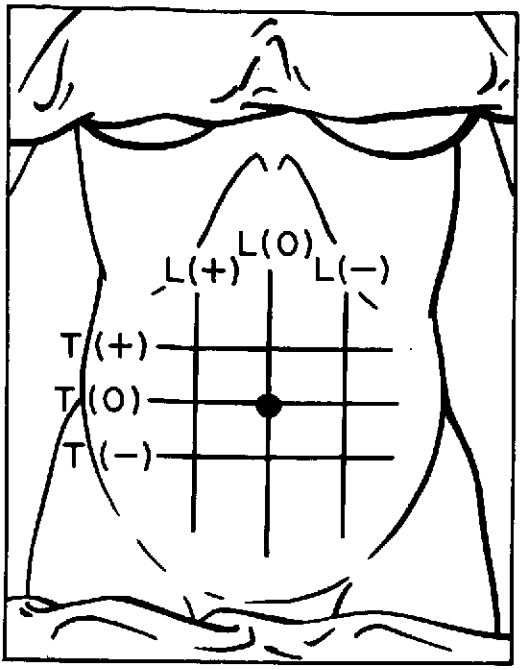

FIGURE 3. Scanning location.

ing to the direction toward which the face of the probe is pointed.

The right side of the sonogram represents a patient's right side in a transverse scan. In the longitudinal scan, the left side of the sonogram is cephalad. It is customary to mark the symphysis with a sharply angled line and the umbilicus with a perpendicular line. In the transverse scan, the midline is also marked with a perpendicular line.

Two-dimensional and A-mode sonograms are calibrated to 3 cm and 2 cm per division respectively.

Normal pelvic organs

A sonogram of the normal pelvic organs is shown in Figure 4. The uterus is pushed slightly toward the sacrum by the full bladder. The uterine cavity is obliterated by close approximation of the anterior and posterior walls of the uterus; therefore, only the uterine outline shows. The vagina appears as double lines forming an angle with the uterus in the vicinity of the internal os. Even during menstruation there are

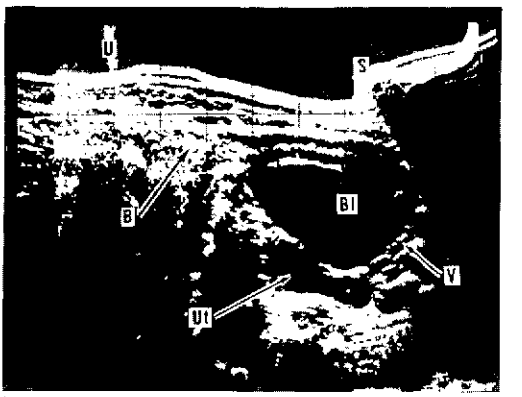

FIGURE 4. Normal uterus.

usually no intrauterine echoes at a normal gain setting. An intrauterine contraceptive device in the uterine cavity, however, can be easily seen (Figure 5). The external diameters of the uterus can be measured accurately. These measurements serve to ascertain uterine growth in normal and abnormal pregnancy. Neither normal fallopian tubes nor ovaries can usually be visualized.

Scattered bowel echoes are produced by reflection of the ultrasonic waves from the serosal surfaces of the fluid- and gas-filled intestines. Ordinarily they occupy a relatively superficial zone in the abdominal cavity, but their depth can vary with their content. Very little can be seen behind the intestines, but their shadows and locations are characteristically altered by intestinal obstruction, massive intraperitoneal hemorrhage, adhesions, and ascites. The echoes

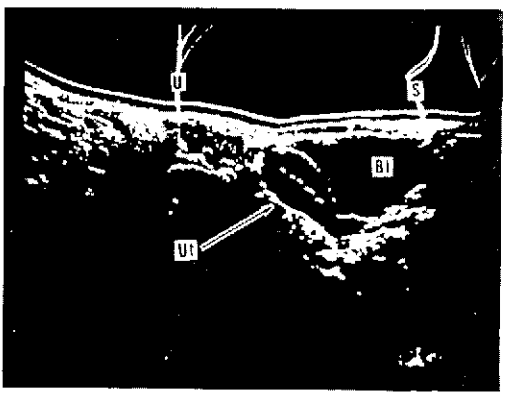

FIGURE 5. Lippes loop *in utero*.

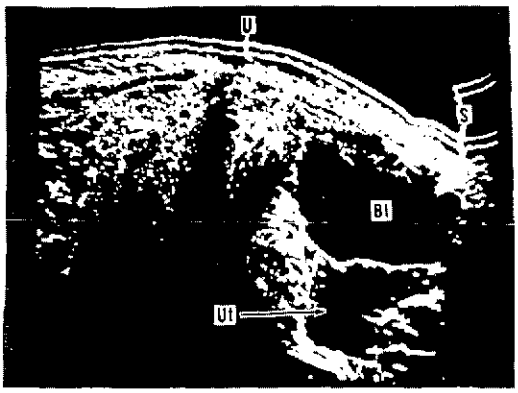

FIGURE 6. Retroverted uterus.

from the cul-de-sac are difficult to interpret and are often misleading because of the depth and many varied reflecting surfaces. Thus a retroverted uterus (Figure 6) lying in the hollow of the sacrum may be difficult to outline.

Fetal growth

Both the Glasgow group and the workers in New York (*3, 5*) have identified human intrauterine pregnancies during the fifth gestational week (menstrual age).

An early normal intrauterine pregnancy is characterized by a typical round cystic-appearing gestational sac located in the uterine fundus (Figure 7). This sac can be measured in several diameters and thus early fetal growth can be followed. The gestational sac is readily visualized until about the tenth week of pregnancy, when fusion of the decidua capsularis and parietalis begins to occur. At this point the sac appears to dissolve and the uterine cavity is filled with disorganized echoes (Figure 7). Continuing enlargement of the uterus furnishes the only quantitative estimate of the growing

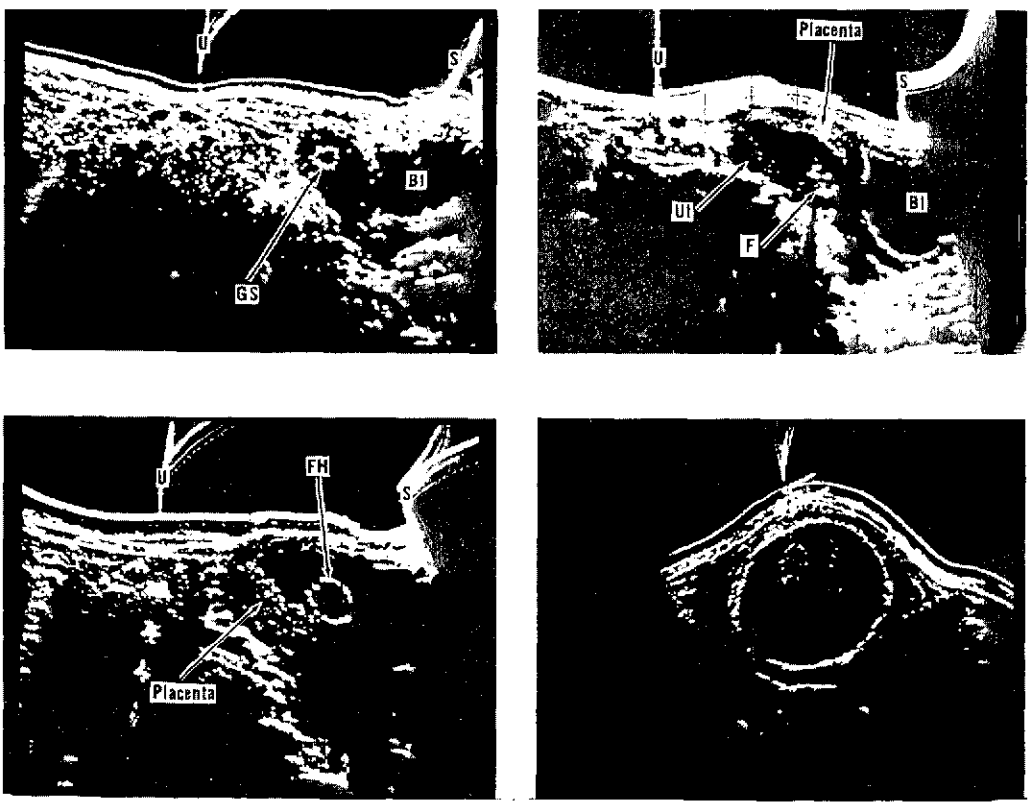

FIGURE 7. Sonograms showing growth of pregnancy from fifth week to term. Top, from left: 5 weeks and 11 weeks. Bottom, from left: 13 weeks and 37 weeks. U, umbilicus; S, symphysis; GS, gestational sac; Bl, bladder; Ut, uterus; F, fetus.

TABLE 1. Comparison between A-scan and B-scan measurements (cm) of biparietal diameter (*4*)

No. of paired observations	88
Absolute mean difference (A-B)	0.202
Mean difference (A-B)	—0.134
t value	—5.66
Probability	<0.001

pregnancy during this period. The fetal head, however, begins to appear between the twelfth and the fifteenth week of pregnancy (Figure 7) and is measurable from this point until term.

Measurement of the fetal head is highly accurate with both the A-mode and two-dimensional scanning, as may be seen in Table 1. Both the biparietal diameter and the occipitofrontal diameter and circumference can be obtained from the scanned sonograms. Usually only the biparietal diameter is measurable with the A-mode. Both techniques require care and meticulous attention to detail for reliable results. Prior to the A-mode measurement (Figure 8) we use scanning to locate the biparietal diameter. The A-scope probe is then adjusted until the proximal and distal pulses produced by the parietal bones are of equal height. The midline structures of the fetal head can also be used to orient the A-scope probe.

The fetal weight after 20 weeks' gestation bears an approximately linear relation to the biparietal and occipitofrontal diameters and to the occipitofrontal circumference of the fetal

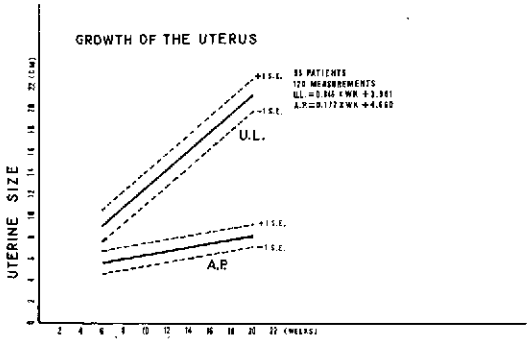

FIGURE 9. Least squares regression lines and standard errors of estimate of relation of duration of pregnancy to uterine size. Uterine size is measured by greatest AP diameter of fundus and length of uterus (*5*).

head from which the following formulas can be derived:

$$WT = BP\ 772.2 - 3{,}973.8$$
$$WT = OF\ 604.5 - 3{,}733.8$$
$$WT = OFC\ 262.3 - 5{,}863.6$$

The standard error of each estimate is less than 400 grams.

The relation between the various measurable diameters and the duration of pregnancy is illustrated in Figures 9 to 12. This correlation is more useful than the weight relationship and perhaps more precise.

Growth of the dizygotic twin pregnancy is shown in Figure 13. The double gestation sac is first visible at the seventh week (menstrual age). The placentas begin to appear at the eleventh week, and the fetal heads are visible

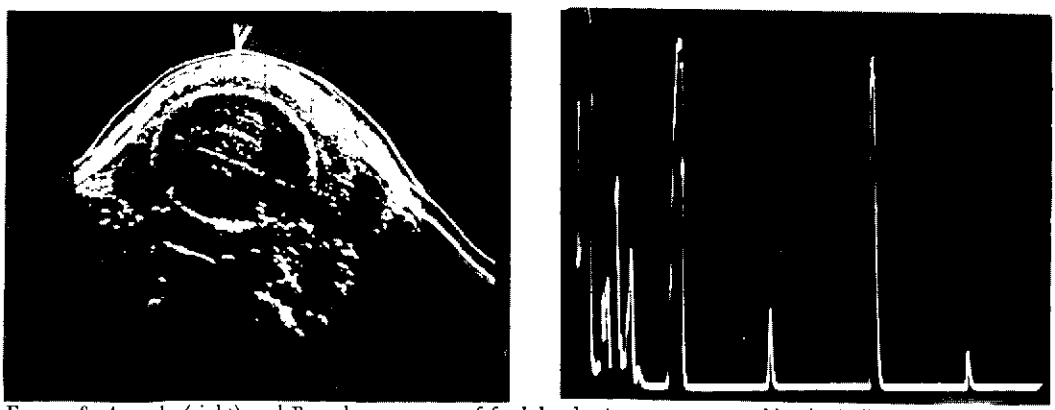

FIGURE 8. A-mode (right) and B-mode sonograms of fetal head. At or near term, biparietal diameter can be measured equally well from either mode.

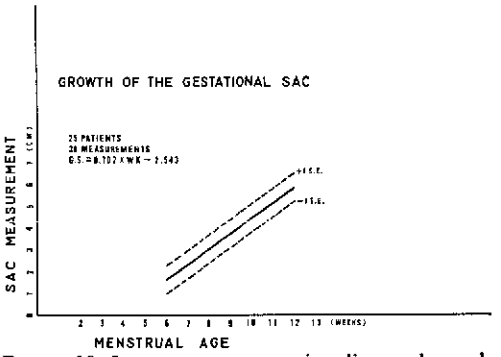

FIGURE 10. Least squares regression line and standard error of estimate of relation between diameter of gestational sac and duration of pregnancy (*5*).

and measurable from the twelfth to fifteenth week onward.

At the present time very few data are available from sonographic studies regarding intrauterine growth retardation or acceleration.

Placental growth

A typical ultrasonic placentogram shows the placenta as a semilunar dotted area bounded by the inner surface of the uterine wall on the maternal side and a linear chorionic plate on the fetal side. There are characteristic multiple echoes contained within the placental area. Although the basal plate of the placenta is not usually visible, the chorionic plate should always be clearly demonstrable for positive identification of the placenta. The chorionic plate appears linear with occasional interruptions. It is best

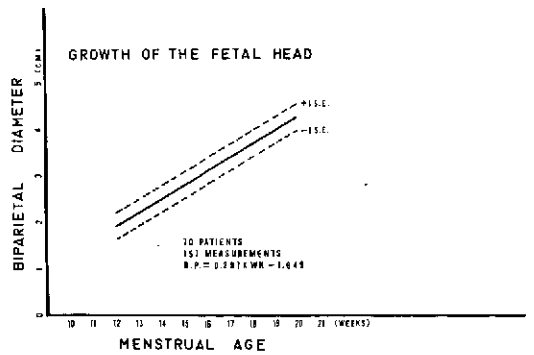

FIGURE 11. Least squares regression line and standard error of estimate of relation of fetal biparietal diameter to duration of pregnancy (*5*).

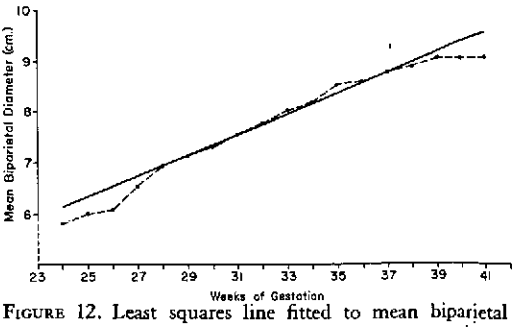

FIGURE 12. Least squares line fitted to mean biparietal diameter by weeks of gestation in 91 normal gravidas. BP = 0.21 wk + 1.14 (*4*).

demonstrable where it is not in contact with any part of the fetal body and there is some intervening amniotic fluid. The multiple-echo pattern in the placenta varies with the sensitivity setting, the scanning speed, and the position of the placenta, but there should always be sufficient characteristic echoes to differentiate the placenta from the amniotic fluid.

The growth of the placenta is illustrated in Figure 14. It becomes visible about the tenth week of gestation, and thereafter both its chorionic plate and its thickness are measurable. Information is too incomplete to permit the definition of errors in these measurements or to construct their regression lines. The importance of placental growth mensuration, however, is obvious.

Abnormal embryonic development

Knowledge regarding ultrasonic diagnosis of abnormal fetal development is in its infancy. Some obvious abnormalities are shown in Figure 15.

Ultrasonic techniques have made all but obsolete other methods of diagnosis of hydatid mole. First cited by the Glasgow group, the characteristic multiple echoes that appear to fill the enlarged uterine cavity make the diagnosis almost certain. These echoes have no fixed pattern, although they resemble those of normal placental villi. There is, however, no limiting chorionic plate. These echoes are most prominent at high gain settings and tend to disappear as gain is lowered.

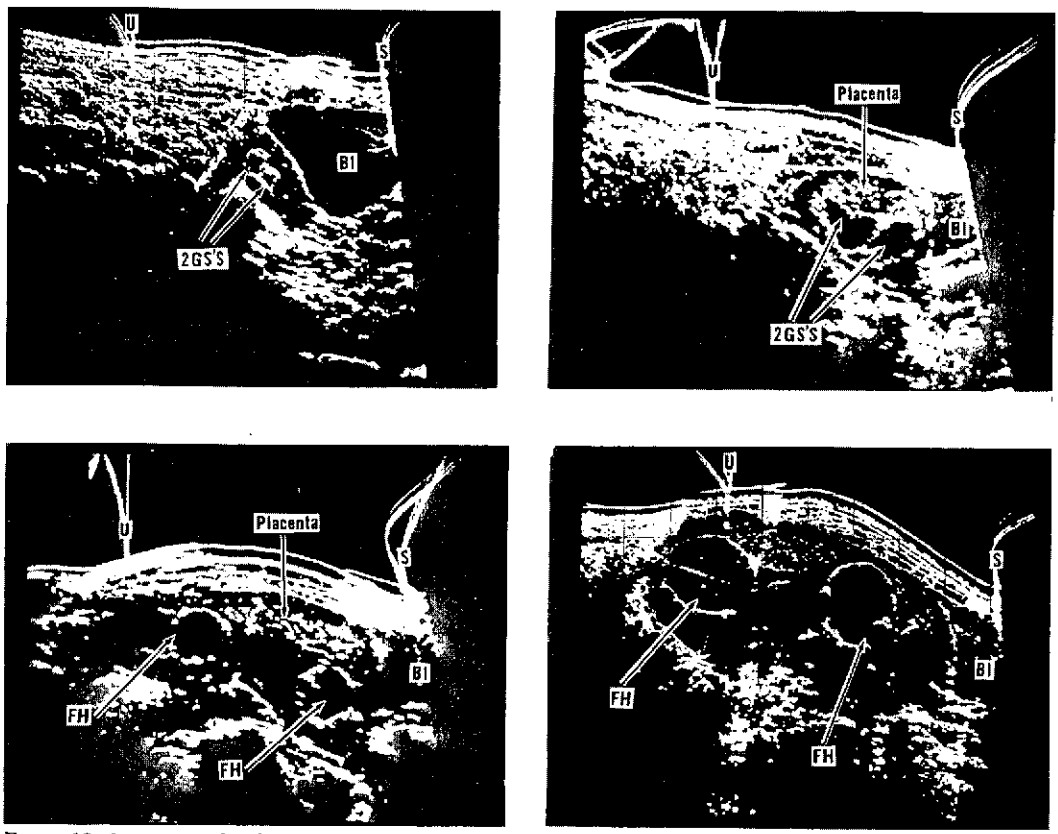

FIGURE 13. Sonograms showing growth of double-ovum twins. Top, from left: 7 weeks and 11 weeks. Bottom, from left: 17 weeks and 23 weeks. (See Figure 7 for abbreviations.)

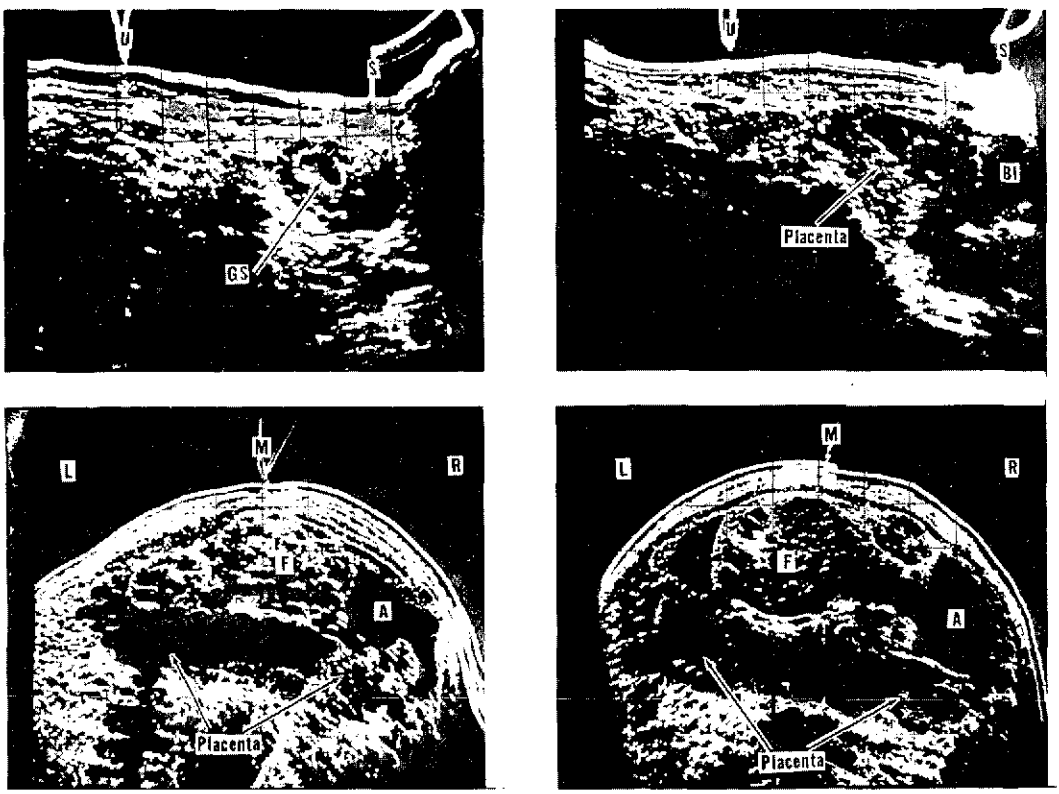

FIGURE 14. Sonograms showing growth of posteriorly implanted placenta. Top, from left: 8 weeks and 13 weeks. Bottom, from left: 32 weeks and 37 weeks. (A, amniotic cavity; see Figure 7 for other abbreviations.)

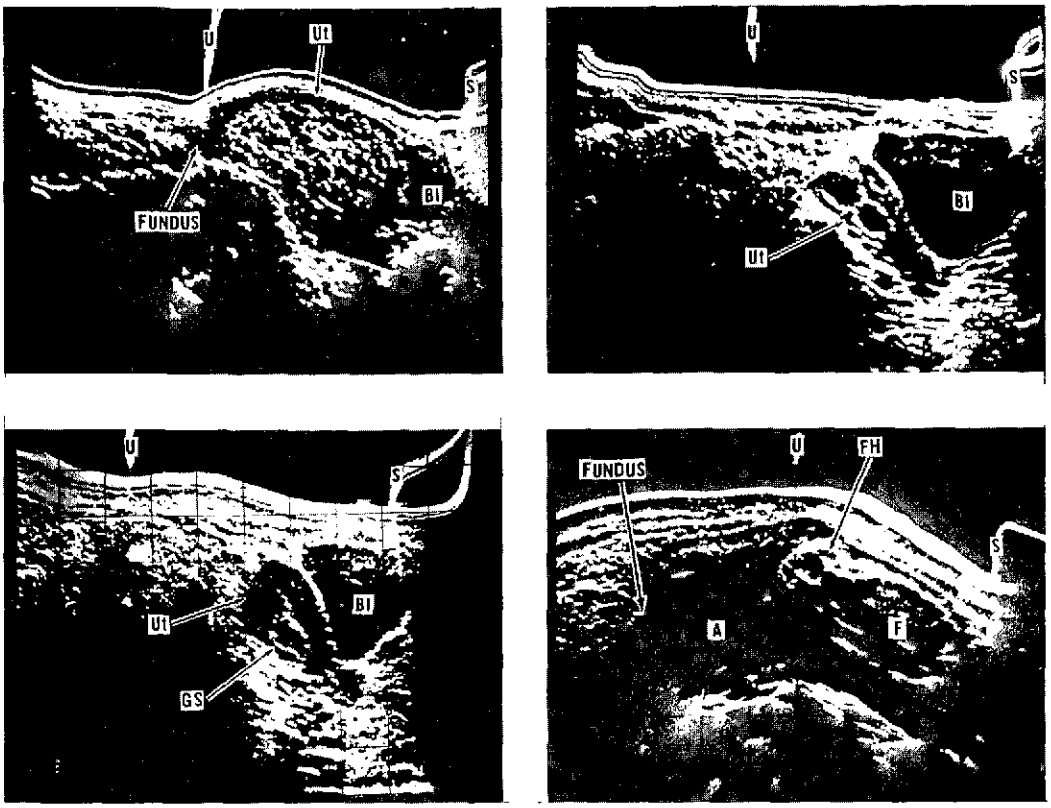

FIGURE 15. Sonograms showing several types of abnormal pregnancies. Top, from left: hydatidiform mole; double gestational sacs (10 weeks), with subsequent abortion. Bottom, from left: abnormal gestation (9 weeks); anencephaly (26 weeks). (See Figures 7 and 14 for abbreviations.)

Gross malformations of the fetus, except for those of the fetal head, are not readily seen with ultrasonic techniques and present equipment. Abnormalities of the fetal head, such as anencephalus or moderate to severe hydrocephalus, are easily visualized. The rest of the body is difficult to outline, and one cannot always be sure of the completeness of the sonogram. An incomplete fetal skull is shown at lower right in Figure 15D. In this case the X-ray appeared normal. At birth the infant had a rachischisis of the frontal bone, and autopsy revealed an incomplete anencephalus.

Three relatively common abnormal early pregnancies are also shown in Figure 15. The double gestational sac probably represents single-ovum twinning. It appears to be much more common than the usually cited prevalence of 0.5 per cent and very frequently ends in abortion. Similarly, low implantation is more prevalent than the

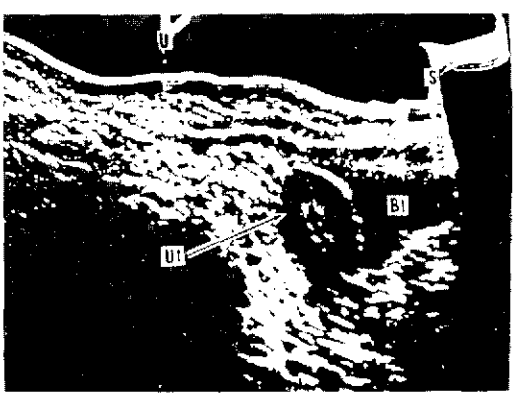

FIGURE 16. Abnormal ovum at 6 weeks (menstrual age). Scanning was done 2 days before the patient began to bleed and pass necrotic decidua (5).

0.5 per cent rate for placenta previa and usually terminates in abortion. The elongated ovum illustrated in Figure 16 represents a chorionic sac devoid of an inner cell mass; these ova inevitably abort.

Summary

In brief, the recently developed sonographic techniques have made it possible to depict the growth of pregnancies from early date until term. It now seems apparent that future studies will reveal defects in fetal development and growth rates. Sonography has already produced significant information and promises an important advance in fetal medicine.

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UTERO-PLACENTAL CIRCULATION: AN ANGIOGRAPHIC STUDY

J. Bieniarz, W. Julio, and L. Grainer [1]

It has been widely assumed that occlusion of the inferior vena cava causes supine hypotension by reducing venous return to the right heart (*20, 22, 26*). Venous return is the fulcrum of circulation, since the heart can pump only as much blood as it receives (*34*). Cardiac output and systemic arterial pressure are largely determined by venous return (*18*).

Recent investigations of various vascular regions by simultaneous pressure recordings (*5, 7, 12, 13, 16, 25, 31, 32*) and by iliocavography (*23*) have demonstrated that the inferior vena cava is completely occluded by the gravid uterus in late pregnancy when the women are in the supine position. But it has never been clearly explained why, if this is so common—it is seen in 10 out of 12 women (*23*)—supine hypotension develops only in a minority.

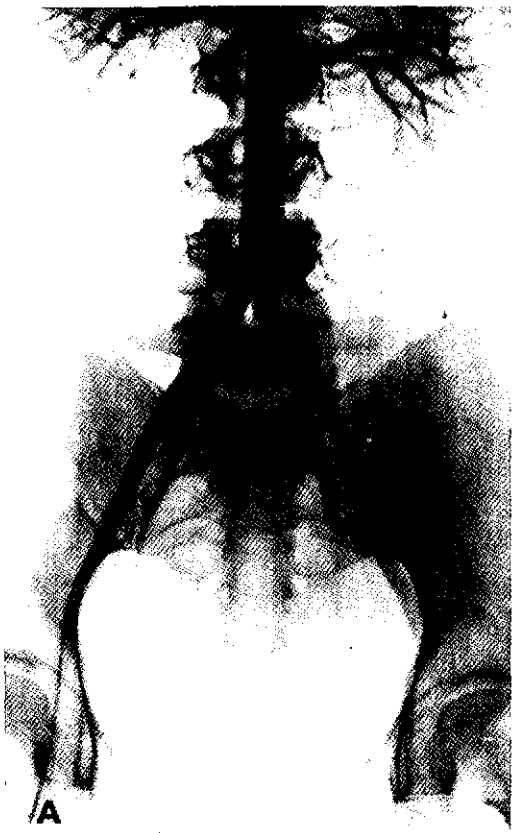
Further investigation disclosed that a similar compression is exerted by the gravid uterus on the aorta and its branches (*2, 4, 6*). During hypertension, however, high intra-arterial pressure withstands uterine compression. During normotension, the aorta is partly obstructed; the compressive effect becomes progressively more marked when hypotension develops (*6*). The question that arises immediately is, How can the placenta meet the metabolic needs of the rapidly growing fetus in late pregnancy if in normal conditions the main supply and drainage routes —the aorta and inferior vena cava—are obstructed?

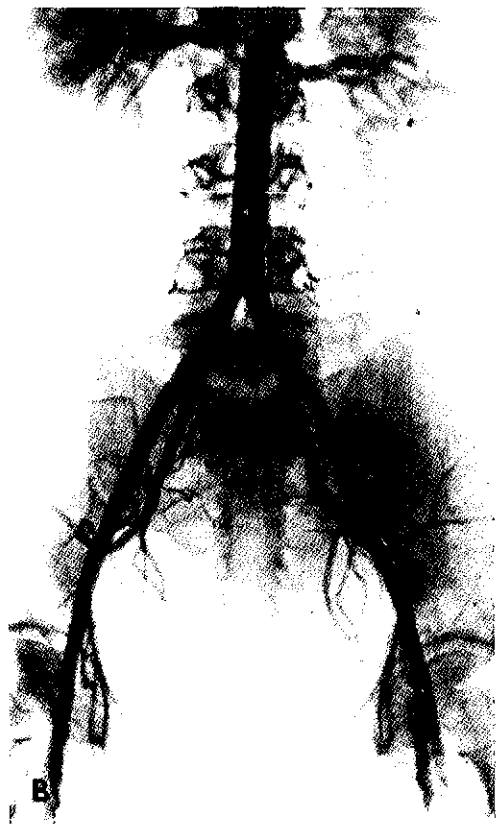
[1] Presented by Dr. Bieniarz.

Bieniarz *et al.* (*4, 9*) have performed abdominopelvic arteriographies in 100 women during late pregnancy (after the twenty-eighth week) for the study of arterial supply to the placenta in conditions of aortocaval obstruction. The vascular system visualized in 30 nonpregnant women for medical or urologic indications served as control. Studies by Ramsey and associates (*29, 30*) and by Borell and Fernström (*10, 11, 15*) have proved that angioradiography is a valuable tool in the investigation of utero-placental circulation.

In the arteriograms obtained in nonpregnant women (Figure 1), the aorta was seen as a straight vessel of uniform width and density projected near the midline. Ovarian arteries were visible in no more than 20 per cent of the arteriograms as fine vessels, reaching the ovaries but not the uterus. Contrast medium injected into the aorta cleared with higher velocity and density through the straight external iliac arteries than through the angulated and narrow internal iliac arteries, and from branches of the latter more rapidly through parietal pelvic gluteal arteries than through uterine arteries. The latter were visualized late and poorly, tapering in a distal direction, so that the arcuate arteries were hardly visible and the spiral arteries were never visualized.

In late pregnancy (Figure 2), the aorta was displaced usually to the left, frequently narrowed, and less opacified in the retrouterine region and in its branches crossing the vertebral column. Arterial hypotension enhanced these





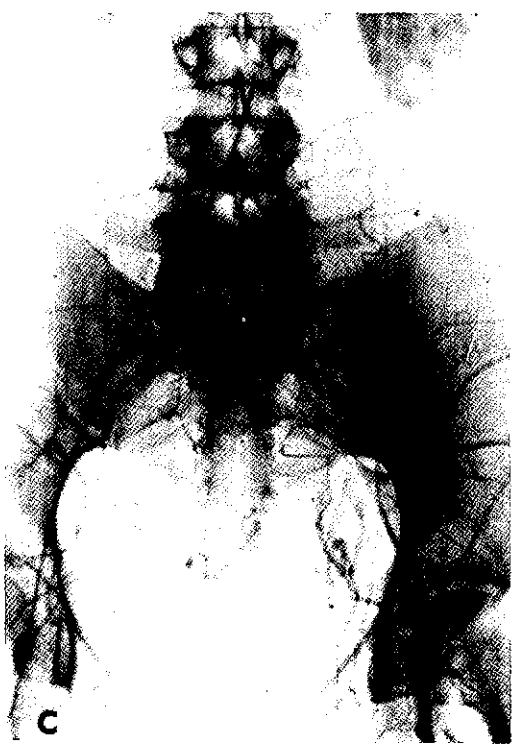


FIGURE 1. Angiogram obtained in nonpregnant woman. Dye clears from straight midline aorta more rapidly and with higher density through external iliac arteries than through internal (A, 1.5 sec). Gluteal arteries are visualized earlier and more densely (A; B, 3 sec) than uterine arteries (C, 5 sec), which taper distally so that their arcuate and spiral branches are not visible.

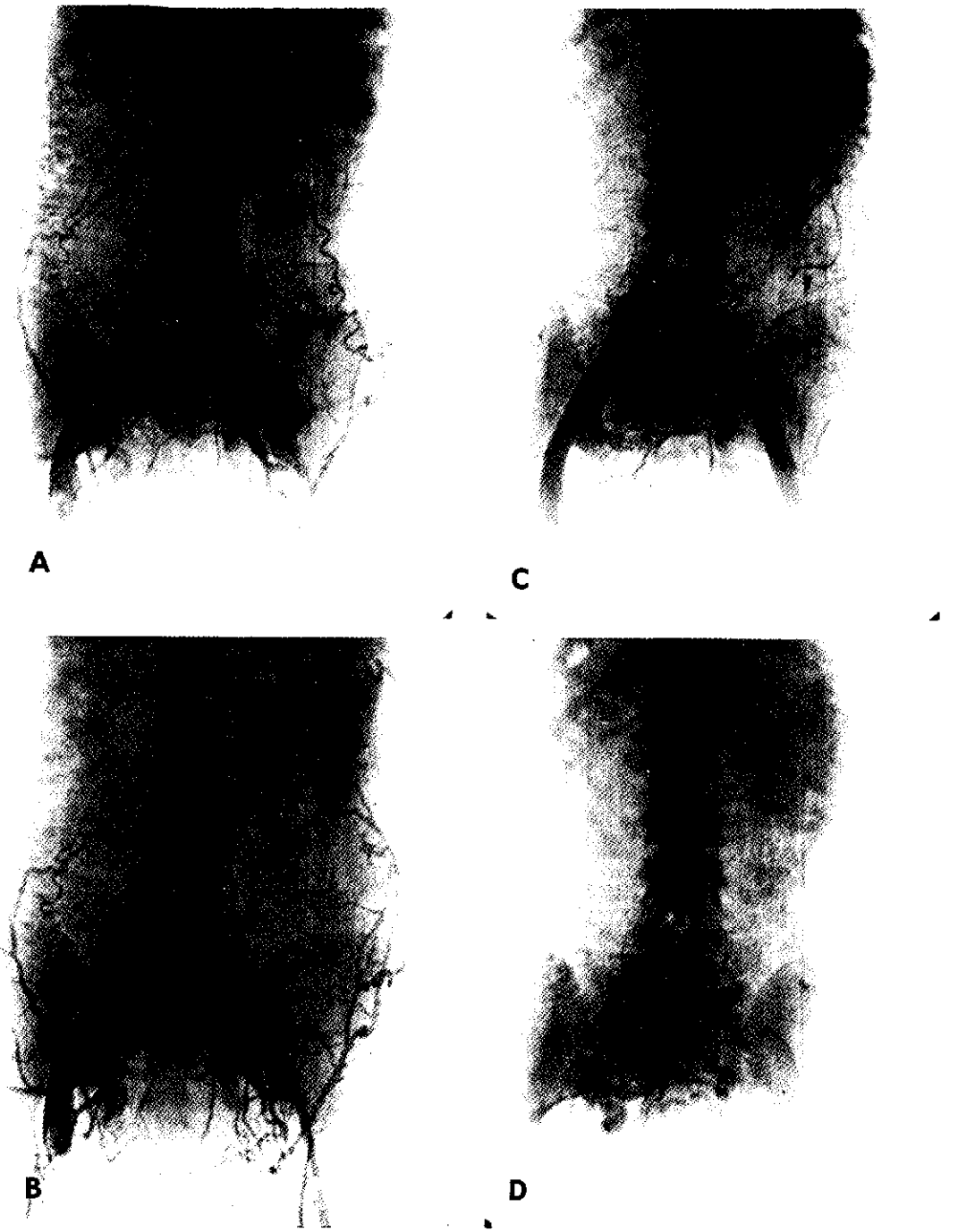


FIGURE 2. Concomitant iliocavography and arteriography in normotensive primipara. Venous return is occluded at iliac confluence, with moderate distension of pelvic venous reservoirs. Preferential perfusion of placenta at expense of distal parietal circuits is visualized (A, 2 sec; B, 3 sec). Circulating blood is distributed uniformly between principal reservoirs: pelvic veins, arterial system (A, B), and placenta (C, 6 sec; D, 10 sec). See text for detailed description.

compressive effects. Compensation for the obstructed arterial supply consisted of the following vascular adjustments (*9*):

1. Recruitment of all possible supply routes. The main stem of uterine arteries, dilated 3 times, was joined in 70 per cent of the angiograms by widened ovarian arteries and in 40 per cent by canalized round ligament arteries, which were usually obliterated. Communications between these arteries on each side and between their arcuate branches from one side to the other formed a virtual arterial circle surrounding the placenta.

2. Selective overgrowth of arteries which supply the placenta. Corkscrew-like arcuate arteries and helical spiral arteries that approached the placenta increased in tortuosity and width 10 and 30 times with respect to their width in the nonpregnant state. Extraplacental vessels remained straight and narrow.

3. Preferential perfusion of the placenta. The placenta became the center of uterine circulation, where blood flow converged. Dye injected into the aorta cleared twice as rapidly through internal iliac and uterine arteries supplying the placenta than through external iliac and gluteal arteries supplying the lower extremities and parietal pelvic circuits. This is exactly the opposite of conditions seen in angiograms obtained in nonpregnant subjects, in whom there was more rapid dye clearance through external iliac and gluteal arteries. A similar pattern was seen in late pregnancy in only 20 per cent of the angiograms, obtained in women with hypotensive or hypertensive disorders. It was postulated (*9*) that an obstructed inferior vena cava blocks the venous return from the parietal pelvic and lower extremity circuits so that, distended to the limits of their capacity and compliance, they cannot accept more blood. Grafted in parallel to these parietal circuits, placental circulation offers less resistance because its vascular bed is markedly dilated and because the placenta finds an alternate pathway of venous return through the ovarian veins, bypassing the retrouterine vena caval occlusion (*3, 21*). This preferential perfusion of the placenta is considered a major homeostatic adjustment in normal pregnancy that covers the metabolic needs of the fetus and provides for an adequate venous return to maintain normal arterial pressure.

In order to check the postulated physiological role of the inferior vena caval occlusion in the development of preferential perfusion of the placenta, it was decided:

1. To investigate venous drainage conditions in late pregnancy (a) from the regions distal to the occlusion of the inferior vena cava when women are in the supine position, and (b) from the intervillous space of the placenta.

2. To study how occluded or free inferior vena caval return affects (a) systemic arterial blood pressure, (b) blood-flow distribution, and (c) filling of the principal blood reservoirs: placental circulation; venous system distal to the occlusion; and the aorta, representing the systemic arterial reservoir.

Materials and methods

Venous drainage and arterial-blood-flow conditions were studied at exactly the same moment in 31 women in late pregnancy by a concomitant iliocavography and arteriography. This procedure permits the highest economy of time, film, and radiation exposure. The patients tolerate the dual injection without any more apparent discomfort than that associated with an aortogram alone (*27*). The patient was informed of the aim of the study, the possible harm, and the potential benefits both for diagnosis and management of pregnancy and for a better understanding of the underlying disorder. Appropriate permission was obtained in all instances.

The angiographic techniques used were similar to those reported previously (*4, 9*). Briefly, they were as follows: The patient received Phenergan 25 mg intramuscularly as premedication and was placed on the X-ray table over a Schonander automatic 14-×-14-inch cut-film changer. A USCI 50 cm catheter, 8 to 7 French tapered tip, was inserted by Seldinger's replacement technique through the femoral artery and threaded up into the aorta (*33*). The femoral

arteries were not compressed for the purpose of selective filling of the uterine arteries (*15*), in in order not to interfere with the study of blood-flow distribution between placental circulation and parietal circuits. The maternal arterial pressure and heart rate and the fetal heart rate were checked repeatedly before and after angiography or were recorded by direct methods. According to accepted criteria, hypotension was defined as blood pressure below the normal values of 100 mm Hg systolic and 55 mm Hg diastolic; hypertension as blood pressure above the normal values of 140 mm Hg systolic and 90 mm Hg diastolic. For the concomitant iliocavography, both femoral veins were catheterized percutaneously with a Longdwell catheter needle and connected on each side to a 20 cc syringe filled with contrast medium. Bilateral injection produces better visualization of drainage routes.

An intra-aortic injection of 40 ml of 66.8 per cent sodium iothalamate was made in two seconds, using a 4 atmosphere Viamonte-Hobbs injector. After one second, when half of the dye was injected, a series of four exposures at intervals of one second was started; these were followed by two further exposures with a three-second interval. Concomitant iliocavography was done by injecting 20 ml of dye on each side, starting after the first arteriographic exposure in order to avoid superposition of the arteriographic with the phlebographic picture.

Technical data: 65 to 90 kilovolts, 45 milliamperseconds, focus-film distance 100 cm. The irradiation received by the fetus, measured by ionization chambers at the rectum, is equal to 15 to 30 mr during one exposure (*28*). The calculated irradiation received during a serial angiography is no more than 0.2 r, less than that received during routine diagnostic procedures involving a lateral exposure, such as pelvimetry.

Analysis of the angiograms: Routes of venous return

Free venous return was recognized by a wide and slightly dextro-convex shadow projected slightly to the right of the vertebral spine (*19*). The occluded inferior vena cava was diagnosed by blocked dye clearance at the confluence of the common iliac veins, absence of the inferior vena cava shadow, diverted venous return through collateral routes, and retrograde irrigation toward pelvic venous reservoirs with prolonged dye retention there.

The degree of distension of veins distal to the occlusion is directly related to the amount of blood sequestrated and serves as a useful indicator of the volume. Each visualized vessel was measured with a transparent scale gauged to an accuracy of 0.5 mm in segments of uniform width and was tabulated along with the length of the segment. A weighted mean width of the whole length of the vessel was calculated. In order to simplify the assessment of results, the widths of all veins on the right and left sides forming one functional unit were added together to indicate the capacity of the respective system. The following four functional units of venous return have been assessed: (1) the main drainage routes: external iliac veins, common iliac veins, inferior vena cava; (2) collateral routes: ilio-lumbo-azygos trunks, vertebral plexuses; (3) venous pelvic reservoirs irrigated in retrograde: internal iliac veins, segmental sacral communications (from one side to the other and through intervertebral anastomosis to the vertebral plexuses); and (4) placental drainage routes: ovarian plexuses, uterine veins.

The routes of venous return from the placenta are rarely visualized during the venous phase of an arteriography. In seven women with a placenta seated on the anterior uterine wall (*8*) and with a fetus with severe congenital anomalies incompatible with extrauterine life (e.g., acranius), contrast medium was injected directly into the intervillous space through a catheter inserted by percutaneous puncture. Correct location of the tip in the intervillous space was recognized by free passage of dark-red blood and by a distinctive feathery, fan-shaped configuration when dye was injected (*30*). Thirty ml of dye were injected in four to six minutes and exposures were repeated every 60 seconds. After finishing the infusion, two further exposures were taken with an interval of three minutes.

Arterial blood flow

The possible effect of occluded or free inferior vena caval return on arterial blood flow, preferential perfusion of the placenta, and blood mass distribution was studied in the concomitant arteriogram in a way similar to that described in previous publications (*4, 9*). The width of the aorta was considered in this study as representative of the capacity of the arterial system. Uterine compression could exert a greater effect on the anteroposterior diameter of the aorta than on the transverse, especially during systemic hypotension (*4*). A decreased density of dye in the retrouterine region of the aorta indicated a marked compressive effect and reduced capacity of this vessel, whereas a uniform opacity of the whole aorta indicated its normal filling of the arterial system.

The efficiency of placental circulation was assessed by the following indices:

1. The *number of visualized arteries* supplying the uterus: (a) main supply routes—uterine arteries, ovarian arteries, and round ligament arteries; (b) arcuate arteries; (c) spiral arteries supplying the placenta.

2. The respective *summed mean widths* for each of these groups of arteries.

3. The *index of preferential perfusion* of the placenta (*9*), calculated as the ratio between the length of the external iliac artery visualized in the same exposure.

4. The *surface of the intervillous space* visualized in the anteroposterior projection, measured in square centimeters, as an index of the blood volume contained in this vascular reservoir if the placenta is located on the anterior or posterior uterine wall. If the placenta is lateral, this measurement is unreliable.

On the basis of these criteria, placental circulation in each angiogram was classified as normal or insufficient.

Results

Venous return from the region distal to uterine compression

In 31 angiograms obtained in late pregnancy, iliocavography revealed a completely occluded inferior vena cava at the level of common iliac fusion in twenty-three women. Venous return was partly blocked, with pelvic venous reservoirs dilated, and was partly diverted through collateral routes, ilio-lumbo-azygos trunks, sacral segmental communications, and vertebral plexuses on the right and left side (Figures 2 and 5). In eight women, venous return through the inferior vena cava was free as in nonpregnant patients, and in these angiograms collateral routes were visualized poorly and retrograde irrigation not at all (Figure 6). These results confirm those of Kerr *et al.* (*23*).

The possible effect of free or obstructed venous return and blood sequestration in venous reservoirs on maternal systemic pressure is shown in Table 1.

All seven women with supine hypotension presented an occluded inferior vena cava, and no one with free venous return was hypotensive. However, venous return was occluded in the majority of late pregnant women who were normotensive (39 per cent) or even hypertensive (14 per cent). Therefore, there must be factors other than occluded venous return present in some of these women that reveal their tendency to hypotension. On the other hand, of the eight women with unobstructed venous return, seven presented arterial hypertension and one was normotensive. This incidence of hypo-, normo-, and hypertension is very unlikely to have arisen by chance and may be related to different conditions of venous blood

TABLE 1. Inferior vena caval return in 31 women in late pregnancy

	OCCLUDED		FREE	
CONDITION	NO.	% [a]	NO.	% [a]
Supine hypotension	7	22	0	0
Normotension	12	39	1	3
Hypertension	4	14	7	22
Total	23	75	8	25

[a] This incidence is not representative for the entire population. It is biased by a high incidence of patients with hypertensive or hypotensive disorders of pregnancy selected for this preliminary study.

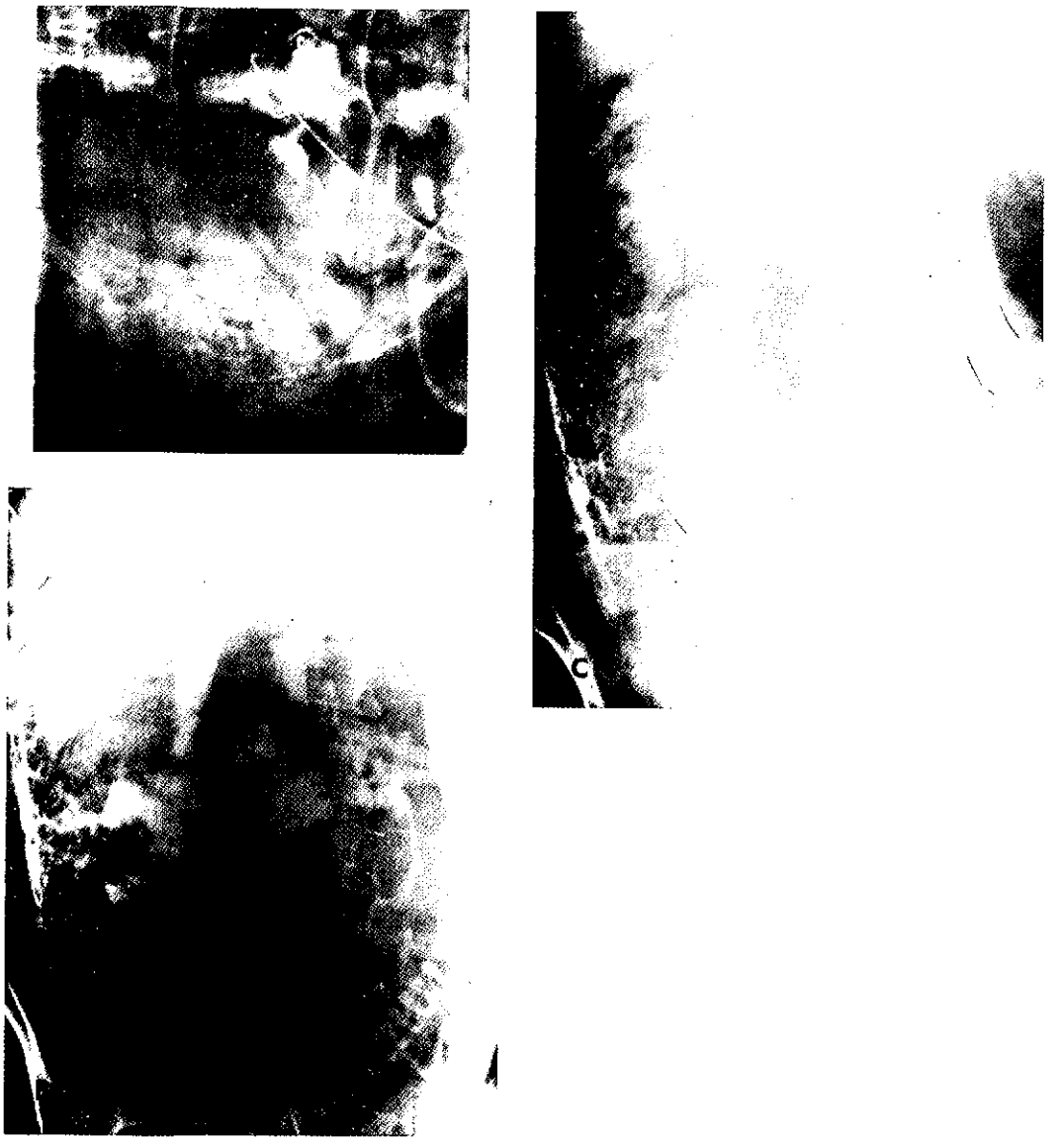


FIGURE 3. Clearance of contrast medium injected into intervillous space. Dye reaches marginal lakes on both sides through intramyometrial veins on right side (B, 6 min). Dye clearance is directed cranially through right ovarian plexus and not caudally through uterine veins. Two minutes after dye injection is completed, clearance through ovarian plexus is visualized (C, 8 min.)

return and consequent blood redistribution in late pregnancy.

Venous return from the placenta

Contrast medium injected into the intervillous space escaped either through the basal veins of the original cotyledon or passed to neighboring cotyledons and marginal lakes of the placenta. Figure 3A presents characteristic drainage conditions seen in a normotensive multipara with an anencephalic fetus at the thirty-seventh week. With a further infusion of dye, a network of myometrial veins was visualized draining the congested right marginal lake; on the left side the lake was not drained at all (Figure 3B). Dye clearance from stratified veins of the lateral uterine wall is far more prominent cranially through the right ovarian vein than caudally through the uterine vein. Of the seven patients studied, uterine and ovarian vein drainage in both directions was visualized in one during uterine contraction (*3*) and in another with a low seated placenta (*1*).

Concomitant iliocavography and arteriography

Figures 2, 5, and 6 illustrate conditions of venous return and arterial blood flow distribution that are typical for women with normotension, hypotension, and hypertension, respectively. Figure 2 was obtained in a normotensive primipara at the thirty-eighth week of a normal pregnancy. Dye injected into wide iliac veins on both sides is blocked at the common iliac confluence (Figure 2A). Inferior vena caval return is occluded, diverted slightly in retrograde through both internal iliac veins (Figures 2A and B) and through sacral segmental communications (Figures 2C and D), draining eventually through both vertebral plexuses Figure 2D). In spite of the scarcity of venous return routes, the aorta is well filled and opacified. All previously described vascular adjustments to pregnancy are visualized. The uterine arteries are joined by the ovarian arteries (Figure 2A) and form a virtual arterial crown of dilated arcuate and spiral branches surrounding the placenta. In comparison, the extraplacental myometrium is poorly supplied (Figure 2B). The contrast medium clears more rapidly through the internal iliac and uterine arteries (Figure 2A) than through the gluteal and external iliac arteries, which appear delayed and poorly opacified (Figure 2B). This preferential perfusion of the placenta results in multiple entries into the intervillous space and good placental irrigation (Figures 2C and D). Venous return through the ovarian plexuses, bypassing the vena caval occlusion (Figures 3 and 4) provides for an adequate cardiac output and uniform blood mass distribution between placental circulation, arterial system, and pelvic venous reservoirs. Adequate vascular adjustments in normal pregnancy provide for homeostasis of placental and systemic circulation.

Of the thirteen normotensive women only two had insufficient placental perfusion, one of whom was the patient with free inferior vena caval return (Table I). Except in these and in another with a double loop of cord around the fetal neck, all the babies were born in good condition (Apgar score 7 or above), with a weight adequate for the date.

Figure 5 was obtained in a nullipara at the thirty-ninth week of pregnancy who presented

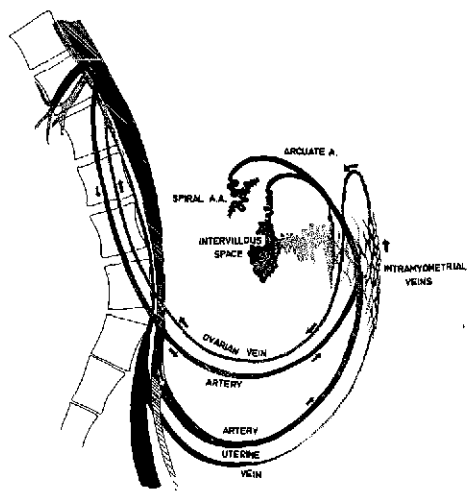


FIGURE 4. Schematic representation of circulatory conditions in normal late pregnancy, as visualized in angiograms (Figures 2 and 3).

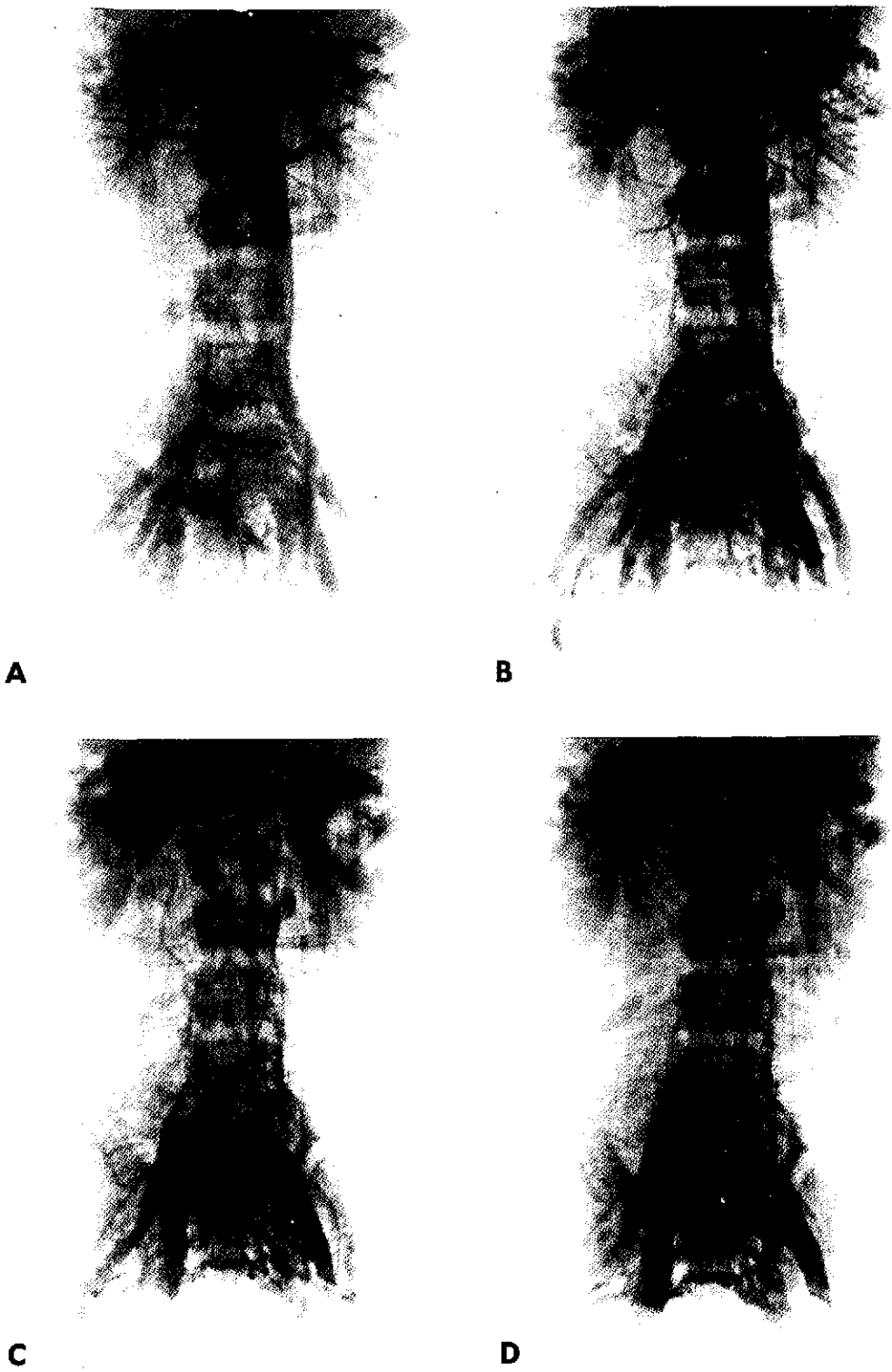


FIGURE 5. Circulatory conditions visualized during supine hypotension in a nullipara. Marked distension of pelvic venous reservoirs is seen sequestrating large amounts of blood from circulation for prolonged periods. Venous return diverted through left ilio-lumbar trunk and vertebral plexus (C, 6 sec; D, 12 sec) is scarce, with consequent systemic hypotension and placental ischemia. Aorta is displaced and poorly opacified at retrouterine region (A, 2 sec). Dye is cleared through external iliac and gluteal arteries (B, 4 sec), while uterine and placental circulation are poorly visualized and do not act as bypass for venous return.

supine hypotension 95/50 mm Hg during the angiographic study. The most prominent vessels in the angiographic picture are the markedly dilated pelvic venous reservoirs distal to the occlusion of the inferior vena cava. The internal iliac veins are interconnected from one side to the other through sacral segmental communications that drain further through vertebral plexuses. Venous return is scarce, diverted through the left iliolumbar trunk and left vertebral plexus. In these vast pelvic reservoirs, large amounts of blood can be removed from circulation and sequestrated, resulting in systemic arterial hypotension. In the concomitant arteriogram, the aorta is displaced, narrowed, and poorly opacified in the retrouterine region, suggesting marked compression and poor filling. Dye clears more rapidly through the external iliac arteries than through the internal. There is no preferential perfusion of the placenta.

Placental circulation was insufficient in five of the seven women who presented supine hypotension during angiography. In the remaining two women, hypotension lasting more than 20 minutes tended to recover spontaneously and placental perfusion was good, with wide spiral arteries. All the babies were born in good condition (Apgar score 7 or higher).

Figure 6 was obtained in a nullipara with hypertension 170/120 mm Hg during angiography. The inferior vena cava is visualized as a wide vessel to the right of the vertebral column. The iliac veins are collapsed, and dye injected here clears without any retrograde irrigation or sequestration, suggesting rapid drainage through the vena cava toward the heart. On the arterial side the aorta is densely opacified in the retrouterine region (Figure 6A), efficiently withstanding uterine compression. In a pattern simulating that seen in nonpregnant women, dye clears more rapidly through the external iliac and gluteal arteries than through the uterine artery. The latter is visualized poorly on the left side only; its arcuate branches are straight and tapering (Figures 6B and C). There are only a few spiral arteries and entries into the intervillous space, with a limited spread of dye (Figure 6D). With a free vena caval return, the blocking effect on parietal circuits that diverts blood flow towards placental circulation is missing. Circulating blood is driven toward the heart, overloading the arterial system and resulting in hypertension.

Of the eight angiograms with free vena caval return (seven women with hypertension and one with normotension), five presented insufficient placental circulation. The newborns were small for the date and depressed, with an Apgar score of 6 or below. Two of them died a few hours after delivery. The remaining three women with hypertension and free vena caval return had good placental perfusion, suggesting that vasodilatation of spiral arteries caused by hormonal and metabolic factors may be sufficient in diverting blood flow toward the placenta. The four women with hypertension and an occluded inferior vena cava had good placental perfusion, except for one with angiosclerotic changes, partially blocked placental circulation, and a dystrophic baby small for the date. In pregnancies with good placental circulation, the course of hypertension was usually mild and the babies were born in good condition.

While uniform distribution of the circulating blood mass characterized normal pregnancy, a predominant blood sequestration in venous reservoirs distal to vena caval occlusion, with systemic and placental ischemia, was typical in supine hypotension. Inversely, overloading of the arterial system, with empty pelvic venous reservoirs and placental ischemia, was seen in hypertensive disorders of pregnancy. Table 2 presents the mean widths of the principal blood reservoirs as indices of their distension in the three groups of women with hypo-, normo-, and hypertension. Filling of the intervillous space indicates normal or insufficient placental circulation. A wide mean width of the inferior vena cava was found in women with hypertensive disorders of pregnancy, as compared to a low value in normotensive patients and an absence of this vessel in angiograms obtained during supine hypotension. Inversely, the mean

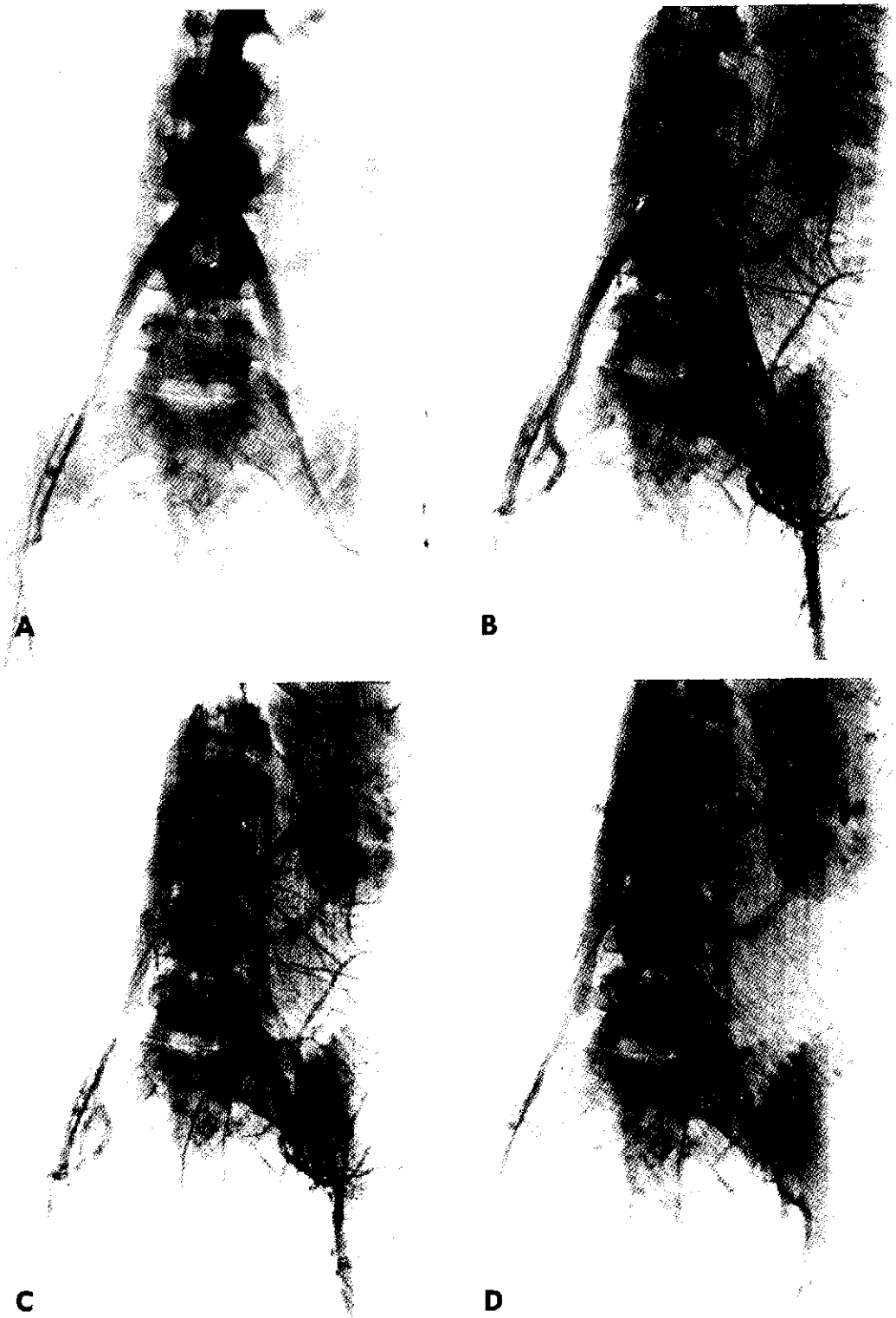


FIGURE 6. In hypertensive nullipara, venous return is free, inferior vena cava is wide, and pelvic veins are collapsed (A, 2 sec; C, 6 sec). Dye injected into aorta clears through parietal circuits, similar to conditions seen in nonpregnant women, while uterine artery is poorly visualized, straight, and tapering (B, 3 sec; C, 6 sec). Entries into intervillous space are scarce and dye spreads poorly (D, 10 sec). Blood is driven through inferior vena cava to heart and evidently overloads arterial system.

TABLE 2. Mean widths of the principal vascular reservoirs during pregnancy

CONDITION AND NO.	INFERIOR VENA CAVA, MEAN±SD	PELVIC VENOUS RESERVOIRS, MEAN±SD	AORTA, MEAN±SD	PLACENTAL CIRCULATION NO. NORMAL	PLACENTAL CIRCULATION NO. INSUFFICENT
Supine hypotension (7)	0.0 ± 0.0	11.2±3.5	16.0±2.3	2	5
Normotension (13)	0.05± 2.2	6.5±3.9	14.5±2.1	11	2
Hypertension (11)	16.0 ±12.0	2.8±4.1	16.5±1.7	6	5

width of pelvic venous reservoirs was greatest in the group of women with supine hypotension and smallest in the group with hypertension. Surprisingly, the aorta did not show clear differences in width between the three groups of hypo-, normo-, and hypertensive women. However, the density of opacification was clearly decreased in the retrouterine region of the aorta during hypotensive disorders of pregnancy, suggesting that compression may decrease the capacity of the aorta mainly in its anteroposterior diameter and not in its width.

The significance of the difference in widths of vascular reservoirs between pregnant women with supine hypotension on the one hand, and the combined group of normo- and hypertensive women on the other, was analyzed by the student's t test (Table 3). The difference for the inferior vena cava is obvious. In patients with supine hypotension, the pelvic venous reservoirs are significantly wider and the time of dye clearance significantly longer than in both normotensive and hypertensive women.

Comment

Occlusion of the inferior vena cava is a common finding when the mother is in the supine position (*23*). Alternative routes of venous return through vertebral plexuses and iliolumbar trunks are narrow, and can hardly explain how blood returns to the heart and why supine hypotension is rare if occluded vena cava is common in late pregnancy. The studies by concomitant iliocavography and abdominopelvic arteriography presented here have shown that a diversion of blood flow through placental circulation may compensate for the insufficient vena caval return. Paradoxically, occlusion of the inferior vena cava does not impede placental circulation but may even improve it by blocking parietal pelvic and lower-extremity circuits that otherwise compete with the placenta for blood distribution. Grafted in parallel to these circuits, placental circulation offers less resistance to flow because its vascular bed dilates under the influence of local metabolic and hormonal factors of feto-placental origin, and because the

TABLE 3. Difference between widths of vascular reservoirs

	MEAN ARTERIAL PRESSURE (MM HG)	INFERIOR VENA CAVA (MM)	PELVIC VENOUS RESERVOIRS (MM)	TIME OF DYE CLEARANCE (SEC)	AORTA (MM)
Supine hypotension	93/91	0.0± 0.0	11.2±3.5	13.6±2.9	16.0±2.3
t test		[a]	5.1491 [a]	4.0116 [a]	0.6478 [b]
p			0.0010	0.0010	
Normotension and hypertension	130/86	7.1±11.0	5.4±5.5	8.2±2.9	15.4±2.0

[a] Significant.
[b] Not significant.

placenta finds an alternate route of venous return through ovarian plexuses, bypassing the retrouterine caval occlusion. This idea has been confirmed by visualization of drainage routes from the intervillous space through the ovarian plexuses to the region of the inferior vena cava proximal to the occlusion, rather than through uterine veins against the pressure gradient to pelvic reservoirs distal to vena caval occlusion.

The resulting preferential perfusion of the placenta is considered an important circulatory adjustment of pregnancy. In spite of aortocaval obstruction, it maintains placental blood flow on a level sufficient to cover the metabolic needs of the rapidly growing fetus and provides for adequate venous return to the heart to maintain normal cardiac output and arterial blood pressure. One further effect of the homeostatic function of placental circulation is a uniform distribution of the circulating blood mass between the principal vascular reservoirs, pelvic veins, placental circulation, and arterial system. This function of the placenta as a circulatory bypass and moderator of blood distribution fails in hypotensive and hypertensive disorders of pregnancy.

Supine hypotension was observed only in those women with occluded vena caval return in whom pelvic venous reservoirs distal to the occlusion dilated markedly, sequestrating large amounts of blood from circulation. Low smooth muscle tone of the vascular wall, attributable to hormonal factors of pregnancy (*24*), may explain increased venous compliance and the appearance of supine hypotension. The occluded pelvic reservoirs may accept and pool large amounts of blood without creating resistance to divert the flow through the placental circulation. Systemic hypotension, which led to cerebral ischemia and blackout, resulted. However, this dramatic picture did not seriously affect the fetus. Hypotension was usually of short duration, easily improved by a change in the patient's position. Even if the patient was obliged to maintain the supine position, placental circulation and systemic blood pressure were eventually re-established by wide opening of spiral arteries (*4*).

In hypertensive disorders of pregnancy, a pattern of blood flow simulating that seen in nonpregnant women was frequently observed. Venous return through the inferior vena cava was free, with no sequestration in pelvic venous reservoirs, while arterial blood flow was directed through parietal pelvic circuits and lower extremities and was not diverted to the placenta. Preferential perfusion of the placenta was rarely seen. In these conditions of an unobstructed venous return, blood was directed predominantly toward the arterial system, whose capacity and compliance was reduced because of the increased vascular tone, resulting in hypertension. In patients with free vena caval return and poor placental perfusion, the course of hypertensive pregnancy was severe and the newborns were small for the date and depressed. In hypertensive patients with an occluded inferior vena cava, placental perfusion was usually favorable and the course of the disorder was mild.

Failure to develop circulatory adjustments to pregnancy may be an important and not sufficiently recognized factor in the pathological mechanism of hypertensive disorders of pregnancy. This idea, although an oversimplification of a complex problem, may suggest new therapeutic approaches. By simulating the physiological conditions of obstructed vena caval return frequently absent in hypertensive disorders of pregnancy, circulatory homeostasis of placental and systemic circulation might be re-established.

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TEST OF FETAL TOLERANCE TO INDUCED UTERINE CONTRACTIONS FOR THE DIAGNOSIS OF CHRONIC DISTRESS[1]

S. V. Pose, J. B. Castillo, E. O. Mora-Rojas, A. Soto-Yances, and R. Caldeyro-Barcia[2]

The uterine contractions of normal labor produce a reduction of blood flow in the uterine vessels and in the intervillous space both in women (*2, 4, 8*) and in monkeys (*21*). It has also been demonstrated in both species (*1, 18, 19, 20*) that they produce a fall in the pO_2 values of fetal tissues (Figure 1) and in the percentage of hemoglobin saturation in the fetal blood (*22*). These results are in accord with the working hypothesis that dips II[3] are produced by transient fetal hypoxia caused by uterine contractions (*8, 11, 15*). Dips II will be produced as a consequence of vagal stimulation when fetal pO_2 falls below a critical level. This level is of 18–20 mm Hg measured in the capillary blood of the fetal scalp (*11*) (Figure 2).

In normal pregnancies (Figure 2A) the pO_2 in the fetal tissues is high, about 24 mm Hg (*11*) between contractions, in the capillary blood of the fetal scalp. Under these normal conditions the falls produced by normal uterine contractions of labor do not reach the critical level required to stimulate the vagus nerve and dips II are not produced. The "fetal reserve" of oxygen is high.

In cases of fetal hypoxemia the "base line" of fetal pO_2 is lower than normal (Figure 1) and closer to the critical level (B and C in Figure 2). A transient reduction of the fetal pO_2 similar in amplitude to that produced by the contractions of normal labor will drive it below the critical level and a dip II will occur.

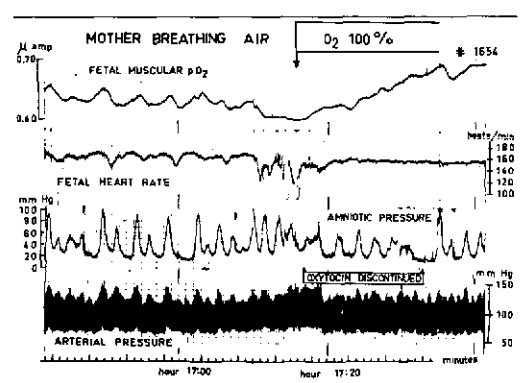

FIGURE 1. Records of fetal muscular pO_2 (polarographic method), FHR, and amniotic fluid pressure. Nullipara, labor induced with intravenous infusion of oxytocin at 2 mU/min. Three different levels of fetal pO_2 can be observed: (1) when mother breathes room air and uterine tonus is normal; (2) during period of hypertonus in amniotic fluid pressure; and (3) when mother breathes pure oxygen. Dips II are evident in first period, amplitude increases during second period, and they are not present in third one (*1*).

[1] This study received support from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization, and from grant HD 00222-06 of the National Institute of Child Health and Human Development, Bethesda, Md., U.S.A.

[2] Presented by Dr. Pose.

[3] Transient falls in fetal heart rate occurring immediately after a uterine contraction in such a way that the bottom of the dip occurs 30 to 60 seconds after the peak of the contraction (*8, 9, 10*). Hon's term "late deceleration" (*15*) is a synonym. Dips II are considered a sign of fetal distress (*8, 9, 10, 11, 15, 16*).

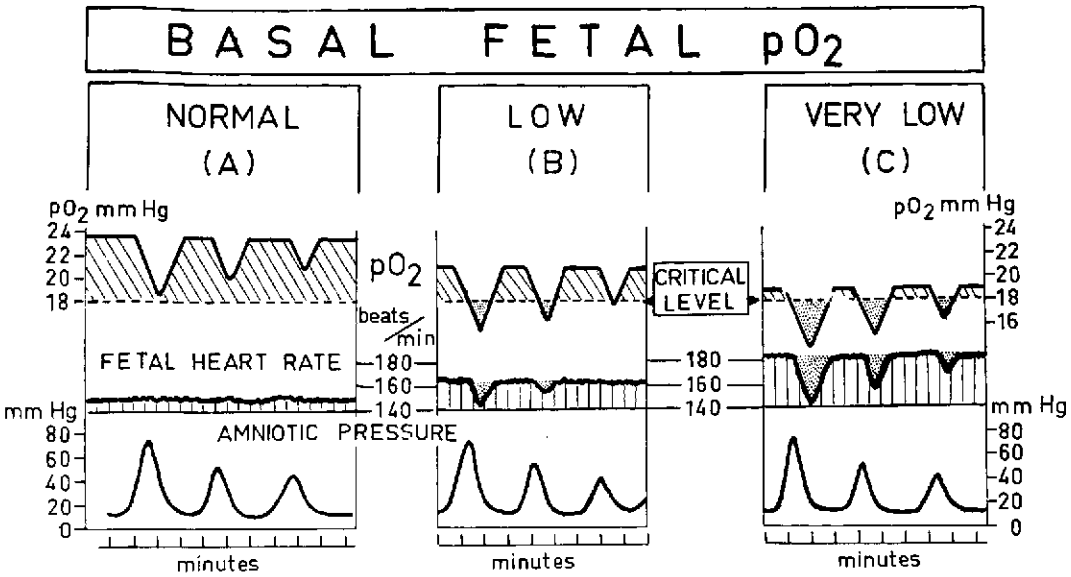

FIGURE 2. Highly schematic representation of working hypothesis concerning effects of uterine contractions on fetal pO_2 and FHR (dips II). Each contraction causes a transient fall in fetal pO_2, proportional in amplitude to rise in amniotic fluid pressure caused by contraction. Basal fetal pO_2 is that recorded between transient falls. A, normal conditions, similar to those of third period in Figure 1. B and C, abnormally low pO_2 as in periods 1 and 2 of Figure 1. In cases of chronic fetal distress, the condition of fetus could be similar to those in B and C.

The "fetal reserve" of oxygen is lower than normal.

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

Material and methods

Thirty-three experiments were performed in twenty pregnant women between the thirtieth and fortieth weeks of gestation. Nineteen of these patients had associated pathology that can produce chronic fetal distress, such as arterial hypertension, toxemia of pregnancy, and diabetes mellitus (Table 1).

In all the cases the amniotic fluid pressure and fetal heart rate (FHR) were recorded simultaneously. In twenty-eight of these records the fetal heart rate was obtained by an external method (Figure 3), based on the Doppler effect with ultrasonic waves (*13*). The FHR was obtained beat to beat with an integrator (model Elemedix, Uruguay). In six cases in which the

TABLE 1. Maternal pathology capable of producing chronic fetal distress in 20 subjects tested [a]

PATHOLOGY	NUMBER
Diabetes Class B	2
Diabetes Class D	6
Diabetes Class F	1
Chronic hypertensive disease	2
Chronic hypertensive disease with toxemia superimposed	3
Acute toxemia	1
Tetralogy of fallot	1
Sickle-cell anemia	1
Systemic lupus erythematosus	1
Rh isoimmunization	1
Myasthenia gravis	1

[a] See text.

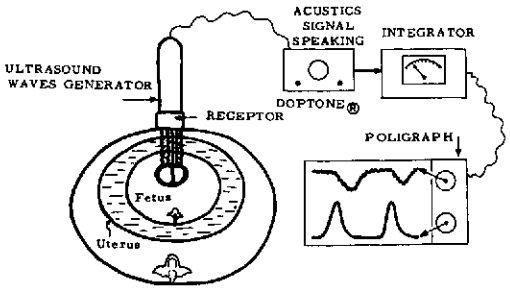

FIGURE 3. Method employed to record FHR using ultrasonic waves (Doppler effect).

interruption of pregnancy had already been indicated, the FHR was obtained using the R wave of the fetal ECG recorded with an electrode placed in the fetus through the abdominal wall of the mother, as previously described by Caldeyro-Barcia *et al.* (*8, 9*). In two of these patients, simultaneous records of FHR using both techniques were obtained (Figure 4). These records were very useful for demonstrating the accuracy of the external method.

After a continuous recording of one hour

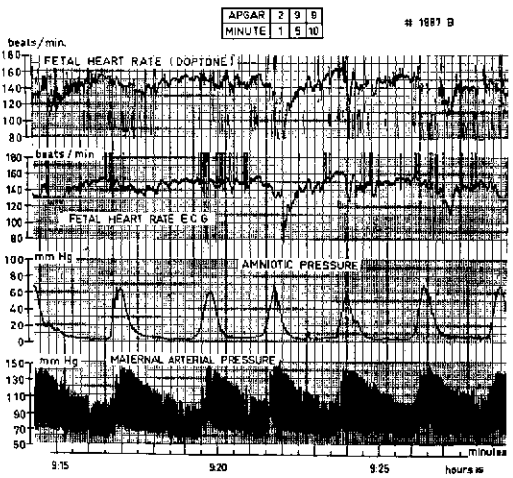

FIGURE 4. Diabetic (Class D) multipara, age 40, thirty-sixth week of pregnancy. Polyhydramnios. Induction of labor with oxytocin infusion commenced at hour 1:53, presently 4 mU/min. Artificial rupture of membranes at hour 5:16; outflow 3,000 ml of amniotic fluid. Cervical dilatation 4 cm, station -5. Cesarean section at hour 11:05. Female newborn 2,560 g, crown-heel length 46 cm. Simultaneous record of FHR using both external method (upper row) and one electrode placed in fetus (second row).

(Figures 5 and 7), uterine contractions similar to those of normal labor were produced by the administration of oxytocin in a continuous intravenous infusion (Figures 6, 8, 9, 11, 12, and 15) at rates ranging from 4 to 16 mU/min depending on the uterine response. The induced uterine contractility was maintained for 30 or more minutes. However, as soon as dips II appeared, the oxytocin infusion was immediately discontinued (Figures 6, 8, 9, 11, and 12). FHR and amniotic fluid recordings were continued in all cases until uterine contractility recovered the values observed in the basal conditions. Prior to the oxytocin administration special attention was paid to the characteristics of the uterine cervix so as to avoid uterine stimulation if the cervix was ripe and induction of labor was not previously indicated.

In ten of our patients the test was repeated one or more times (maximum of four records in the same patient) at a one-week interval (Figures 4, 7, 8, 9, 11, 12, and 13). In all the patients the indications for the time and procedure for delivery were decided by the attending physician according to clinical considerations, regardless of the result of the test.

After delivery the condition of the newborn was evaluated by the Apgar score at the fifth minute of life. The fact that cesarean section was the method of delivery used in fourteen

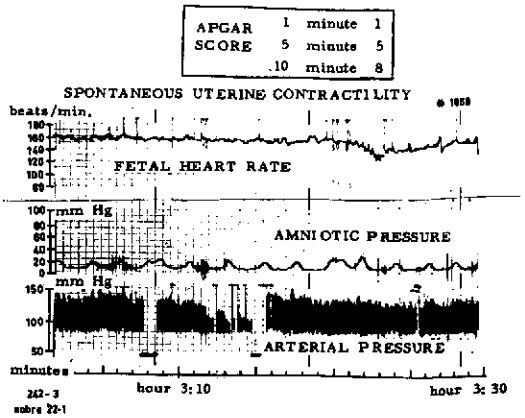

FIGURE 5. Diabetic (Class D) primipara, age 36, thirty-eighth week (265 days) of pregnancy. Records obtained before uterine contractions were induced (see also Figure 8 and 9).

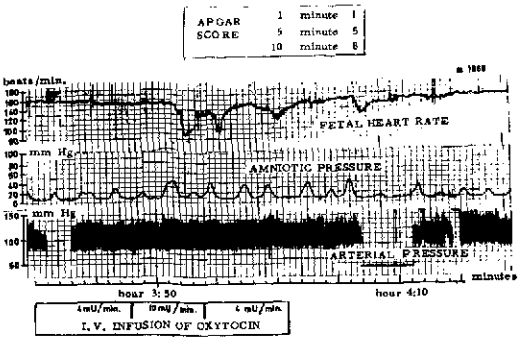

FIGURE 6. Continuation of record in Figure 5. Positive test. Cesarean section performed at hour 5:50. (See also Figure 9.)

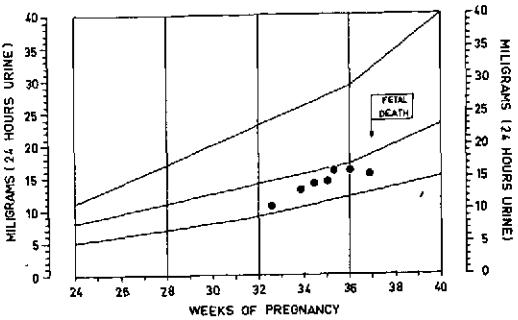

FIGURE 10. Urinary excretion of estriol in same patient as Figures 7 to 9. Moment of fetal death is illustrated.

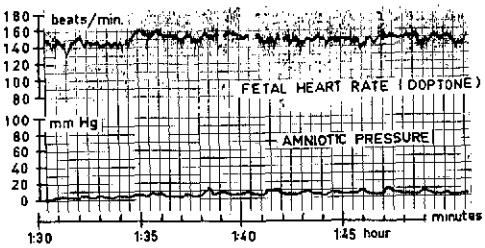

FIGURE 7. Juvenile diabetic (Class F), age 25, thirty-second week (224 days) of pregnancy. Record obtained before induction of uterine contractions. (See also Figures 8 to 10.)

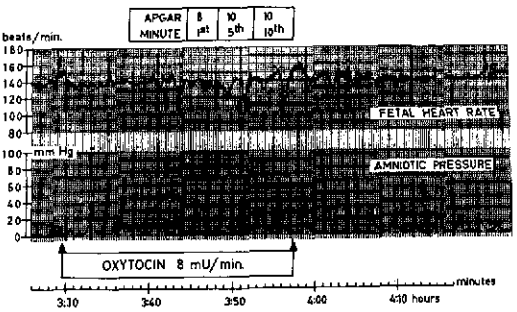

FIGURE 11. Chronic arterial hypertension treated with bed rest and reserpine. Thirty-fourth week (236 days) of pregnancy. Positive test. Cesarean section at 38 weeks (265 days). Two additional positive tests were obtained at 34 and 36 weeks. (See also Figures 12 to 14.)

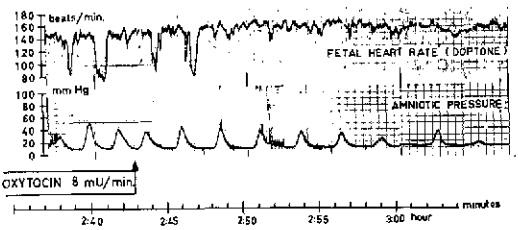

FIGURE 8. Continuation of record in Figure 7. Positive test.

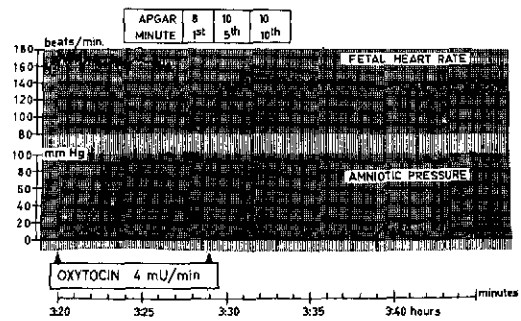

FIGURE 12. Same case as in Figure 11. Record obtained at thirty-seventh week (262 days). Fall in FHR is similar to those described by Hon (*14, 15*) in cases of cord compression.

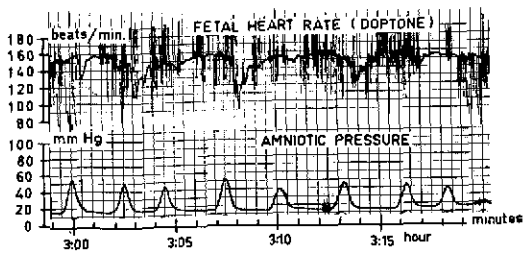

FIGURE 9. Same case as in Figures 7 and 8. Second positive test obtained in thirty-third week (231 days) of pregnancy.

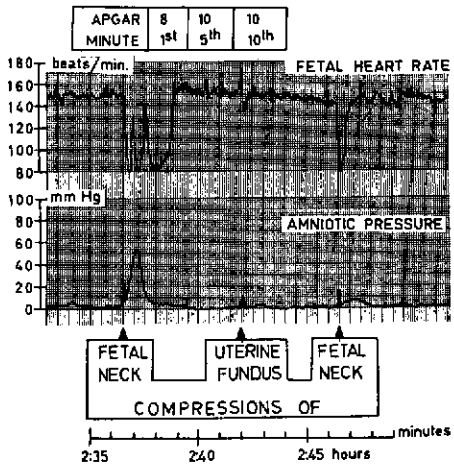

FIGURE 13. Same record as in Figures 11 and 12. Falls in FHR produced by compression of fetal neck. In cesarean section performed immediately after record, two tight loops of umbilical cord were found around neck.

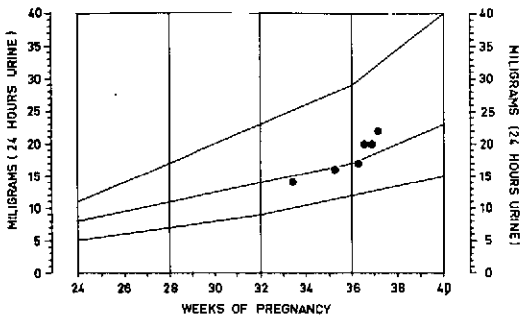

FIGURE 14. Estriol excretion in same patient as Figures 11 to 13.

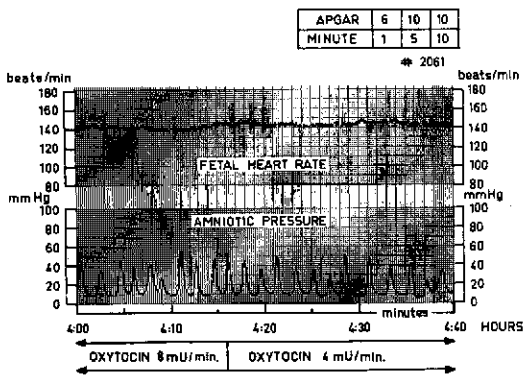

FIGURE 15. Diabetic (Class D) primipara, age 23, thirty-five weeks (245 days) of pregnancy. Normal uteroplacental angiography at day 232. Negative test. Cesarean section following test. See also Figure 16.

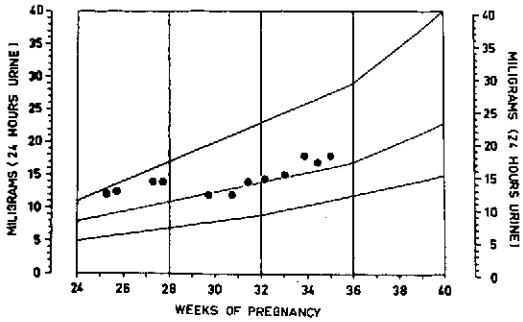

FIGURE 16. Urinary estriol excretion in same patient as Figure 15.

of the twenty cases was an additional consideration in selecting the fifth-minute score, in order to overcome the possible effect of general anesthesia of the mother on the newborn.

In seven patients (Table 2) a uteroplacental angiography was performed according to the technique established by Bieniarz (2, 3).[4] In seven patients the urinary elimination of estriol in 24 hours was measured using the colorimetric technique of Brown (5) (Table 2, Figures 10, 14, and 16).

Results

Interpretation of the test

The test was considered *negative* when uterine contractions with a peak pressure of 35 mm Hg or more did not cause dips II (Figure 15). It was considered *positive* when dips II were produced (Figures 4, 6, 8, 9, 11, and 12). In

TABLE 2. Correlation between results of tolerance test and condition of newborn [a]

RESULT OF TEST	APGAR SCORE, 5TH MINUTE 0–6	7–10	TOTAL
Positive (dips II present)	6	2	8
Negative (dips II absent)	0	12	12
Total	6	14	20

[a] $p < 0.001$.

[4] The angiographies were obtained by Dr. E. Curuchet and interpreted by Drs. J. Bieniarz and H. Julio.

the positive cases, 38 per cent of the contractions with a peak pressure between 15 and 75 mm Hg produced dips II. One attempt was made to study the possible correlation between the intensity of the contractions and the production of dips II. In the positive tests the contractions of a peak pressure higher than 15 mm Hg were grouped in intervals of 10 mm Hg (Figure 17). In a few cases, weak contractions of 15 to 25 mm Hg produced dips II; among all the cases analyzed, 12 per cent of the contractions of this intensity caused dips II. The percentage rose to 39 per cent in the group with contractions of 25–35 mm Hg and to 49 per cent in the group with 35 to 45 mm Hg. There is no significant difference between this last percentage and those of the groups with contractions of higher peak pressures.

Table 2 illustrates the correlation between the results of the test and the condition of the newborn. In all twelve patients in whom the test had been negative, the newborns were vigorous (Apgar score 7–10). In six of the eight patients who had one or more positive tests, the newborns were depressed (Apgar score 6 or less). The correlation between the condition of the newborn and the test was highly significant ($p<0.001$).

The group of six depressed newborns includes three cases of fetal death. In two of these the fetus died *in utero* between the thirty-sixth and thirty-seventh weeks of pregnancy, three and seven days respectively after the last test was performed (Figures 7 to 10 illustrate one of these cases). Neither patient was in labor at the moment of the fetal death. In the third patient, the fetus died during induced labor at the thirty-sixth week of gestation, three days after a positive test. This was a case of chronic arterial hypertension with superimposed toxemia.

In two of the eight positive tests a vigorous newborn was obtained. One of these patients was a diabetic Class D (White's classification) for whom induction of labor was indicated by the attending physician. Dips II appeared during labor four hours after the onset of the induction; at this time the intensity of the contractions was higher than normal (hypersystolia) (Figure 4). Since no free period of time elapsed between the test and the onset of labor, the result of the test was classified as positive. The other case was one of chronic hypertensive disease with superimposed toxemia. Three positive tests were obtained at the thirty-third (Figure 11), thirty-fifth, and thirty-seventh (Figure 12) weeks of pregnancy. In the last of these the falls in FHR proved similar to those described by Hon (*14, 15*) for cases of cord compression. In this patient, the compression of the fetal neck through the abdominal wall produced variations in FHR indicating a possibility that the cord was coiled around it (Figure 13). At cesarean section performed immediately after this record, two loops of the cord were found to be tightly wound around the fetal neck.

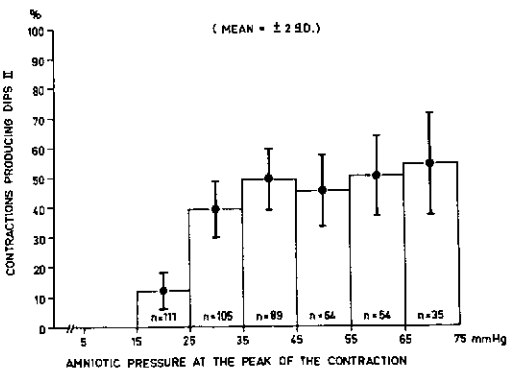

FIGURE 17. Percentage of uterine contractions producing dips II in cases classified as positive (see text).

Uteroplacental angiography

In three of the seven cases studied with this method (Table 3), insufficient uteroplacental circulation (*2, 3*) coincided with a positive test and a depressed newborn (the records in Figures 5 and 6 correspond to one of these cases). In two other patients, a normal angiography coincided with a negative test and a vigorous newborn (Figure 15). There was no correlation in the results of the other two cases, which showed normal angiographies but had positive tolerance tests. Of these patients, one delivered a vigorous newborn (the fetus with a loop of

TABLE 3. Results of uteroplacental angiography and/or urinary elimination of estriol in 10 patients

CASE NUMBER	MATERNAL PATHOLOGY	RESULT OF TEST	UTEROPLACENTAL ANGIOGRAPHY	URINARY ESTRIOL	APGAR SCORE, 5TH MINUTE
1868	Diabetes D	Positive	Insufficient circulation	—	5
1941	Acute toxemia	Positive	Insufficient circulation	—	Intrapartum fetal death
2031	A. hypertension + toxemia	Positive	Insufficient circulation	Below normal	5
2027	Diabetes F	Positive	Normal	Normal	Intrauterine death at 37 weeks
1935	A. hypertension + toxemia	Positive	Normal	Normal	10
1980	Myasthenia gravis	Negative	—	Below normal	10
2036	A. hypertension	Negative	—	Normal	7
2037	A. hypertension	Negative	—	Normal	9
2053	Diabetes B	Negative	Normal	—	8
2061	Diabetes D	Negative	Normal	Normal	10

cord around the neck shown in Figures 11, 12, and 13); the other fetus, of a diabetic patient, Class F, died *in utero* (Figures 7, 8, 9, and 10).

Urinary elimination of estriol in 24 hours

This technique is recently being used in our laboratory. Our normal values are very similar to those published by Brown (*5*).

We studied the urinary excretion of estriol in seven patients (Table 3). In three positive tests, the estriol values were low in one patient and normal in two. The low value corresponded to a depressed newborn. One normal value belonged to a patient with two positive tests and fetal death *in utero* (Figures 7, 8, 9, and 10). The other normal value was from the case with a positive test, nuchal cord, and vigorous newborn (Figures 11, 12, 13, and 14).

In four cases with negative tests and vigorous newborns, estriol values were normal in three (Figures 15 and 16). In the remaining case the estriol excretion fell progressively from 12 to 7 mg in 24 hours in the four determinations made between thirty-fourth and thirty-sixth weeks, at which time labor was induced.

Passage of meconium

The presence of meconium was determined at the time of the amniotic puncture, during labor or cesarean section. It was found in two cases. In one of them, meconium appeared three days after a positive test, during induced labor and before fetal demise. The other case had a negative test and a vigorous newborn; the mother suffered from sickle-cell anemia.

Discussion

The fact that uterine contractions like those of a normal labor produce dips II (positive test) may be explained by a lowering in the fetal oxygen reserve (*1, 11, 18, 19, 20*) probably due to a decrease in feto-maternal exchanges. In these circumstances it is logical to expect that the fetus will not tolerate the aggression of labor. To avoid intrapartum fetal distress, these fetuses should therefore be delivered by cesarean section.

With the results obtained from this study, it may be concluded that a positive test indicates a high probability of a depressed newborn, even if a cesarean section is performed. Taking this in connection with the fact that two fetuses died three and seven days after a positive test, it may be stated that most probably the fetus is in a precarious condition. It cannot be established for how long the fetus will be able to endure this situation.

In cases in which the interruption of pregnancy before term is indicated because of asso-

ciated maternal pathology, a doubt arises as to the most appropriate time for such an interruption. Ideally, it should be deferred as long as possible, to avoid the risks of prematurity. A positive test of fetal tolerance to uterine contractions is an additional argument in favor of the interruption of pregnancy. A negative test indicates a good chance of obtaining a vigorous newborn. Spontaneous or induced labor may be allowed. However, this does not mean that fetal distress will not occur during labor. In the case shown in Figure 4 signs of fetal distress (dips II) appeared even when the fetus had tolerated uterine contractions of labor during four hours.

Uteroplacental angiography and the test of fetal tolerance to uterine contractions seem to complement each other. The advantages of the test are that it is simpler to perform and that it can be repeated several times in the same patient, thus making possible an early discovery of fetal distress during pregnancy.

The experience in our laboratory with the values of urinary excretion of estriol is insufficient. The fact that in two cases there was no agreement between the estriol values and the condition of the newborn, even though suggestive, does not provide enough support to the viewpoint of those (*17*) who minimize the importance of estriol excretion in the management of chronic fetal distress.

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FETAL TOLERANCE TO MATERNAL EXERCISE HYPOXIA

Z. K. Štembera

In all countries where perinatal care is well developed, the importance of the prenatal period is more and more being taken into account. An analysis of perinatal mortality in Czechoslovakia (Table 1) shows that of 204,927 newborns weighing more than 2,500 grams born in the country in 1967, 1,550 died perinatally—a rate of 7.5 per 1,000. Almost half of these died *in utero* in the last weeks of pregnancy, even before the beginning of labor. Of those who died during delivery or during the first seven days of life, the cause was prenatal in origin in 80 per cent (*4*). Even more important, from the standpoint of parents and society, are the cases in which intrauterine hypoxia did not cause perinatal death but affected the infant's further development unfavorably; exact data on these are lacking, but it is estimated that their number is about double the figure for perinatal mortality. We therefore realized the necessity of establishing a method to enable us to determine, in women with high-risk pregnancies, the existence of fetal distress that so far could not be discovered by the usual diagnostic methods.

From two earlier reports (*1, 2*) we knew that uteroplacental circulation decreases in various pathological conditions that hinder the intrauterine development of the fetus (for example, late toxemia) and also that maternal exercise decreases this circulation, with the fetus responding by a change in heart rate. These findings, we thought, would be useful for the timely detection of intrauterine fetal distress in women with high-risk pregnancies. We presumed that the greater the distress of the fetus, the more it would respond to hypoxia provoked by an acute maternal physical load.

We started by using a step test as the physical load in 50 women. Fetal heart sounds were recorded in the form of a phonocardiogram on the Galileo polygraph, at 24 five-second intervals immediately before and immediately after the test; thus, 10 sounds in five seconds would mean a rate of 120 a minute, and so on. In most cases there were conspicuous changes in heart rate where the fetuses had been distressed (*3*).

On a second occasion, 40 women also pedaled for three minutes on a stationary bicycle fixed to

TABLE 1. Perinatal mortality in Czechoslovakia, 1967

	TOTAL		WEIGHT 2,500 G OR OVER	
	NO.	RATE PER 1,000	NO.	RATE PER 1,000
Births	217,421		204,927	
Perinatal death	4,696	22.1	1,550	7.5
Late fetal death				
During pregnancy	1,319	6.2	675	3.3
During labor	389	1.9	248	1.2
Early neonatal death	2,988	14.0	627	3.0

the bed, so that recording could continue throughout the test. This was to ascertain whether a change in heart rate occurred during the exercise. But the majority of cases presented changes only after the termination of the physical load. In a minority of cases, the changes had occurred before the end of the test and continued in the first minutes thereafter; these cases did not differ from the others (to be published). In most of these 40 cases as well, an association was found between changes in the fetal heart rate and intrauterine distress.

Table 2 shows the criteria used for evaluating the results in each case and the score given for each alteration in heart rate. A total score of 0 or 1 represents a negative test. A score of 2 or above is positive and demonstrates fetal distress. The reliability of the test increases if it is repeated after one to three days; if the score remains high or rises, the likelihood of fetal distress becomes higher, and if it remains low or if an elevated score drops to 0 or 1 the fetus is developing normally.

TABLE 2. Criteria for scoring step test

	SCORE
A. *Period of 24 five-second intervals before test*	
Absolute frequency:	
1. Bradycardia 2 x 9 or lower	1
2. Tachycardia 3 x 14 or higher	1
Variation of frequency:	
3. 2 x divergence of 3	1
or	
2 x divergence of 4	2
or	
"Silence" (unvarying at least 20 times)	2
B. *Period of 24 five-second intervals after test*	
Absolute frequency:	
4. Bradycardia 3 x 10	1
or 2 x 9	2
or 2 x 8 or lower	3
5. Tachycardia 3 x 14 or more	1
Variation of frequency:	
6. "Silence (unvarying at least 20 times)	2
Decrease of lowest rate after test in comparison with lowest rate before test:	
7. Two levels from 1	1
or	
Several levels from 1	2
or	
Two levels from 2	2
or	
Several levels from 2	3

The clinical condition of the newborns and the occurrence of symptoms of intrauterine hypoxia (meconium staining and bradycardia as shown by dips II) were compared with the heart rate changes after the step test in the 90 cases of the two groups mentioned.

As an illustration, let us take the case of a 28-year-old patient whose previous pregnancy had ended in death *in utero,* with no evident cause, three days before predicted term. In the thirty-seventh week of pregnancy she came to the hospital because of a transitory rise in blood pressure to 150/100 mm Hg. After two days of bed rest only, her blood pressure returned to normal and she was in no difficulty. The following week a step test was performed (Figure 1). Before the test an almost unvarying rate of 132 beats/min was recorded at 24 five-second intervals. Afterwards there was a brief period of bradycardia; a rate of 96 beats/min (two levels lower—that is, 24 beats/min—than the lowest before the test) was recorded twice in 24 five-second intervals. The total score was 7; in other words, the test was highly positive. A repetition of the test unfortunately proved impossible because fetal movements ceased two days later. Labor was induced and a dead fetus weighing 2,600 grams, with a crown-heel length of 48 cm, was delivered; no cause of death was apparent.

Few of the 217 obstetrical institutions in Czechoslovakia have phonocardiographs, and most of these are old models that only register

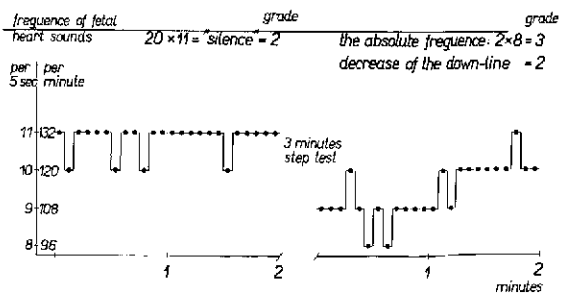

FIGURE 1. Schematic record of ascertained changes of heart sounds frequency during step test.

separate fetal heart sounds but will not give a continuous record. We next tried, therefore, to simplify the test so that it could be performed anywhere. A specialist holding a stop watch counts the heart rate at five-second intervals and reports it, in an agreed-upon code, to a midwife, who writes it down. The entire test (two minutes' auscultation before the test, three-minute test, two minutes' auscultation after the test, and evaluation) can be carried out in ten minutes. Using this method, we conducted 389 step tests in 109 women with high-risk pregnancies. To verify the reliability of the test, we divided the cases into three groups.

Group I consisted of 51 cases in which no symptoms of fetal hypoxia were recorded and the clinical condition of the newborn was excellent, with an Apgar score of 10 at the first, fifth, and tenth minutes after delivery. In Group II were 28 newborns who were also quite healthy clinically but in whom bradycardia (dips II) or meconium staining or both was ascertained during labor. Group III contained 28 newborns with low Apgar scores, in most of whom symptoms of intrauterine hypoxia were found during labor. Two deaths were also included in this last group—the case described above in detail, and an anencephalus that was born alive with an extremely low Apgar score and died subsequently.

TABLE 3. Comparison of step-test scores with condition of newborns and symptoms of hypoxia during labor [a]

STEP-TEST SCORE	NO. OF NEWBORNS			✝
	GROUP I	GROUP II	GROUP III	
8	0	0	1	0
7	0	1	0	1
6	0	2	2	0
5	2	3	5	1
4	2	6	2	0
3	3	8	9	0
2	3	1	7	0
1	6	0	1	0
0	35	7	1	0
Total	51	28	28	2

[a] Group I, healthy, no symptoms; Group II, healthy, dips II and/or meconium staining; Group III, low Apgar scores, symptoms.

The individual cases in each of these groups were classified in accordance with the last step-test score received within three days of labor (Table 3). This classification gave us 10 healthy newborns (with no symptoms of intrauterine hypoxia during labor) for whom the step test had been positive, and 7 distressed and 2 depressed newborns for whom the test had been negative. At first sight it would appear that the diagnosis of intrauterine fetal distress in 109 women with high-risk pregnancies was falsely positive for 9 per cent and falsely negative for 8 per cent. But since labor was induced in 4 of the false-positive cases (test scores 5 or 4), it is possible that we thus prevented the fetal hypoxia that would have occurred if we had waited for labor to begin spontaneously. Furthermore, when we compare the step-test results with the clinical condition of the infant immediately after delivery (Table 4), we find that in the 9 false-negative cases only 2 newborns with low Apgar scores (4 and 7) were delivered and the condition of both improved in five to ten minutes.

Another, more detailed verification of the reliability of the step test is the relationship between the step-test score and the occurrence of symptoms of fetal hypoxia—meconium staining and/or bradycardia (dips II). As Figure 2 shows, when the test score is 0 or 1, the occurrence of these symptoms—12 to 25 per cent—is only a little higher than in a normal population sample. With a test score of 2, the occurrence of these symptoms increases to 60 to 70 per cent; with a test score of 5, to 80 to 100 per cent.

The frequency of need for operative termina-

TABLE 4. Comparison of step-test score with Apgar score of newborn

STEP-TEST SCORE	NO. CASES	APGAR SCORE					✝
		10	9–8	7–6	5–3	2–1	
0–1	50	48	0	1	1	0	0
2–4	42	23	6	4	6	3	0
5–8	17	9	1	3	2	0	2
Total	109	80	7	8	9	3	2

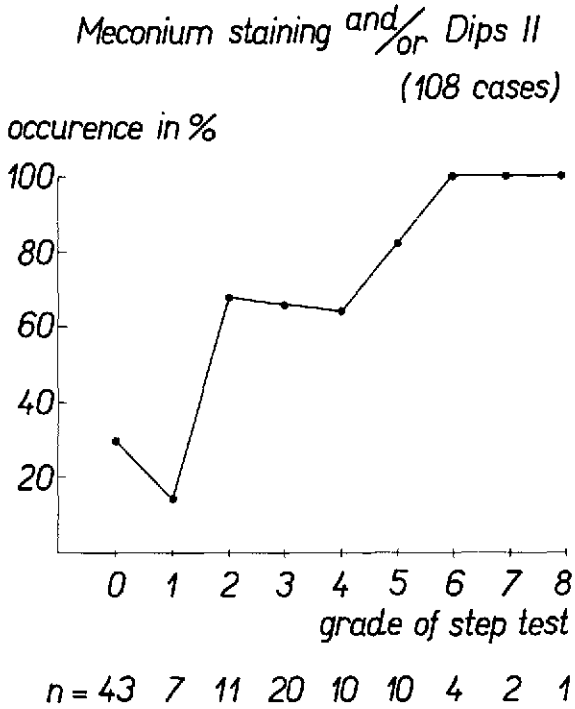

FIGURE 2. Relation of occurrence (%) of meconium staining and/or dips II to step-test score

tion of delivery, by forceps or cesarean section, because of serious fetal hypoxia is a final but relatively rough criterion of the reliability of the step test (Table 5). The difference between negative and positive step tests in this respect is highly significant.

TABLE 5. Frequency of operative termination of labor because of fetal hypoxia, by results of step test

	STEP TEST	
	NEGATIVE	POSITIVE
Total cases	50	59
Forceps	2	15
Cesarean section	0	5

Though the number of cases followed so far is very small, still a total of two perinatal deaths (one of the cases an anencephalus) in 109 high-risk pregnancies is a very good balance, from the standpoint of preventing perinatal mortality. The most frequent reasons for performing the step test were pregnancy prolonged beyond 294 days (47 cases) and late toxemia (36 cases). Other indications, such as habitual decease of fetus, broke down into small groups. Umbilical

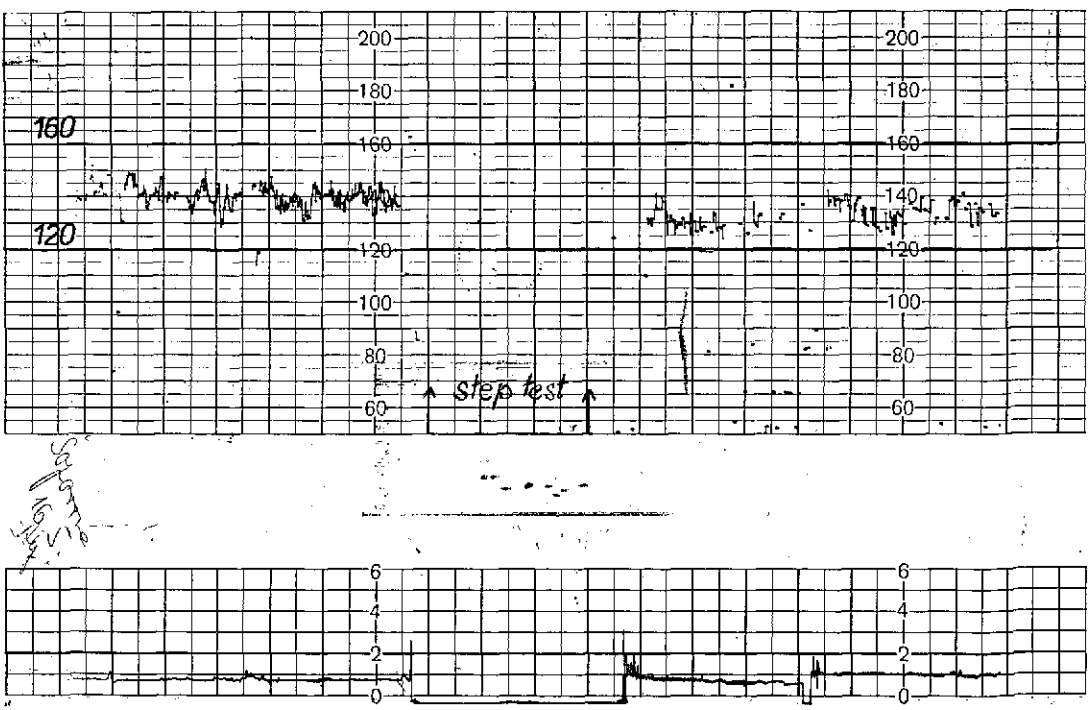

FIGURE 3. Original record of negative step test. Both before and after physical load, fetal heart rate fluctuates between 124 and 150 sounds a minute

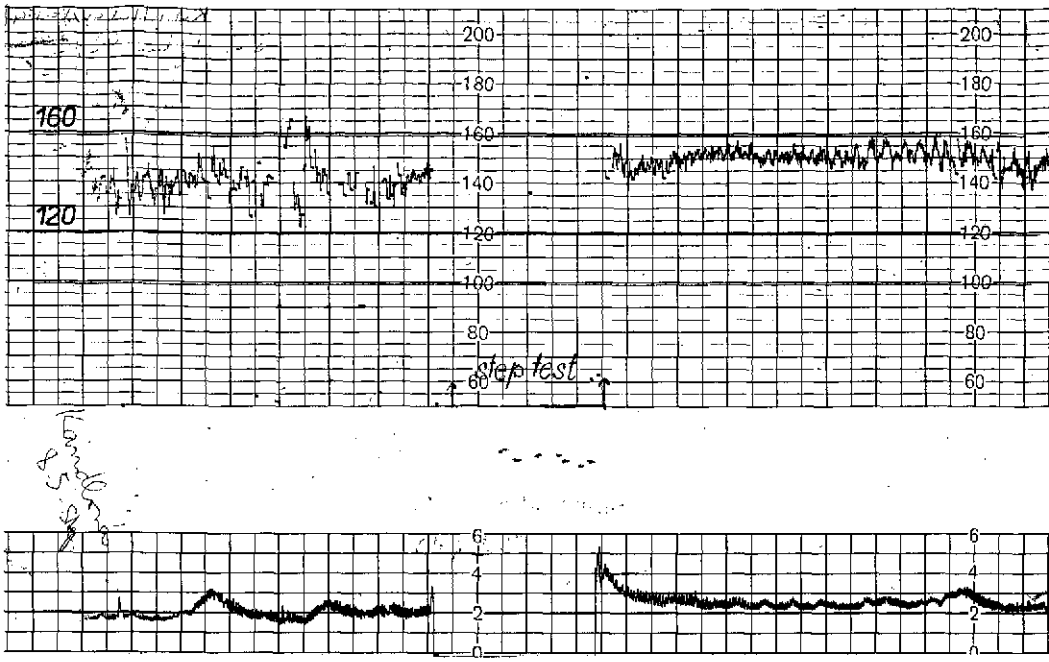

FIGURE 4. Original record of positive step test (score 2). Before physical load, fetal heart rate fluctuates; afterward, "silence," i.e., it remains for three minutes between 146 and 158.

cord complications occurred in about the same proportion in healthy fetuses as in distressed and compromised ones, 28 to 32 per cent, which is higher than in a normal population sample.

Only recently have we acquired a fetal phonocardiograph that records continuously (Hewlett-Packard). Three step-test records made with it appear as Figures 3, 4, and 5.

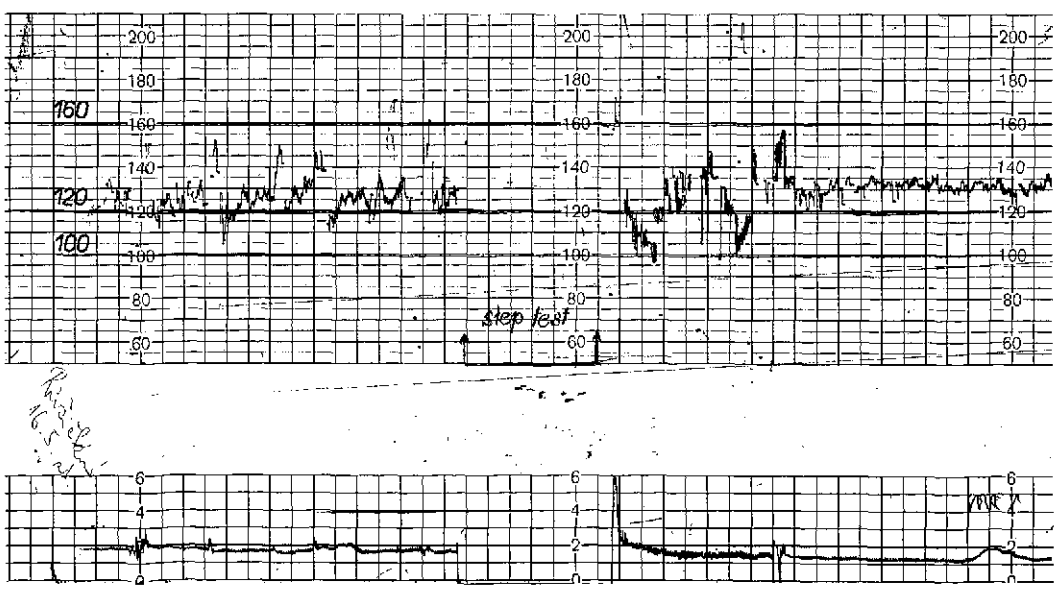

FIGURE 5. Original record of positive step test (score 7). Before physical load, pathological oscillation of fetal heart sounds between 110 and 162 beats/min; afterward, transitory bradycardia down to 98 beats/min with following pathological oscillation between 100 and 158.

Summary

Step-test results in 109 women with high-risk pregnancies showed that high scores were closely associated with frequent occurrence of meconium staining and dips II during labor, depressed newborns, and need for operative termination of pregnancy because of fetal distress. This test, when used in high-risk pregnancies approaching term, makes it possible to identify with 83 per cent reliability which fetuses will be distressed. The test can be used to predict which labors will require either special attention, induction of labor, or cesarean section, not only to avert perinatal death but also to prevent serious hypoxia that could impair the infant's subsequent development.

Acknowledgements

The author would like to express appreciation for technical assistance to M. Šedivá.

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DISCUSSION

Gruenwald: I should like to ask any of the speakers what one finds in growth-retarded fetuses during pregnancy at the time studied here, when they are not in any acute trouble. Do they usually show some aberrations or not?

Pose: In the majority of our fetuses with positive tests, the weight is lower than normal. But there is one point that makes the whole thing unclear: the fact that the majority of our patients are cases of diabetes, and the fetuses of diabetics are, in general, bigger than those of normal cases. We thus have a contradictory situation.

Bieniarz: In angiographic studies we observe a higher incidence of insufficient placental circulation in cases where the fetus is small. This occurs most frequently in chronic hypertensive vascular disease of the patient.

Churchill: Dr. Hellman's presentation on sonography is very exciting, I think, since it gives us for the first time an opportunity to plot the development of the individual child throughout the course of gestation.

All of us who are studying intrauterine growth retardation are blocked by the inability to measure the rate of growth of individual fetuses. Sonography appears to offer a solution to this vexing problem.

Now, there seems to be a bit of difficulty in positioning the baby's head to get proper planes for measurements. One of Dr. Hellman's slides was beautiful; it showed sharp definition of midline cerebral structure with scattering of sound waves right down the falx cerebri and through the midline structures of the brain. The cephalic index, which is the product of the fronto-occipital and biparietal diameters and is a useful measure for anthropology, could easily be obtained.

How can one find the proper planes consistently? Are there any technological advances on the horizon that would, in a sense, make ultrasound waves coherent enough to use in constructing holograms? If this were possible, then reconstitution of the holograms would produce a three-dimensional image that could be rotated, in effect, and looked at from any point of view. Dr. Hellman may know something about this.

Hellman: Thank you for your kind remarks, Dr. Churchill.

Some very crude holograms have been made by Dr. Donald in Glasgow. You have to have a good deal of imagination to see these in three dimensions. Nevertheless, the possibility does exist that this method could be perfected.

What we have done is slice the fetal head in two- or three- or even one-centimeter slices by moving the machine mechanically and then making negatives and holding them up so you can look through a block and actually see the fetal head in three diameters. I do not think this is necessary, because, if you take more than one slice of the fetal head, you can get the occipital, frontal, and biparietal diameters pretty clearly and you can get the circumference from a series of sonograms.

We have done such measurements and compared the accuracy of one dimension, two dimensions, and three dimensions against actual measurements taken just before and after cesarean section. The variance is known: plus or minus two millimeters or a little greater.

Adamsons: I should like to comment on the very interesting presentations of Dr. Pose and Dr. Štembera. Obstetricians have been concerned for quite a number of years with the development of some sort of tolerance test on the fetus prior to the onset of labor. Interest has been concentrating on the relationship between fetal needs and availabilities.

In this situation, the principal requirement has been to establish a standard test that will modify the fetal internal environment somewhat.

The standardization of the stimulus has been, I think, our major problem.

I believe Dr. Pose has come closer with his test than most other previous investigators. There are, however, certain unknowns that may require further refinements of the test.

Most of us are aware that the induction of uterine contractions by oxytocin not infrequently leads to the elevation of resting tone, particularly if this is conducted earlier in gestation. We have induced labor with oxytocin in a number of rhesus monkeys in late pregnancy, and not infrequently the intrauterine pressure has risen, before discernible contractions are elicited, to a level at which this is likely to interfere with normal circulation. This may then lead to an alteration of the actual fetal circumstance on which the higher uterine tone is imposed. Perhaps with more refined measurements it would be possible to screen out those patients in Dr. Pose's test in whom some sort of embarrassment resulted from elevated tone rather than interruption in intervillous space perfusion.

It may be asked what we are actually determining by Dr. Pose's test. To me it seems that we are trying to ascertain the relationship between the quantity of oxygen available in the intervillous space and the fetal needs.

It can be estimated that normal intervillous space stores a quantity of oxygen that will suffice for fetal needs toward the end of pregnancy for approximately 45 seconds to one minute and a half. Dr. Pose's test may be useful in unmasking situations in which the blood volume of the intervillous space is smaller and thus the oxygen content is less. This will pertain especially to patients with conditions like erythroblastosis or diabetes, in which there may be some relative loss in volume due to trophoblastic edema. I am not so sure whether these tests may be as revealing in conditions where both the fetus and the placenta are small, because fetal needs may also be reduced; although the quantity of blood stored is less, there may be no imbalance.

I was less satisfied with the step test as a quantitation of the adequacy of placental circulation supplied to the fetus. Its shortcoming seems to be the uncertainty of the magnitude of the stimulus. We all know that the same mechanical performance as stated by the step test may infer a very different physical load to the cardiovascular system in different patients, depending on their body mass and their previous exposure to physical exercise. Perhaps these patients could best be tested while performing a quantitative workload rather than lifting their body masses to a certain kind of height. I also wonder whether the step test may not be more informative if changes in the fetal heart rate are recorded during the test rather than in the recovery period. The recovery period may produce a relatively normal heart rate that is tachycardia following rather significant bradycardia occurring during the actual deprivation of oxygen while the test is in progress.

Hon: In reply to Dr. Churchill's question about the possibility of using coherent signals in ultrasonic work, it is possible to improve the resolution of ultrasonic devices by tying the transmitting pulse to trigger a group-averaging computer and averaging the echo. In this way the echoes are time-locked to the stimulus. We have not done B scans, but one of my students has been doing A scans work and we find that this improves the resolution considerably. I think it would avoid some of the scatter we see in the B scan.

With respect to the question on the low-birth-weight baby and its limits of tolerance, our experience would suggest that it has a lower tolerance for the stresses of labor or the individual uterine contraction than the normal baby. This is not always true—if you have a smaller baby, you may have a smaller placenta—but I should think that by and large it is.

Our experience with the exercise test and with using uterine contractions as a stress also suggests that it is much more difficult to quantitate the extent of the stress with the exercise test. Indeed, this is why we abandoned it some time ago: the variability on a high-risk population was so great.

However, using the fetal heart rate early in labor, it is possible to predict with almost 100 per cent accuracy whether a particular baby will tolerate labor or not. That is, if the baby is

having type II dip decelerations with minimal contractions, it will not tolerate labor. These dips II seem to be bad for the babies, as is attested to by studies done in conjunction with their heart rates. We see changes in the electrocardiogram, which is expected, and in the umbilical cord blood and in the blood of the newborns as we follow them through the first hour of life.

Dawes: A good deal of interest has been shown today in manipulation of maternal-placental blood flow. Presumably these tests are based on a reduction of maternal-placental blood flow. Therefore, one looks to the experimental physiologist to see what is known about this subject.

Until very recently, there has been no adequate method for measuring maternal-placental blood flow quantitatively. But during the last 18 months this situation has changed radically, with the introduction of the isotope-labeled microsphere technique. Duncan and Lewis have made some observations that do not directly answer the questions posed today but are relevant. I shall mention only three points.

The observations have been made on rabbits. In this species there are favorable and unfavorable positions in the uterine horn; in the unfavorable position maternal-placental flow is low not only absolutely but relatively, so that flow per gram of fetus or of placenta is much below average.

Secondly, if the number of fetuses per horn is substantially increased, the reduction in maternal-placental flow to the less-favored fetus is even greater.

Finally, there is an interesting point about the mechanism of control of maternal-placental flow. If you produce hypoxemia in the pregnant rabbit, maternal-placental flow is greatly reduced but myometrial flow is not changed—which is surprising because they are fed by the same uterine artery. This suggests that we have a great deal to learn about the basic physiology on which these tests should be designed.

Méndez-Bauer: I have two questions for Dr. Štembera. One is the same as that of Dr. Adamsons, about what happened with the fetal heart rate during exercise. The second has to do with what might be a by-product of his work—whether maternal exercise may modify uterine contractility, increasing or decreasing it.

Štembera: I think you are right that there is a difference between the same step test for one woman and for another. We do use a metronome; we use 80 steps up and down a minute; but it is different for a woman of 70 kilograms from what it is for one of 90 kilograms. But we have no choice.

We too were interested in what happens with heart sounds during this physical load, and so in one group, as I say in my paper, we used a special bicycle and measured the heart sounds during the physical load. We found, in these pathological cases, changes in the fetal heart sounds at the end of the load and also afterward, but it was too complicated for many of the women. We therefore returned to the step test.

In reply to the other question, we recorded the uterine contractility before and after the maternal exercise but found no changes.

Adamsons: I wonder whether you could improve the uniformity in your step test by making allowances for differences in weight and by forcing your patients to perform the work in a specified time interval.

We have also been thinking about the possibility of interrupting intervillous space flow, without the necessity of invoking uterine contraction, by external compression of the uterus. In theory, this seems straightforward and easy because no other variables are modified and the uniformity of the duration of the stimulus could be guaranteed. Unfortunately, the uterus does not seem to be a very suitable structure for such maneuvers. The compression of abdominal wall infrequently leads to increased muscle tone of the mother and there is no guarantee that intrauterine pressures have risen appropriately.

I think this is something that perhaps should be examined more thoroughly, to see whether certain appropriate devices could not be constructed.

Pose: I should like to make a comment on Dr. Adamsons' first statement, about the possibility of producing hypertonus with the adminis-

tration of oxytocin. Of course, I do not have time to explain all the details of the technique employed, but what we used to do was start with oxytocin infusions at low rates, then increase the velocity of the infusion until the moment normal uterine contractions were obtained.

Figure 6 of my paper shows the percentage of contractions producing dips II in the positive test in relation to the peak pressure developed by the contraction (including the tonus plus the intensity of the contraction). There is an increase in the number of contractions producing dips II up to the peak pressure of 40 mm Hg or so, but from that point on there are almost no variations in the number of contractions producing dips II. I think that the way to perform the test would be to produce mild contractions, not strong ones.

In relation to Dr. Hon's comments about the size of the fetus and the tolerance to labor, we have some cases that we followed with negative tests from the thirty-second week on. In general, we obstetricians have to deal with cases in which the decision is whether to interrupt pregnancy between the thirty-fourth and the thirty-eighth week of pregnancy for reasons of fetal risk. We are not actually dealing with very small fetuses. Even if the test is positive or estriol is very low, or other signs show that the fetus is in very bad condition, we do not dare remove a fetus before the thirty-fourth week.

Myers: If the type II dip ultimately represents a challenge with lower partial pressures of oxygen, the most direct and uncomplicated provocative test would appear to be one in which the mother is given an atmosphere with diminished levels of oxygen. Such a regulated and timed exposure would get around the complexities inherent in using the exercise test with variation in patient size. By regulating the concentration of oxygen in the inspired air of the mother, a very precise control of the degree and length of the provocation can be achieved. Further, if elevated CO_2 is an important ingredient in the provocation, its concentration can also be controlled by regulation of the partial pressures of carbon dioxide in the atmosphere being breathed.

Has this sort of provocative test been tried clinically in the human?

Moderator: It has been tested, yes, but we found that the uterine contraction was the most reliable and easy to repeat—the least dangerous for the mother and fetus, and one that also reproduced what was going to happen in labor. Of all the tests we assayed, this seems to be the most reliable, because it mimics the histological situation.

PRESSURE EXERTED BY UTERINE CONTRACTIONS ON THE HEAD OF THE HUMAN FETUS DURING LABOR[1]

R. L. Schwarcz, G. Strada-Sáenz, O. Althabe, J. Fernández-Funes, and R. Caldeyro-Barcia[2]

Ingelman-Sundberg *et al.* (*12*) and Lindgren (*14, 15, 16*) have reported that under certain conditions during labor the pressure exerted by uterine contractions on the fetal head may be two to four times higher than that exerted on the amniotic cavity at the same time. Schwarcz and Salaber (*18*) reported that manual compression of the fetal head through the anterior abdominal wall against the promontorium caused a sudden and marked fall in fetal heart rate (FHR), which was perceived by clinical auscultation—a finding confirmed by many authors and recently studied with greater precision by means of the electronic record of FHR by Hon (*10*), Chung and Hon (*7*), and Arellano-Hernández *et al.* (*1*). These falls in FHR are mediated by the vagus nerve, since they are completely blocked by atropinization of the fetus (*17*).

During advanced labor, particularly after rupture of the membranes, each uterine contraction may cause a transient fall in FHR (dip I), which is simultaneous with the contraction in such a way that the bottom of the dip I coincides with the peak of the contraction (*5*). It has been postulated (*5, 6*) that each dip I is caused by a strong compression exerted on the fetal head by the corresponding uterine contraction. Cephalic compression would produce vagal stimulation. Dips I have similar characteristics to the "early decelerations" described by Hon and Quilligan (*11*), who have postulated the same pathogenic mechanism.

The purpose of the present paper is to record and measure the compression received by the fetal head during each uterine contraction, correlating it with the rise in amniotic pressure and the amplitude of the dip I (if present) caused by the same contraction.

Methods

This study was made in 18 normal, term pregnant women during labor, with vertex presentation. The pressure received by the fetal head during labor is recorded by means of three flat pressure receptors, which are introduced between the uterine cervix and the fetal head (Figure 1) outside the ovular membranes (*12, 18, 20*).

Each pressure receptor is a flat tambour (Figure 2) formed by two latex membranes, which are glued to the edges of a circular hole on a thin plastic blade. The diameter of each receptor is 15 mm, and the distance between the centers of two consecutive receptors is 30 mm. Each receptor is filled with water and connected to a recording pressure transducer by a thin polyethylene tube. The three re-

[1] This study received support from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization, and from grant HD 00222-06 of the National Institute of Child Health and Human Development, Bethesda, Maryland, U.S.A.

[2] Presented by Dr. Schwarcz.

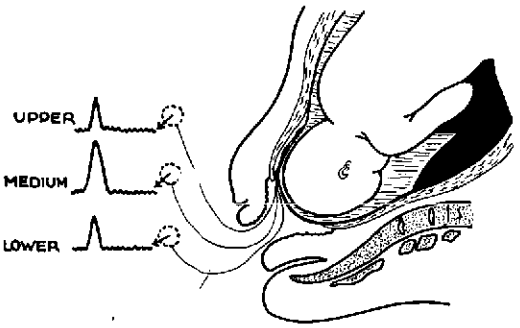

FIGURE 1. Method of recording pressure between fetal head and birth canal with three receptors.

ceptors are centered in line on the blade; they are known as "upper," "medium," and "lower" according to their position in relation to the uterus. The plastic blade—100 mm long, 30 mm wide, and 1 mm thick—is very flexible.

The blade is introduced between the membranes and the uterus toward the fundus (Figure 2). One surface of the receptor touches the lower pole of the amniotic sac (eventually the fetal head) and the other faces the uterine wall. The lower end of the blade is sutured to the uterine cervix at the external os (Figures 1 and 2).

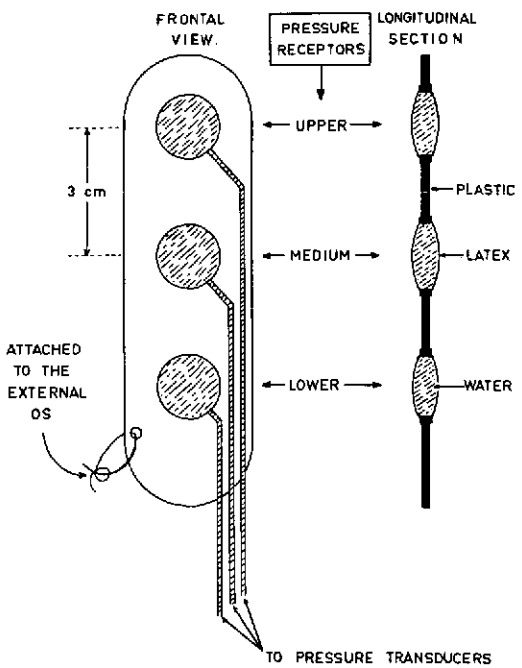

FIGURE 2. Detailed diagram of pressure receptors inserted between fetal head and uterus (see also Figure 1).

The position of the receptors relative to the fetal head is determined by radiology; it changes with the progress of cervical dilatation or with the station of the fetal head. As labor progresses, there is a relative displacement of the blade and receptors from the vertex toward the base of the fetal head (Figures 5 and 7).

The intrauterine (amniotic) pressure is recorded by means of a catheter introduced through the abdominal and uterine walls into the amniotic sac (*2*) and connected to a pressure transducer. The FHR is recorded by means of an instantaneous cardiotachometer triggered by the fetal electrocardiogram (*3*). The ECG is obtained almost free of maternal interference by means of electrodes inserted under the skin of the fetus in either the buttock (*3*), the scalp, or both (*8*). The amniotic pressure, the FHR, and the pressures between the fetal head and birth canal are all inscribed on the same recording paper (Figures 3, 4, 6, and 8) to facilitate the study of their interrelations. The fetal EEG is also recorded, as will be reported at this meeting by García-Austt *et al.* (*9*).

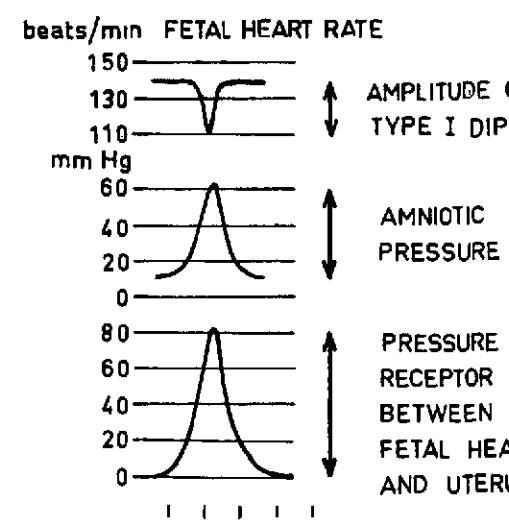

FIGURE 3. Method of measuring amplitude of type I dips and rise in pressure caused by each uterine contraction in several simultaneous tracings.

Results

Correlation between cephalic compression and amniotic pressure

During each uterine contraction, the pressure recorded by the cephalic receptors rises almost simultaneously with the amniotic pressure (Figures 3, 4, 6, and 8). The amplitude of the rise is measured in every tracing for each contraction (Figure 3). The pressure rise in each cephalic receptor is plotted against the corresponding rise in the amniotic pressure (Figures 5 and 7). For any given period of labor in which the cervical dilatation and station remain unchanged, a given direct linear relationship is found between the pressure in each cephalic receptor and the amniotic pressure (Figures 5 and 7). The correlation coefficients (r) are very high—0.95 or more.

When the receptors are displaced and change their position relative to the fetal head (as a consequence of the progress of cervical dilatation or of the station), a new linear correlation is established between the pressure in each cephalic receptor and the amniotic pressure, the value of the intercept and of the regression coefficient changes depending on the new relative position of the receptor (Figures 5 and 7).

When a cephalic receptor is more than 2 cm above or below the equator of the fetal head, the pressure it records at the peak of each uterine contraction is very similar to that in the amniotic cavity (Figures 5 and 7). When the receptor is displaced and comes closer to the equator of the fetal head, the pressure it records at the peak of the contraction becomes higher than that in the amniotic sac. The ratio (pressure in cephalic receptor/amniotic pressure) is higher than 1 and is significantly different ($p<0.001$) from that for receptors distant from the equator (Table 1). This is clearly shown in Figures 5 and 7, where the regression coefficients corresponding to receptors near the cephalic equator are higher than those for receptors distant from it. For example, in Figure 5C the lower receptor (at the equator) records much higher pressures than the other two.

The difference in pressure between the receptor near the equator and those distant from it has been found both when the membranes are intact (Figures 5A) and when they are ruptured (Figures 5B and 5C). However, the greatest pressure differences have been observed after rupture of the membranes (Figure 5C). In Figure 8, the pressure at both receptors (medium and lower) is always greater than the amniotic pressure, but the exact relationship between each receptor and the amniotic pressure varies according to the stage considered. In section A, the pressure at the medium receptor is approximately 2.6 times greater. In section B, the pressure at the lower receptor is approximately 2.5 times greater than the amniotic pressure; at the medium receptor it is a little less than at the lower receptor, though still greater than the amniotic pressure. In section C (ending in delivery of the newborn), the pressures at the two receptors are practically identical; both are much lower than those recorded

TABLE 1. Analysis of variance of the ratio between pressure in cephalic receptor * and amniotic pressure

SOURCE OF VARIATION	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARES	$F_{(1, 4)\ 5\%} = 7.71$
Between groups	17.7551	1	17.7551	
Within groups				$F_{(1, 4)} = 21.2942$
Between periods	3.3351	4	0.8338	
Within periods	9.6726	164	0.0590	
	30.7628	165		

* Comparison between data obtained from the receptor near the cephalic equator and those distant from it in record No. 1475, illustrated in Figures 4 and 5.

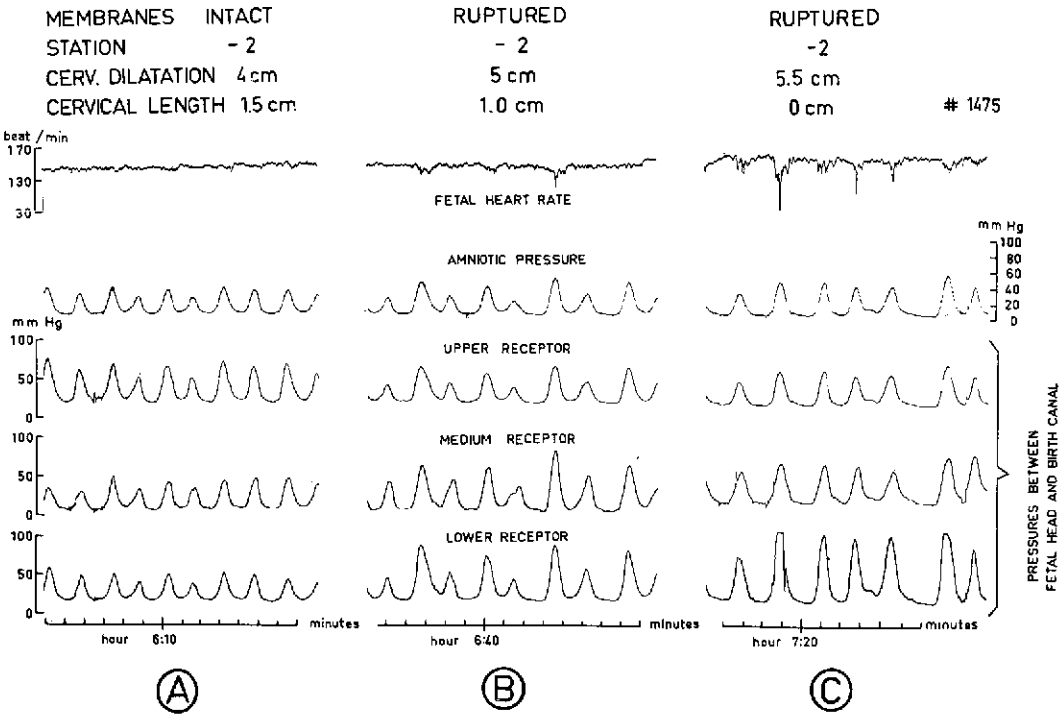

FIGURE 4. Three segments of record obtained during spontaneous labor at term pregnancy (newborn weight 3,320 g, Apgar score 9). Multipara in supine position. Vertex presentation. In A, pressure tracings recorded from receptors placed between fetal head and birth canal are not much different from tracing of amniotic pressure. In B and C, after rupture of membranes, uterine contractions exert much higher pressures on receptors near equator of fetal head (see Figure 5) than on amniotic cavity. Type I dips appear in FHR tracing. Record is quantitatively analyzed in Figure 5.

in section B and only 1.3 times greater than the corresponding amniotic pressure.

These results are interpreted as follows: In the three sections (A, B and C), both receptors are near the cephalic equator and thus record higher pressures than the amniotic. In section A, the cephalic equator is nearer the medium receptor. Upon the descent of the presentation (section B), the cephalic equator gets nearer to the lower receptor, which thus records the highest pressures. When the descent of the head is completed (section C), both receptors are above the cephalic equator; this explains the relative reduction in the pressure they record.

Correlation between cephalic compression and dips I

If the fetus is not suffering from systemic hypoxia and acidosis, uterine contractions cause no changes in FHR as long as the pressure received by the fetal head during each uterine contraction is not much higher than the amniotic pressure (Figure 4A). Under these conditions the FHR tracing shows the normal "rapid" oscillations, the baseline is close to 140 beats/min, and there are no dips I.

When the compression exerted by one uterine contraction on the fetal head is much higher than that on the amniotic cavity, a transient fall (dip I) occurs in FHR (Figure 4, sections B and C; Figure 6, sections A and B; and Figure 8). In Figure 6C, uterine contractions cause dips I even though there are no differences between the amniotic pressure and that recorded by the cephalic receptors. However, these receptors are above and distant from the equator (Figure 7C) and thus do not report the maximal pressure received by the fetal head.

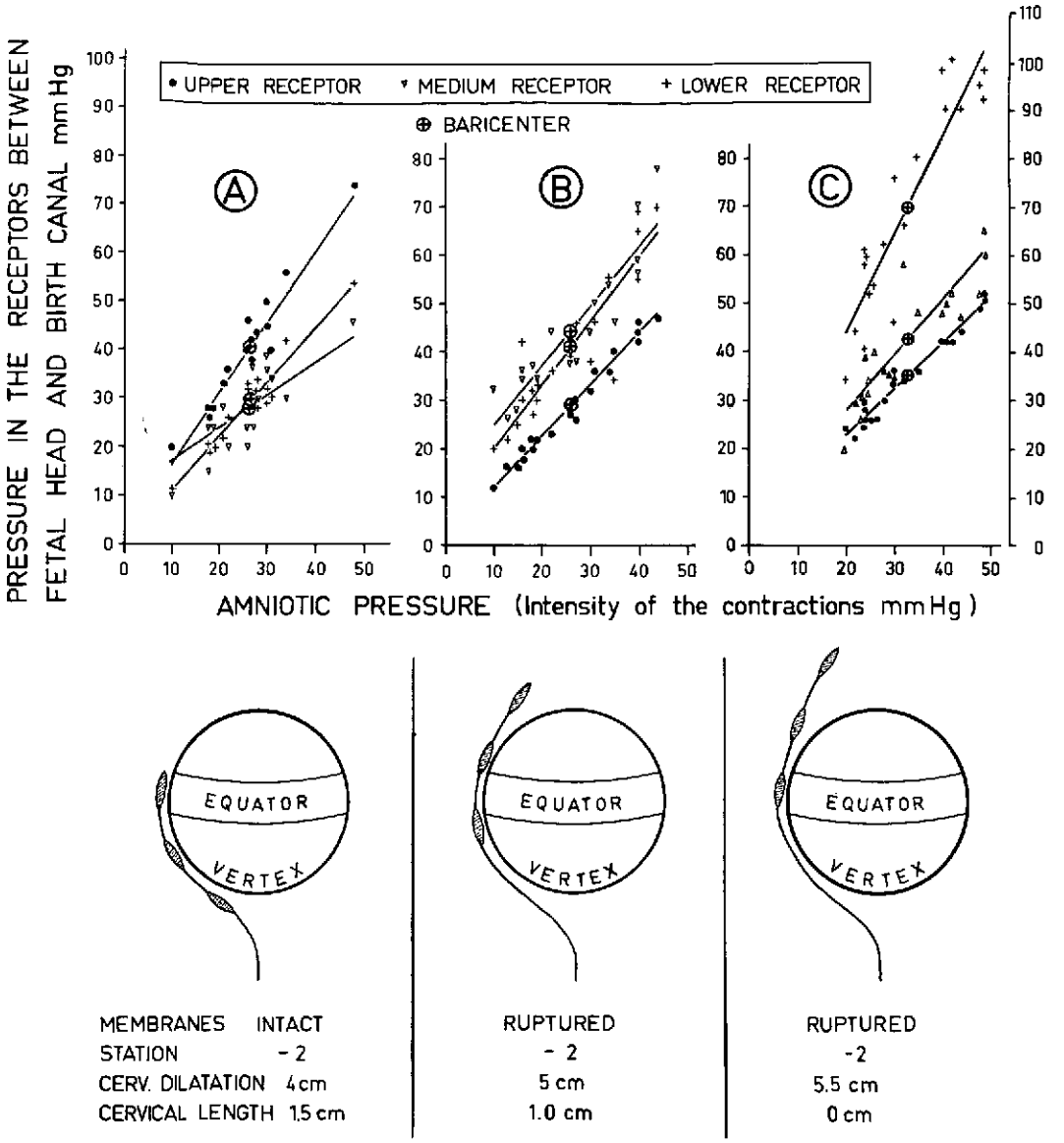

FIGURE 5. Upper half: correlation between pressure on cephalic receptors and in amniotic cavity measured at peak of each uterine contraction (Figure 3). A, B, and C refer to three periods illustrated in Figure 4. Diagrams in lower half of figure show, for each period, position of receptors in relation to fetal head.

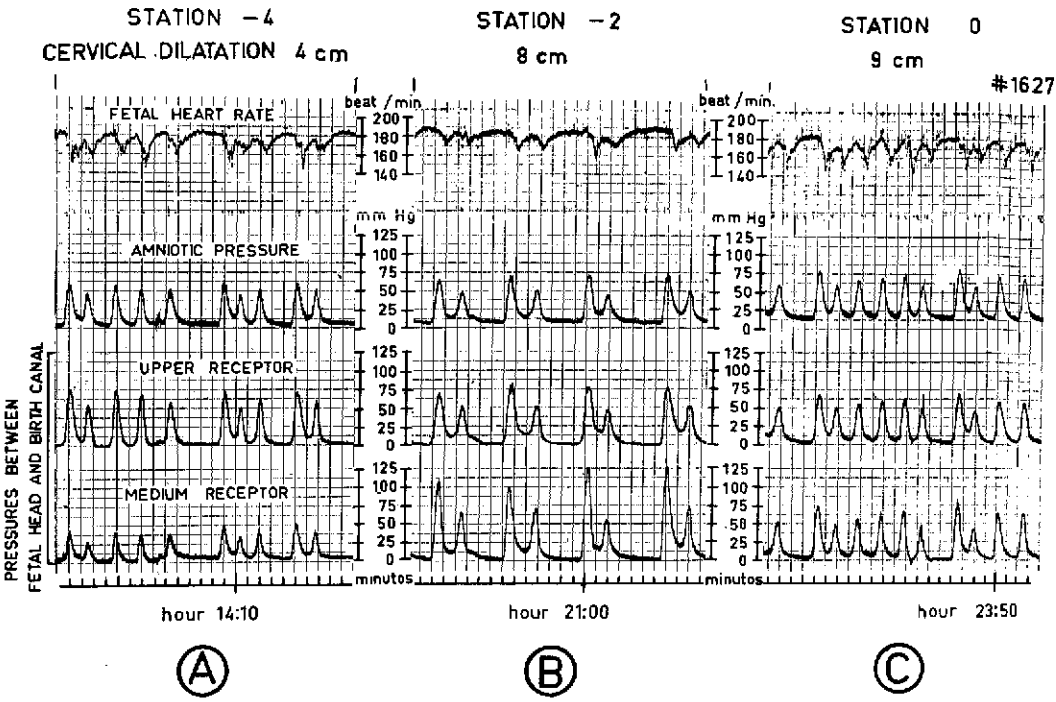

FIGURE 6. Three segments of record obtained during labor induced with oxytocin infusion at term pregnancy (newborn weight 3,460 g, Apgar score 6). Membranes were ruptured at hour 12:30. Receptor placed near equator of fetal head (upper receptor in Section A and lower receptor in section B) record pressure higher than that in amniotic cavity. In section C both receptors are distant from cephalic equator, and pressures recorded are similar to those in amniotic sac. Uterine contractions cause dips I in all 3 sections. This record is quantitatively analyzed in Figure 7.

The greater the pressure exerted by the uterine contraction on the fetal head, the larger the amplitude of the corresponding dip I in FHR (compare sections B and C in Figures 4 and 5). In Figure 8 almost every uterine contraction causes a dip I. Several contractions cause, in addition, a dip II—that is, a second transient fall in FHR recorded immediately after the dip I. Dips II will not be discussed in this paper. The amplitudes of dips I are larger in section B of Figure 8 than in sections A and C, probably because in section B the fetal head was receiving a stronger compression than in sections A and C, as is shown by the corresponding cephalic pressure receptors.

Figure 9 shows the direct linear relationship present in record No. 1475 between the amplitudes of dips I and the pressures recorded in the cephalic receptors at the peaks of the corresponding uterine contractions. When this pressure was higher than 50 mm Hg, almost every contraction caused a dip I in the FHR tracing.

Discussion

Relation between amniotic pressure and cephalic compression

Our results confirm Lindgren's report (*14, 15, 16*) that under given conditions the pressure exerted by uterine contractions on receptors placed between the fetal head and the uterine wall may be much higher than the pressure in the amniotic cavity. They also confirm Lindgren's statement (*14, 15*) that the receptor placed at the equator of the fetal head is the one that records the highest pressure.

The ratio (pressure in cephalic receptor/amniotic pressure) is much higher in Lindgren's

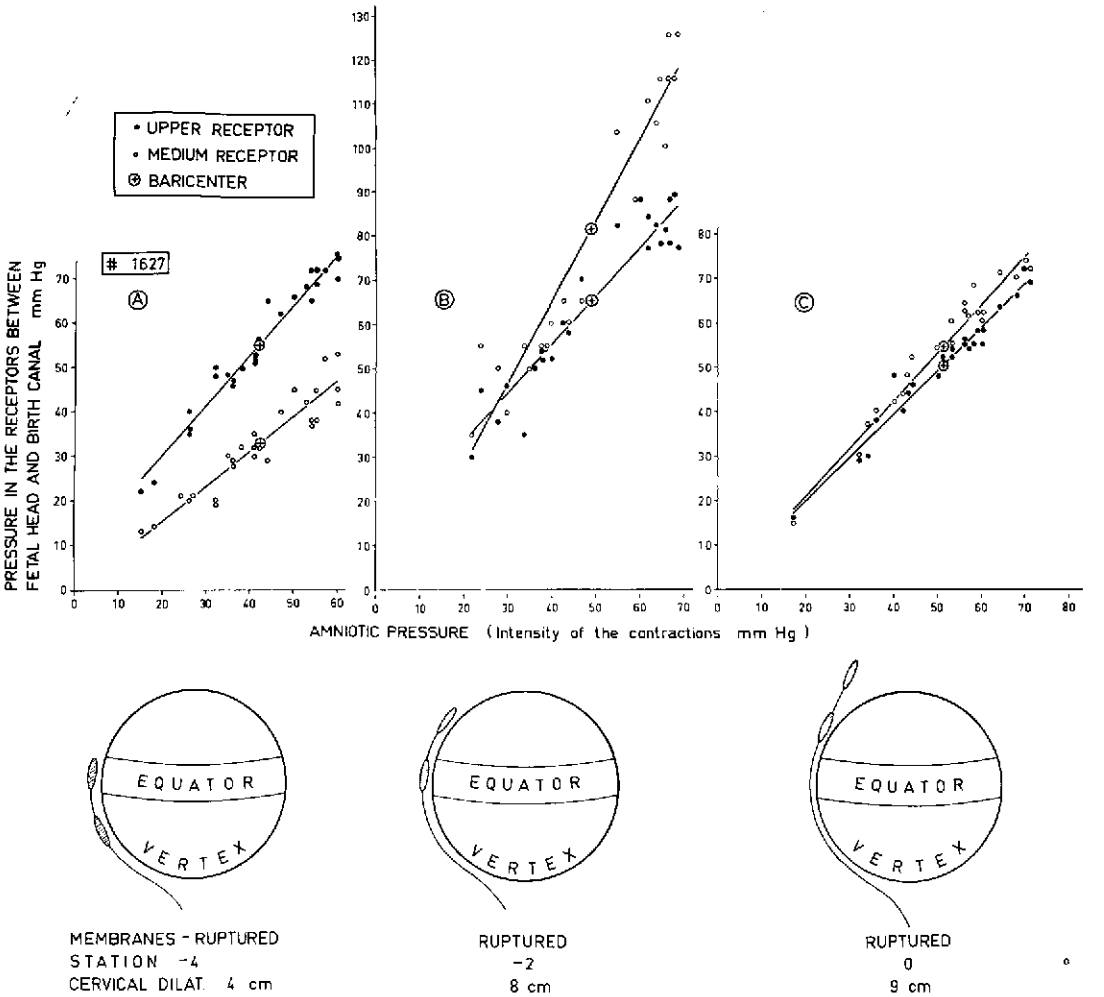

FIGURE 7. Upper half: correlation between pressure on cephalic receptors and in amniotic cavity measured at peak of each uterine contraction (Figure 3). A, B, and C refer to three periods illustrated in Figure 6. Diagrams in lower half of figure show, for each period, position of receptors in relation to fetal head.

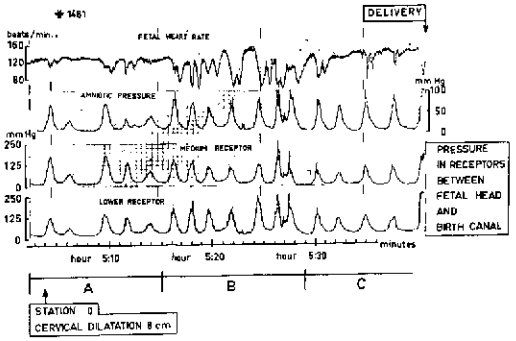

FIGURE 8. Record obtained during last 40 minutes of normal spontaneous labor at term pregnancy (newborn weight 3,375 g, Apgar score 8). Membranes were ruptured at hour 2:45. In section B, uterine contractions cause very strong compressions of cephalic receptors (up to 200 mm Hg) and dips I of very large amplitude. In sections A and C, pressure recorded by cephalic receptors and amplitude of dips I are smaller than in section B.

results (*16*) than in those reported here, even for similar obstetrical conditions (Figure 10). Whereas we found a linear relationship between the pressure in the cephalic receptors and the amniotic pressure, Lindgren finds (*16*) that when the amniotic pressure increases beyond a certain limit, the linear relation is lost, since the pressure in the cephalic receptor does not rise accordingly. These discrepancies may be due to differences in the type of cephalic pressure receptors employed.

Pressure required to produce dips I

The correlation found between the pressure in

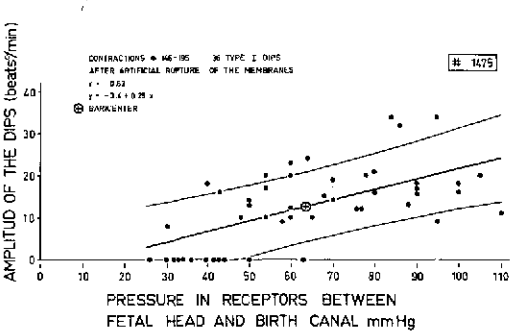

FIGURE 9. Correlation between amplitude of type I dips in FHR tracing and pressure received by fetal head at peak of corresponding uterine contraction. Best-fitted line and 95 per cent confidence belt are shown.

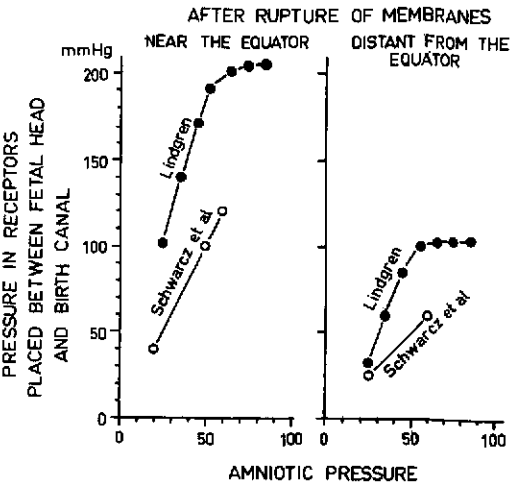

FIGURE 10. Comparison of results presented in this paper with those previously reported by Lindgren (*16*).

the cephalic receptors and the amplitude of dips I (Figure 9) is in accord with the hypothesis (*6*) that these transient falls in FHR are caused by a strong compression exerted by the uterine contraction on the fetal head. To cause a dip I, the cephalic compression should be greater than 40 mm Hg (Figure 9). This value agrees with those recorded by Arellano *et al.* (*1*) employing similar cephalic receptors; when a transab-

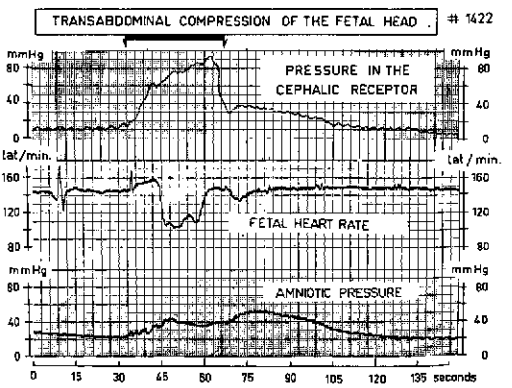

FIGURE 11. Manual compression of fetal head through abdominal wall causes pressure rise in receptor placed between head and uterine wall. When pressure reached 60 mm Hg, FHR fell abruptly. Compression caused rise of 20 mm Hg in amniotic pressure. During manual compression, a uterine contraction started and reached peak about 10 sec after end of compression, causing rise of 30 mm Hg both in amniotic pressure and cephalic pressure receptor but no effect on FHR (after *1*).

dominal manual compression was applied to the fetal head, the cephalic receptor indicated a pressure higher than 50–60 mm Hg before the fall in FHR was produced (Figure 11). Somewhat lower values (30–40 mm Hg) were obtained by Chung and Hon (*7*) with direct compression of the fetal head by the vaginal route. Kelly (*13*) estimated that when the amniotic pressure is 40 mm Hg the fetal head would be supporting a force of 11 pounds, assuming the head to be spherical and to have a diameter of 10 cm.

Consequences of cephalic compression

Cranial hypertension and cerebral ischemia. Since the bones of the fetal skull are not fused, it is natural to assume that compression on the fetal head will produce cranial hypertension (Figure 12). The correlation between intracranial pressure and pressure in the receptor outside the fetal head was studied by simultaneous recording in the same fetus. Intracranial pressure was recorded in a dead fetus by introducing a catheter into the fetal head, which was punctured through the sagittal suture. Figure 13 shows that there is an acceptable correlation between direct intracranial pressure and the record obtained with the cephalic pressure receptors. In a living fetus, increased intracranial pressure may result in reduced blood flow through the brain. The resulting hypoxia and hypercapnia of the central nervous system would stimulate

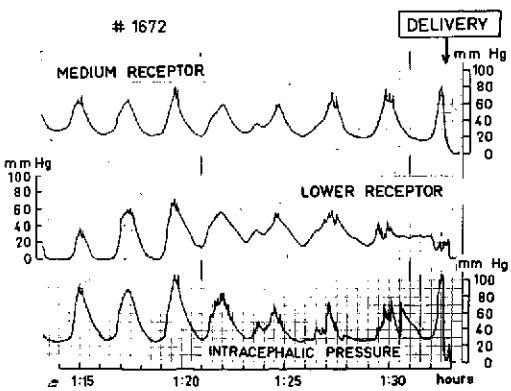

FIGURE 12. Pathophysiology of fetal disturbances resulting from cephalic compression produced by uterine contractions (working hypothesis).

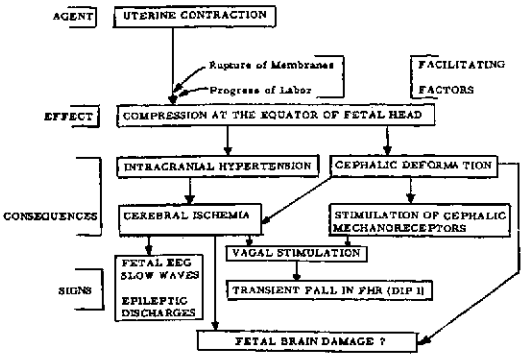

FIGURE 13. Lower tracing is record of intracephalic pressure obtained in dead fetus at 36th week of pregnancy by means of catheter introduced into head by puncturing cranium through sagittal suture. Elevations of intracephalic pressure caused by uterine contractions are similar to those recorded by pressure receptor placed between fetal head and uterine wall.

the vagus center and contribute to dips I (Figure 12). The complete disappearance of dips I after fetal atropinization is in accord with the hypothesis (*5, 6*) postulating that increased vagal tone is the mechanism involved in their pathogenesis. A transient cerebral ischemia can also explain the changes observed in the fetal electroencephalogram (slow waves of high voltage) (*9*) occurring during the peaks of strong uterine contractions that also produce dips I (Figure 12).

Cephalic deformation. Even in normal conditions, the compression of the equatorial zone of the fetal head is stronger than in other areas (*16*) and may cause a deformation (molding) of the head (Figure 12). Borell and Fernström (*2*) have shown radiologically that during labor the parietal bones are usually "disaligned"—that is, more prominent than the occipital and frontal bones (Figure 14A). It should be recalled that the larger portion of the parietal bones are in a zone distant from the equator—that is, one that receives a lower pressure. The frontal and occipital bones are in the equatorial zone, receive a stronger compression, and are relatively depressed inward (Figure 14).

The deformation of the head may stimulate cephalic mechanoreceptors, which may elicit a reflex vagal stimulation and thus contribute to

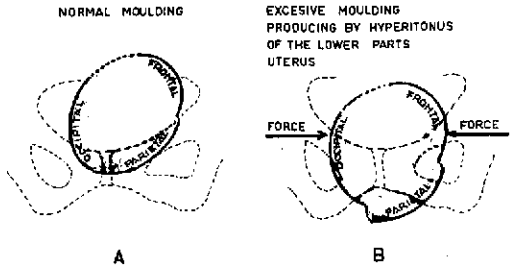

FIGURE 14. Molding of fetal head during labor. In normal conditions (A), parietal bone is moderately displaced outward and disaligned in relation to occipital and frontal bones. In abnormal conditions (B), parietal dsiplacement becomes more pronounced, with great bony disalignment more marked at lambdoid suture. (Drawn after radiological pictures from Borell and Fernström.)

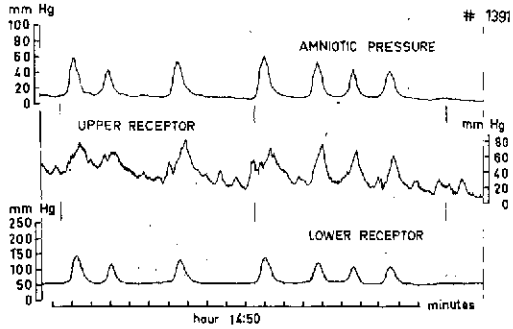

FIGURE 15. Hypertonus of lower uterine segment. Record obtained during labor at term pregnancy. Cervical dilatation is 5 cm. Vertex presentation in LOA, station -1. Upper cephalic receptor shows augmented contractility and tonus of lower part of uterus.

the pathogenesis of dips I (*5, 17*). By distorting cerebral vessels, cephalic deformation may additionally aggravate cerebral ischemia caused by increased intracephalic pressure (Figure 12).

Factors facilitating equatorial compression and deformation of the fetal head

Hypertonus of the lower uterine segment. The abnormal increase in the tone of the lower uterine segment (hypertonic lower segment, "spasm," inversion of contractile gradient) (*4*) augments the compression on the equatorial zone (*15*) and magnifies the deformation of the fetal head (*2*) (Figure 14B). One example of increased tone and contractility of the lower part of the uterus is shown in Figure 15. The record obtained by the upper cephalic receptor shows much more contractile activity and higher pressures than the lower cephalic receptor or the amniotic pressure record.

Rupture of the membranes. When the membranes are intact and the fetal head is completely surrounded by amniotic fluid (Figure 16A),

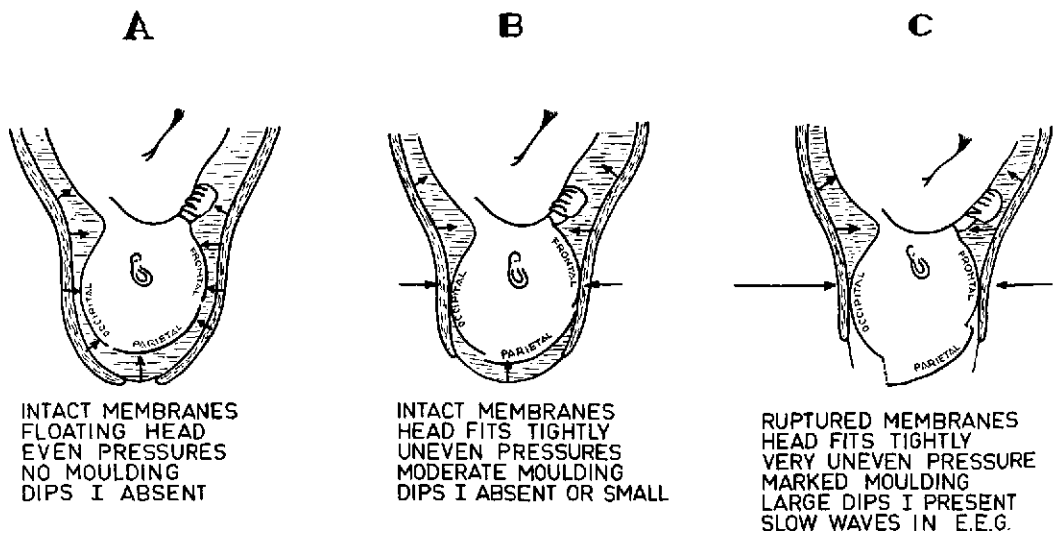

FIGURE 16. The three hydrostatic conditions in which fetal head may be during labor. In A there is no deformation of the fetal head; in B, only moderate molding; in C, marked deformation.

the pressure received is the same in all areas of the head. During uterine contractions there is no cephalic deformation. Blood flow through the brain is not disturbed, because the rise in cephalic pressure is similar to that occurring in other body fluids of the fetus, including the arterial pressure. Dips I are not produced.

When the equatorial zone of the head is in contact with the uterine wall (Figure 16B), this zone receives a higher pressure than the remaining areas of the cephalic pole. However, if the membranes are intact, some counterpressure will be exerted by the forewaters on the parietal bone, preventing excessive disalignment and molding.

This counterpressure markedly diminishes after the rupture of the membranes (Figure 16C), facilitating the bulging of the parietal bone. Molding is increased even further because the pressure on the equatorial zone augments after rupture of the membranes (*14*). The rise in intracranial pressure will be higher than that in amniotic pressure (and in fetal arterial pressure), with a consequent reduction in blood flow through the fetal brain. It follows that the rupture of membranes may facilitate cerebral ischemia and deformation of the fetal head by uterine contractions and thus the production of dips I.

Fetal brain damage

It is logical to assume that a repetition of successive episodes of cerebral ischemia and also the deformation of the brain may lead to permanent damage of the central nervous system of the fetus. This subject has not yet been properly investigated, although it deserves high priority. If cerebral damage may result from this mechanism, obstetricians should be very cautious before deciding to perform the rupture of membranes.

Summary

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 uterine contraction produced a compression of the fetal head equal to or greater than the pressure rise caused in the amniotic cavity, depending on the obstetrical conditions.

For each period of labor and for each given receptor, there is a direct linear relationship between the pressure recorded by that receptor and the amniotic pressure. The receptors placed near the equator of the fetal head record higher pressures than those at a greater distance. In the latter the pressure is equal to the amniotic pressure, whereas in the former the pressure may be up to 2.5 times higher than the amniotic pressure.

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 at the equatorial zone.

During each uterine contraction, the intracephalic 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 rate (dip I), which is simultaneous with the 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.

Acknowledgment

The authors acknowledge their gratitude to Dr. Roberto Yabo, Consultant in Biostatistics of the Pan American Health Organization, for his advice in the analysis of the data.

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EFFECTS OF UTERINE CONTRACTIONS ON THE EEG OF THE HUMAN FETUS DURING LABOR[1]

Elio García-Austt

Human fetal electroencephalograms were first obtained by Lindsley (*13*) by means of electrodes applied on the maternal abdominal walls. Later, similar results were reported with an improved technique using intravaginal electrodes (*2, 3, 4, 5, 17, 19*).

With this technique human fetal EEGs were recorded during advanced labor. It would be important to establish the possible influence on the EEG of fetal anoxia and acidosis during the last stages of labor, when uterine contractions provoke or increase the systemic metabolic disorders. Moreover, a number of findings indicate that uterine contractions causing transient falls in fetal heart rate (FHR) (*1, 20*) also produce a compression and deformation of the fetal head (*20*) and probably a transient reduction in fetal brain blood flow.

It is thus of interest of find out what changes occur in the fetal EEG during uterine contractions and whether these modifications are correlated with the strength of the contraction and the variations in FHR The initial results obtained in nine fetuses will be presented in this paper. Preliminary observations have been submitted recently (*9*).

[1] Research performed pursuant to Contract No. NIH–69–6 with the National Institutes of Health, Bethesda, Maryland, U.S.A. Support also received from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization.

Material and methods

Nine full-term pregnant women were studied during labor, six of them under carbocaine epidural and/or caudal anesthesia. The effect upon the EEG of 124 uterine contractions was analyzed.

The fetal EEG was recorded during advanced labor after rupture of the membranes and with cervical dilatations greater than 4 cm. In every case the head was at or beyond station 0. Three to six electrodes were inserted in the scalp over both parietal and occipital bones, which were the easiest zones to reach through the birth canal. The electrodes were hook-shaped platinum needles, enamel-insulated except at the tip. An 8-channel Grass electroencephalograph (Model III) was used. The EEG was obtained by means of bipolar leads between all the electrodes but one which was grounded. The paper speed was 15 mm/second.

The uterine contractions were inscribed by recording the intrauterine pressure with a thin polyethylene catheter introduced into the amniotic sac by the transabdominal or transvaginal route (*6*). The catheter was connected to a pressure transducer and the latter to an 8-channel recording Poly Viso, with a paper speed of 10 mm/minute. In the first recording the transducer was also connected to the electroencephalograph by means of a Grass Balance Demodulator Unit, in order to have the record of the contraction on the same paper as the EEG. This

simultaneous recording, of course, made it possible to study the relationship between the two variables.

The FHR was recorded by means of an instantaneous cardiotachometer, which was triggered by the R waves of the fetal ECG. The ECG was obtained with a scalp electrode that supplied a fetal signal free from maternal interference (*6*). The FHR was recorded in the Poly Viso.

All these variables, including the EEG in the last five cases, were recorded on magnetic tape in an instrumental tape recorder (Stanborn-Ampex Model 2007). Subsequently the playback of the tape was recorded on a 6-channel Grass Polygraph (Model V), and all these data were compared at a convenient speed (15 mm/sec) and amplification. Different time constants were used (½ amplitude low frequency 0.6/sec and ½ amplitude high frequency 3/sec and 15/sec).

The Apgar score was determined twice, one and five minutes after birth. A neurological examination was carried out within the first 48 hours of life and between the third and fifth days. Postnatal EEGs were obtained in the same electroencephalograph using the 10/20 system for electrode position.

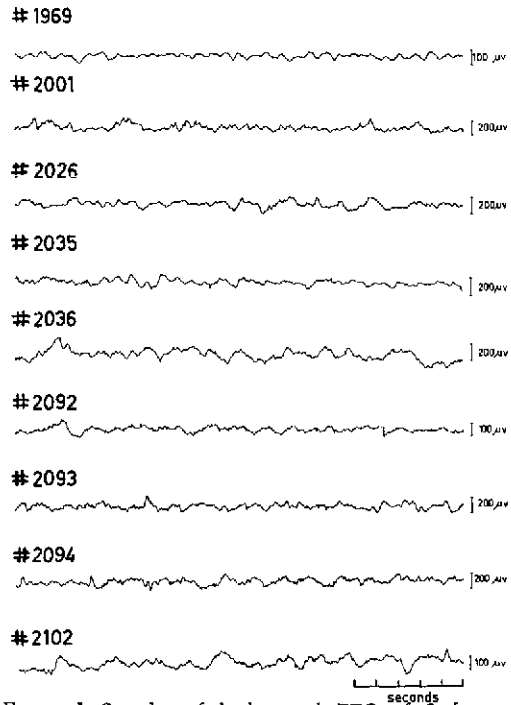

FIGURE 1. Samples of background EEG of 9 fetuses studied. Most common pattern is slow irregular activity of 2–5/sec and amplitude of 50–150 μV (2026 and 2093). Slower waves of 0.5–1/sec are also observed (2036 and 2102). 2001 shows rhythm of 2/sec in middle of record. In 2093 and 2094 irregular low-voltage fast activity is superimposed on slow waves.

Results

The fetal EEG exhibited constantly slow waves during most of the uterine contractions. In some instances epileptiform activity was also recorded. The characteristics of the background fetal EEG—that is, the recording obtained between contractions when the uterus was relaxed—the slowing of the EEG observed during contractions, and the epileptiform activity will be described successively.

Background fetal EEG during labor

The most constant pattern recorded (Figure 1) was a slow irregular activity with a frequency of 2–3/sec and an amplitude of 50–100 μV (cases 2026 and 2093). Slower waves of 0.5–1/sec were also currently observed (cases 2036 and 2102). In one case a regular rhythm of 2/sec was quite consistent along the record (case 2001). In some instances irregular low-voltage fast activity was superimposed on the slow waves (cases 2093 and 2094).

Changes in the EEG not related to the uterine contractions, and apparently spontaneous, were observed (Figure 2). An increase in the amount and amplitude of slow waves, the appearance or increase of low-voltage fast activity, and a considerable reduction in amplitude were the most common variations observed. On the whole, these changes were not consistent, the various patterns alternating throughout labor. In some cases, however, a reduction in amplitude was noted as labor progressed (case 2094). In two cases (2094 and 2102) that exhibited both a low Apgar score and epileptiform activity related

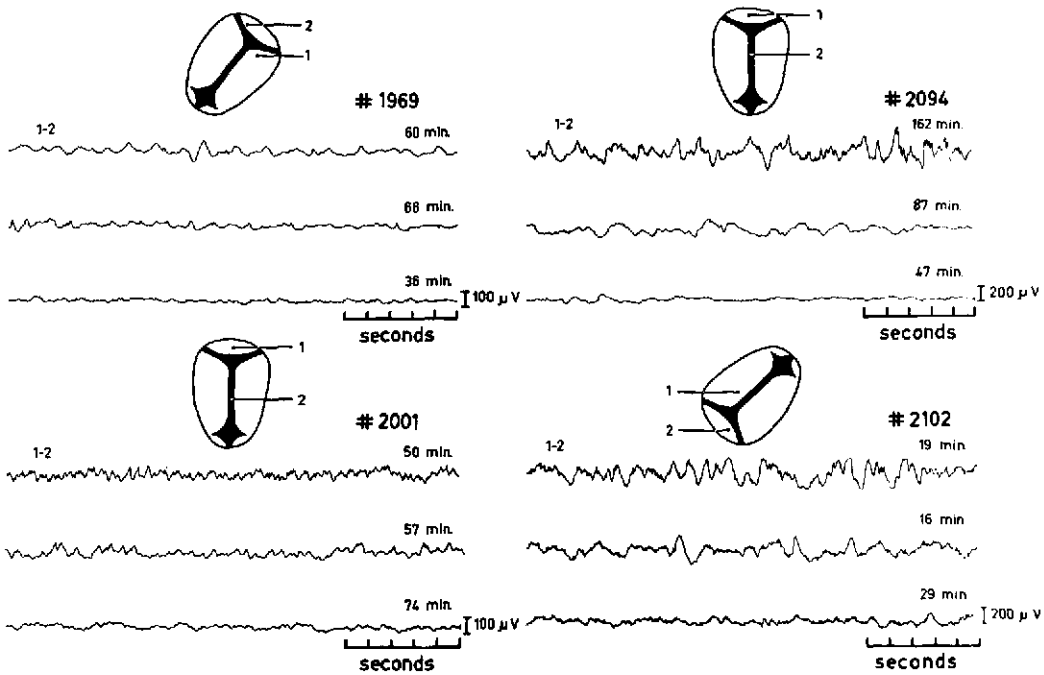

FIGURE 2. "Spontaneous" changes of background fetal EEG during labor. Samples obtained with leads indicated are arranged according to decreasing amplitude in each case. Time is minutes before delivery. Case 1969 (high Apgar score) has irregular slow activity without low-voltage fast activity superimposed. Case 2001 (also high Apgar score) has faster EEG with low-voltage faster activity superimposed. Cases 2094 and 2102 were born with low Apgar scores. Both show considerable amount of low-voltage slow waves with faster activity superimposed. In case 2094 only, reduction in EEG amplitude was progressive throughout labor.

to uterine contractions, patterns of high-voltage slow waves were found to predominate.

Suppression-burst periods were never observed in these full-term fetuses.

Slowing of the EEG during uterine contractions

Of the 124 contractions studied, 76 (61 per cent) provoked consistent changes in the EEG (Table 1). The most frequent variation was the appearance of irregular high-amplitude slow waves of 100–200 µV and 0.5–1/sec (Figures 3 and 4). These changes were present in all the fetuses studied, whether or not the contractions were accompanied by bearing-down efforts.

This slowing of the EEG was gradual and was observed with a latency of 5 to 15 seconds from the beginning of the contractions. The maximum slowing coincided with the peak of the contractions and subsided a few seconds before they ended. In those cases in which it was possible to obtain various simultaneous leads with several electrodes distributed over the scalp, it was found that the slowing of the EEG was generalized and appeared simultaneously in all the leads studied (Figure 5). No statistical dependency between the strength of the contractions and the slowing of the EEG was found.

TABLE 1. Slowing of EEG and dips I during uterine contractions

	PRESENT	ABSENT	TOTAL
EEG slowing			
No.	76	48	124
%	61	39	100
Dips I			
No.	60	62	122
%	49	51	100

$\chi^2 = 8.2$; $r = 0.21$; $p < 0.05$.

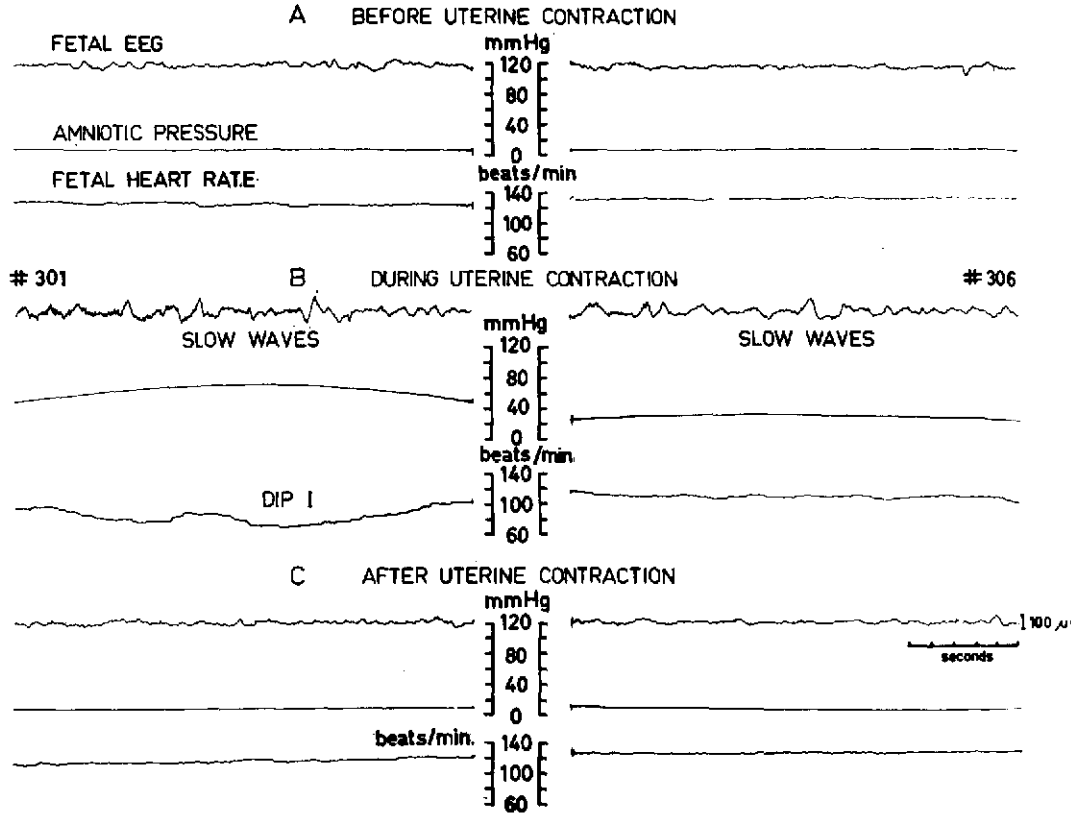

FIGURE 3. Slowing of fetal EEG during uterine contractions. Effects of two contractions (left and right). Before contraction patterns are similar. During contractions similar slowings are observed though contraction 306 (left) is weaker and provokes no changes in FHR (dips I). After contraction both EEG's show same pattern as before.

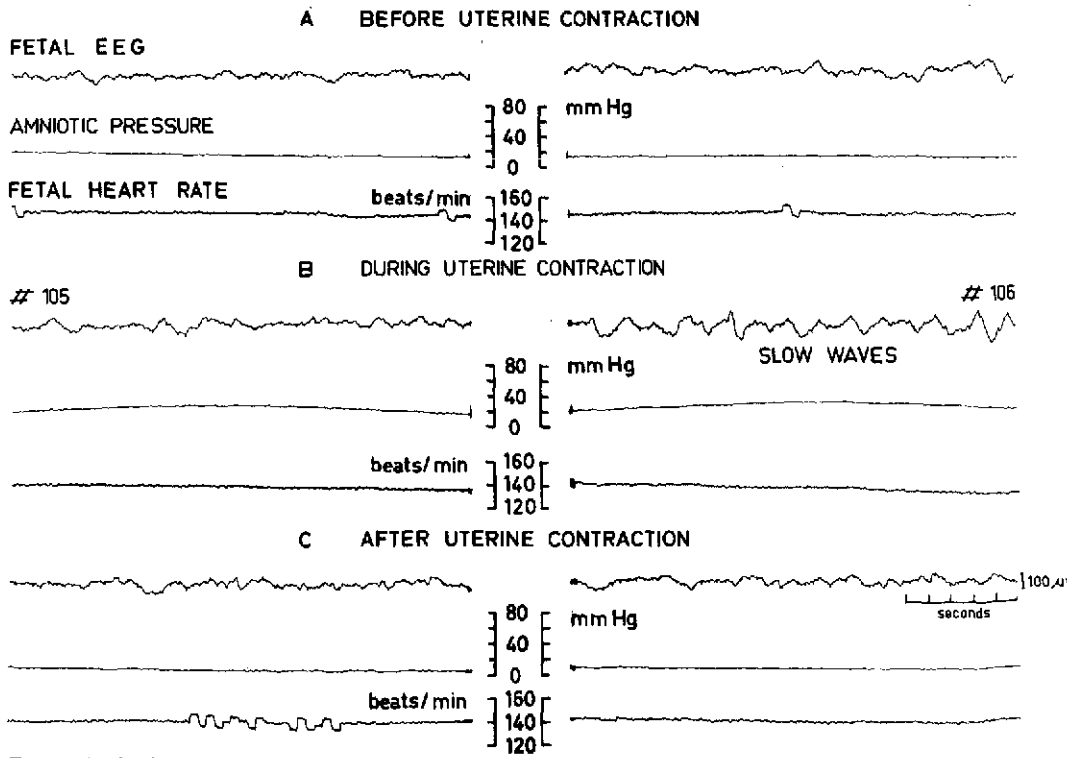

FIGURE 4. Slowing of fetal EEG during uterine contractions. Effects of two contractions (left and right). Before contractions EEG patterns are similar. During and after contraction 105 (left) no significant changes. During contraction 106, considerable slowing of EEG, which reacquires its initial characteristics after contraction. No FHR changes in either contraction.

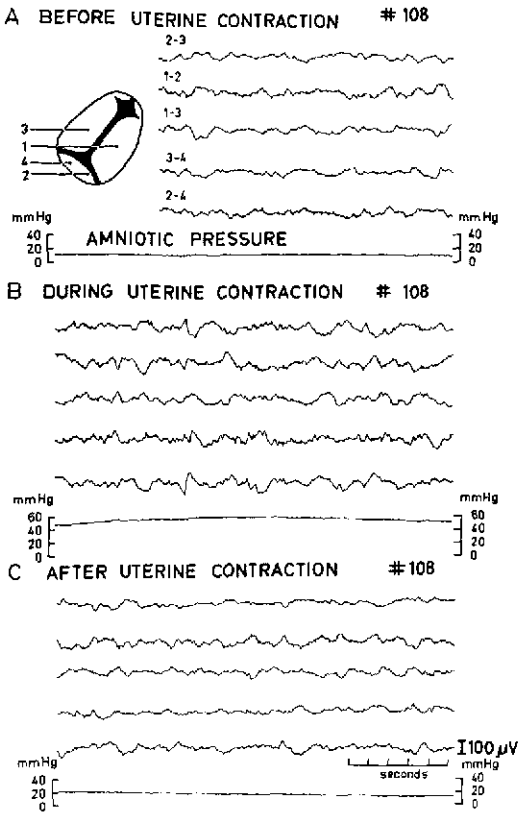

FIGURE 5. Generalized slowing of EEG during uterine contraction. First five records are EEGs obtained simultaneously from different regions of scalp at electrode positions indicated; bottom record is amniotic pressure. Background EEG (A) shows only slight differences between leads. At peak of contraction (B), generalized slowing of EEG, with certain predominance in some leads. After contraction (C) EEG reacquires its initial characteristics.

In 60 of the 124 contractions (49 per cent), transient falls in FHR (dips I) were observed, which were synchronous with the peak of the uterine contractions (Table 1). A statistical dependency between the two phenomena was found (χ^2 8.2) but there was not a significant correlation ($r = 0.21$) between the intensity of the contractions and the slowing of the EEG (Figures 3 and 4).

This slowing simultaneous with the uterine contractions was evident in all fetuses, even those that at birth were in apparently good condition as evaluated by the Apgar scores. In two cases exhibiting a low Apgar score the

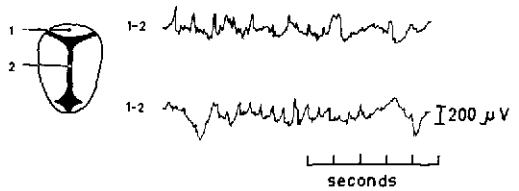

FIGURE 6. Random and rhythmic fetal epileptic activity. Samples obtained from same fetus at different moment with same lead at electrode position indicated. Above, random single sharp waves; below, same waves are repeated rhythmically.

slow waves persisted after the contractions or reappeared a few seconds later. These changes coincided with descents in FHR that appeared or persisted after the contraction (dips II). Under these circumstances the changes were complex ones, as will be discussed below.

Epileptiform activity

Some of the fetuses evidenced random and/or rhythmic epileptiform activity during labor (Figure 6). Random epileptiform activity consisted of slow sharp waves of 200–300 msec duration and 200–400 μV amplitude. These sharp waves were single or repeated many times at a random frequency (Figure 7).

But the most common finding was rhythmic epileptiform activity (Figure 7). Regular

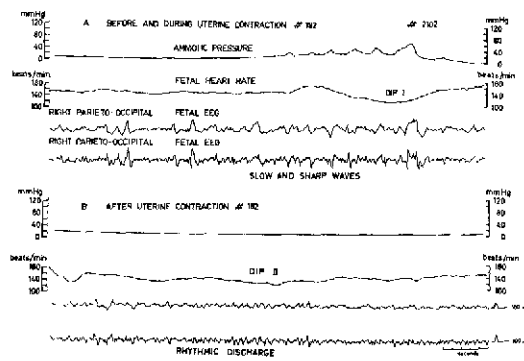

FIGURE 7. Random and rhythmic epileptiform activity during uterine contraction. A and B continuous records. Fetal EEG was recorded simultaneously with two different time constants: long (upper), with slow waves best observed, and short (lower), with faster waves. Before contraction (A), a few high-voltage slow waves and occasionally single sharp waves; during contraction (A), increase in slow waves and a dip I. After contraction (B), a rhythmic discharge develops, best seen in lower EEG, and a dip II is observed.

rhythms of sinusoidal or half-rectified waves with progressive changes of frequency were observed during 5 to 50 seconds. Sometimes the initial frequency was higher (4–5/sec) and decreased at the end of the discharge (1–1.5/sec). In other instances the opposite sequence was recorded. The amplitude of these discharges was of the same order as or lower than that of background activity. As the discharge progressed the amplitude increased. This recruitment or build-up of epileptiform discharge was a common finding.

The epileptiform discharges did not exhibit a great tendency to propagate. On some occasions it was possible to observe propagation over one hemisphere from one electrode to the next. In other instances discharges were seen in both hemispheres, although not synchronous. Bilateral synchronous activity was never observed.

In most cases the epileptic discharges coincided with the uterine contractions (Table 2, Figure 7). They usually appeared a few seconds after the contraction, coinciding with the descents in FHR observed about 40 seconds after the contractions (dips II). This relationship was observed in two fetuses born with a low Apgar score (cases 2094 and 2102). In three others, born with a high Apgar score and not showing dips II, the discharges likewise had the same time relationship with the contractions. Less frequently the epileptiform activity appeared at the onset or at the peak of the contraction. A statistical dependency and correlation between dips II and the fetal epileptiform activity was found ($\chi^2=52.7$; $r=0.672$) (Table 2).

In the two cases with a low Apgar score a number of epileptiform discharges unrelated to the contractions were also observed. In one fetus rhythmic epileptiform activity was set up when compressing the anterior fontanel and upon placing the forceps.

All but one of the cases in which epileptiform activity was recorded during labor exhibited activity of the same type in the EEGs obtained after birth (Figure 8).

The number of cases studied is as yet not large enough to substantiate data of statistical significance. We shall confine ourselves to three typical examples (Table 3):

TABLE 2. Epileptic activity and dips II during uterine contractions

	PRESENT	ABSENT	TOTAL
Epileptic activity			
No.	35	89	124
%	28	72	100
Dips II			
No.	44	80	124
%	35.5	64.5	100

χ^2 52.7; four-fold point correlation = 0.672; $p<0.001$.

Case 2035 had a normal delivery. Its heart rate presented only dips I. The Apgar score at the first and fifth minutes was 7 and 10, respectively, and the neurological examinations were normal. The fetal EEG showed slow waves during contraction but no epileptiform activity. The subsequent EEGs obtained at one hour, two and a half months, four months, and one year of life were normal. In this case all the findings concurred to confirm the normal delivery of a normal baby.

Case 2094 presented a great amount of epileptiform activity during delivery, in addition to slow waves coincident with uterine contractions. Dips II were observed along with dips I. The Apgar scores were low and the neurological examinations abnormal. The postnatal EEG studies exhibited epileptiform activity up to the fifth day of life. An EEG taken two and a half months later was normal. In this case abnormal signs were apparent in labor (epileptiform activity and dips II) and persisted for some time after birth (low Apgar score, abnormal neurological examinations, and epileptiform activity).

In case 2026, in addition to slow waves epileptiform activity appeared during labor. Dips II were not present. After birth the Apgar scores were high and the neurological examinations normal. On the sixth postnatal day the EEG persisted abnormal. The last EEG, recorded one year later, was normal. Evidently in this case there was a discrepancy between the EEG find-

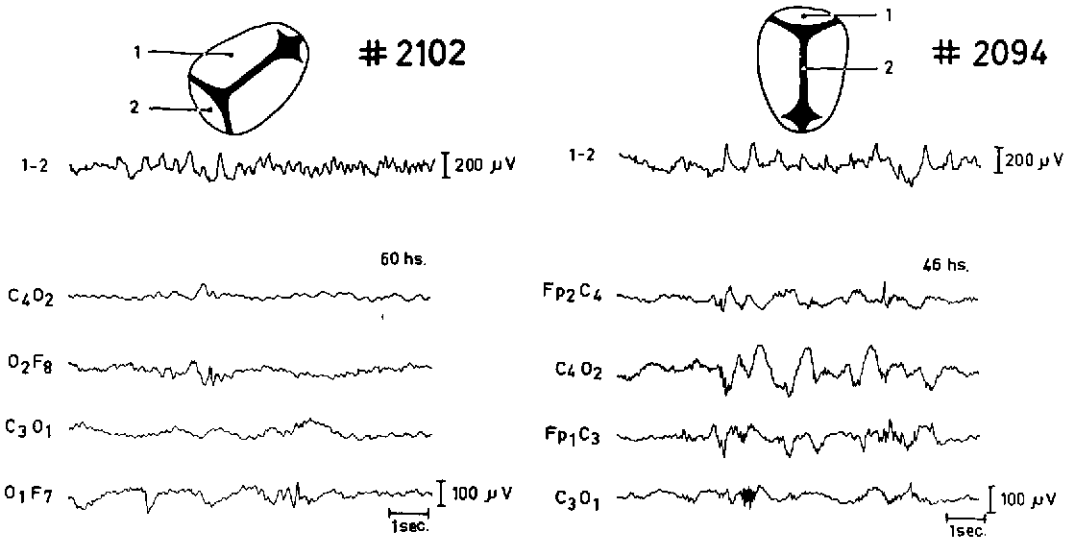

FIGURE 8. Epileptiform activity in fetal and postnatal EEGs. In case 2120, fetal EEG (top, lead indicated) shows rhythmic discharge. Other recordings are multilead EEG registered 60 hours after delivery using 10/20 system for electrode positions; asynchronous sharp waves in both hemispheres. In case 2094, fetal EEG shows waves repeated rhythmically at frequency of 1.5/sec. EEG 46 hours after birth shows rhythmic and random epileptiform activity synchronous and asynchronous in both hemispheres.

ings showing epileptiform activity before and after delivery and the remaining findings, which were all normal.

Discussion

During the uterine contractions and owing to movements of the mother, artifacts were usually recorded, but these can be differentiated by their shape and amplitude from the other slow waves registered during contractions. Moreover, the EEG waves attributed to the effect of contractions were recorded with epidural anesthesia in the absence of pain and mother movements. Artifacts produced by fetal movements that are commonly observed during uterine contractions can be also recognized. The PGR have a different temporal course from that of the slow waves. However, we do not know the characteristics of the electrical activity originating in the fetal cutaneous glands.

It could be postulated that the slow waves recorded on the fetal scalp during contractions are a reflection of the electrical activity of the uterine muscle, or electrohysterogram. Thus, in addition to a slow electrical potential whose time course is concomitant with that of the uterine contraction (*12*) faster activity of 0.5–2/sec of sinusoidal or more or less irregular wave forms has been described (*21*). Sometimes these waves have the same shape as that of the waves recorded on the scalp. However, no electrohysterogram with these characteristics

TABLE 3. Comparative EEG and clinical study of three cases

CASE NO.	FETAL EPILEPTIC ACTIVITY	POSTNATAL EPILEPTIC ACTIVITY					APGAR SCORE		NEUROLOGICAL EXAMINATION	
		1ST	2ND	3RD	4TH	5TH	1ST MIN	5TH MIN	48 HOURS	3–5 DAYS
2035	No	No	No	No	No	—	7	10	Normal	Normal
2094	Yes	Yes	Yes	Yes	Yes	No	1	4	Abnormal	Abnormal
2026	Yes	Yes	Yes	No	—	—	10	10	Normal	Normal

has ever been recorded from the cervix and inferior segment by means of intravaginal electrodes (*22*). Furthermore, the EEG slowing was observed in only 61 per cent of the uterine contractions studied, the electrohysterogram being a constant phenomenon when the contractions are normal, as indeed they were in all the cases studied. Therefore, we believe that the electrical activity recorded on the scalp during the contractions was not of uterine origin.

Epileptiform activity had the same wave shape as in newborn infants and children. The possibility that this activity might be an artifact is eliminated by the fact that it persists after birth with similar characteristics.

The amplitude and frequency of fetal background EEG found in these studies correspond with the descriptions of other authors (*2, 3, 4, 5, 17, 19*). Obviously the EEG slowing is a consequence of uterine contractions even though no relationship between the EEG change and the strength of the contractions was found.

The changes in the EEG of the human fetus reported in this paper occur under conditions in which the fetal head is quite likely being very strongly compressed by the uterine contractions. This transient compression may cause an increase in intracranial pressure, cephalic deformation, and consequent reduction in cerebral blood flow. Ischemia of the brain may explain the occurrence of slow waves and rhythmic discharges in the EEG during the peak of the contractions. The dependency between dips I and the slowing of the EEG in the same stage of labor agrees with this hypothesis, since dips I are known to occur when the fetal head is strongly compressed by uterine contractions (*1, 20*). Moreover, the reduction in brain pO_2 during intracranial hypertension has been demonstrated in animals (*16*) and in the human fetus (*15*). Changes in the EEG pattern similar to those occurring during the peak of uterine contractions have been classically described during brain anoxia in man (*7, 10, 11, 18*). Similar changes have also been reported by Mann (*14*) in the fetal lamb when the ewe is made anoxic by breathing pure nitrogen.

So far there is no evidence that these transient periods of brain ischemia and anoxia may cause permanent damage to the brain. As far as is inferable from the Apgar score of the newborn, there is no correlation between the incidence of dips I during labor and the condition of the newborn (*20*).

In addition to the reduction in brain pO_2 as a possible mechanism of production of slow waves, a direct mechanical action on the brain could also be postulated. The considerable cephalic deformation observed during uterine contractions would seem to support this interpretation.

Dips I were not the cause of the slow waves observed during contractions, because this slowing could be observed in their absence. This eliminates the possibility that decreased heart rate would reduce arterial pressure and blood flow through the brain.

A different problem is involved in the persistence of slow waves and the presence of epileptiform activity immediately after the contractions correlated with dips II. All these fetal signs might also be the result of fetal brain anoxia and/or brain lesion caused by cephalic deformation. These changes were observed only in cases showing a low Apgar score. It should therefore be assumed that in these cases the changes were more marked than in the rest. Moreover, the EEG continued to exhibit epileptiform activity several days after birth. This finding indicates that fetal epileptiform activity observed during labor was caused by abnormal brain conditions that persisted in the newborn. Presumably, after many contractions producing brain anoxia the brain function is consistently disturbed; this makes epileptiform discharges and slow waves appear independently of the contractions.

The presence of epileptiform activity in the fetal EEG is not surprising because the immature brain has a high sensitivity to the hypersynchronous discharge. It is well known that the newborn and the infant develop convulsions with relative ease. In the chick embryo it has been reported (*8*) that EEG epileptic activity

may be present almost simultaneously with the onset of the background electrical activity. The presence of focal cortical seizures with slight or no tendency to propagation is likewise a characteristic of the abnormal EEG in the newborn infant. Hence it is not surprising that the fetus should present similar patterns.

The cases showing discrepancies between EEG and clinical data, of which an example was presented, pose the question of the possible significance of fetal EEG in the management of labor. It is worth noting that in all these cases abnormal EEG patterns were recorded after delivery, a likely indication of important changes in brain function. All the same, in order to gain a better understanding of the future implications of the findings derived from these babies, a more extensive experience is clearly required.

Summary

Fetal EEGs were recorded during advanced labor by means of enamel-insulated platinum needle 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 heart rate was also recorded.

The background EEG activity (recorded between uterine contractions) had a frequency of 2–3/sec and an amplitude of 50–100 μV, occasionally with superimposed faster activity. Apparently spontaneous variations in the patterns were observed.

Most of the uterine contractions provoked consistent EEG changes, which consisted in the appearance of irregular, high-amplitude slow waves of 100–200 μV and 0.5–1 sec. These changes were present in all the fetuses studied.

Some fetuses exhibited random and/or rhythmic epileptiform activity, which also coincided with the uterine contractions. In these cases the newborn EEGs also demonstrated epileptiform activity. This finding indicates that the fetal epileptiform activity observed during labor was caused by abnormal brain conditions that persisted in the newborn.

The changes caused in the fetal EEG by 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 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.

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THE HUMAN FETAL ELECTROENCEPHALOGRAM: 2. CHARACTERIZING THE EEG DURING LABOR[1]

Mortimer G. Rosen and Joseph J. Scibetta[2]

The summated cortical changes of the electroencephalogram (EEG) are a sensitive indicator of metabolic alterations within the brain. Interest in the human fetal EEG has existed for many years, yet a successful technique for continuous monitoring of it has not been available.

The historical development of attempts to study the human fetal EEG began with the work of Lindsley (*5*), who attempted to study his then-unborn son with the use of abdominal electrodes and techniques normally used in fetal heart rate studies. Perhaps the next significant approach was attempted by Bernstine *et al.* (*1*), who attempted to record EEG both with abdominal and with vaginal electrodes. Numerous investigators, including some in this laboratory (*7*), have previously attempted fetal EEG monitoring techniques without more than transient success.

This report documents the patterns, frequencies, and voltages of the fetal EEG *in utero* during labor and correlates them with known patterns after birth. Examples of common electrical artifacts and problems in recording techniques that may be encountered when recording conditions are not satisfactory will be presented. The electrode and the technique for its application have been reported previously (*8*) and therefore will be only briefly outlined here.

[1] Project supported by the John A. Hartford Foundation, Inc.

[2] Presented by Dr. Rosen.

An acceptable fetal EEG monitoring system must incorporate the following principles: (1) the scalp electrode must be harmless and easily applied early in labor; (2) the recording point must be isolated from the conductive vernix and amniotic fluid that normally surrounds and coats the fetal skin; (3) the electrode construction must minimize artifacts produced by uterine contractions, maternal pulses, respirations, and body movements; (4) the electrode must eliminate the fetal heart beat from representation on the tracing.

With these principles in mind, a monitoring system has been developed for the continuous recording of the human fetal EEG. This system makes it possible to record from the fetal scalp during labor with tracings as clear as similar recordings in the newborn infant. A suggested program for the use of this method of fetal study and its place among the already applied parameters in fetal monitoring will be presented.

Technique

The electrode (Figure 1) consists of two suction rings surrounding an inner platinum needle electrode. The outer ring is soft silastic and contains pure powdered silver embedded along its circumference. The silver ring acts as a patient ground. The suction helps to prevent contact with the highly conductive extrauterine environment and also holds the electrode in place.

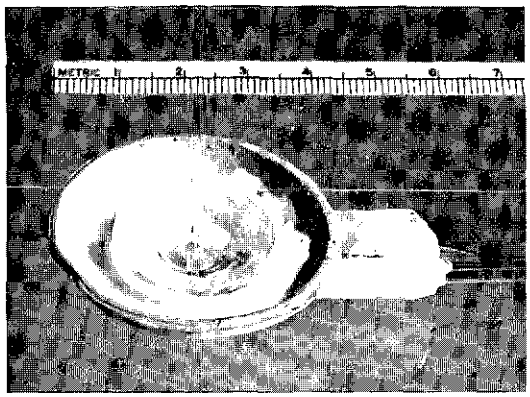

FIGURE 1. Actual size of electrode with needle point in center of firm lucite disc. Outer gray-shaded area is soft silastic impregnated with powdered silver (see text).

The inner cup, of firm lucite, is one millimeter deeper than the needle is long. Besides providing a firm base, this disc prevents accidental deep penetration of the needle beneath the scalp. The inner suction draws the underlying skin up to the needle, making a stable electrical contact. The recovery time (electrical stability) for a needle electrode after even small movements that may occur during labor is much more rapid than for electrodes with larger surfaces. The schematic drawing of this electrode can be obtained on request.

Three cartoons (Figure 2) illustrate the monitoring and the most common pitfall encountered. In Figure 2A we note the fetus surrounded by conductive fluid with a well-isolated electrode. Here the EEG potentials are not attenuated by loss into this environment and the tracing is of good quality. In contrast, in Figure 2B, although the electrode makes contact with the skin, fetal heart rate patterns are the only apparent information. This will occur when the two suction rings do not form a complete seal. In these cases the needle point is not isolated from the vaginal and uterine fluids. Following birth, the previously recorded tracing (Figure 2A) should be duplicated in the neonate (Figure 2C) in normal cases.

A bipolar recording technique is used. Two identical but separate electrodes are applied after 3 centimeters of cervical dilatation with

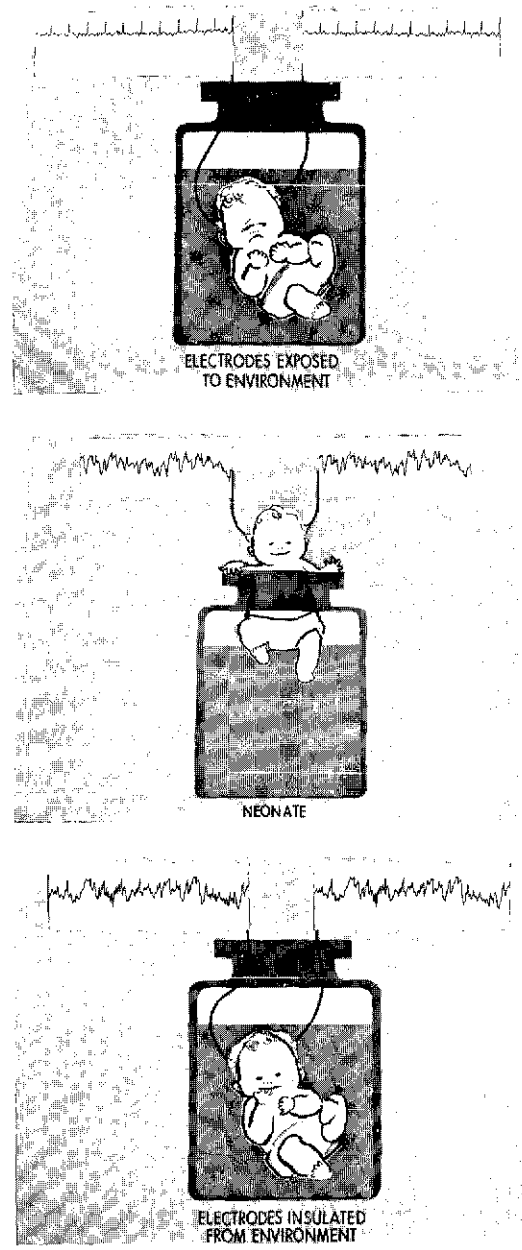

FIGURE 2. Cartoons illustrate monitoring. A, good-quality tracing from fetus *in utero,* with needle points of electrodes isolated from amniotic fluid and skin of fetus. B, poor-quality tracing with fetal heart patterns and almost no fetal EEG, obtained when needle points of electrodes are not isolated from environment. C, good-quality tracing after birth, similar to that obtained *in utero.*

the amniotic membranes ruptured. Attempts are made to achieve biparietal location, but this is not mandatory. With the electrodes securely against the scalp, the suction is turned on. Ten to 15 centimeters of water pressure is adequate.

The usual EEG recording parameters are used with a Type R Beckman Dynograph. The paper speed is 30 mm/sec, and filtering to admit wave frequencies between 1/2 and 32 cycles/second is used. Generally, 50 μV/cm amplification makes it possible to discriminate wave forms clearly. If the voltage is lower, a 20 μV/cm amplification may be used.

Results

General statement about studies completed

Twenty satisfactory tracings have been obtained with these electrodes. A problem still encountered is the contamination of the recording with the fetal heart complex (Figure 3, Line A). This will occur if the electrodes are not applied securely against the scalp or if there is a defect in the electrode insulation.

There have been no complications due to the use of suction. At times small abrasions—outlines of the inner lucite disc with the punctate mark of the needle—can be seen, but these are superficial and disappear rapidly. Even after eight hours of continuous recording it may be difficult to find the site of electrode location. In comparison to forceps marks or scalp microblood incisions, these are inconspicous marks.

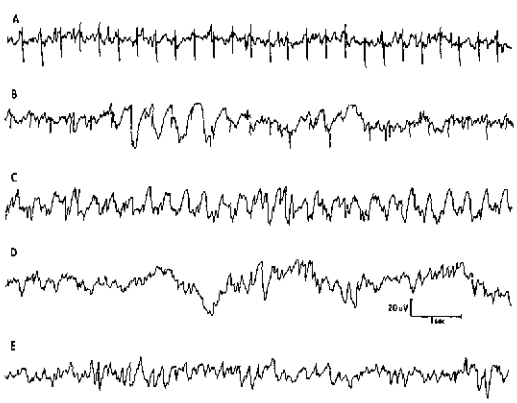

FIGURE 3. Line A, Fetal EEG early in labor. Line B, fetal EEG immediately prior to birth. Line C, neonatal EEG shortly after birth. Line D, neonatal EEG third day after birth.

Defining the fetal EEG

From our previous experiences in fetal surgery in the guinea pig (*6*) and the sheep fetus (unpublished data), we did not anticipate that the patterns found *in utero* would be different from those found immediately after birth. This was confirmed in these studies. In Figure 3, we note the EEG before birth (Lines A and B) and then 30 minutes after birth (Line C) with the same electrodes in place. There appears to be little change in voltage, patterns, or frequencies.

However, to make this comparison, the time that the tracing is obtained is most important. For example, early in a recording, prior to the use of medications, the tracing may differ from that obtained later when the presence of an EEG drug effect is documented by altered EEG patterns.

In Figure 4 we note a series of recordings taken before (Line A) and after the use of meperidine (Lines B through E). The tracing shows classic EEG voltages (20–75 μV/cm) and frequencies (2–25 cycles/sec), similar to those described in term neonates (*3*). At first the recording time is continuous without areas of flattening (Lines A and B). The EEG patterns in Lines C and D demonstrate what is described in the neonate as the *trace-alternant*-type EEG. The trace-alternant pattern consists of bursty wave forms (3–7 cycles/sec) in the theta range separated by short intervals of voltage depression. This will occur naturally in most infants after the thirty-fourth week of life and also after certain medications have been administered. As noted earlier, this mother had received 50 mg of meperidine intravenously. In Line E, a different EEG pattern, now prior to birth, indicates low-voltage fast activity predominantly

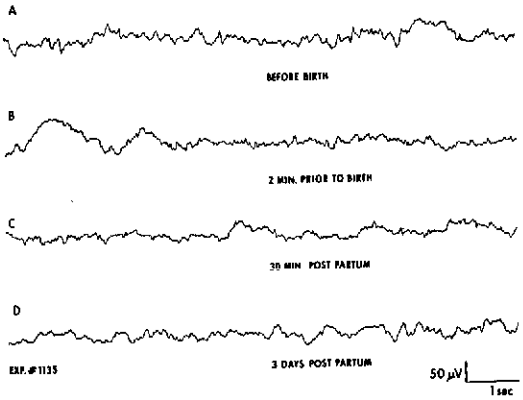

FIGURE 4. Line A, fetal EEG prior to administration of 50 mg of meperidine intravenously to mother in labor. Line B, minimal drug effect. Line C, first indication of trace-alternant pattern. Line D, later in recording trace-alternant pattern more apparent. Voltage of tracing is lower. ECG exists as a contaminant of electrical recording. Line E, marked depression of voltage (1½ hours later) with 25 cycles/sec activity most prominent. Line F, neonatal EEG immediately after birth documenting persistence of pattern.

in the beta range (25 cycles/sec), which continued into the neonatal period (Line F). This infant was born with an Apgar score of 7 and was without overt distress. After its initial cry, it promptly returned to a lethargic state and needed repeated physical stimulation to restore crying and movement. This pattern

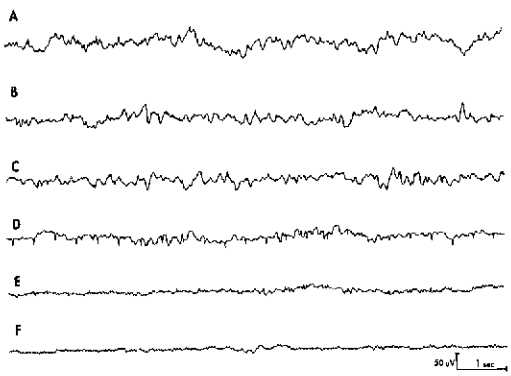

FIGURE 5. Line A, poor-quality fetal recording with EEG almost entirely obscured by fetal heart patterns. Line B, occasional high-voltage delta-like artifact in poor-quality tracing. Line C, a less-common pulsation artifact, which was synchronous with fetal ECG (not shown). Line D, good-quality tracing with slow baseline movement artifact present during contraction. Line E, good-quality fetal EEG.

of low-voltage fast activity has been reported in the neonate as long as 24 hours after birth and correlated with the medications given in labor (*9*) and neonatal neurologic examinations (*2*). The subject of drug transfer across the placenta is being studied more extensively with this technique and will be the subject of a forthcoming paper. At this time we can say that these patterns are a repeatable occurrence following the use of meperidine.

EEGs and artifacts

In Figure 5, Line A, we note (as discussed earlier) an unacceptable tracing because of fetal ECG contamination. If the electrodes are applied well, there should be little or no contamination with heart rate. The recordings should remain stable and clear even during uterine contractions.

At times slow-wave artifacts may be present; they are most often found in less stable recordings (Figure 5, Lines B, C, and D). These wave forms may vary, but generally differ from the normal patterns found in that they are higher in voltage, different in shape, and transient in time without repeatable patterns. They may be found more commonly when there is patient movement in bed and particularly electrode wire movement. Delta-wave frequencies (½ to 2½ cycles/sec) persisting in runs longer than 10 seconds have a more ominous prognosis in the neonate (*4*). Therefore, it is most important to be certain of the origins of this information in fetal recordings.

Occasionally the electrode records pulsations that are synchronous with maternal or fetal heart rates (Figure 5, Line C). This is identified by comparison with synchronous ECG tracings. Finally, the extremely slow baseline movement noted in Figure 5, Line D, may most often be present during a contraction and is considered to reflect electrode sway or movement during that contraction. Figure 6 documents 50 consecutive seconds of acceptable recording without artifact and at the higher amplification of 20 μV/cm.

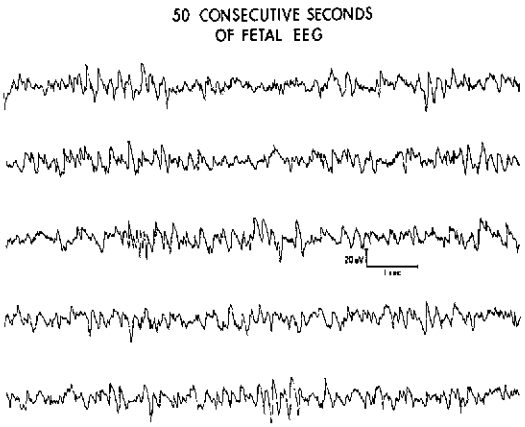

FIGURE 6. Fifty consecutive seconds of good-quality recording without artifact (note 20 μV/cm amplification).

The artifacts described in detail are for purposes of illustrating the pitfalls in recording and reading fetal tracings. Generally, less than 1 per cent of recording time is eliminated by such changes. However, this cannot be obtained unless extreme care is paid to the electrode preparation, its application, and EEG recording techniques.

Electrode failures

During the past five years countless attempts have been made to arrive at a clinically acceptable, continuous monitoring system. Many kinds of surface electrodes, such as discs, have been tried and found unsatisfactory even when isolated with suction rings. These surface discs are more difficult to isolate from the vagina because of their large area. Following gross movements the recovery time of a disc-type electrode may be several seconds; thus maternal movements and contractions will cause loss of pages of tracing during critical periods. Variations of skin-clip-type electrodes such as are used for fetal heart monitoring were also tried without success. These electrodes were not used with suction for isolation.

Discussion

Attempts to study the fetal EEG are not new and have been briefly reviewed earlier. This method allows successful and continuous fetal brain wave recording in an atraumatic manner. The technical application of the electrodes is easily mastered and does not hinder the obstetrician in the normal conduct of labor. Patient acceptance has been high. Once the electrodes are in place, the patient is relatively unaware of their presence.

The principles of EEG suggest that the wave forms and voltages are reflections of the superficial areas of the brain underlying the bipolar electrode location. Focal electrical abnormalities representing areas of pathology are occasionally seen. The technique does not lend itself to the identification of focal lesions without the use of numerous electrodes scanning large areas of the vertex. As yet, this is not easily performed.

The cortical and subcortical voltages reflected in the EEG occur from cells quite sensitive to general metabolic changes also taking place in deeper areas of the brain. For example, if patterns compatible with drugs such as meperidine are seen, it is reasonable to expect similar changes to be taking place in deeper portions of the brain.

In a like manner, asphyxial changes, although recorded from cortical and subcortical areas, may also be representative of analogous patterns deeper in the brain. In rhesus monkeys Windle (*11*) has recorded documented pathology both in the cortex and the basal ganglia following prolonged neonatal asphyxia. Towbin (*10*) has described prenatal lesions attributed to hypoxia. It is reasonable to suspect that the monitoring of EEG may document the time of injury if it takes place during labor.

This report does not document such changes. It is suggested that the addition of fetal EEG studies to the other accepted fetal monitors, such as the fetal cardiogram and acid-base studies, and the maternal uterine contractions will allow its development as a valuable diagnostic laboratory test in the study of fetal brain damage.

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INFLUENCE OF THE RUPTURE OF MEMBRANES ON COMPRESSION OF THE FETAL HEAD DURING LABOR[1]

O. Althabe, G. Aramburú, R. L. Schwarcz, and R. Caldeyro-Barcia[2]

In a previous paper (*10*) it has been shown that when uterine contractions of labor exert a strong compression on the fetal head, and this pressure is higher than the pressure in the amniotic fluid cavity, the fetal vagus is transiently stimulated and a transient fall (dip I) occurs in the tracing of the fetal heart rate (FHR).

Dips I occur simultaneously with the contraction (*2*) in such a way that the bottom of the dip is recorded almost at the same time as the peak of the contraction (Figure 1).[3] They are similar to the "early decelerations" described by Hon and Quilligan (*6*).

In this paper we shall present the influence of some obstetric factors, such as the rupture of membranes, on the incidence of dips I throughout labor and shall also discuss the probable mechanism of action.

Twenty-six pregnant women at term were studied during labor. Intrauterine (amniotic) pressure and FHR were continuously recorded from the beginning of labor to delivery by methods described previously (*2*). The progress of cervical dilatation and that of the station of

[1] This study received support from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization and from grant HD 00222-06 of the National Institute of Child Health and Human Development, Bethesda, Maryland, U.S.A.

[2] Presented by Dr. Althabe.

[3] Dips II, which occur 30 to 60 seconds after the contraction (*2*), will not be discussed in this paper.

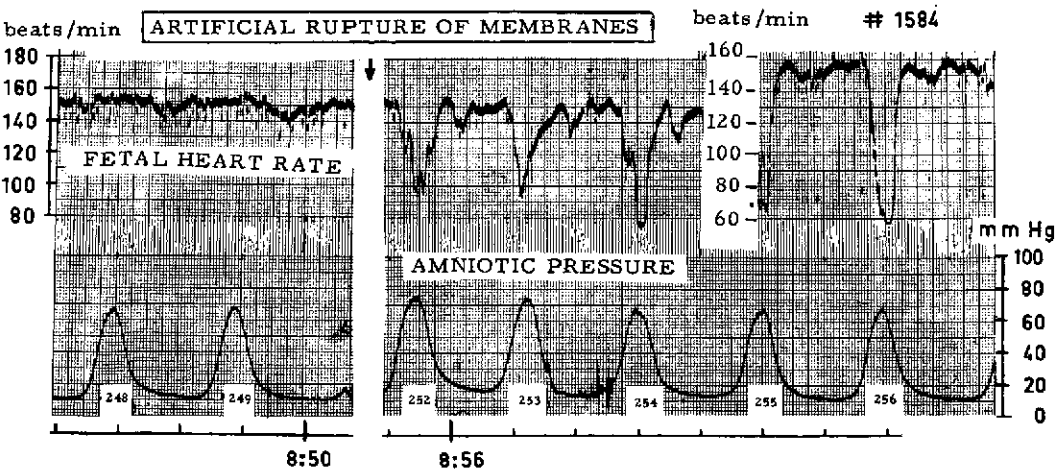

FIGURE 1. Record obtained during first stage of labor. Cervical dilatation 6 cm. Before rupture of membranes, dips I are absent from the FHR tracing. After rupture, each uterine contraction causes a dip I of large amplitude.

the fetal head were periodically checked by vaginal examination.

Effect of the rupture of membranes

The production of dips I by uterine contractions was greatly increased by the rupture of membranes. Figure 1 shows one typical record that illustrates such effects. Before the rupture, the contractions did not cause dips I (they only produced dips II of very small amplitude). After rupture of the membranes each uterine contraction caused a dip I of large amplitude (a small dip II follows each dip I).

Figure 2 and Table 1 show the results obtained in all 26 women. Before rupture of the membranes, 2,157 contractions were recorded and only 82 of them (3.8 per cent) produced dips I. After the rupture of membranes, 2,243 contractions were recorded and 747 of these (33.3 per cent) caused dips I. The difference between the percentages before and after the membranes were ruptured is highly significant ($p<0.001$).

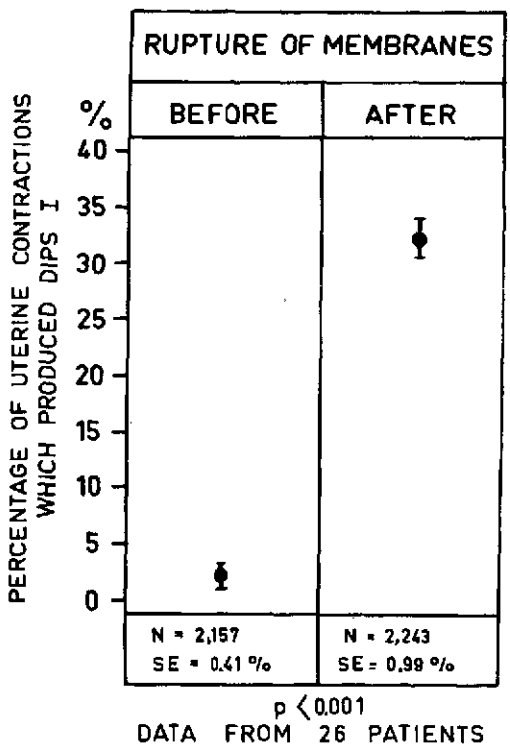

FIGURE 2. Incidence of dips I is significantly higher after rupture of membranes than before.

TABLE 1. Number of contractions causing dips I before and after rupture of membranes

	TOTAL CONTRACTIONS	CAUSING DIPS I		NOT CAUSING DIPS I
		NO.	% [a]	
Before rupture of membranes	2,157	82	3.8	2,075
After rupture of membranes	2,243	747	33.3	1,496
Total	4,400	829		3,571

[a] $p < 0.001$.

Interpretation

Our working hypothesis is schematically shown in Figure 3. When the membranes are intact and the head is floating (the cephalic equator being above the inlet), there is amniotic fluid all around the fetal head and it transmits the pressure of the uterine contractions equally in all directions (Pascal's law). The head receives the same pressure on its entire surface and is not deformed during the contractions (Figure 3A). Furthermore, the same pressure is also exerted on the fetal body, umbilical cord, and placenta. The contractions produce no changes in blood flow through the fetal brain. Under these conditions they do not produce dips I.

During engagement and descent of the head, the cephalic equator fits tightly in the lower uterine segment (Figure 3B). There is no longer free communication between the amniotic cavity and the forewaters. The pressure exerted by the uterine contractions on the cephalic equator is greater than that above and below the equator (*8, 10*). The fetal head is slightly deformed (molding) and it becomes lengthened from chin to occiput and shortened in all other directions; as a result, the parietal bones bulge and become disaligned with the frontal and occipital bones. The rise in intracephalic pressure during the contractions may be

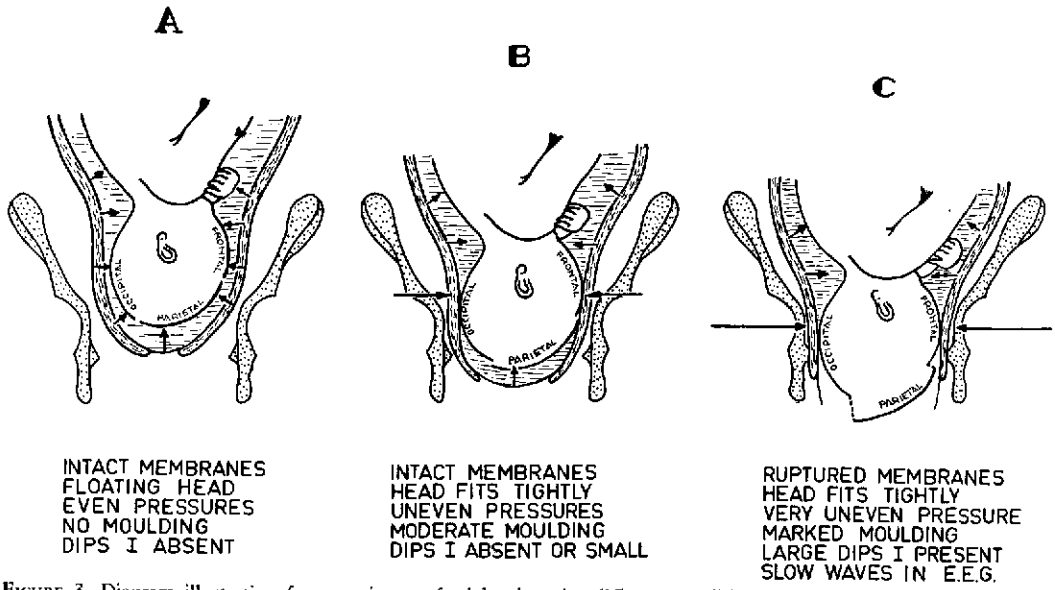

FIGURE 3. Diagram illustrating forces acting on fetal head under different conditions of labor and resulting cephalic deformation (molding).

greater than that occurring in the amniotic cavity and in the fetal body fluids; the consequence is a transient reduction of cerebral blood flow. In these conditions, the incidence of dips I is low and their amplitude small.

After the rupture of membranes, there is no longer any counterpressure exerted by the bag of waters against the lower part of the head and the pressure on the cephalic equator during contractions is increased (*9*) (Figure 3C). The rupture of membranes thus facilitates the deformation of the fetal head by the contractions (Figure 3C) and the disalignment of the parietal bones is very marked.

The rise in the intracranial pressure during uterine contractions is now markedly greater than that occurring in the amniotic sac and the fetal body fluids and may cause a significant reduction in cerebral blood flow. The resultant ischemia, hypoxia, and hypercapnia of the brain are known to cause direct stimulation of the vagal center, a mechanism that explains the transient fall in FHR occurring simultaneously with these contractions.

Cerebral ischemia may explain the change in the EEG pattern (high-voltage slow waves) observed at the time of the peak of strong contractions that produce dips I (*5*). Cerebral ischemia also stimulates the vasomotor center and may cause fetal arterial hypertension, which in turn, acting through the baroreceptors of the carotid sinus and aortic arch, will reflexively stimulate the vagus, causing the dip I (*7*).

The deformation of the fetal head may stimulate mechanoreceptors (*3*) in the face and head, which may also reflexively stimulate the vagus and contribute to producing dips I. The deformation of the cranial cavity may also disturb blood flow and contribute to cerebral ischemia, eliciting the mechanism described above. Since the rupture of membranes increases the compressive effects of uterine contractions on the fetal head (deformation and cranial hypertension), it naturally encourages the production of dips I.

Effects of the progress of cervical dilatation

This study was made in the same 26 patients. Labor was divided into eight consecutive periods according to cervical dilatation (Figure 4). The second stage was included in the eighth period. All the uterine contractions recorded during each of the eight periods in all 26 patients were pooled. The percentage of contractions causing

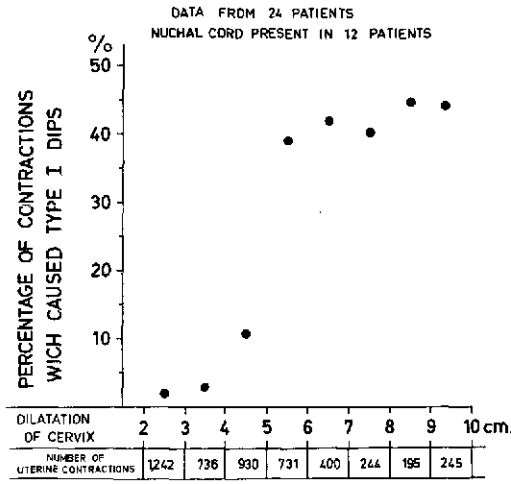

FIGURE 4. Incidence of dips I increases as cervical dilatation augments. A marked rise is produced between 4 and 6 cm of dilatation.

dips I—that is, their incidence—was very low for the first three periods (cervical dilatation from 2 to 5 cm) and increased markedly (about 40 per cent) for the remaining periods. This confirms previous reports by Faúndes *et al.* (*4*) and Aramburú *et al.* (*1*).

For statistical analysis, labor was divided in

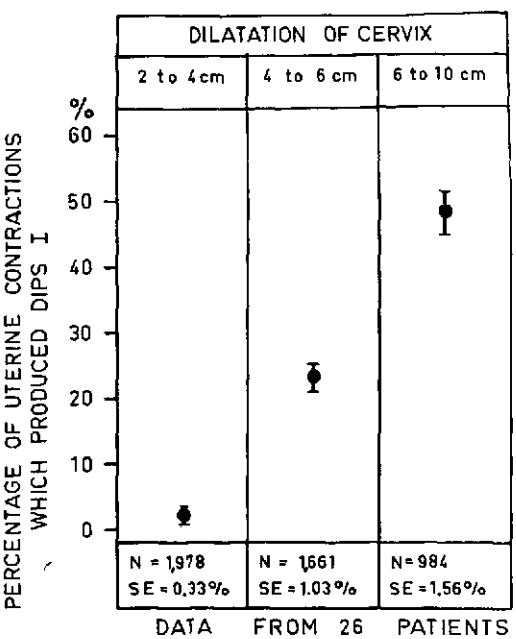

FIGURE 5. Incidence of dips I is significantly different in the three periods of labor divided according to dilatation of cervix.

TABLE 2. Number of contractions causing dips I in relation to progress of cervical dilatation

DILATATION	TOTAL CONTRACTIONS	CAUSING DIPS I NO.	CAUSING DIPS I %	NOT CAUSING DIPS I
2–4 cm	1,978	44	2.22	1,934
4–6 cm	1,661	385	23.18	1,276
6–10 cm	984	470	47.76	514
Total	4,623	899		3,724

three periods: early first stage (dilatation 2–4 cm); mid-first stage (dilatation 4–6 cm); and advanced labor (dilatation 6 to 10 cm and second stage) (Figure 5). The difference between the three periods in the incidence of dips I was highly significant (Table 2).

Three factors may explain these results:

1. *Cervical dilatation by itself.* When the cervix is closed (Figure 3A) the part of the lower uterine segment that faces the lower part of the head would reinforce (if membranes are intact) or exert (if membranes are ruptured) the counterpressure that could minimize cephalic deformation. This counterpressure diminishes gradually as cervical dilatation progresses, facilitating cephalic deformation.

2. *Coincidence of progresss in cervical dilatation with rupture of membranes.* In about 80 per cent of the 26 patients studied, the membranes were artificially ruptured when cervical dilatation was between 4 and 6 cm (Figure 6).

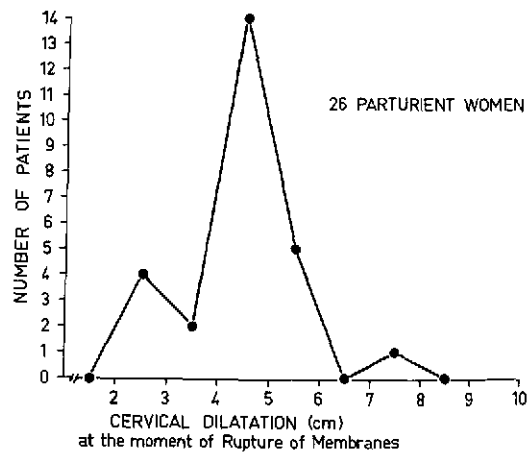

FIGURE 6. Frequency polygon showing cervical dilatation in 26 patients at moment of rupture of membranes.

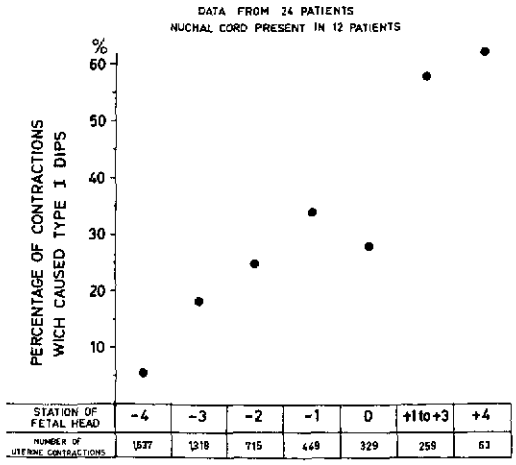

FIGURE 7. Incidence of dips I rises as fetal head engages and descends in birth canal.

This may explain the abrupt rise in the incidence of dips I when cervical dilatation progressed to this point (Figure 4).

3. *Coincidence of the progress in cervical dilatation with progressive engagement and descent of the fetal head in the birth canal.* This factor will be discussed below.

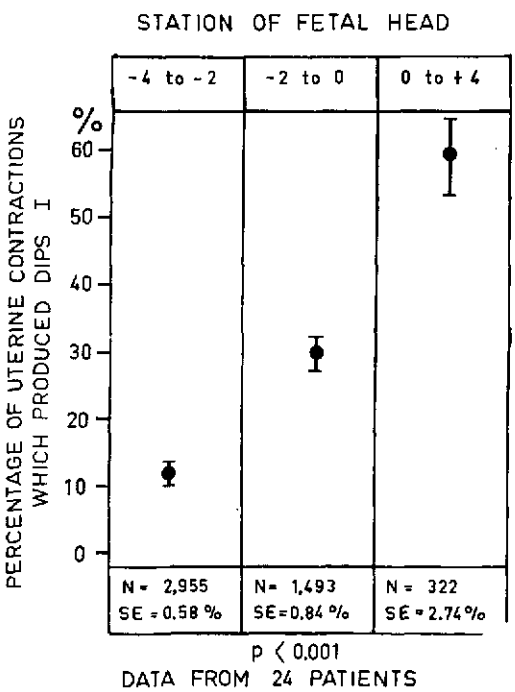

FIGURE 8. Incidence of dips I differs significantly in the three periods of labor divided according to the station of the fetal head.

Influence of station of fetal head

Figure 7 shows that the incidence of dips I rises progressively as the fetal head descends in the pelvis, confirming previous reports of Aramburú *et al.* (*1*).

To study this problem statistically, labor was divided into three periods according to the station of the fetal head (Figure 8, Table 3). In the first period (station –4 to –2) the incidence of dips I was only 11 per cent. It increased to 30 per cent when the station was between –2 and 0, and to 60 per cent when the head was between stations 0 and +4. The difference in incidence between these three periods is highly significant ($p<0.001$).

The progress of the fetal head through the birth canal may in itself increase the incidence of dips I, because as the head becomes more engaged the compression exerted by the uterine contractions on the cephalic equator augments (Figure 3B and C). However, these effects may be influenced by the coincidence with simultaneous progress in cervical dilatation, which might have a direct effect of its own.

Furthermore, the number of cases with ruptured membranes increases as the fetal head descends, and this may also influence the results. The linear relationship illustrated in Figure 8 between incidence of dips I and the station of the fetal head suggests that the timing of the rupture of membranes has been more or less evenly distributed between stations –4 and –1.

There is a need for studies to evaluate the influence of each of the three factors mentioned

TABLE 3. Number of contractions causing dips I in relation to progress of fetal head through birth canal

STATION	TOTAL CONTRACTIONS	CAUSING DIPS I NO.	CAUSING DIPS I %	NOT CAUSING DIPS I
—4 to —2	2,995	333	11.27	2,622
—2 to 0	1,493	444	29.74	1,049
0 to +4	322	189	58.70	133
Total	4,770	966		3,804

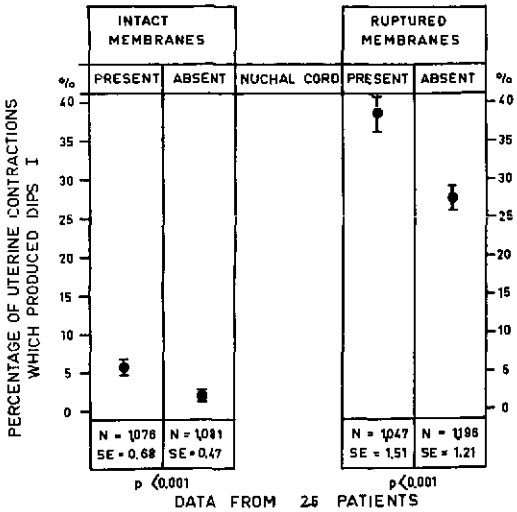

FIGURE 9. Presence of nuchal cord increases incidence of dips I. Differences between groups with and without nuchal cord are significant, both with intact and with ruptured membranes.

—rupture of membranes, cervical dilatation, and descent of the fetal head.

Influence of the presence of nuchal cord

Nuchal cord was present in 13 of the 26 patients studied. With intact membranes the incidence of dips I was 2.4 per cent when nuchal cord was absent and 5.2 per cent when it was present. The difference is significant ($p<0.001$) (Table 4). With ruptured membranes, the incidence was 28 per cent without nuchal cord and 39 per cent with. This difference is also highly significant ($p<0.001$) (Table 5).

TABLE 4. Number of contractions causing dips I before rupture of membranes in patients with and without nuchal cord

NUCHAL CORD	TOTAL CONTRACTIONS	CAUSING DIPS I NO.	CAUSING DIPS I % [a]	NOT CAUSING DIPS I
Present	1,076	56	5.20	1,020
Absent	1,081	26	2.41	1,055
Total	2,157	82		2,075

[a] $p < 0.001$.

TABLE 5. Number of contractions causing dips I after rupture of membranes in patients with and without nuchal cord

NUCHAL CORD	TOTAL CONTRACTIONS	CAUSING DIPS I NO.	CAUSING DIPS I % [a]	NOT CAUSING DIPS I
Present	1,047	410	39.16	637
Absent	1,196	337	28.18	859
Total	2,243	747		1,496

[a] $p < 0.001$.

The presence of nuchal cord increases the production of dips I, both when the membranes are intact and when they are ruptured. However, its influence is far less striking than that of the rupture of membranes.

The presence of one or several loops of the cord around the fetal neck may facilitate the compression or stretching of the umbilical vessels by uterine contractions. These stimuli are known to elicit a reflex fall in FHR (6).

Summary

Dips I are transient falls of fetal heart rate (FHR) occurring simultaneously with uterine contractions. Much evidence indicates that they are caused by 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 result.

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 the incidence was significantly greater after the rupture of membranes (33 per cent) than when these were intact (4 per cent). It 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—significantly higher than in early labor (intact membranes, cervical dilatation smaller than 4 cm, and fetal head above –3 station), when it was about 2 per cent.

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.

Acknowledgment

The authors acknowledge their gratitude to Dr. Roberto Yabo, Consultant in Biostatistics of the Pan American Health Organization, for his advice in the analysis of the data.

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DISCUSSION

Leon I. Mann: The Effect of External Cephalic Compression and Uterine Contractions on Fetal EEG, Heart Rate, and Cephalic Metabolism

The forces that act to compress the fetal head during labor and the effects of those forces on the patterns of fetal heart rate and EEG have been identified in the presentations.

These forces may be separated into two groups: first, those that arise from the increase in pressure within the amniotic cavity during a contraction; second, those due to the resistance of the cervical tissues and the muscular and bony pelvic wall. The force exerted on the fetal head by a contraction can be approximated by determining the pressure within the amniotic cavity and by considering mean cephalic diameters. The force (kilograms or pounds) is equal to the product of pressure and area. The occipito-frontal diameter (mean 11.75 cm) identifies the plane of largest dimensions (equatorial plane), which would have a maximum area of 108.5 cm^2 if assumed to be circular. A pressure of 50 mm Hg would result in a maximum force of 16.3 lb (7.4 kg) at that plane (1 mm Hg = 1,333 dynes per cm^2; 1 dyne = 2.25 x 10^{-6} lb; 1 kg = 2.204 lb). The force would decrease as the plane of the diameter decreased or the pressure decreased, so it is difficult to know exactly the magnitude of the force exerted on the total head. The force will be distributed equally, however, while the membranes remain intact and the fetal head is unengaged.

When the fetal head engages within the pelvis (generally station 0 or beyond), the resistance of the cervix and of the muscular and bony pelvic wall offers an additional compression force, particularly if cephalo-pelvic disproportion exists. The pressure exerted on the fetal head recorded by means of a pressure-sensitive device placed between it and the pelvic wall would be larger than that recorded from intrauterine measurements by an amount approximately equal to the force due to the resistance of the pelvic wall. The pressure should be greatest at the plane of largest dimensions, since the head at this level is in closest proximity to the pelvic wall during a contraction. With flexion of the fetal head during descent, however, the plane defined by the suboccipital bregmatic diameter (mean 9.5 cm) is the first to meet the resistance of the pelvic wall. It is above the area of this plane that molding usually occurs and not that of the occipital-frontal. It would seem that, once the fetal head is engaged, the intactness of the membranes would have little influence on the course of these events. It would seem more reasonable to assign the effects of the rupture of membranes to the force imposed by the resistance of the more closely applied cervix, the resistance of the pelvic wall, and the increase in intensity of contractions and intra-abdominal pressure that usually follow it.

The changes that have been noted in fetal heart rate and EEG during a contraction could be due either to the force on the fetal head or

to the fall in fetal oxygen tension that occurred during the contraction.

As part of our interest in the developmental aspects and environmental influences on fetal cephalic metabolism and EEG, we have obtained some preliminary observations on the effect of both external cephalic compression and uterine contractions on these parameters. The experiments were designed to dissociate the effect of cephalic compression from that of uterine contraction and study each independently.

Materials and methods

The sheep fetus was prepared *in utero* with the mother anesthetized with Fluothane .6–1.2 per cent. Bipolar extradural electrodes were placed over the frontal-parietal aspect of each hemisphere, and the EEG was recorded on two channels of a Beckman Dynograph. Pressure in the carotid artery (CA) and jugular vein (JV) was measured continuously with calibrated strain-gauge transducers (Statham P23db). Cephalic metabolic rates (CMR) were calculated from the product of the CA-JV difference and the cephalic blood flow (Ultrasonic perivascular flowmeter—Ward Associates) and expressed as ml or mg/100 gm of brain tissue/min. A pediatric rib retractor was modified so that the distal end of each arm was attached to a 1½-inch-square metal plate. Force was calibrated electronically by means of a strain gauge placed in one of the arms of the device, the output of which was recorded continuously on the dynograph. The steel bar connecting the arms of the device was measured in centimeters so that deformation changes could be recorded. Forces approximate to those occurring clinically (2–15 kg, calculated from the above formulas) were applied through the myometrium over the temporal-parietal area of the fetal head. The force was held constant for various time intervals and was released after the onset of the isoelectric stage of the EEG when this occurred. Uterine contractions were difficult to initiate but did occur frequently after the infusion of a solution containing 2 cc of Pitocin (1 cc = 10 units; Parke Davis) at a rate of 1–2 cc/min (.04–.08 units/min). Rhythmic contractions could not be induced.

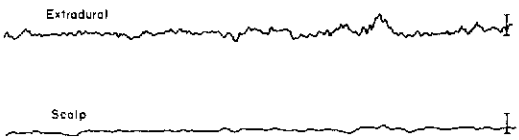

FIGURE 1. Fetal EEG recorded simultaneously from same hemisphere by means of extradural and scalp electrodes. Gestational age 118 days. Vertical bar equals 50 microvolts.

Results

EEG tracings have been obtained under steady-state conditions from a chronic preparation and during hypoxia from an acute preparation (*6*). These recordings emphasize the species variations in EEG ontogeny and the variations due to the technique used in obtaining the EEG.

Figure 1 shows the difference in frequency and amplitude of the EEG when recorded simultaneously from scalp and extradural electrodes. The lower amplitude of the slow waves and loss of the low-amplitude fast frequencies when recordings are obtained from scalp electrodes is shown clearly. It is obvious that normal baseline EEG characteristics would be determined by the technique employed.

The ontogeny of the fetal EEG is shown in Figure 2. From 105 to 145 days the EEG shows first an increase in frequency from 1–6 cps to 6–14 cps, with an increase in amplitude from <50 μV to 50–100 μV, and later the appearance of 1–3 cps waves with an amplitude of 100–150 μV. Tracing A represents the type of record obtained throughout gestation in the human and reported by Dr. García-Austt and by

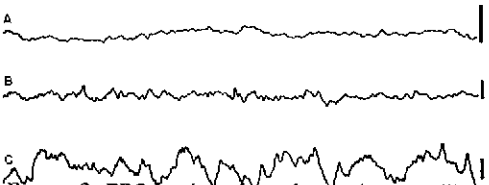

FIGURE 2. EEG tracings from fetuses *in utero* illustrating changes with maturation. A, 110-day fetus; B, 130-day fetus; C, 137-day fetus. All epochs are 10 sec in length and vertical bars equal 100 microvolts.

others.[1, 2] Further development of the EEG that occurs *in utero* in the sheep proceeds over approximately two to three months in the newborn monkey[3] and two to three years in the human.[4]

In addition to the development of frequency and amplitude characteristics during this gestational period, chronic observations of a single fetus over periods as long as 40 days have shown the development of various states of arousal. From 135 days to term (145–150 days) tracings such as shown in Figure 3 have been obtained. For about half the period of observation the EEG is characterized by high-amplitude slow waves characteristic of light to deep sleep (top 3 tracings); during the rest of the time the record consists of low-amplitude fast waves. The length of either cycle is from 5 to 10 minutes. The question is whether the fast activity represents REM sleep or a state of fetal arousal. In order to differentiate these patterns an electromyogram (EMG) and electrooculogram (EOG) must be recorded simultaneously with the EEG. REM sleep in other species, including man,[5] is generally associated with rapid eye movements and a quiet EMG. However, it was noted in the present experiments that during the period of rapid activity the ewe appeared uncomfortable in the cart while fetal movements were noted by observation of the maternal abdomen and by direct palpation.

During a period of acute fetal hypoxia induced by respiring the ewe with a gas mixture containing 7.5 per cent O_2 and N_2 the EEG showed characteristic changes (Figure 4). We have defined the first appearance of a change in the EEG as the first pathological change. This consisted of a decrease in amplitude in the 6–14 cps frequencies. A similar decrease in amplitude in the 1–6 cps frequencies in younger fetus was also evident but could not be recognized as accurately.

Computer power spectral analysis of coded magnetic tape recordings has confirmed these first changes but has not added to the accuracy of predicting them.

Dropping out of the faster frequencies and unmasking of the slower activity preceded the

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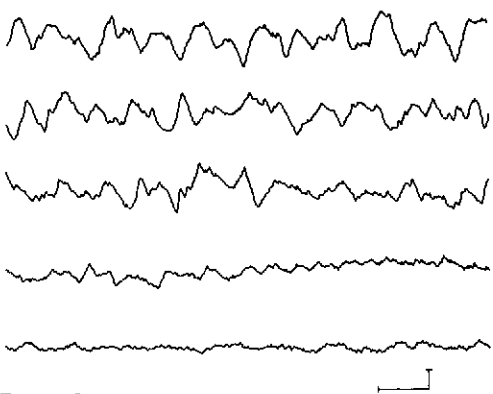

FIGURE 3. Fetal EEG recorded from chronic fetal preparation of 140 days' gestation. Though not continuous, all tracings were obtained within 5-minute period. Vertical bar equals 50 microvolts, horizontal bar equals one second.

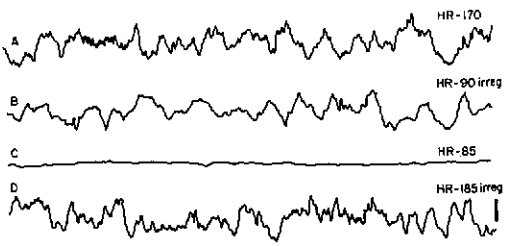

FIGURE 4. EEG records from 137-day-old fetus during hypoxia. Fetal hypoxia was induced by respiring ewe with 7.5 per cent oxygen. A, prior to hypoxia; B, "first pathological change" and unmasking of slow activity during hypoxia; C, isoelectric stage; D, recovery record 5 minutes after reintroduction of O_2 to ewe. Fetal heart rates (HR) at various EEG recordings are shown. Vertical bar equals 50 microvolts.

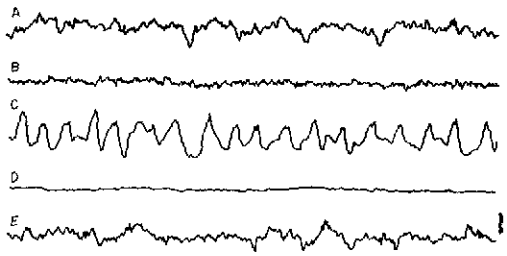

FIGURE 5. Effects of acute hypoxia on adult sheep EEG. A, control record; B, activation phase; C, synchronous slowing after 13 minutes breathing 7.5 per cent; D, isoelectric phase after 14 minutes breathing 7.5 per cent O_2; E, prompt recovery to control levels 3 minutes after restoration of high O_2. Light Fluothane anesthesia.

onset of the isoelectric stage. After the reintroduction of O_2 to the mother, the slower frequencies reappeared first and were followed by an increase in both frequency and amplitude.

The changes that occurred in the EEG of the adult ewe during hypoxia are shown in Figure 5. The classic pattern during hypoxia described for other species is seen.[6] The initial decrease in amplitude is followed by a stage of desynchronization (low amplitude, fast frequencies), which is followed by a stage of synchronized slow waves prior to the onset of the isoelectric stage. The difference in EEG alterations during hypoxia between the fetal and the adult records is most likely explained by the development of the reticular activating system postnatally. The modulating effect of this system on cortical activity has been described.[7]

The changes in EEG, heart rate and cephalic perfusion pressure, flow, and resistance that occurred after external cephalic compression are

[6] Gastaut, H., H. Fischgold, and J. S. Meyer. Conclusions of the International Colloquium on Anoxia and the EEG. In H. Gastaut and J. S. Meyer (eds.), *Cerebral Anoxia and the Electroencephalogram.* Springfield, Illinois, Charles C Thomas, 1961, p. 599.

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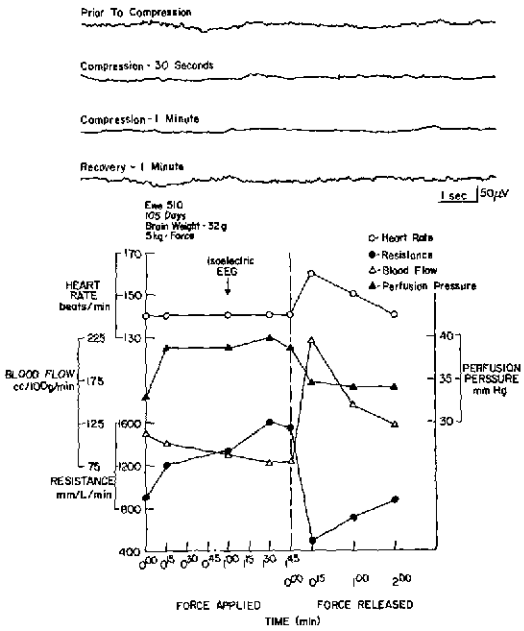

FIGURE 6. Changes in fetal EEG, heart rate, cephalic resistance, perfusion pressure, and blood flow during application of external cephalic compression force of 5 kg. Fetus 105 days.

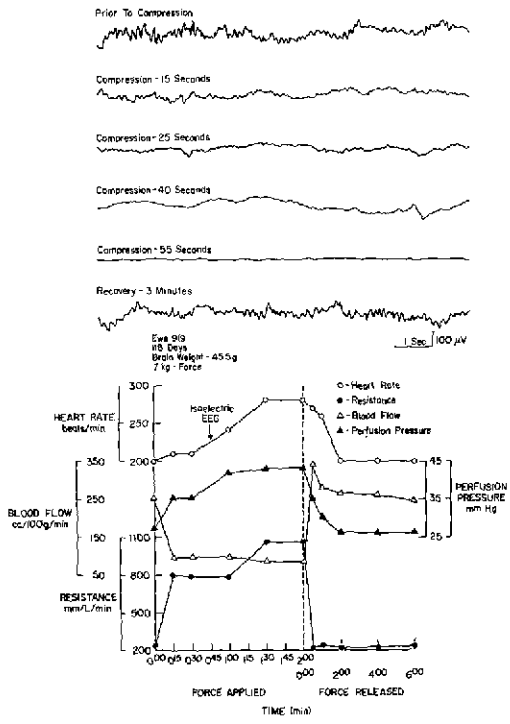

FIGURE 7. Changes in fetal EEG, heart rate, cephalic resistance, perfusion pressure, and blood flow during application of external cephalic compression force of 7 kg. Fetus 118 days.

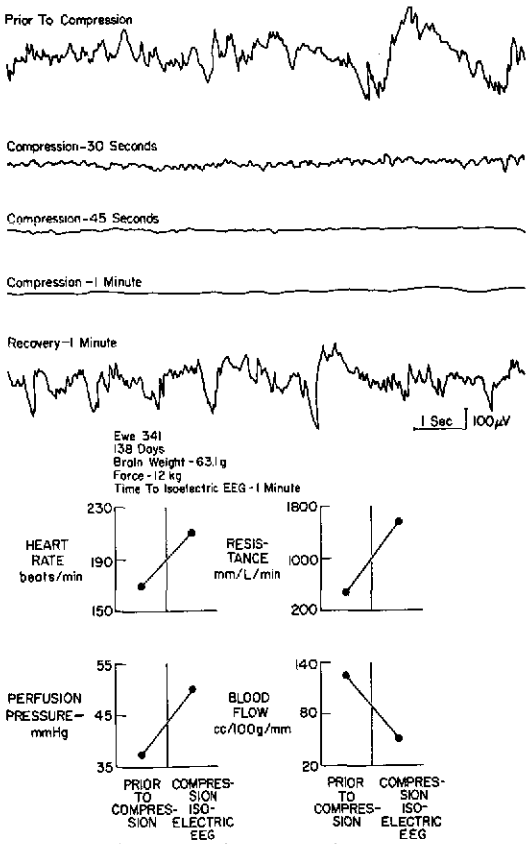

FIGURE 8. Changes in fetal EEG, heart rate, cephalic resistance, perfusion pressure, and blood flow during application of external cephalic compression force of 12 kg. Fetus 138 days.

shown in Figures 6, 7 and 8. The experiments presented are representative of the observations obtained at different gestational ages when the EEG became isoelectric following compression.

The EEG revealed frequency and amplitude changes similar to those observed during more progressive and prolonged hypoxia (Figure 4). The main characteristic was a rapid, though progressive, decrease in amplitude in all frequencies regardless of gestational age prior to the onset of the isoelectric stage. "Unmasking of slow activity" was evident in most tracings as well, particularly when the time to the onset of the isoelectric stage was 45 seconds or longer or when the isoelectric stage did not occur after prolonged compression. Recovery of the EEG to baseline frequency and amplitude occurred rapidly after release of the force, regardless of the length of time it was applied (up to 3 minutes). We have observed previously [8] that as the isoelectric stage was prolonged after a period of hypoxia of approximately 13 minutes, the time to full recovery of the EEG was similarly lengthened. This difference in recovery observations under the two experimental conditions would seem to be explained by more marked metabolic alterations that resulted during the prolonged periods of hypoxia (see below).

A marked increase in cephalic resistance and perfusion pressure occurred within 5 to 15 seconds of the compression, and was associated with a rapid fall in cephalic blood flow. These changes, of course, preceded the onset of the isoelectric EEG. In those experiments in which the onset of the isoelectric stage occurred beyond one minute or in which no isoelectric stage appeared, only a mild to moderate rise in resistance and pressure and decrease in flow was noted initially. These changes increased as the force was continued until the onset of the isoelectric stage or until the force was released. A reactive hyperemia followed release of the force in all the experiments.

Metabolic observations were limited to only a few experiments. Prior to the application of the 5 kg external cephalic force in ewe 510 (Figure 6), cephalic oxygen consumption was 2.37 ml/100 gm/min; carotid artery pO_2, 20 mm Hg; pCO_2, 40.5 mm Hg; O_2 content, 9.6 vol.%; and A-V O_2 content difference, 1.94 vol.%. One and a half minutes after the application of the force during the isoelectric stage, cephalic oxygen consumption was 0.90 ml/100 gm/min; carotid artery pO_2, 19 mm Hg; pCO_2, 41.5 mm Hg; O_2 content, 8.8 vol.%; and A-V O_2 content difference, 1.2 vol.%.

Ewe 919 (Figure 7) was moderately asphyxic prior to a 7 kg cephalic compression with a carotid artery pO_2 of 15 mm Hg; O_2 content, 5.01 vol.%; and pCO_2, 54 mm Hg. We have

[8] Mann, L. I., J. Prichard, and D. Symmes. EEG, EKG and metabolic observations during acute fetal hypoxia. *Amer. J. Obst. & Gynec.* In press.

previously noted[9] that under these conditions the fetal heart rate is generally tachycardia (200 beats/min) and cephalic blood flow is increased (258 ml/100 gm/min; mean at this age, 135 ml/100 gm/min).[10] Cephalic O_2 consumption decreased from 4.18 ml/100 gm/min (A-V O_2 1.62 vol.%) to 0.99 ml/100 gm/min (A-V O_2 1.1 vol.%) 15 seconds after the onset of the isoelectric stage. This marked decrease in oxygen consumption was the result of a 65 per cent reduction in blood flow (258–90 ml/100 gm/min) and only a 32 per cent decrease in A-V O_2 difference (1.62 vol.% − 1.10 vol.%). Oxygen tension in the carotid artery decreased only 1 mm Hg, while CO_2 increased 2 mm Hg.

The fetal heart rate showed minimal variation from baseline values during cephalic compression prior to the onset of the isoelectric stage. A tachycardia that was never greater than 10 per cent occurred on occasion. However, after the onset of the isoelectric stage it was not uncommon to see tachycardias 40 to 50 per cent above baseline values. A bradycardia of 30 per cent (150–105) occurred during cephalic compression in only one experiment. Heart rate returned rapidly to baseline values after release of the cephalic compression.

The relation between the force exerted and the time to the onset of the isoelectric stage is shown in Figure 9. The younger fetuses generally responded to less of a cephalic compression force in a shorter period of time than the more mature fetuses. Further, a force-time relation appears to exist in both groups in that less of a force held longer may result in the onset of an isoelectric EEG. However, this may be the result of variation in the time necessary to apply the force and the location of the application of the force.

[9] *Ibid.*

[10] Unpublished data.

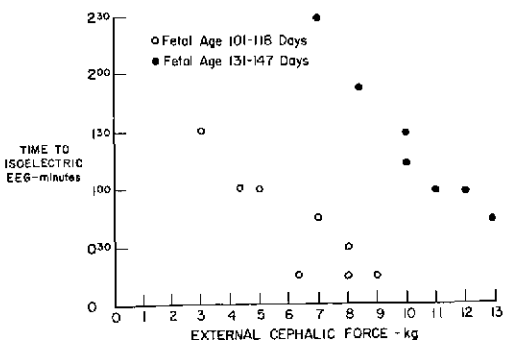

FIGURE 9. Time to onset of isoelectric stage of EEG as function of external cephalic compression force at two different gestational ages.

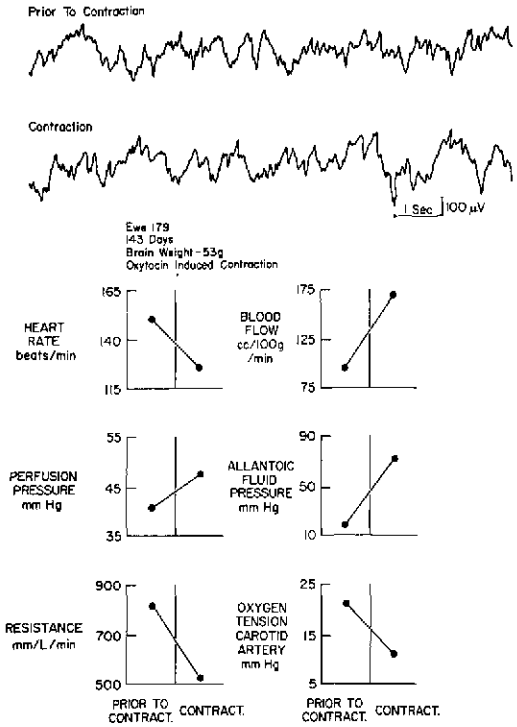

FIGURE 10. Observations of fetal EEG and other parameters during induced uterine contraction. Fetus 143 days.

The course of events resulting from a uterine contraction was quite different from the changes noted during cephalic compression (Figure 10). During the contraction the fetal head was free from external forces other than those within the allantoic-amniotic cavity. There were no recognizable differences in the EEG during contractions with an intensity as high as 70 mm Hg. It is possible, however, that power spectral analysis might uncover changes not apparent on visual examination. During the contraction oxygen tension in the carotid artery fell from 21 mm Hg to 11 mm Hg in ewe 179. As the result of a simultaneous rise in perfusion pres-

sure and fall in resistance, cephalic blood flow increased. Heart rate decreased in most experiments by as much as 40 per cent. These observations are quite similar to those obtained during acute-hypoxia experiments, when pO_2 in the carotid artery was in the range of 10–15 mm Hg.[11] Further reductions in pO_2 in those experiments resulted in the EEG changes described above, a marked bradycardia, and a fall in blood flow.

Discussion

The ontogenetic pattern of functional activity of the brain in terms of EEG and the maturation of the central nervous system in general in the fetal sheep provides an experimental preparation that offers many opportunities for studying and evaluating environmental influences on fetal CNS development. As in most animal preparations used in this area, it is limited in terms of the detection of long-term neurological, mental, and behavioral abnormalities. The subhuman primate preparation will certainly provide more valuable information on the long-term effect of induced fetal distress.

The effect of external cephalic compression and uterine contractions on fetal cephalic metabolism and EEG was studied by approaching each condition separately. It is recognized that during labor and delivery these conditions are occurring simultaneously. Indeed, compression of the fetal head is maximal during the uterine contraction as the fetal head meets the resistance of the pelvic wall. However, by dissociating these factors we hoped to gain an understanding of the effects of each, so that their simultaneous action could be interpreted correctly. Further, the effect of compression forces resulting from forceps application for delivery is closely simulated by the application of the external cephalic force used in these experiments.

An external cephalic compression force results in an increase in cephalic resistance and cephalic perfusion pressure and a fall in cephalic blood flow. Generally these changes occur rapidly, and as a result of the marked decrease in flow the cephalic oxygen consumption falls precipitously and the EEG becomes silent. Oxygen tension and A-V O_2 content are minimally to moderately depressed. A lesser force applied over a longer period produces, particularly in older fetuses, more gradual changes prior to the onset of the isoelectric stage. The skull of the older fetus in this species is much more developed, thick, with most suture lines fused. A larger force was required to elicit EEG changes, probably because of the increased resistance offered. The delayed time to the onset of the isoelectric stage may be due therefore to the time required to overcome this resistance in terms of molding and spatial rearrangements. Most of the force applications did not result in an isoelectric EEG even when prolonged. However, a decrease in amplitude and unmasking of slow activity was noted. Apparently a critical force exists, producing an intracranial pressure greater than that in the vascular system, that was not reached in these experiments. Intracranial pressure measurements are paramount to a complete understanding of this problem. The EEG returned rapidly after the release of the force, as did the vascular parameters and oxygen consumption. This can be compared to the more prolonged recovery of the EEG following acute hypoxia of approximately 12 to 13 minutes. This difference is probably accounted for by the accumulation of lactate within the brain during longer periods of hypoxia when anaerobic glycolysis is providing energy requirements. Further experimentation is necessary to elucidate the effect of excess lactate or metabolic acidosis on fetal cerebral function.

The EEG during induced uterine contractions was essentially unaffected or revealed only minor decreases in amplitude. The increase in cephalic perfusion pressure and blood flow and the decrease in resistance associated with a fall in carotid artery oxygen tension are similar to the responses observed previously during acute-hypoxia experiments. It is likely that cephalic oxygen consumption is only moderately

[11] Unpublished data.

depressed and changes in the EEG are not noted. These observations reflect the autoregulation of cerebral flow that has been adequately documented in adults of several species.

Heart rate changes are more difficult to interpret. Bradycardia was commonly observed during induced uterine contractions. There were essentially no heart rate changes during external cephalic compression prior to the onset of the isoelectric stage, beyond which a tachycardia was more commonly observed. The explanation of these observations may be related to the fact that during compression O_2 and CO_2 tension in the carotid artery and peripheral circulation was unaffected, whereas during a contraction a moderate hypoxemia developed. Recent evidence to be presented at this meeting has demonstrated the role of the peripheral chemoreceptors (aortic in particular) in regulating the fetal heart rate and circulation.[12] It is possible, therefore, that the failure to observe significant heart rate changes during external cephalic compression was due to the absence of chemoreceptor activation.

The changes that were observed in the fetal EEG and heart rate during uterine contractions in human parturients were associated with both a decrease in fetal oxygen tension and an increase in cephalic compression. The minimal decrease in fetal oxygen tension that occurs at this time could be expected to result in an increase in fetal cephalic blood flow. The autoregulation of cephalic blood flow would maintain an adequate cephalic oxygen consumption, and the EEG would therefore be unaffected. However, as the external cephalic forces increase as a result of an increase in amniotic pressure and pelvic resistance, cephalic pressure and resistance increase while blood flow and cephalic oxygen consumption decrease.

A critical point is reached at which frequency and amplitude changes in the EEG would be expected. The normal characteristics of the fetal EEG in the human must be known before the changes can be diagnosed with accuracy. Slowing of the dominant rhythm has been reported by García-Austt. This is the usual occurrence during hypoxia in human adults and may represent a predictable pattern in the fetus.

The change in heart rate pattern during a contraction may be due to peripheral chemoreceptor activation as a result of the fall in oxygen tension, or to a central mechanism as a result of the decrease in cephalic oxygen consumption. The experiments in fetal sheep have suggested the former, but differences between species in CNS and chemoreceptor functional development limit their interpretation.

It is reasonable to suggest that prolonged fetal hypoxia, increasing degrees of cephalic-pelvic disproportion, and difficult forceps application and delivery would act to increase the compression force to the fetal head and magnify the effect of such force on cerebral function and heart rate. Certainly an understanding of the effect of the changes observed on both the immediate and long-term condition of the fetus represents the challenge in this field of investigation.

General Discussion

Adamsons: I should like to ask whether, in the opinion of the specialists, the level of discrimination of the electroencephalogram as an indicator of fetal adequacy of oxygen supply is higher than that of fetal heart rate or fetal electrocardiogram. It was interesting for me to see, in the presentation by Dr. Mann, that the EEG recorded under ideal circumstances was virtually identical, while fetal heart rate had changed from 170 to 90 and the fetus probably showed every sign of severe asphyxia. There is little doubt that the injection of agents such as carbocaine or other CNS stimulants will be reflected more readily, but I think that the clinician is chiefly concerned with the opportunities to identify mild degrees of fetal asphyxia.

I wonder whether the animal experiments so far suggest that fetal EEG under these circum-

[12] Dawes, G. S., S. L. B. Duncan, B. V. Lewis, C. L. Merlet, J. B. Owen-Thomas, and J. T. Reeves. Hypoxemia and aortic chemoreceptor function in foetal lambs. *J. Physiol.* 201:105, 1969.

stances will be more sensitive in identifying minor departures from the state of normality than measurements of acid-base component or continued surveillance of fetal heart rate.

A final comment about the changes in fetal heart rate resulting from head compression: I hope Dr. James will give some of the preliminary information we have on intracranial pressure recordings in baboons during labor, but we have observed in the rhesus monkey that compression of the head is mild, followed by a prompt rise in blood pressure, and it is likely that the type I dip may be a low chemoreceptor response. Bradycardia occurs so promptly that I doubt very much whether it is an expression of brain asphyxia and chemoreceptor stimulation.

Mann: I think that two clinical situations can be identified. In one, the fetus is hypoxic because of a failure of maternal-fetal exchange at the placenta site; under these circumstances, the heart rate is probably a better indicator of the condition of the fetus than the EEG.

In a large series of experiments conducted under induced hypoxia, the heart rate changes preceded those of the EEG in each instance. However, I think we have identified today a second clinical situation that may explain the false negatives reported with the acid-base data. That is, a situation in which the newborn is obviously depressed but the pH is within normal limits; everything from an acid-base standpoint looks good. Under these conditions, the depression of the infant may be related to the forces we have discussed today and the depression of electroencephalographic activity may be due to the decreased oxygen consumption of the total head, in my experiments, or of the brain in particular. Here the EEG would certainly be more sensitive than the heart rate—on the basis of the experiments I have just presented, the only sensitive indicator.

Rosen: I think that at this point we really do not have enough data in the human to make a statement. I will say, in reply to Dr. Adamsons, that we do find a correlation. When the fetal heart rate changes, the EEG changes; it flattens out. This is almost time-synchronous, but I cannot give hard data as yet because we have few cases. When the heart rate returns to normal, the EEG returns to normal. Even at this point, with 40-odd cases, we have already identified several infants as having come into labor with abnormal EEG patterns that persisted in labor and as then having convulsed on the second and third day postpartum and shown the same waves. Thus the EEG may define what occurs before labor as related to what may occur during labor and to what damage may occur later—a problem we have been searching for answers to for a long time.

A second thing occurred in some of the guinea pig studies. We produced an asphyxial stress. The brain wave and heart rate changes were so rapid I shall not attempt to say which came first, but I should expect that the heart rate fell first and then the brain wave flattened. During the recovery interval the reverse occurred. Invariably the heart rate came back to normal before the EEG reached the same picture as prior to the asphyxial stress. I repeat that these studies were done in guinea pigs, not humans. They were done with the abdomen open, not closed.

Fuchs: Now that we have work from north and south of the equator, from Stockholm as well as from Montevideo and Buenos Aires, showing that the pressure around the equator of the head is higher, we have some important information that I think we ought to discuss. We were presented twice with slides that raised the question whether early rupture of the membrane could be the cause of fetal brain damage in some cases. I should like to ask whether the Perinatal Study could not provide some data that would resolve this question.

One comment immediately comes to mind. When we rupture the membranes during labor we usually shorten labor. We have heard that the percentage of contractions leading to dips I was smaller as long as the membranes were intact than after rupture. Thus, the total number of such insults might remain the same, if the percentage is raised but the shortening of labor reduces the length of exposure to them. I would hesitate to believe that the process of birth to which the human race has been subjected for so many generations can be as dangerous as this

would imply. I urge those who have the material from the Perinatal Study to put the material through the computers and get a fast answer.

Moderator: The moderator has the privilege of posing some questions. If labor is not interfered with by the attending person, at what time do membranes rupture spontaneously, on the average? The question is to Dr. Fuchs.

Fuchs: I do not think it is possible to talk about an average, because the range is from before any labor is present and visible to after the entire parturition process has been completed. Some are born with intact membranes and the sac has to be ruptured afterwards. This was called "the shirt of victory"; the suggestion raised here could support the view that perhaps the best thing would be to be born with intact membranes. I do not think, however, that this is necessarily true.

Moderator: I have no data from our unit, but all the books say that the membranes rupture spontaneously very late in labor. Modern obstetrics has changed this so that the membranes are ruptured much earlier. I should like to raise the question whether this is beneficial or detrimental to the fetus. I think this is an important point. I have no information, but I am glad Dr. Fuchs brought up the subject.

Churchill: Dr. Rosen has given us a very nice beginner's lesson about artifacts in electroencephalography, and I think we should all be mindful that half the effort in electroencephalography deals with this stubborn and persistent problem. In short, to be reasonably certain that a recording is brain activity rather than artifact, it is necessary to have electrodes on or in the brain itself. Of course, with few exceptions, this is impossible to do in humans.

Dr. Rosen did a good job, I think, in pointing out that one of the ways to determine whether one has brain waves or not is to look for the signature of brain activity as given from drug effects and from evoked potentials coupled with computer averaging of transient waves. Visually evoked potentials are better than auditory to work with, but one cannot very well give visual stimuli *in utero*. Hyperventilation (HV) produces EEG changes. Whether HV of the mother would produce fetal EEG changes I do not know, but perhaps it could be tried.

Motion artifact is a major problem, particularly movement of the eyeball dipole. If the individual is external, it is possible to apply electrodes around the orbits and identify them. I do not know how this could be done *in utero* or how much fetal eye motion causes. Miniature strain gauges that can pick up movement artifacts could be placed near recording electrodes. Perhaps this should be done.

A class of microphonic movement artifact is difficult to identify. These can be very deceitful, looking like alpha, sleep spindle, or other rhythmic waves. Microvibrations are hard to detect by instruments.

If salt bridges between electrodes occur, as Dr. Rosen implied, their presence should be identified by a short circuit or zero potential difference as measured by ohmmeter. Such shorts may open and shut, giving marked potential sways.

In the newborn infant skin resistance is quite high, and it is hard to reduce it to the acceptable level of 3,000 ohms; getting it down to 6,000 ohms is good luck. High impedance increases artifact from external electrical interference, such as ECG. The use of needle electrodes should obviate most impedance problems.

None of the papers presented on EEG here mentioned whether the electrodes were tested for conductance.

Each new advance in EEG has been beset by the artifact criticism. The inconvenient location of the fetal head imposes extraordinary difficulty upon the investigator, who may have to devise ingenious ways to identify and exclude artifact.

Adamsons: One technical question, which Dr. Hon might care to answer. What is the advantage of using platinum rather than silver chloride electrodes, in dealing with problems of movement and other artifacts that would result from polarization of the salt medium?

Hon: Personally, I should prefer to use a nonpolarizable type, a silver chloride electrode. It does not make very much difference, but I should think that silver chloride would be advantageous if one wants—and one certainly does—

to reduce the low-frequency artifacts. I suspect that platinum is more convenient to use.

I have a question for Dr. Rosen. He implied that the ECG potential came across the skin of the fetus and that since this was apparently guarded out by the suction ring he did not get this interference into his signal. This confused me, because my experience has been that the electrocardiographic potential came through the fetus somewhat as a volume conductor and did not travel very much along the surface.

Rosen: I shall take the difficult question—Dr. Hon's—and answer it first. I am not sure how the fetal electrocardiographic activity gets to the needle point, but it has occurred whenever our recording points have been exposed to the environment. We can check for total isolation, because we can get the salt-bridge effect and check our resistances across the two recording points, but when our resistances drop down about to 3,000 we know we are in trouble as far as ECG activity goes.

You must remember that we are dealing in terms of different kinds of resistances. We are using a needle point. Good clinical EEG in the fetus occurs at around 15,000 to 18,000 ohms, in contradistinction to a disc with a larger surface area, with which acceptable resistance should be around 3,000 ohms. If the needle point or disc is exposed, we drop down to about 3,000 and pick up ECG. If it goes through the body as a volume conductor, then I do not know why it is not there at other times. I can only describe what is happening here and the hypothesis we have used.

With the clip electrode, for example, the ECG is simply much higher in potential and overwhelms whatever recording we have.

García-Austt: Even placing electrodes directly on the cerebrum will not solve the very difficult problem of artifacts. All of us who have had experience in working with electrodes implanted in animals know that these recordings too are often full of artifacts.

With regard to the problem of eye movement, it is often difficult to determine whether an artifact is or is not due to these movements, but in the conditions under which we have worked they are very unlikely to be recorded because the variations of voltage as determined by the ocular dipole are never recorded in the posterior half of the scalp.

We differ from Dr. Rosen in having recorded electroencephalograms simultaneously with cardiac frequencies and uterine contractions. We have tested all of these for artifacts. Undoubtedly many artifacts may take place in electroencephalograms during labor. We are absolutely certain that some of the slow waves recorded during contractions are of cerebral origin. But in many of these contractions important artifacts were also recorded. All I can say is that after some 27 years I believe I know how to recognize an artifact.

About our technique, I should like to say that the speed we use to record electroencephalograms is absolutely routine in Europe—15 mm per second. We in the underdeveloped countries use this speed because paper is very expensive, but this is a routine speed for recording.

As to the presence of slow waves, it has been known since the very beginning of EEG history that slow waves—from half to two per second—are what predominates in the newborn. Therefore, I do not believe that slow waves appearing in the fetal EEG must be catalogued as artifacts. I did not see any in the tracings of newborns shown by Dr. Rosen; perhaps they had been filtered out.

EFFECT OF UTERINE CONTRACTIONS ON MATERNAL BLOOD FLOW THROUGH THE PLACENTA[1]

J. J. Poseiro, C. Méndez-Bauer, S. V. Pose, and R. Caldeyro-Barcia[2]

The maintenance of normal fetal homeostasis is basic to cellular growth and development. Fetal homeostasis is largely dependent on metabolic exchanges with the mother through the placenta. A reduction in these exchanges causes a diminution in the supply of anabolites to the fetus and also a retention of catabolites, with several harmful consequences such as acidosis.

Insufficient feto-maternal exchanges may be produced by several factors. Uterine contractions are the most important cause in reducing the blood flow through the intervillous space of the placenta (IVS) because they are always present in labor (other causes, if present, add their effects to that of the contractions), because they may in themselves produce fetal distress, because they act through different mechanisms that potentiate each other, and because they are often iatrogenically augmented by the administration of oxytocic drugs.

Mechanisms of action

Uterine contractions reduce the maternal blood flow through the placenta by means of at least two mechanisms: the compression of the intramyometrial vessels and the compression of the aorta and iliac arteries by the contracting uterus.

[1] This study received support from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization, and from grant HD 00222-06 of the National Institute of Child Health and Human Development, Bethesda, Maryland, U.S.A.

[2] Presented by Dr. Poseiro.

Compression of the intramyometrial vessels

The placental blood flow is a function of the difference between the mean arterial blood pressure and the intramyometrial pressure. It is directly proportional to the mean arterial pressure and indirectly proportional to the resistance of flow. This relationship can be expressed by the equation

$$\text{Placental blood flow} = K \frac{\text{perfusion pressure}}{\text{resistance opposed to blood circulation}}$$

Figure 1 illustrates the pressure system when the uterus is relaxed. Under these conditions

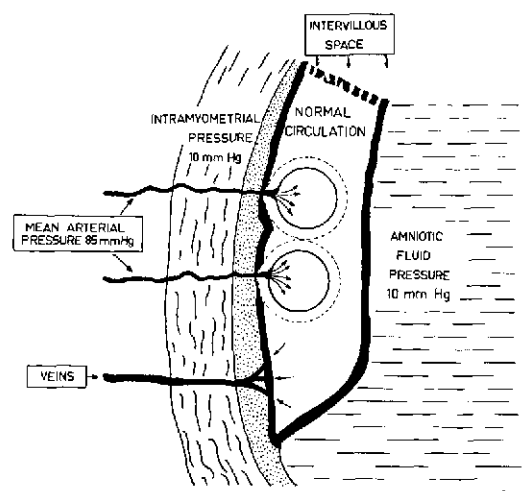

FIGURE 1. Schematic representation of circulatory conditions when uterus is relaxed. Blood circulates freely through IVS (*17*).

the amniotic pressure is around 10 mm Hg; the intramyometrial pressure is also low, 8–10 mm Hg (see also Figure 2); the blood in the arteries crossing the myometrium has a mean normal pressure of 85–100 mm Hg and has no difficulty in entering the IVS, circulating through it, and leaving via veins that have a pressure of 8 mm Hg.

When the uterus contracts, the circulatory conditions are completely different. Caldeyro-Barcia *et al.* reported in 1952 (*12*) that during contractions, even in normal conditions, the intramyometrial pressure reaches values two to three times higher than the amniotic pressure (Figure 2). The muscular fibers act like sphincters completely surrounding the intramyometrial vessels and may even occlude them.

The following equation may be used instead of the one above:

$$\text{Placental blood flow} = K_1 \frac{\text{perfusion pressure}}{\text{intramyometrial pressure}}$$

From these results Caldeyro-Barcia postulated in 1956 (*15*) that each contraction apparently reduced or even suppressed the maternal blood flow through the IVS (Figure 3). When the contraction starts, on its ascending branch, the first vessels to undergo this compression are the veins that drain the IVS; the blood accumulates backward, and the arteries (having a higher pressure) continue to supply blood to the IVS. Later, when the contraction exerts a greater pressure, the arteries are also compressed. The compression pressure exceeds the mean arterial pressure; at this stage the blood neither enters or leaves the IVS. As a consequence of this circulatory stasis, the blood in the IVS lacks oxygen and anabolites, which are continuously being used by the fetus, and at the same time accumulates catabolites, which are continuously being produced by the fetus. Hypoxemia, hypercapnia, and acidosis are produced both in the IVS and in the fetal blood (*17*) (Figure 3).

Figure 4 schematizes the relationship between the pressures. It has been assumed that the mean arterial pressure is 100 mm Hg and does not change during contractions (this is not entirely true). Each uterine contraction is represented by the value of its corresponding intramyometrial pressure. The placental flow at a given time (in the figure, periods of 10 minutes) is proportional to the dotted area between the two pressures. Five situations are represented. Even in normal conditions there are about 15 seconds at the top of the contraction during

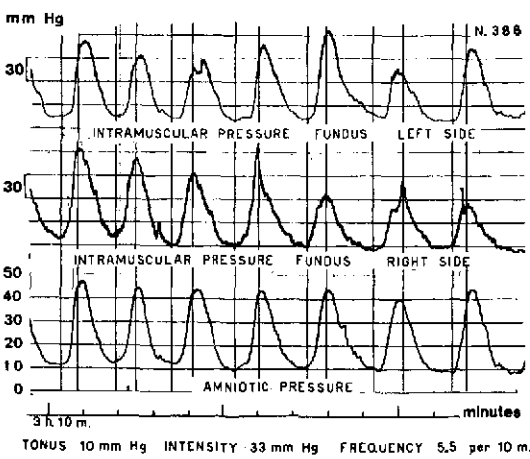

FIGURE 2. Records of intramyometrial pressure obtained with microballoons inserted into thickness of uterine wall. Contractions cause much greater rise in intramyometrial pressure (60–120 mm Hg) than in amniotic pressure (35–40 mm Hg). Intramyometrial aspect of vessels supplying IVS is exposed to intramyometrial pressure, which during contractions becomes high enough to occlude them (*16*).

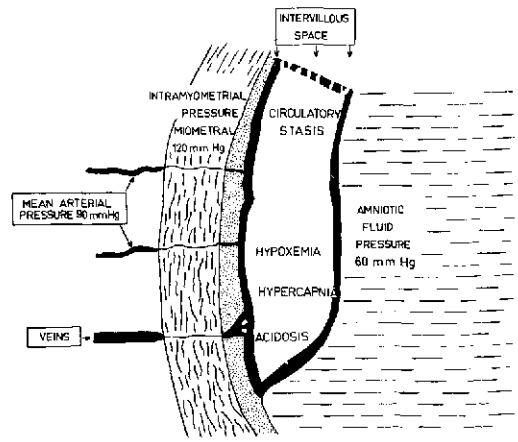

FIGURE 3. Circulatory stasis when the uterus is contracted (*17*).

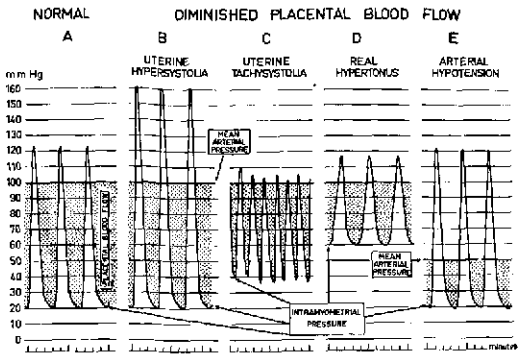

FIGURE 4. Placental blood flow (dotted area) is function of difference between mean arterial blood pressure and intramyometrial pressure. Dotted area is markedly reduced in B to D because of abnormal uterine contractility and in E because of maternal arterial hypotension. (Highly schematic.)

which the intramyometrial pressure is higher than the mean arterial pressure and thus no blood is circulating. We postulate that this is the mechanism by which each uterine contraction causes a transient episode of fetal hypoxia (see below). When abnormally high uterine contractility exists (Figure 4B, C, and D) the circulatory stasis is more marked and its consequences are more serious. These abnormalities in contractility can in themselves be a definite cause of fetal distress (*53*). It must be borne in mind that while here they are represented singly, they can occur in combination and thus worsen the condition of the fetus (*23*). An additional cause of fetal distress, under certain conditions, may be maternal arterial hypotension (*51*) (Figure 4E).

The intramyometrial vessel compression has been demonstrated by several methods:

1. *Clearance of radioisotopes injected in the IVS.* In 1953 Browne *et al.* (*11*) reported the first results injecting ^{24}Na. A lot of work has been done up to now (*39, 40, 41, 43, 45, 66*), but little evidence of the effect of uterine contractions has been reported. In a recently published thesis Lagorce (*42*) made a good review of the literature and documented very well the study of uterine and placental blood flow with Xenon 133. He did not study the effects of uterine contractions but promised to do so in the near future.

Caldeyro-Barcia in 1956 (*14, 17*) and Poseiro in 1958 (*50*) studied the influence of uterine contractility on the flow of maternal blood through the IVS. Three phenomena were recorded: maternal arterial pressure, amniotic pressure, and the clearance of a radioisotope, ^{131}I, injected in the IVS. This experiment has been performed in cases of intrauterine fetal death because uterine hypercontractility was induced and in order to avoid any passage of radioisotopic material into the fetal circulation that would interfere with the results.

Figure 5 shows a typical result of this study. In the upper part of the figure the arterial pressure was normal and uterine contractility had values corresponding to those observed in the days preceding labor. Under these conditions 2 microcuries of ^{131}I were injected into the IVS. Placental radioactivity increased rapidly and then decreased, following an exponential curve that reached the background line in one and a half minutes. The half period (T ½) was 30 seconds. In the lower part of the figure, ¼ unit of pituitrin injected intravenously produced a great increase in uterine contractility. A second injection of the same amount of ^{131}I

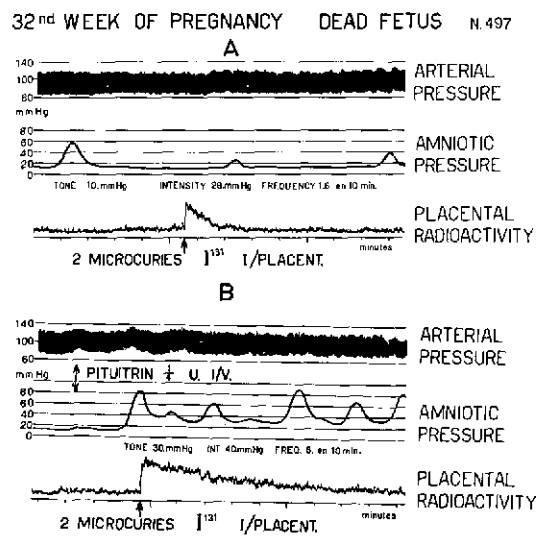

FIGURE 5. Influence of uterine contractility on flow of maternal blood through IVS, studied by clearance curve of radioactive ^{131}I injected in IVS. In A, contractions are normal; in B, hypercontractility was induced by injection of Pitocin (*14*).

disappeared much more slowly than in normal conditions, taking more than 9 minutes to reach the baseline. The T ½ was 144 seconds. Maternal blood flow through the placenta was about five times less during hypercontractility than in normal conditions. We can conclude that uterine hyperactivity markedly reduced the blood flow through the IVS.

2. *Angiographic studies.* Ramsey *et al.* (*56, 57*), using radioangiocinematographic methods in the rhesus monkey, found that during uterine contraction the IVS blood flow was arrested and only restarted when the uterus relaxed.

Using similar methods in pregnant women, Borell *et al.* (*8, 9, 10*) found a suppression or slowing of utero-placental circulation during uterine contractions. Figure 6 shows schematically the results of an angiogram obtained when the uterus was relaxed (*9*). The spurts into the IVS appear in large number—25. When the uterus is contracted the intramyometrial vessels are compressed, and a similar study (*9*) shows a great diminution in the number of spurts; there are 6 completely tinged and 6 incomplete (Figure 7).

FIGURE 6. Schematized results of angiogram with relaxed uterus. Thickness of lines is proportional to diameter of vessels. Number of spurts to IVS (black circles) is high—25 (*8*).

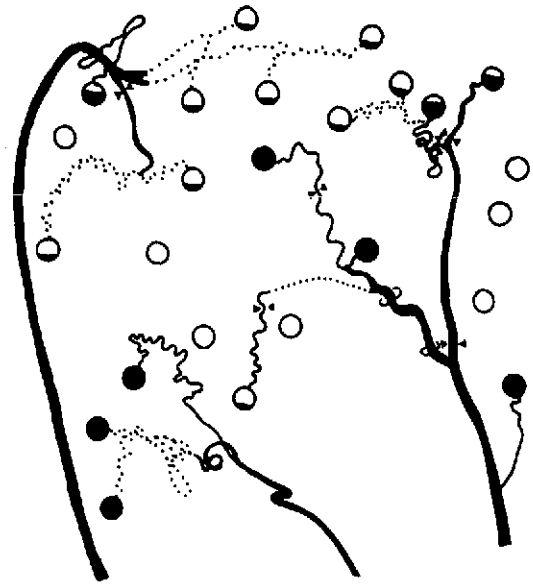

FIGURE 7. When uterus is contracted, number of spurts is markedly smaller than in Figure 6. There are 6 incompletely tinged spurts (incomplete black circles) (*8*).

Bieniarz *et al.* (*6, 7*) used serial abdomino-pelvic arteriography to visualize the aorta as well as the utero-placental blood vessels in more than 150 women whose pregnancies were past the twenty-seventh week. A catheter was inserted into the aorta through the femoral artery using the Seldinger technique (*61*), similar to that used by Borell *et al.*, Fernström (*29*), and Ramsey *et al.* Four exposures were made in six seconds. Figures 8 and 9 summarize schematically the findings shown by X-ray films taken at different times. The film taken at the sixth second shows (Figure 8, relaxed uterus) a good quantity of the opaque substance in the IVS, whereas that taken at the same time during a uterine contraction (Figure 9) shows none.

3. *Measurements of uterine blood flow.* In 1947 Ahlquist *et al.* (*1*) reported the first direct observation of uterine blood flow during labor in the pregnant bitch. They observed that the flow diminished when the uterus contracted. In 1958 Assali *et al.* (*3, 4*) found in the ewe that each contraction caused a transient decrease of blood flow in the uterine artery, which was recorded with electromagnetic flow-meters. They observed that uterine blood flow decreased

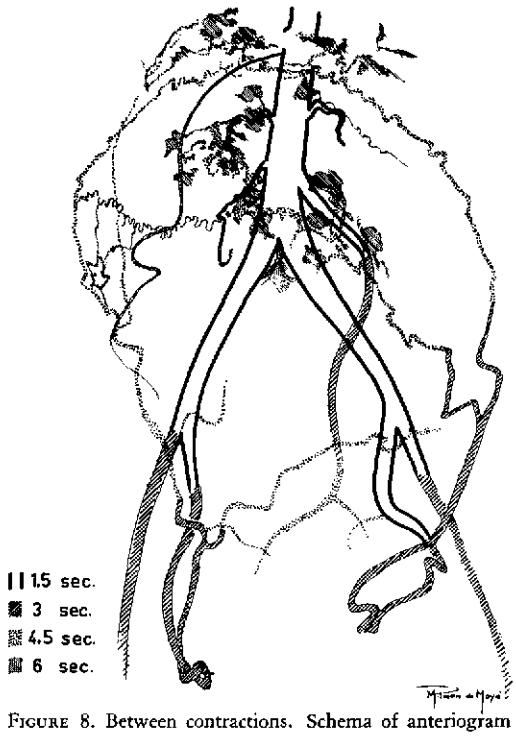

FIGURE 8. Between contractions. Schema of anteriogram in a normal full-term pregnant woman. Superposition of pictures demonstrates progress of dye clearance in sequential exposures of series. IVS shadow is dense, showing good blood circulation (*6*).

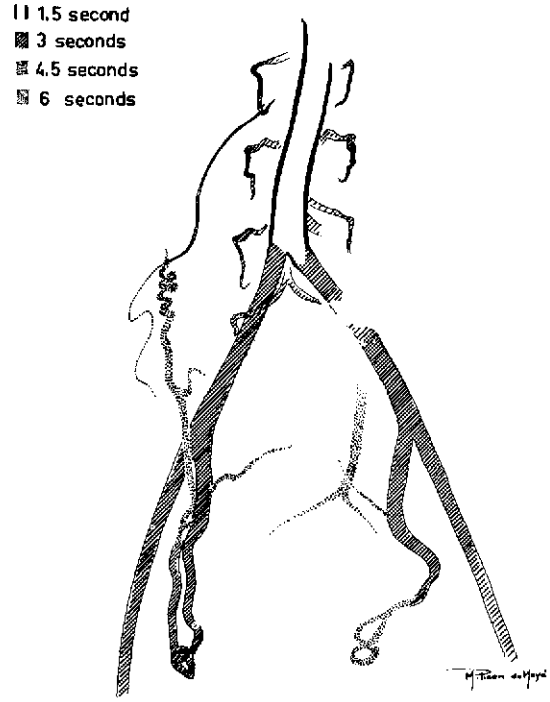

FIGURE 9. During contraction. Same case as in Figure 8. Right uterine artery, which mainly irrigates IVS, is occluded by uterus. IVS does not appear (*6*).

with each contraction and that the degree of flow reduction correlated with the intensity of palpable contractions.

Most recently, Greiss *et al* (*32, 33, 34*) implanted electromagnetic flow probes and occlusion loops around the uterine arteries and the descending aorta. Intrauterine pressure and maternal arterial pressure were measured simultaneously. Figure 10 (*34*) illustrates the effect of a single contraction. The uterine blood flow diminishes gradually as intrauterine pressure rises. The recovery of the baseline of the blood flow is slow, related to the very prolonged descending limb of the contraction wave. The basal flow was reached only when the contraction descended to the normal level of uterine tonus.

Figure 11 (*34*) illustrates the effect of an excessive dose of oxytocin. When intrauterine pressure reached high hypertonus the uterine blood flow decreased to the zero level. Hypersystolic and tachysystolic contractions produced falls in the flow, giving a mirror image of the tracing of the contractions.

Greiss and Anderson (*34*) conclude that "the uterine blood flow varies inversely with the intensity, frequency and duration of uterine contractions and with the level of the tonus." Maternal hypotension due either to hemorrhagic

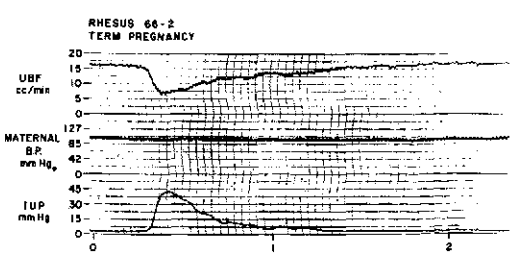

FIGURE 10. Relationship between uterine blood flow and uterine contractions during spontaneous labor in rhesus monkey (*34*).

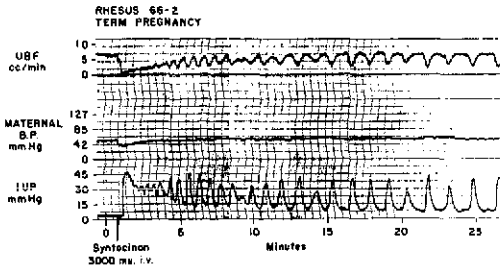

FIGURE 11. Hypercontractility due to excessive administration of oxytocin (lower tracing). Tracing of maternal blood pressure shows small lowering, coinciding with injection of Pitocin. Marked fall in uterine blood flow coincides with hypertonic uterine contractions (*34*).

shock or to sympatholytic mechanisms diminishes the uterine blood flow (*32*).

Compression of the aorta and iliac arteries by the contracting uterus

During labor, when the mother is in the supine (dorsal recumbent) position, the contracting uterus may compress the aorta against the spine, reducing or suppressing the arterial circulation of blood through the occluded vessels.

In 1955 this effect was described (*35*) in about 20 per cent of the records of maternal femoral arterial pressure. Figure 12 shows how the relaxed uterus rests on the main vessels. When the uterus contracts it tends to take a more spherical shape; its antero-posterior diameter augments, compressing the inferior vena cava and the aorta against the spine. Usually this compression occurs at the end of the aorta or at one of its divisions, right or left iliac arteries. The compressive effect was found in 28 per cent of the blood pressures recorded in one femoral artery (*44, 54*). It is possible that this percentage would be greater if the pressure were recorded in both femoral arteries. Each uterine contraction produces a marked fall in the systolic and a less marked one in the diastolic pressure of the femoral artery (Figure 13). The systolic fall is so marked that the pulse pressure disappears and the tracing appears as a line around the diastolic values.

The effect described is strictly local. The tracing of the brachial artery in Figure 13 (*54*) shows no fall in pressure during uterine contractions. The same fact can be observed in aortic tracings, as shown in Figure 16. The compression of the main abdominopelvic vessels can be demonstrated by several methods:

1. *Clinical findings.* As the pulse pressure disappears, clinical palpation of the femoral region can easily detect this phenomenon during contractions and note how the pulse reappears when the contraction ends. It can also be observed by performing the oscillometry in the legs of the parturient.

2. *Angiographic studies.* Figure 14 shows schematically the findings obtained with X-ray films taken at different times in the intervals

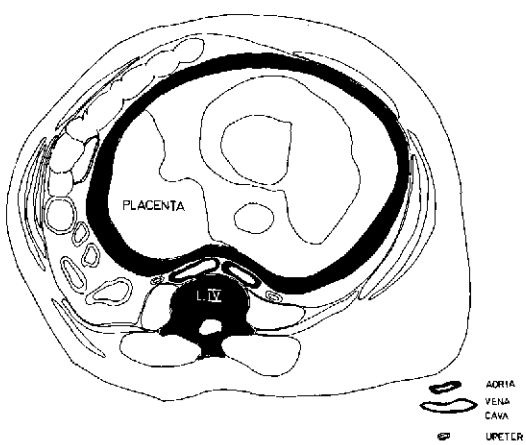

FIGURE 12. Transverse section, modified from Couvelaire's, of 32-week-pregnant woman, illustrating how weight of pregnant uterus may compress aorta against vertebral column just as it obstructs inferior vena cava.

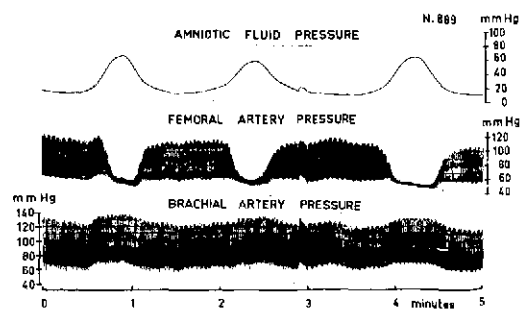

FIGURE 13. Responses to uterine contraction: each coincides wtih transient fall in systolic and pulse pressure in femoral artery and rise in brachial artery pressure, proving complete separation of the two vascular regions.

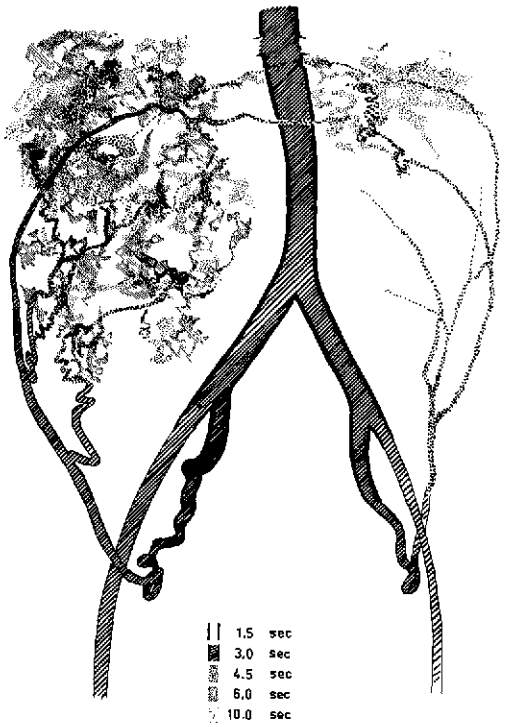

FIGURE 14. Superposition of pictures taken between contractions in angiographic study demonstrates progressive dye clearance through all supplying arteries into IVS.

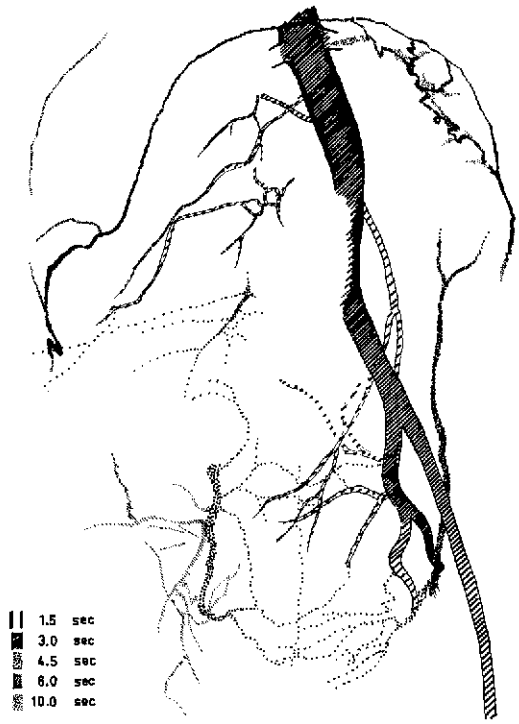

FIGURE 15. During contraction, superposition of pictures in series similar to Figure 14 shows marked obstruction of the aorta and occlusion of right common iliac artery by contracting uterus. Retro-uterine fulcrum (L_{4-5}) is completely ischemic; placental irrigation is deficient despite compensatory retrograde irrigation.

between contractions (*52*). As can be seen, the contrast medium circulates more rapidly through the right artery than through the left. Multiple spurts and good visualization of cotyledonary pools can be seen at the right upper uterine quadrant (films taken at the sixth and tenth seconds). The contraction displaces the aorta to the left (Figure 15), partially obstructing its flow and completely occluding the flow of the right common iliac and consequently of the hypogastric and uterine arteries (*51, 52*). Only the left iliac and uterine arteries maintain the uterine blood supply. Furthermore, the entrance of the vessels into the contracted myometrium is occluded. The effects of the contraction both on the main arteries (X-ray film taken at 1.5 seconds in Figure 15) and on their intramural branches (4.5 to 10 seconds) are additive and no spurts are seen in the placental location.

3. *Hemodynamic studies* (*52, 54, 55*). The same occlusive effect of each contraction that

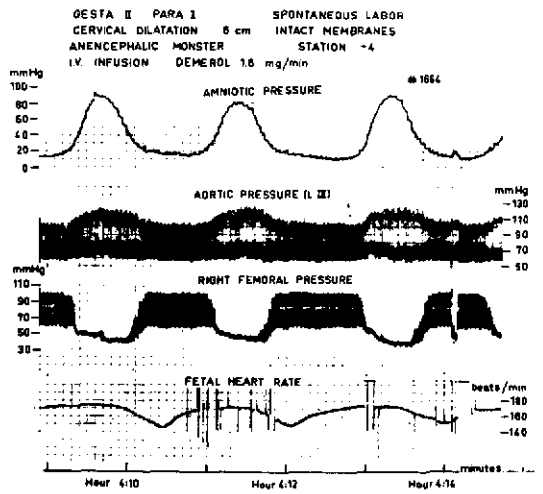

FIGURE 16. Occlusive effect of each contraction recorded in same woman as in Figure 15: transient hypotension in right femoral artery, coinciding rise in aortic pressure, proving complete separation of these vascular regions. Descent in fetal heart rate follows (dip II), related to tidal hypoxia due to interference with placental circulation during contraction.

was visualized in the angiograms of Figures 14 and 15 was observed in the simultaneous recording of aortic and femoral pressures and amniotic pressure (Figure 16). Each contraction is accompanied by a marked fall in systolic blood pressure in the femoral artery, whereas in the aorta a small increase in both systolic and diastolic values is noted (*12, 35*). This demonstrates that the effect is exclusively local. The effect does not appear in the lateral position. In Figure 17, when the patient is in the supine position each contraction causes a fall in femoral pressure and also a dip II (see below); when she turns to the lateral position, similar contractions produce neither of these effects, because the uterus does not compress the main vessels. The utero-placental blood flow is assumed to have increased.

Effect of contractions on fetal oxygenation

Caldeyro-Barcia *et al.* (*22*) postulated in 1961 that the above demonstrated effects of uterine contractions on maternal blood flow through the placenta caused fetal asphyxia. This has been demonstrated by Pose *et al.* (*28, 47, 48, 49*), who performed simultaneous recordings of the amniotic pressure and the partial pressure of oxygen (pO_2) in fetal tissues. They concluded (*48, 49*) that each uterine contraction caused a slow and transient fall in fetal pO_2

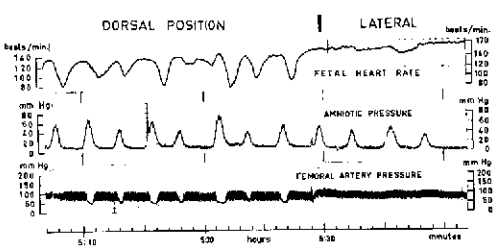

FIGURE 17. With mother in dorsal position, each contraction causes marked Poseiro effect in femoral artery pressure (pressure in uterine artery assumed to have fallen similarly) and dip II of large amplitude in FHR; in lateral position, Poseiro effect disappears and amplitude of dips II diminishes markedly. Record obtained in a severe pre-eclampsia with arterial hypotension, after arterial pressure had fallen because of infusion of Demerol and Chlorpromazine. Loop of cord around neck. Cervical dilatation 3 cm. Intact membranes.

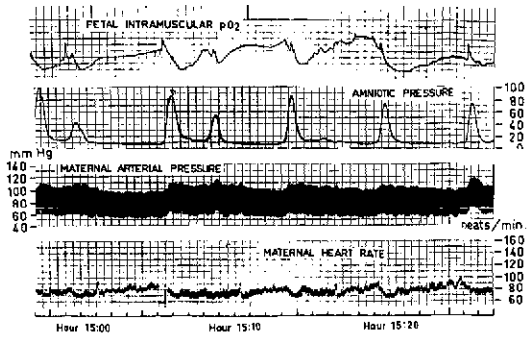

FIGURE 18. Record of fetal muscular pO_2 ($FMpO_2$) obtained with polarographic electrode inserted into buttock muscle of fetus. Each uterine contraction causes a marked fall in $FMpO_2$, starting a few seconds after onset of contraction and reaching bottom 30–45 seconds after its peak. Recovery to initial level after each fall is very slow—2–5 minutes (*49*).

(Figures 18 and 19), which reached bottom about 30 to 45 seconds after the peak of the contraction—a lag-time similar to that of a

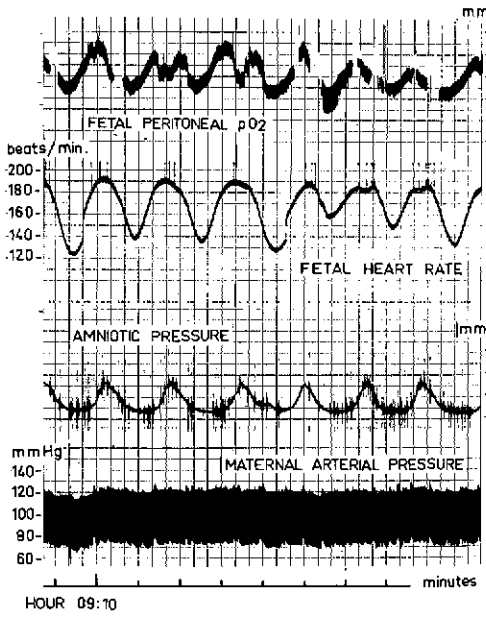

FIGURE 19. Records obtained in full-term (159 days) monkey. Each uterine contraction is followed by slow drop in fetal peritoneal pO_2 and this, after about 10 seconds, by dip II. Intravenous infusion of Demerol at 0.02 mg/kg/min and of oxytocin at 0.1 mU/kg/min. Three doses of 0.2 mg of atropine were given i/m to mother at hours 05:13, 06:33, and 08:40. Artificial respiration with pure oxygen. At time of this record, arterial pressure of the mother was much lower than at beginning of experiment (180/120 mm Hg) (*46, 48, 49*).

dip II (*13, 15, 22, 23, 37, 38*), which is a transient fall in fetal heart rate produced by one uterine contraction (Figures 16 and 19), mainly by hypoxic mechanisms (*22, 23*). These results agree with those of Dawes *et al.* (*27*) obtained in the rhesus monkey. These authors reported that 30 seconds after each contraction, a transient fall occurred in the oxygen saturation of fetal arterial blood; similar effects have been found by Paul (*46*) in the fetal lamb. Saling (*59, 60*) found that a fall in oxygen saturation of hemoglobin with O_2 in fetal capillary blood follows the uterine contraction.

Conclusions

It is concluded that each uterine contraction causes a reduction of maternal blood flow through the IVS and that this is reflected in the internal milieu of the fetus, causing a lowering of the pO_2 of the fetal tissues and a fall in the saturation percentage of hemoglobin with O_2 in fetal capillary blood.

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FACTORS INFLUENCING THE ACID-BASE STATE OF THE FETUS DURING LABOR[1]

K. Adamsons, H. O. Morishima, and A. C. Comas-Urrutia[2]

It has been recognized that a substantial proportion of human fetuses experience measurable degrees of oxygen deprivation during the course of labor and delivery. Indirect evidence of this was first obtained by comparing the degree of oxygenation and acid-base state of blood obtained from the umbilical cord at the time of delivery with what were known to be normal values of newborns and of fetuses of experimental animals (*8, 13*). Direct evidence of changes in fetal acid-base state in the human during the course of labor became available after the introduction of fetal blood sampling by Saling in 1961 (*11*). The evaluation of the physical condition of the fetus immediately after delivery provided another measure of the degree and relative frequency of asphyxia accompanying the birth process. Using the criteria proposed by Apgar it was found that in an unselected population not more than 20 per cent of newborns were in optimal physical condition at the time of delivery and that about 20 per cent had experienced a degree of oxygen deprivation that was likely to have an effect on their subsequent neurological development (*2*). Among patients with obstetric complications known to be associated with increased fetal morbidity, the proportion of severely depressed infants (Apgar score 0–3) was in excess of 10 per cent (*14*). A similar distribution was also observed when the pH of the fetus was used as an indicator. In most studies the mean pH of the fetus at the time of delivery has been less than 7.30, and, even in obstetric units with highly intensified intrapartum care of the fetus, as many as 25 per cent of randomly chosen patients had pH values of the fetal capillary blood of 7.20 or less (*4*). Among patients with obstetric complications the proportion with this degree of acidosis was even higher. Thus, Wood (*19*) reported an incidence of 41 per cent in a series of 256 patients. Because of the high frequency of varying degrees of acidosis and hypercarbia observed during the course of presumably uncomplicated labor, this change in fetal acid-base state was considered normal and perhaps even physiological. Several observations, however, make the validity of this assumption dubious. In most series the mean values for pH and other acid-base indicators vary greatly, reflecting changes in fetal oxygenation during the course of labor and delivery; furthermore, the difference between the means of the corresponding variables at beginning and end of labor is usually reported to be less than the standard deviation. Perhaps the strongest evidence implicating abnormal events as a cause of fetal acidosis is the fact that a small but distinct population can be identified in which there is no evidence of developing acidosis and hypercarbia up to the point of, and sometimes even through, delivery.

Attempts have been made to ascertain the

[1] Research supported by grants HD 00118 and GM 09069 of the United States Public Health Service.

[2] Presented by Dr. Adamsons.

changes in fetal acid-base state that have preceded the delivery of high-score infants born to mothers without medical or obstetrical complications. Such data are available from a recent study by Bretscher and Saling representing 306 patients selected from a total material of 1,500 cases (*5*). The mean pH of fetuses at the onset of labor was 7.33, and that at the beginning of the second stage was 7.34. The slightly lower value obtained late in the second stage was 7.30. It is of interest to note that even in this rather homogeneous material the individual pH values varied considerably, as reflected by a standard deviation for the means of approximately 0.06.

Using our own material of 355 randomly chosen subjects and choosing a pH of umbilical venous blood >7.30 as the selecting variable, 52 cases meeting this criterion were identified.

The mean pH of blood obtained from the umbilical vein was 7.33, and of that from the umbilical artery, 7.28. The mean Apgar score was 8.1 Of particular interest was the observation that serial samples obtained during the course of labor and delivery did not indicate the development of fetal acidosis and hypercarbia. In 25 out of the 29 cases studied, the initial pH of capillary blood was actually lower than that found at the time of delivery in the umbilical vein. The mean of the initial pH was identical to that of the pH of the umbilical artery sample. A review of the individual cases indicated substantial fluctuations in pH in either direction as labor progressed, amounting in some instances to as much as 0.10. Blood samples obtained from the fetal scalp within minutes before delivery correlated poorly with the values obtained from either the umbilical artery or the umbilical vein, being often substantially lower. Thus, in 4 cases in which the pH of capillary blood immediately preceding delivery was less than 7.19, the corresponding pH in the umbilical vein was 7.24 or more. This is indicative of transient cord occlusion or venous stasis in the tissues of the scalp.

The two series of data referred to above support the contention that labor is not necessarily an asphyxiating process, and that the frequently observed hypercarbia and acidosis of the newborn may be due to pathological factors.

A variety of events have been identified that may contribute to fetal asphyxia. The following seem to be of particular significance: metabolic acidosis of the mother; hypotension; elevated intrauterine pressure between contractions; brief contraction-free periods; transplacentally acquired agents suppressing fetal cardiovascular system, such as certain local analgesics; and hyperexcitability and anxiety state.

Metabolic acidosis of the mother

Metabolic acidosis of the mother occurs not infrequently during labor and delivery. It originates chiefly from the formation of ketones during the period of restricted carbohydrate intake and from the formation of lactic acid in skeletal muscles and in myometrium during uterine contractions. It has also been proposed that the appearance of lactate in maternal blood during labor constitutes an influx from the fetal compartment. This is unlikely to play a significant role, since it has been demonstrated that under normal conditions the fetal output of lactate is small or even absent.

The relative frequency of metabolic acidosis during labor in a random population is estimated to be approximately 20 per cent. It is higher among patients deprived of carbohydrate intake prior to elective induction of labor and in patients with prolonged labor who do not receive carbohydrates intravenously. The mechanism by which acidosis of the mother affects fetal homeostasis is only partly understood. A lowering of maternal pH is known to be associated with a larger-than-corresponding lowering of pH in fetal blood. This would suggest a slight reduction in placental gas exchange. In a group of 9 mothers in whom the mean pH was 7.36 and a base deficit was 4.8 mEq/L, Bowe and coworkers (*4*) found the mean pH of fetal blood to be only 7.15, in contrast to 7.25 for a group in which the maternal pH was 7.42 and the base deficit was 2.16 mEq/L. An additional study

by Beard, Morris, and Clayton (*3*) indicates that fetuses of mothers with metabolic acidosis are more prone to become more acidotic during the course of labor than those born to mothers in an essentially normal acid-base state. In a population of 18 mothers in whom the mean of base deficit was 7.14 mEq/L the mean pH of the fetus during the second stage was 7.17, in contrast to 7.29 for a group comprising 66 patients in whom the mean value of base deficit in the mothers was only 4.2 mEq/L. It should be pointed out, however, that infants born to mothers with metabolic acidosis are not necessarily depressed at birth as judged by the Apgar score, unless subjected to other adverse experiences during the course of labor.

Hypotension

Hypotension is relatively frequent among patients receiving epidural or spinal analgesia during labor and delivery. Its milder and more transient forms do not appear to constitute a particular hazard to the fetus. When prolonged or severe it may lead to fetal asphyxia and even fetal death. The adverse sequelae are more frequently observed in patients that have received systemic analgesics and hypnotics. Our experience with rhesus monkeys indicates that even small amounts of barbiturates administered rapidly by the intravenous route may lead to sufficient hypotension and reduction in placental perfusion to result in fetal death, while at the same time producing only a transient impairment of the mother's cardiovascular performance. It is of note that fluorinated hydrocarbons, such as halothane, may produce appreciable reduction in systemic blood pressure in the mother without adversely affecting placental perfusion (*9*).

The adverse effects of the supine position upon uterine circulation have been demonstrated by means of radiographic studies by Bienarz and co-workers presented at this session. The effect is due to interference in arterial supply to the uterus brought about by the compression of the aorta or the iliac arteries by the contracting uterus, and by the reduction in cardiac output due to interference in venous return resulting from the compression of the vena cava. Our experience with the rhesus monkey is in agreement with the clinical findings reported by these investigators. Figure 1 illustrates the changes in fetal and maternal arterial blood pressure and heart rate brought about by changing the mother from the lateral to the supine position. It can be seen that the supine position has an adverse effect on placental perfusion, even when the mother's cardiovascular performance is affected to only a minor extent. This is demonstrated by the transient rise in fetal blood pressure and by a persistent progressive fall in fetal heart rate and in pH of fetal blood. When the mother is moved back to a lateral position, the condition of the fetus gradually returns to normal: the heart rate is restored to normal levels and a partial recovery from acidosis occurs. The adverse effects of the supine position are more pronounced in animals that have received systemic analgesics or hypnotics or anesthetic agents that interfere with the integrity of the autonomic nervous system. Figure 2 illustrates changes in fetal blood pH after the mother has been moved from the lateral to the supine position. Case 444 developed profound acidosis until the mother was returned to the lateral position, whereas case 494 revealed no significant

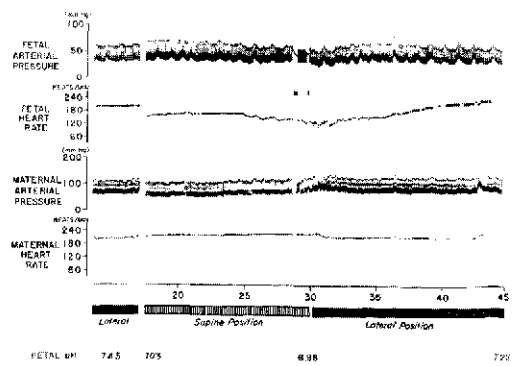

FIGURE 1. Influence of change in maternal posture on cardiovascular performance of mother and fetus of rhesus monkey near term. Fetal blood pressure is recorded via catheter previously inserted into carotid artery. Maternal blood pressure is recorded from femoral artery. Heart rate is recorded electronically from beat-to-beat interval obtained from pulse wave. Note marked acidosis developing in fetus with mother in supine position.

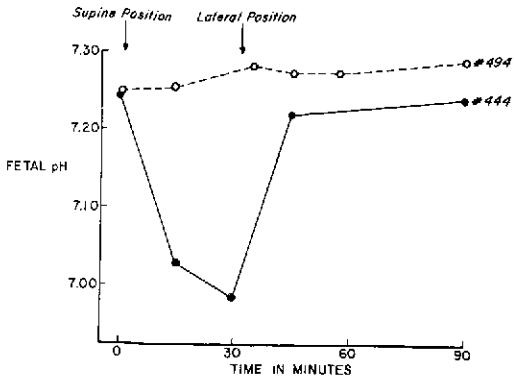

FIGURE 2. Effect of maternal position on fetal pH in two rhesus monkeys near term.

changes. It is probable that the adverse effects are particularly pronounced in patients with strong abdominal muscles and in whom the uterine contractions are of high intensity.

Uterine contractions

It has been commonly inferred that the reason for the frequently observed progressive acidosis of the fetus during the course of labor is a reduction in placental perfusion due to uterine contractions. In analyzing this phenomenon four components must be identified: the intrauterine pressure between contractions, the pressure generated during the contraction, the duration of the contractions, and the duration of the contraction-free period. Although no systematic studies on the relative importance of each of these components have been carried out in experimental animals, the data available suggest that an elevation of intrauterine pressure between contractions and a short interval between contractions is much more likely to affect placental perfusion adversely than a high frequency of uterine contractions *per se* and high maximum values of intrauterine pressure reached at the peak of the contraction. We have observed the development of acidosis and hypercarbia in the fetal rhesus monkey even before the onset of appreciable uterine contractions during early phases of uterine stimulation by oxytocin infusion when the principal change was an elevation of intrauterine pressure from a few mm Hg to 10 to 15 mm Hg. Although this pressure was significantly lower than the presumed perfusion pressure on the arterial side of the uterine circulation, the reduction in intervillous space perfusion must have been considerable and disproportionately greater than the change in the net perfusion pressure. On the other hand, strong uterine contractions, either occuring spontaneously or induced by oxytocin, did not affect fetal homeostasis if the intrauterine pressure between the contractions was low (less than 5 mm Hg) and when the ratio of the area under the pressure curve to the total area of one cycle was less than 0.4 to 0.3. This is not unexpected, since it has been demonstrated previously by Ramsey and coworkers that uterine perfusion essentially ceases during the contraction period; furthermore, it has been calculated that the quantity of oxygen stored in the materal blood of the intervillous space is sufficient to meet fetal needs for at least one minute before oxygen tension is reduced to abnormally low values (*1*).

Hyperexcitability and anxiety of the mother

Information is still lacking as to the effect of anxiety states or hyperactivity of the sympathetic system of the mother on placental perfusion and gas exchange. The administration of small amounts of epinephrine and norepinephrine to the pregnant sheep has been found to have no adverse effect upon the pH and cardiovascular performance of the sheep fetus. These data, however, have little bearing on situations in which prolonged stimulation of the adrenergic system may occur, as a result of either endogenous or exogenous stimuli. Since circulation to abdominal viscera is known to be markedly affected by sympathetic stimuli, this problem evidently deserves more attention.

Agents suppressing fetal cardiovascular system

The fetal cardiovascular system does not seem to be particularly susceptible to most anesthetic agents. When fetal acidosis is observed as the result of deep anesthesia of the mother, it is

usually due to impaired placental perfusion rather than to a reduction of fetal cardiac output *per se*. This has been demonstrated at least for halothane using the sheep fetus as an experimental model (*9*). Local analgesics may, however, be an exception. Transient fetal bradycardia is commonly observed after the administration of mepivacaine into the paracervical tissues of the human patient. Although in most instances fetal bradycardia is transient in nature and is not associated with development of significant fetal acidosis, a lowering of Apgar scores of the newborns has been observed (*12*). Fetal bradycardia has been uniformly observed when the mepivacaine concentration in blood obtained from the fetal scalp exceeded 12.8 μg per ml (*7*).

It is generally appreciated that these factors exert a particular influence on fetal acidosis in patients with fetuses of more than 42 weeks' gestation and in conditions of presumably reduced volume of intervillous space (such as erythroblastosis fetalis, clinical or preclinical diabetes of the mother, or syphilitic infections of the fetus). It has also been suggested that fetal acidosis is more likely to develop when the body temperature of the mother, and thus that of the fetus, is substantially elevated. This impression, however, requires additional data for confirmation.

Summary

In most instances labor and delivery lead to moderate acidosis and hypercarbia of the fetus. The changes in fetal acid-base state are particularly pronounced in the period immediately preceding delivery. They are likely to be caused by interferences in the circulation through the umbilical cord. The reasons for the milder forms of fetal asphyxia observed during labor are less well understood. Some of them have been identified and briefly discussed, and their preventability has been stressed. It is proposed that intrapartum acidosis and hypercarbia are not an inevitable consequence of normal labor, and that under optimal conditions the fetal acid-base state remains essentially unchanged. It is further suggested that the supine position imposed upon the laboring patient in most Western countries may have an adverse affect upon placental perfusion, particularly when the integrity of the autonomic nervous system of the mother is modified by the administration of anesthetic, analgesic, or hypnotic agents. Finally, it is suggested that when an effort is made to alleviate the physical discomfort of the mother during labor, increased surveillance of the relevant functions of the mother and fetus is necessary to ensure fetal well-being.

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CHANGES IN FETAL HEART RATE ASSOCIATED WITH ACUTE INTRAPARTUM FETAL DISTRESS[1]

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In present-day obstetrics, it is very important to diagnose acute intrapartum fetal distress as soon as possible, before irreversible damage is produced to the fetus. Early diagnosis, if followed by immediate treatment, may prevent fetal lesions that would otherwise handicap the individual for the rest of his life.

There are various criteria for assessing the validity of any method of diagnosing acute intrapartum fetal distress. Usually it is accompanied by changes in fetal blood composition (*35, 36, 45*) and followed by the delivery of a depressed newborn (excluding pharmacological depression). Thus, either of these may be used to diagnose fetal distress (*12, 35, 36*).

The two phenomena are intimately related. The depression of the newborn (together with some permanent neurological sequelae) is mainly due to damage to fetal cells, particularly those of the nervous system. There are two main causes of fetal cell damage. The abnormal composition of fetal blood during acute intrapartum fetal distress (*1, 7, 16, 32, 34, 35, 36, 43, 45*), in consequence of impaired exchanges between the mother and the fetus (*7*), produces fetal acidosis, hypoxia, hypercapnia, and similar conditions (*7, 34, 46, 48, 49*). Further, the circulation of fetal blood may not assure an adequate supply of metabolites to all fetal organs and tissues (*8, 17, 18, 19, 20, 21, 22, 38*). The two causes may function simultaneously.

It follows that the diagnosis of fetal distress can be reliably based on a study of the composition of fetal blood or on the determination of the Apgar score of the newborn (*2*). A very good correlation between the two criteria has been found (*16, 32, 33*).

From a practical standpoint, both criteria have drawbacks. The fetal blood composition cannot be analyzed when the obstetrical conditions make fetal sampling impossible; moreover, the information obtained from this procedure is discontinuous and a well-equipped laboratory is necessary. On the other hand, to diagnose fetal distress retrospectively, based on a low Apgar score, has no clinical application.

Our aim is to develop a method for the analysis of the fetal heart rate (FHR) that can be used for an early, reliable, and practical diagnosis of acute intrapartum fetal distress. Monitoring of the FHR can provide a very useful tool for this purpose (*5, 6, 8, 10, 27, 28*) if it can be proved that changes in the fetal blood composition are related to certain variations in FHR and that these, in turn, are related to the delivery of a depressed newborn.

[1] This study received support from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization, and from grant HD 00222–06 of the National Institute of Child Health and Human Development, Bethesda, Maryland, U.S.A.

[2] Presented by Dr. Méndez-Bauer.

Abnormal FHR patterns

Changes in FHR, detectable by clinical methods (*8*), have been found in cases of fetal distress. Possibly as a result of chronically impaired feto-maternal exchanges, transiently aggravated by uterine contractions, the composition of the fetal blood is altered. In these abnormal conditions, several adaptive reactions may occur (*8, 13*) that apparently tend to minimize the possible harmful consequences of these homeostatic disturbances and to prolong fetal survival. The cardiovascular response of the fetus is one of the most important and best-known of these adaptive reactions and includes changes in FHR, which can be used for the clinical diagnosis of fetal distress (*9, 10, 11, 16*).

The FHR records obtained from distressed fetuses show a great variety of patterns (*6, 9, 10, 11, 15, 27, 28, 29, 35, 37, 38, 39, 41, 42, 43*). These patterns combine two main components: (1) sustained and prolonged tachycardia of the baseline (*22, 39*), and (2) dips II (see below). In combination, these components may give rise to a great variety of syndromes.

Rise of basal FHR over 155 beats/min (tachycardia)

The FHR tracings show at least four different kinds of variations, which have been designated as "small rapid oscillations" (*38, 40, 51*), "spikes" (*25*), "transient ascents" (*40*), and "dips" (*14, 24, 39*). The baseline upon which these variations are superimposed is the basal FHR (*30, 31, 39*) (Fig. 1).

The basal FHR, or baseline of the tracings (*30*), is measured during the intervals between dips, transient ascents, and spikes, and is defined as the average value between the peaks and valleys of the small rapid oscillations usually present in FHR records (Figure 1). During normal labor, the basal FHR averages 143 beats/min (S.E. 2 beats/min) (*31*). A rise to above 155 beats/min (tachycardia) is considered a sign of fetal distress (*5, 8, 31, 35, 36*) (Figures 1 and 2).

The tachycardia may appear alone—that is, not be interrupted by dips II or other changes in FHR (Figure 2B). It may be intermittently masked when dips II do occur (Figure 2C). The interruptions in the baseline are more prolonged when several consecutive dips II

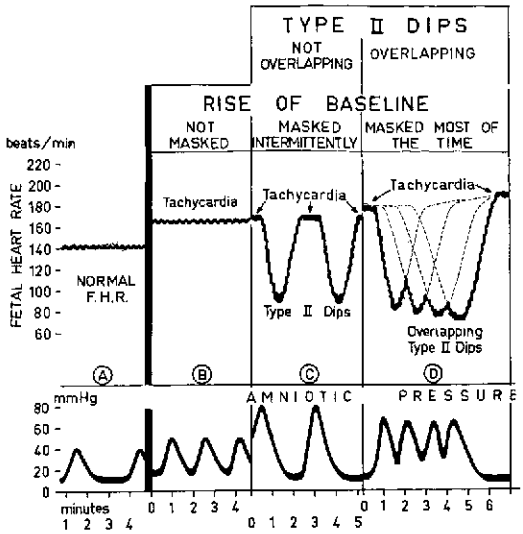


FIGURE 1. Parameters analyzed in tracings of FHR and chronological relationship to uterine contractions (*38*).

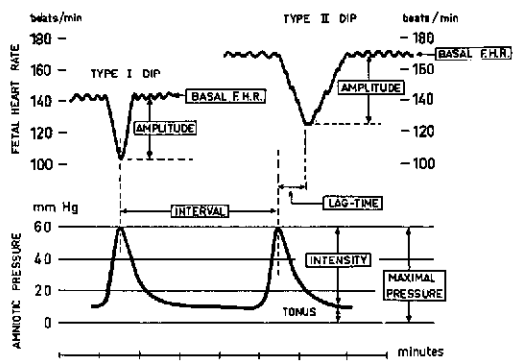


FIGURE 2. Highly schematic representation of basic FHR patterns found in fetal distress. Severity of distress increases from left to right. At bottom, uterine contractions (intraamniotic pressure) assumed to be immediate cause of distress. In A, contractility is normal; in B, moderate uterine tachysystolia; in C, marked uterine hypersystolia; in D, uterine tachysystolia and hypertonus. FHR is normal in A, averaging 140 beats/min; no dips II. Baseline rises abnormally in B, C, and D. In C and D each contraction causes one dip II, totally independent in C and partially overlapped in D. Broken lines in D indicate masked portion (descending and ascending limbs) of individual dips II. Tachycardia of baseline, also masked by overlapping dips II, is indicated similarly (*13*).

overlap (Figure 2C); in these conditions, the tachycardia may be masked most of the time and very difficult to recognize.

Dips II

A dip II is a transient fall in FHR produced by a uterine contraction and occurring some time after it (*10, 14, 23, 35, 36*). The mean lag-time between the peak of the contraction and the bottom of the dip II is 41 seconds (S.D. = 11 seconds) (Figure 1). A dip I is also a transient fall in FHR caused by a uterine contraction, but it occurs at practically the same time as the contraction. The mean lag-time between the peak of the contraction and the bottom of the dip I is 3.5 seconds (Figure 1). This difference in lag-time is a reliable criterion for distinguishing dips II from dips I. An extended discussion and statistical analysis of this point have already been published (*6*).

Dips I and dips II are produced by different mechanisms (*15, 38*), appear under different conditions (*3, 24*), and have different diagnostic and prognostic significance (*3, 8, 31*). Dips II are a sign of fetal distress, whereas dips I apparently have no such ominous connotation (*10*).

Dips II are easily recognized in simultaneous tracings of FHR and uterine contractions and can also be detected by adequate clinical auscultation (*8*). Their appearance usually coincides with a rise in basal FHR above 155 beats/min (Figure 2C). Dips II may be recorded as individual units, totally independent of each other and clearly recognizable, or they may overlap partially, losing their individuality and merging to produce a more prolonged and marked fall of FHR (Figure 2D).

In addition, dips I and II may be produced by the same uterine contraction. This pattern can easily be recognized from FHR tracings, but its recognition by clinical auscultation alone may be rather difficult.

To confirm the hypothesis that tachycardia and/or dips II are associated with fetal distress, in the following sections the presence of both signs will be studied in relation to the occurrence of changes in fetal blood composition and to possible depression of the newborn.

Relationship between variations in FHR and changes in fetal blood composition

Basal FHR and composition of fetal blood

The results of simultaneous studies of fetal blood composition according to Saling's technique (*49*) and FHR have already been published (*7, 35, 36*). It can be concluded that the basal FHR increases to over 155 beats/min when fetal pH falls below 7.20 (Figure 3), whereas no clear relationship has been found between changes in basal FHR and pCO_2, base deficit, or oxygenation of the fetal blood.

Dips II and composition of fetal blood

Dips II are usually associated with fetal hypoxia, acidosis and hypercapnia (Figures 4, 5, and 6). They are not associated with an increased base deficit of fetal blood (*36*).

Relationship between variations in FHR and Apgar score

Complete studies on the relationship between the condition of the newborn, as evaluated by

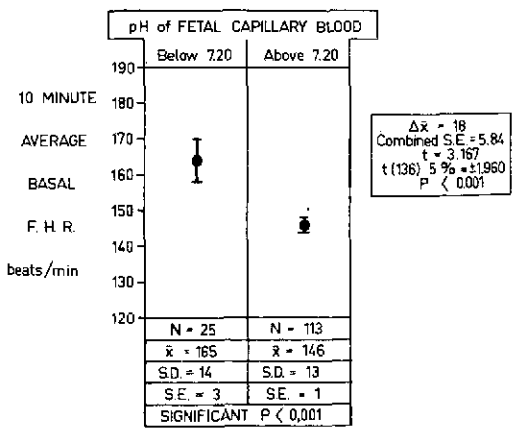


FIGURE 3. Average basal FHR in 10-minute period preceding sampling from fetal scalp was measured for 138 samples divided into two groups (pH values over and below 7.20), and group means were calculated. Difference is highly significant ($p < 0.001$).

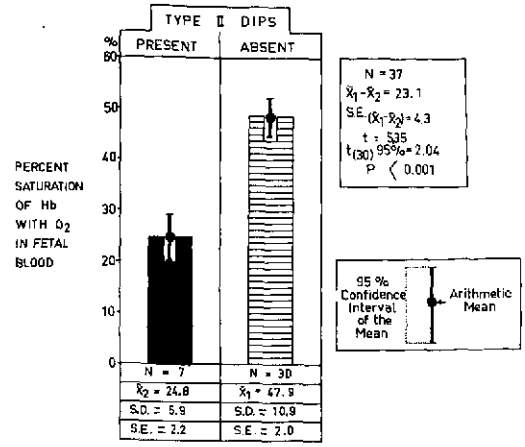


FIGURE 4. Mean percentage of oxygen saturation of Hb in fetal blood samples is significantly lower when dips II were present in FHR tracing than when they were absent (7).

the Apgar score at the first minute of life, and changes in FHR have recently been published (*8, 36*).

Basal FHR and Apgar score

The group of vigorous newborns (Apgar score 7–10) had an average basal FHR of 143 beats/min, in comparison with an average of 166 beats/min for the "depressed" group (Apgar

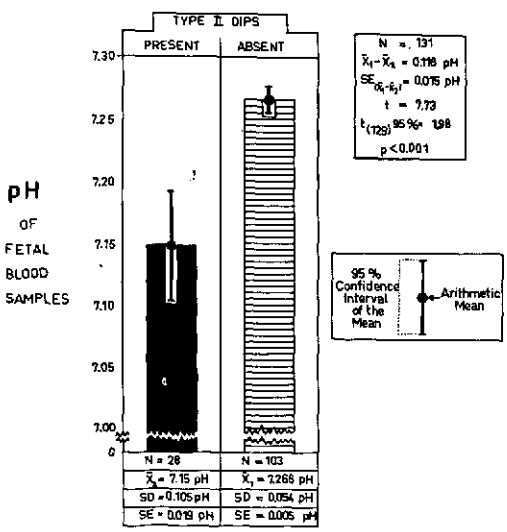


FIGURE 5. Mean pH of fetal blood samples is significantly lower when dips II were present in FHR tracings than when they were absent (7).

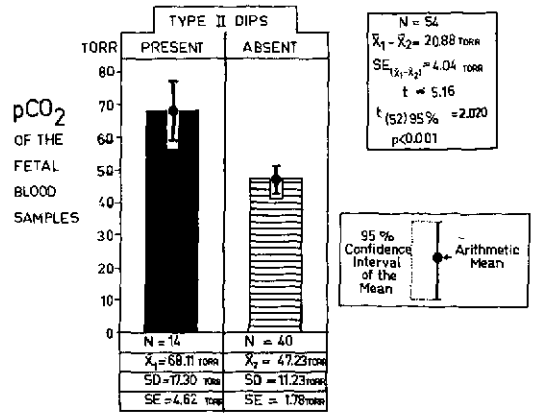


FIGURE 6. Mean pCO_2 in fetal blood samples is significantly higher when dips II were present in FHR tracing than when they were absent (7).

score 1–6). The difference is highly significant. The rise in the baseline above a tentative limit of 155 beats/min is considered a sign of fetal distress. The higher and the more prolonged the rise of the baseline, the worse the prognosis for the infant.

Dips II and Apgar score

Possible correlations were sought between the Apgar score of the newborns at the first minute of life and various quantitative characteristics of the dips II that had occurred in each case.

Mean amplitude of dips II. No significant differences have been found in the mean amplitude of dips II between labors delivering depressed newborns and those delivering vigorous ones. In both groups it was about 20 amplitude units (beats/min).

Total number of dips II. In the group of depressed newborns the average number of dips II recorded during each labor was 91, whereas in the group of vigorous newborns the mean was 11. The difference is highly significant (Figure 7).

It has been suggested (*7, 8*) that dips II should be virtually absent in a normal labor and that their appearance should be regarded as a sign of fetal distress. However, if the total number of dips II recorded during a complete

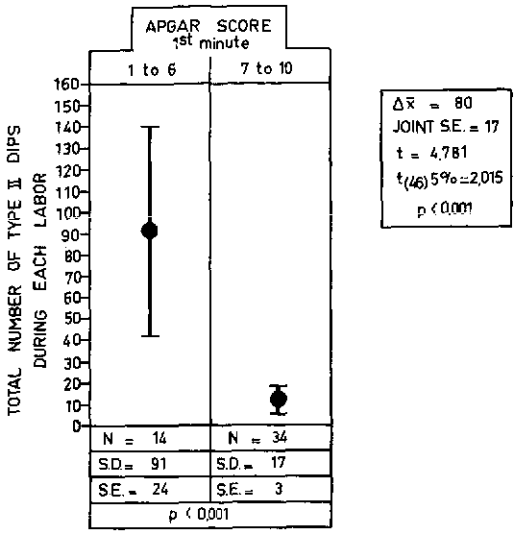
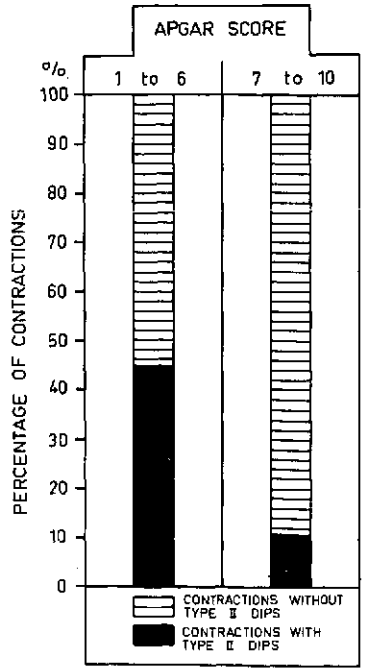


FIGURE 7. Mean total number of dips II recorded during labor in group of 14 depressed newborns is 91. In group of 34 vigorous infants, mean value is 11. Both mean and fiducial limits (95 per cent) are indicated for each group; difference is significant ($p < 0.001$) (*8*).



labor is below a tentative upper limit of 20, the fetal disturbance will not be severe enough to cause a low Apgar score. Above this number the newborn is usually depressed. The few exceptions to this rule were cases in which dips II were recorded in early stages of labor and then disappeared, the FHR tracing being normal for several hours before delivery.

Percentage of contractions causing dips II (Figure 8). In a pool made of all the 3,499 uterine contractions recorded in 34 labors from onset until the delivery of vigorous newborns, only 377 (11 per cent) caused dips II. In the group of 14 labors delivering depressed newborns, 1,273 of the 2,852 contractions recorded (44.6 per cent) produced dips II.

From these results it can be concluded that two signs of FHR (tachycardia of baseline over 155 beats/min and the occurrence of more than 20 dips II) can be used for a reliable diagnosis of fetal distress. In particular, dips II are associated with hypoxia, hypercapnia, and low actual pH of fetal blood; when more than 20 of them occur during labor, the newborn is usually depressed.

UTERINE CONTRACTION	APGAR SCORE 1 to 6	APGAR SCORE 7 to 10	TOTAL
WITHOUT TYPE II DIPS	1.579	3.122	4.701
WITH TYPE II DIPS	1.273	377	1.650
TOTAL	2.852	3.499	6.351

P < 0,001

FIGURE 8. In 14 labors delivering depressed newborns, 45 per cent of contractions caused dips II; only 10 per cent caused dips II in 34 labors delivering vigorous newborns (χ^2 test, $p < 0.001$). Total number of contractions analyzed was 6,351 (*8*).

A practical test for evaluating fetal condition in acute intrapartum fetal distress, based on dips II

The difficulty with using the criterion of 20 or more dips II during labor is that by the time

distress is diagnosed the fetal damage has probably already occurred. The following study was carried out with the aim of finding a way to detect as early as possible any departure from normal in the condition of the fetus.

Material and methods

In a retrospective study of the available records of labor at the Obstetrical Physiology Service in Montevideo, Uruguay, 20 cases were found to have a good FHR tracing in the period immediately preceding the second stage or intrapartum fetal death. These 20 newborns were classified, according to the Apgar score at the first minute of life, into three groups: I (10 newborns), with a score of 7 to 10; II (5 newborns), with a score of 4 to 6; and III (5 newborns), with a score of 0 to 3. Group III included two fetuses who died during labor. Cesarean sections were excluded. Except in one case (No. 1500), in which the umbilical cord was found at birth to be loosely wound around the fetal neck, no cord complications were known to exist.

Several characteristics of dips II were studied in the 20 contractions that preceded the second stage of labor, in order to determine whether any of them were related to the delivery of a depressed newborn.

Results and discussion

Dips II were rare in group I. They did occur in groups II and III, but there was no significant difference in amplitude between the two groups (Figure 9). Thus amplitude cannot be used for predicting the condition of the newborn.

The incidence of dips II was also studied by calculating what percentage of the 20 contractions produced them. In group I (Figure 10) this percentage was 5.5 per cent. The fiducial limits statistically calculated (99 per cent) ranged between 1.5 and 10 per cent. This implies that when up to 10 per cent of the contractions cause dips II, the fetus—if immediately delivered—will have an Apgar score of

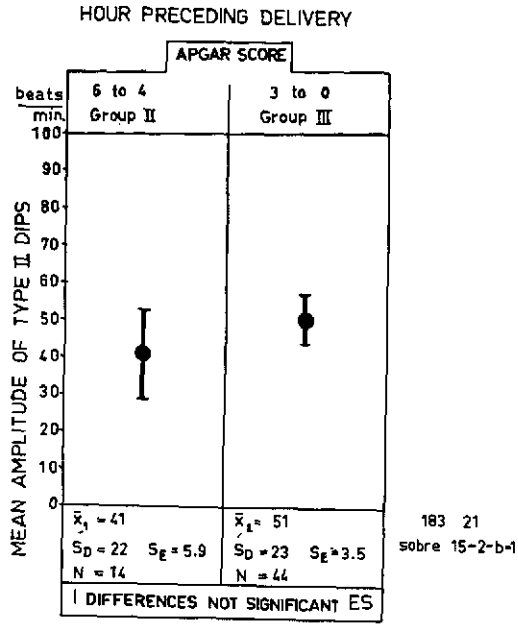


FIGURE 9. Comparison of mean amplitude of dips II in Groups II and III reveals no significant differences (*37*).

7 to 10 (with 99 per cent confidence). In group II the percentage of contractions causing dips II was 21 per cent (Figure 11). The fiducial limits calculated (99 per cent) ranged from 11 to 31 per cent. Within this range the newborns will be moderately depressed (Apgar score 4–6). In group III a mean of 44 per cent

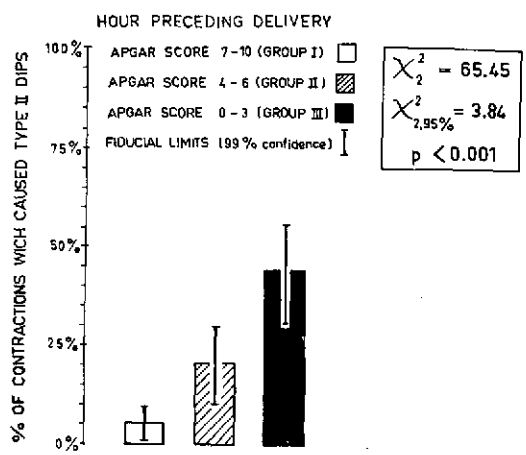


FIGURE 10. Percentages of 20 contractions preceding second stage that caused dips II in Groups I, II, and III. In χ^2 test with two degrees of freedom, differences are highly significant ($p<0.001$) (*37*).

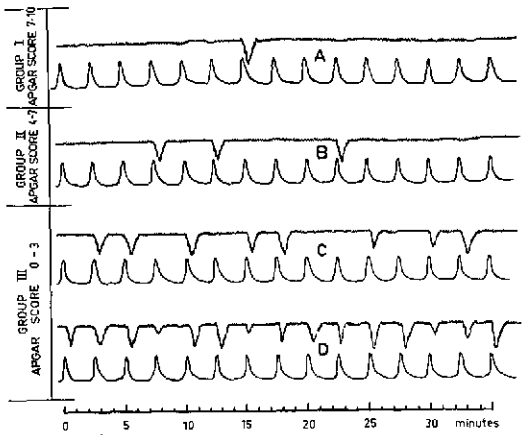


FIGURE 11. Schematic representation of records of FHR and amniotic pressure. Severity of fetal distress increases from top to bottom. At left, theoretical Apgar score (if fetus were delivered immediately). Percentage of contractions causing dips II may indicate, at any moment of labor, condition of fetus (*37*).

of the contractions produced dips II. The 99 per cent fiducial limits for this group ranged from 32 to 56 per cent. Thus, if more than 32 per cent of the contractions cause dips II the fetus will be delivered extremely depressed or will die during labor.

The percentages of uterine contractions causing dips II in each group were studied by means of a χ^2 test with two degrees of freedom. The difference between these percentages was found to be highly significant ($p<0.001$) (Figure 10). These differences cannot be accounted for by differences between groups in the maximal pressure of the contractions; all 20 fetuses were exposed to contractions of similar maximal pressure.

In summary, a study of 15 to 20 contractions prior to the second stage of labor to determine what percentage of them produces dips II is enough to enable the obstetrician to predict the Apgar score of the newborn if it is delivered immediately; the amplitude of the dips II, as has been said, may be ignored. The contractions to be considered should have a maximal pressure ranging between 30 and 70 mm Hg, such as are usually found during labor.

If such a test served only to predict the condition of the newborn a few minutes before delivery, its usefulness would obviously be limited. However, these results can be used to develop a test whereby the clinician can diagnose acute intrapartum fetal distress at any moment during labor.

It may be predicted that fetus A in Figure 11, if immediately delivered, would have an Apgar score of 7–10, since less than 10 per cent of the contractions (6.6 per cent) have produced dips II and consequently its condition can at the moment be described as excellent. Fetus B, with 20 per cent of the contractions producing dips II, would have an Apgar score of 4–6; thus, it is in distress. Fetuses C and D are extremely distressed, as can be suspected from the fact that more than 30 per cent of the contractions are producing dips II; they will die very soon, or be severely depressed if immediately delivered.

Practically speaking, it is enough to monitor 15 consecutive uterine contractions with simultaneous auscultation of the fetal heart and uterine palpation. The method to enable the obstetrician to detect dips II easily by clinical procedures has been published elsewhere (*8*).

For each contraction, the presence or absence of dips II should be represented on a chart similar to that shown in Figure 12. If a contrac-

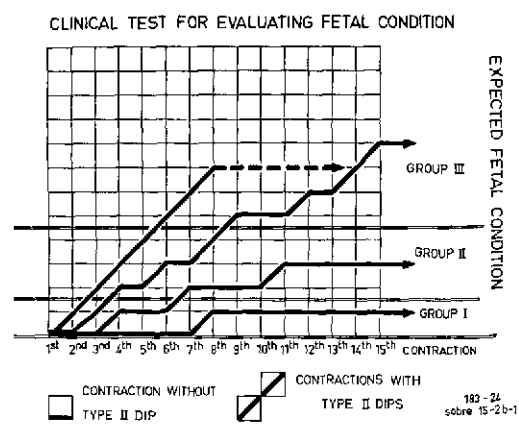


FIGURE 12. Double horizontal lines define groups I, II, and III (expected good, poor, or extremely severe fetal condition). Each vertical line corresponds to one monitored contraction. Heavy lines represent presence (diagonal) or absence (horizontal) of dips II; thus position of continuous line shows after each contraction the condition of the fetus. Number of contractions required to achieve diagnosis of acute intrapartum fetal distress decreases as fetal condition gets worse.

tion does not produce a dip II, a horizontal line is drawn in the square corresponding to it; if it does, an oblique line. If no dips II are detected in the 15 consecutive contractions studied, a continuous horizontal line will be superimposed on the bottom line of Figure 12. One dip II found among the 15 contractions will raise the line slightly, but the fetus will still be in good condition because the percentage (6.6) is within the limits of group I. If 3 or 4 dips II occur in the 15-contraction period, the fetus is distressed and, if immediately delivered, would be depressed (Apgar score 4–6). If more than 4 occur, the fetus is in extremely severe distress and would have a very low Apgar score (0–3).

It can be observed that the number of contractions to be studied diminishes with the severity of fetal distress. For instance, in situation D of Figure 11, in which all the contractions produce dips II, it is unnecessary to wait for the end of the series of 15, because the percentage is already over 47 by the time of the seventh consecutive contraction. At the usual frequency of 3 to 5 contractions every 10 minutes, the diagnosis of severe distress can thus be made in 12 to 20 minutes. This is the case of the fetus represented by the top line of Fig. 12, in which, after the seventh contraction, it can be stated that the fetus is definitely within the area of group III. The dotted line from the seventh contraction onwards emphasizes the fact that the diagnosis of extremely severe fetal distress has already been made. If this situation is allowed to continue, the consequent fetal damage will be increasingly aggravated; if its cause is corrected by adequate treatment as soon as fetal distress has been recognized, the percentage of contractions causing dips II will diminish, showing the improvement of the fetal condition.

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THE FETAL EFFECTS OF UMBILICAL CORD COMPRESSION[1]

Edward H. Hon

In clinical obstetrics umbilical cord complications appear to be frequent causes of fetal distress leading to perinatal morbidity and mortality. It is important, therefore, to be able to recognize them as early as possible. Unfortunately, with intermittent stethoscopic sampling of the fetal heart rate (FHR), fetal distress can only be detected in extreme circumstances (*2*). Recently, however, with the development of techniques for continuous monitoring of the FHR (*3, 8*), it has become possible to identify definite FHR patterns in the human fetus which are similar to those described in fetal animals by Barcroft, Reynolds, Paul, Dawes, and coworkers (*1, 4, 18, 19*).

The similarity of FHR patterns in human and animal fetuses during cord compression has been confirmed by observing the pattern where there has been prolapse of the cord (*10*) or by direct compression of the umbilical cord at elective cesarean section (*16*). In addition to specific FHR changes caused by cord compression, there are also alterations in the configuration of the fetal electrocardiogram, with sinus depression (*7*) sometimes to the point of arrest (*9*).

The introduction of fetal scalp blood sampling by Saling (*20*) has permitted an examination of acid-base changes associated with umbilical cord compression. 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 (*15*).

Preliminary studies of auditory evoked potentials obtained from the fetal scalp during the course of labor indicate that there are alterations in waveform and latency during episodes of umbilical cord compression (*5*). This report will review some effects of compression on the fetus.

Patients and procedures

The data presented in this study were recorded from patients admitted to the Yale-New Haven Hospital in early or active labor. The records have been selected to illustrate various fetal effects of umbilical cord compression. The biophysical techniques employed have been previously described (*6*). In brief, the fetal electrocardiogram (FECG) was obtained by attaching a silver/silver-chloride electrode (*11*) directly to the presenting part of the fetus, and the instantaneous FHR computed with a peak-to-peak cardiotachometer. For pressure measurements a 16-gauge I. D. Teflon catheter was introduced transcervically into the uterus and connected to a Statham strain gauge. After appropriate amplification, the data were recorded on an Offner Type R Dynograph for visual display and on an Ampex FR1100 magnetic tape recorder for later electronic data processing.

Group averages of the FECG were com-

[1] Investigation supported in part by research grants HD 01467–03, HD 03338–02, and 5K03 HD 18,295 from the National Institute of Child Health and Human Development, Bethesda, Maryland, U.S.A.

puted on a CAT computer [2] and recorded on an oscillograph (*12*). The auditory evoked potentials were obtained by placing silver/silver-chloride electrodes on either side of the sagittal suture in the parietal areas of the fetal skull and recording the potentials after amplification and group averaging on the CAT computer. A 50-millisecond auditory stimulus was applied every two seconds to the right ear of the fetus by means of a plastic tube (*14*). The biochemical studies were done with the technique developed by Saling (*20*) except that 13-inch heparinized glass capillaries were used rather than plastic tubing for the collection of blood samples. The pH determinations were done with a Radiometer micro-electrode, and the pCO_2 measurements were made directly with a pCO_2 electrode and Instrumentation Laboratories equipment.

Results

Our early interest in FHR patterns was stimulated largely by the observations made by Barcroft on the FHR changes associated with compression of the umbilical cord of the fetal goat (*1*). Figure 1 shows some of his observations. In describing this FHR change, Barcroft pointed out that with umbilical cord occlusion there was an abrupt drop in FHR, which rapidly returned to baseline levels following cord release. If the same stimulus was repeated after vagotomy, there was a delay in the onset of the bradycardia. This is indicated in Figure 1 by the dotted line. As a result of these and similar observations, Barcroft came to the conclusion that the initial abrupt bradycardia was largely reflex in origin, while the delayed bradycardia had asphyxial overtones and was probably due to hypoxic depression of the fetal myocardium. Implicit in this description is the notion that the initial abrupt drop in the FHR was relatively innocuous (since it was largely reflex) while the delayed bradycardia was ominous (since it probably reflected fetal asphyxia).

The data of our early human studies were carefully reviewed to determine whether similar FHR patterns might be found in the human fetus during the course of labor and delivery. Figure 2 shows an FHR pattern recorded during late labor from a fetus where the umbilical cord had prolapsed between the fetal thighs in a double footling breech presentation. With each uterine contraction the umbilical cord was probably being compressed (*8*). The marked simi-

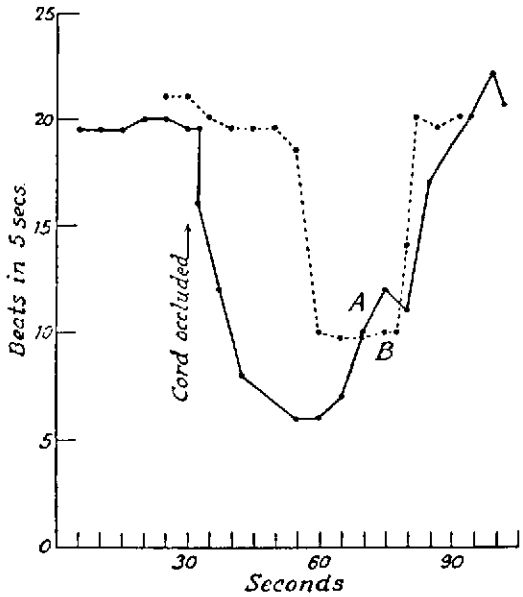

FIGURE 1. Comparison of two types of bradycardia of fetal goat associated with umbilical cord occlusion. Thick line, vagi intact; broken line, vagi cut. (Reproduced with permission of publisher from J. Barcroft, *Researches on Pre-natal Life*, Springfield, Illinois, Charles C Thomas, 1947.)

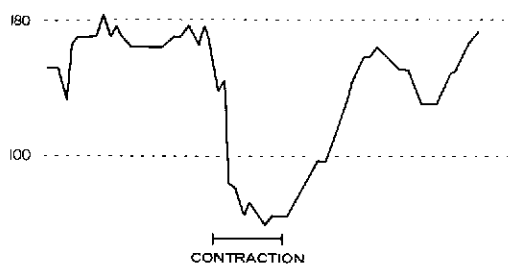

FIGURE 2. Abrupt drop in FHR recorded during late labor where umbilical cord had prolapsed between fetal thighs in double footling breech presentation. With each uterine contraction umbilical cord was probably being compressed. (Reproduced with permission of publisher from E. H. Hon, *An Atlas of Fetal Heart Rate Patterns*, New Haven, Connecticut, Harty Press, 1968.)

[2] Technical Measurement Corporation, North Haven, Connecticut.

larity between this FHR pattern and that observed by Barcroft in the fetal goat is obvious.

The possibility that a specific FHR pattern was associated with umbilical cord compression was further explored at the time of elective cesarean section by making a window in the lower uterine segment of the uterus and pulling up a loop of cord before delivery. A 19-gauge needle to which was attached a catheter was then inserted into the umbilical artery and the cord was compressed for short periods of time (*16*). Figure 3 shows the abrupt fall in FHR whenever the umbilical artery (3A) or the umbilical vein (3B and 3C) is compressed. Although a marked drop in FHR is present in either circumstance, the changes in umbilical arterial blood pressure are different. The concept that cord compression causes specific FHR pattern changes in the human fetus has also been confirmed by later studies.

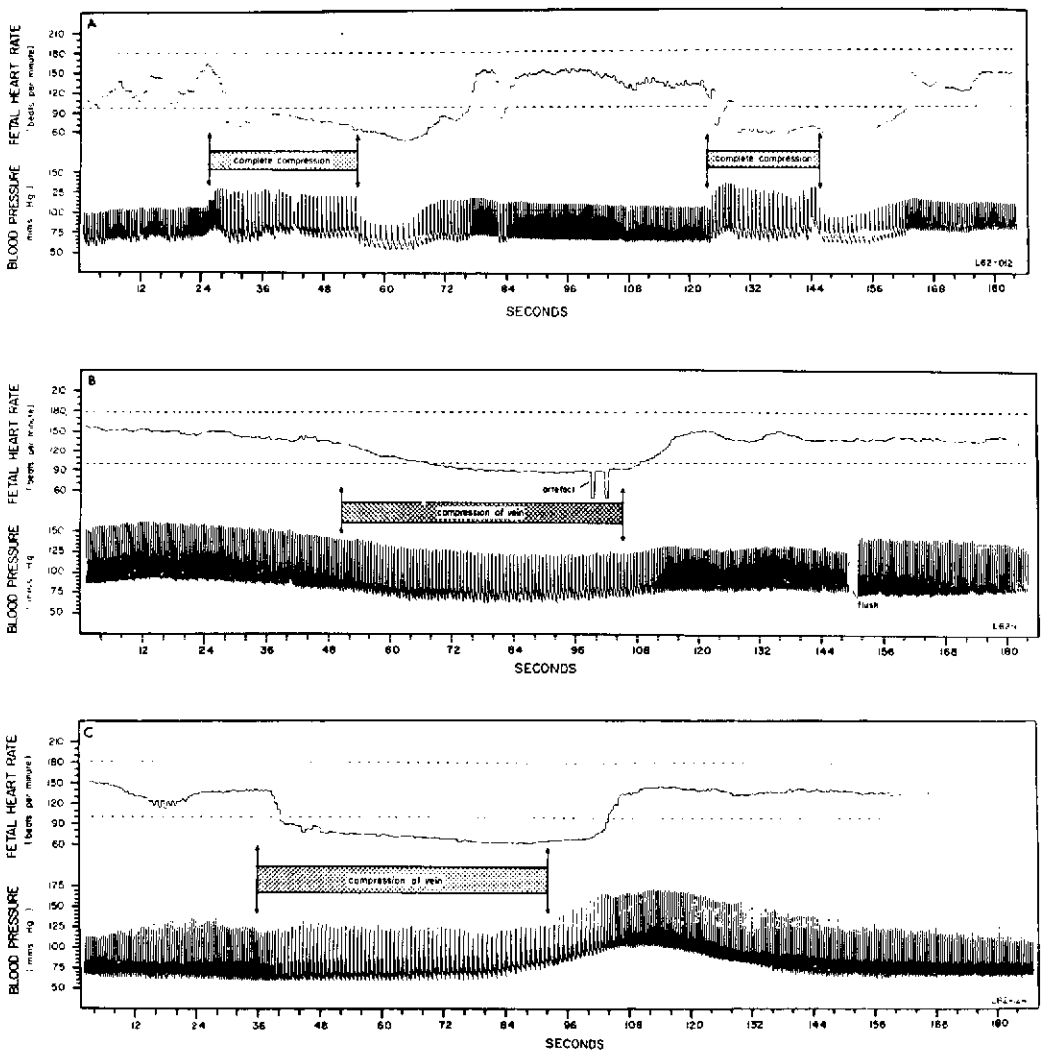

FIGURE 3. A shows abrupt fall in FHR associated with complete compression of umbilical cord; note fetal hypertension. In B and C, abrupt fall in FHR associated with compression of umbilical vein alone. Note hypotension in B and normotension in C. (Reproduced with permission of publisher from *The Heart and Circulation in the Newborn and Infant,* New York, Grune & Stratton, 1966, p. 37.)

In order to provide background data for a consideration of the FHR patterns associated with umbilical cord compression, it is necessary to distinguish specific FHR changes associated with uterine contractions (periodic FHR changes) from those occurring at other times (baseline FHR changes). Periodic rises in FHR are labeled acceleration and periodic falls in FHR are labeled decelerations, to distinguish them from corresponding changes in the baseline (*13*).

Figure 4 describes some of the characteristics of three specific FHR deceleration patterns that appear to be of clinical significance. Figure 4A is a pattern of uniform shape that reflects the shape of the associated intrauterine pressure curve. The deceleration has its onset early in the contracting phase of the uterus. Hence it has been labeled "early deceleration"; it is thought to be caused by fetal head compression. Figure 4B is an FHR deceleration pattern, also of uniform shape, that again reflects the shape of the associated intrauterine pressure curve. In this case, however, in contradistinction to the uniform pattern of Figure 4A, its onset occurs late in the contracting phase of the uterus and it has therefore been labeled "late deceleration." This pattern is thought to be caused by acute utero-placental insufficiency as a result of decreased intervillous blood flow during uterine contractions. Figure 4C is an FHR deceleration pattern of variable shape that does not reflect the shape of the associated intrauterine pressure curve. The onset of the deceleration occurs at different times during the contracting phase of the uterus. This variable pattern is thought to be caused by umbilical cord occlusion.

Figure 5 shows some of the characteristics of variable deceleration. It varies markedly in shape from contraction to contraction, and does not reflect the shape of the associated contraction curve. Its onset bears a variable time relationship to the beginning of the associated uterine contraction. It usually falls below 100 beats a minute and is frequently as low as 50–60 beats a minute or less. Its duration varies from a few seconds to minutes. It is usually associated with a baseline FHR in the normal or low normal range. It is probably due to umbilical cord occlusion. It is markedly altered by maternal position change or fetal manipulation. It does not appear to be altered by maternal hyperoxia. It is markedly altered by atropine administration. It is not associated with fetal acidosis unless frequent and prolonged.

The FECG changes associated with moderate umbilical cord compression are illustrated by Figure 6. The upper tracing shows the typical FHR pattern of cord compression. A series of averaged FECG's computed at various times during the recording is shown in the lower tracings. The bracket over them from letters D to H indicates the time that variable FHR deceleration was present. The FECG complexes observed prior to the beginning of the deceleration (A to C) are essentially the same. At D, a few seconds after the onset of deceleration, the P wave becomes quite small and remains so until position F, where there is a slight increase in the FHR. From F to G to H there is an increase in P wave amplitude. At H, where the FHR has returned to baseline levels, the P wave is of essentially the same amplitude as it was before the onset of the variable deceleration. T wave changes and S-T segment depression are present toward the end of the tracing. These FECG changes may reflect hypoxic aspects of umbilical cord occlusion and provide some indication of fetal tolerance.

In certain clinical situations a strong vagal stimulus superimposed on mild hypoxia may cause severe sinus depression to the point of cardiac arrest (*17, 21*). Figure 7A illustrates fetal cardiac arrest during labor. The FHR pattern of variable deceleration is identified readily. The initial and last episodes of deceleration are associated with an FHR that drops to zero (indicated here by an FHR level of less than 30 beats a minute). Figure 7B, an FECG tracing made simultaneously with the initial episode of variable deceleration, shows that the FECG is absent for about eight seconds. The small deflections on the FECG record, which

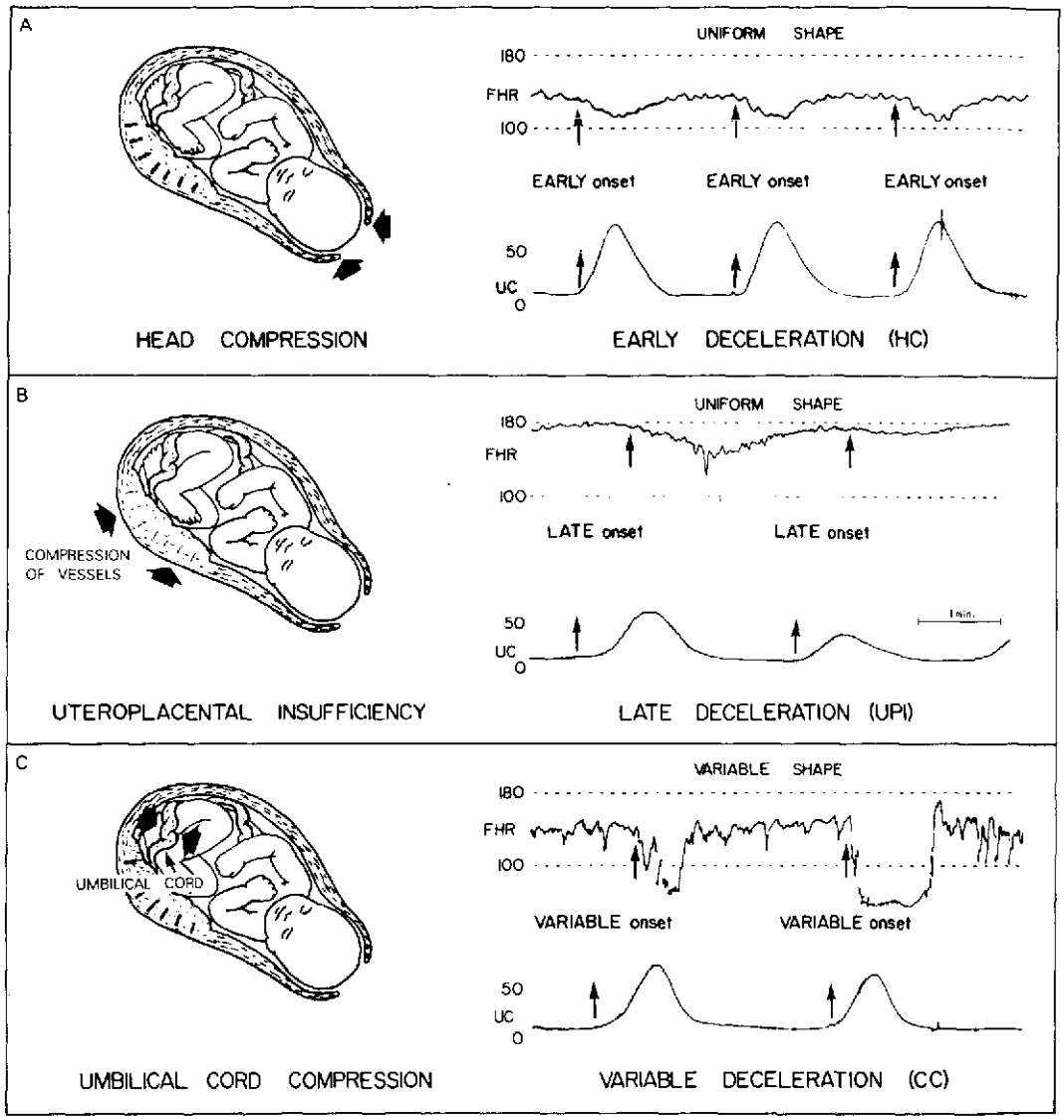

FIGURE 4. A, FHR pattern of uniform shape reflecting shape of associated intrauterine pressure curve; FHR deceleration starts early in contracting phase of uterus; labeled "early deceleration," it is thought to be caused by fetal head compression. B, FHR deceleration pattern also of uniform shape and again reflecting shape of associated intrauterine pressure curve; labeled "late deceleration" because onset occurs late in contracting phase of uterus, it is thought to be caused by acute uteroplacental insufficiency as result of decreased intervillous space blood flow during contractions. C, FHR pattern of variable shape that does not reflect shape of associated intrauterine pressure curve; onset of deceleration occurs at variable times during contracting phase of uterus and is thought to be caused by umbilical cord compression. (Reproduced with the permission of the publisher from E. H. Hon, *An Atlas of Fetal Heart Rate Patterns*, New Haven, Connecticut, Harty Press, 1968.)

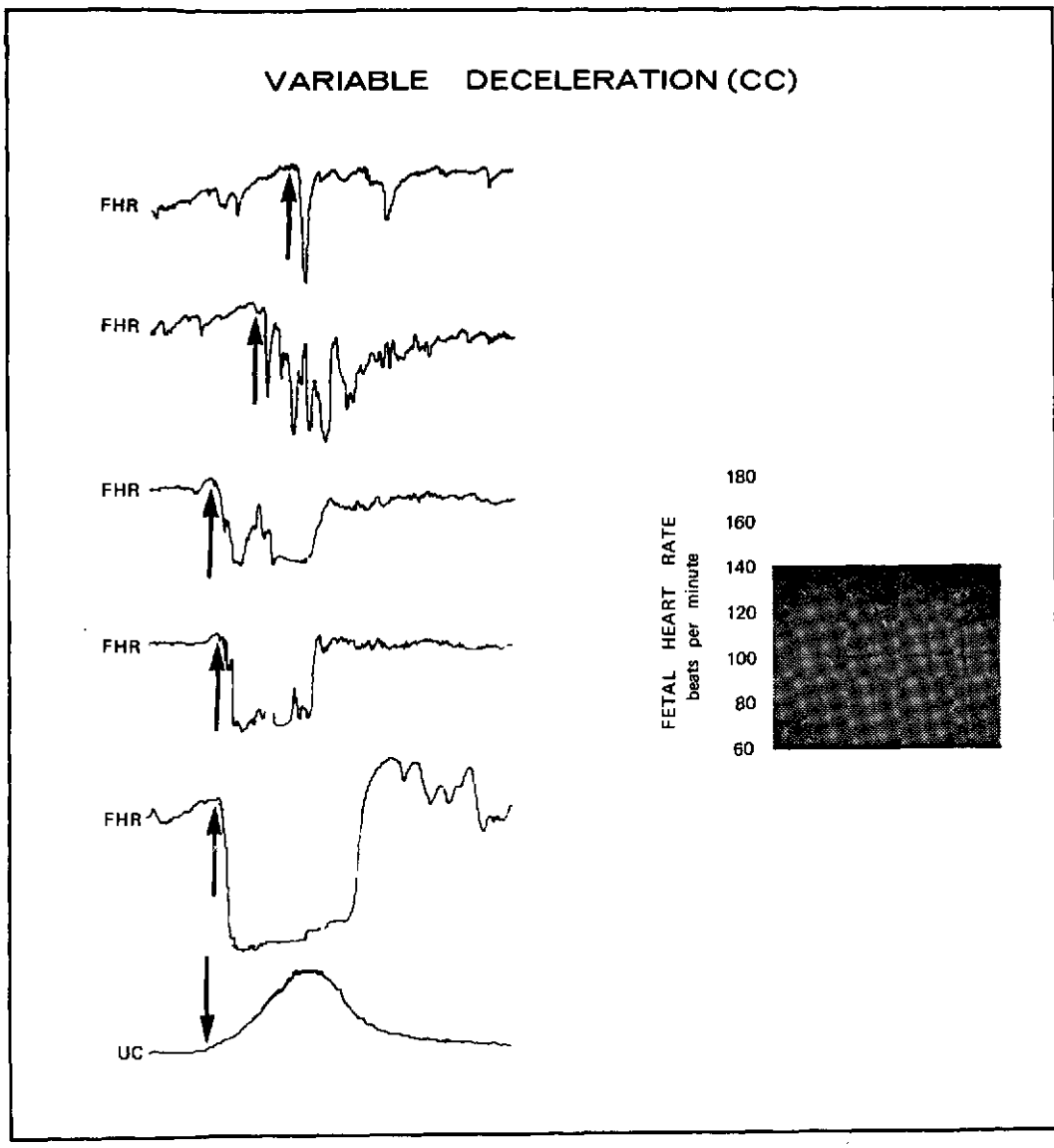

FIGURE 5. Various types of FHR patterns of variable deceleration. Cross-hatched area (right) indicates range in which this type of pattern is usually found. (Reproduced with permission of publisher from E. H. Hon, *An Atlas of Fetal Heart Rate Patterns*, New Haven, Connecticut, Harty Press, 1968.)

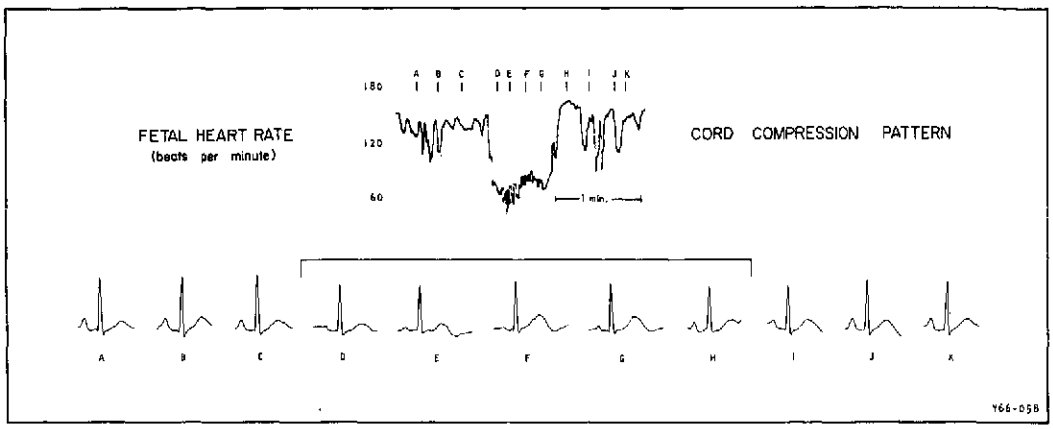

FIGURE 6. Upper trace is typical FHR pattern of cord compression. Lower tracings are series of averaged FECG's computed at various times during recording. Bracket over FECG's from D to H indicates time that variable FHR deceleration was present; FECG complexes before and after are essentially the same. Note marked diminution in P wave immediately following compression (D to F) and gradual increase in amplitude and diphasic nature of T wave as compression is prolonged. Early S-T segment depression can be seen at H. (Reproduced with permission of publisher from *Proceedings of the Fifth World Congress of Gynaecology and Obstetrics*, Australia, Butterworth & Co., 1967, p. 58.)

could be mistaken for fetal P waves, are due to interference from the maternal ECG. Each deflection coincides with a maternal R wave. Maternal ECG interference on the FECG baseline is sometimes a disadvantage; in this particular instance it was an advantage, since it was reassuring to know that the absence of an FECG was not due to malfunction of the electronic equipment. Besides demonstrating the importance of the vagus in sinus depression, this record emphasizes the importance of continuous FECG and maternal ECG records in the study of FHR patterns.

The occurrence of sinus arrest with the FHR pattern of variable deceleration is another piece of evidence to support the hypothesis that vagal

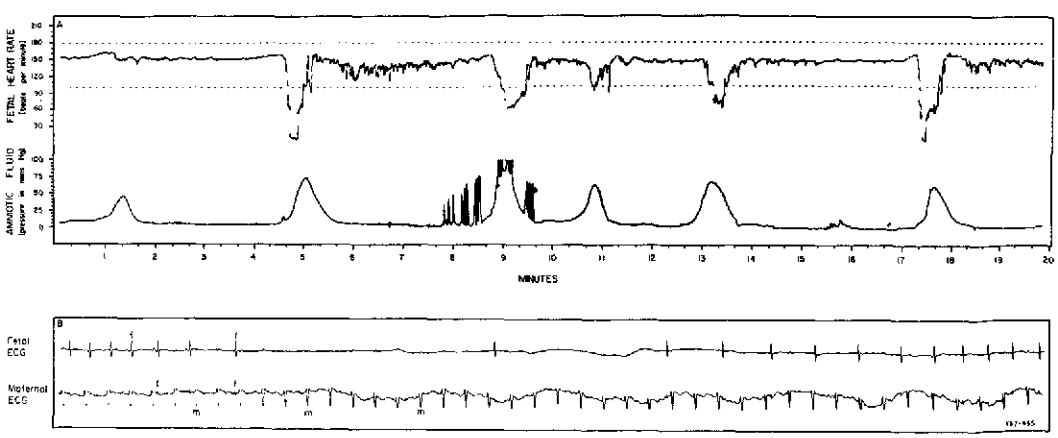

FIGURE 7. FHR pattern of variable deceleration in A is identified readily. Initial and last episodes are associated with an FHR that dropped to zero (indicated here by FHR level less than 30 beats/min). In B, FECG tracing made simultaneously with initial episode of variable deceleration shows FECG absent for about eight seconds; small deflections are due to interference from maternal ECG and are not fetal P waves. (Reproduced with permission of publisher from E. H. Hon, *An Atlas of Fetal Heart Rate Patterns*, New Haven, Connecticut, Harty Press, 1968.)

stimulation and acute transitory hypoxia are probably important elements in the train of events that follow umbilical cord occlusion.

The pH changes associated with the FHR pattern of umbilical cord compression are illustrated by Figure 8. The FHR patterns are easily identified. The blocks immediately beneath the FHR tracing indicate the time during which the fetal scalp sample was collected. In Figure 8A the fetal pH before the onset of variable deceleration is 7.28; during the deceleration it dropped rapidly to 7.23. This rapid drop in fetal pH with umbilical cord compression is again illustrated by Figure 8B. Here additional blood samples were obtained after the FHR baseline had returned to pre-deceleration levels. The rapid fall in pH and the return to normal levels may readily be seen.

Figure 9 shows the rapid changes in the pCO_2 of fetal scalp blood associated with the FHR pattern of cord compression. The initial pCO_2 of 58 mm Hg was obtained during marked variable deceleration. About one minute later, during less severe deceleration, the pCO_2 was 56 mm Hg; some two minutes later, when no variable deceleration was present, it fell to 49 mm Hg, to rise again to 57 mm Hg with variable deceleration.

Figure 10A and Figure 10B are recordings of group averages of 75 auditory evoked potentials obtained from the fetal scalp by attaching silver/silver-chloride electrodes 2 cm on either side of the midline in the biparietal area. Figure 10A was recorded when the baseline FHR was normal except for a moderate degree of irregularity; Figure 10B was made when the FHR pattern of variable deceleration was present. The difference in waveform and latent interval is quite apparent.

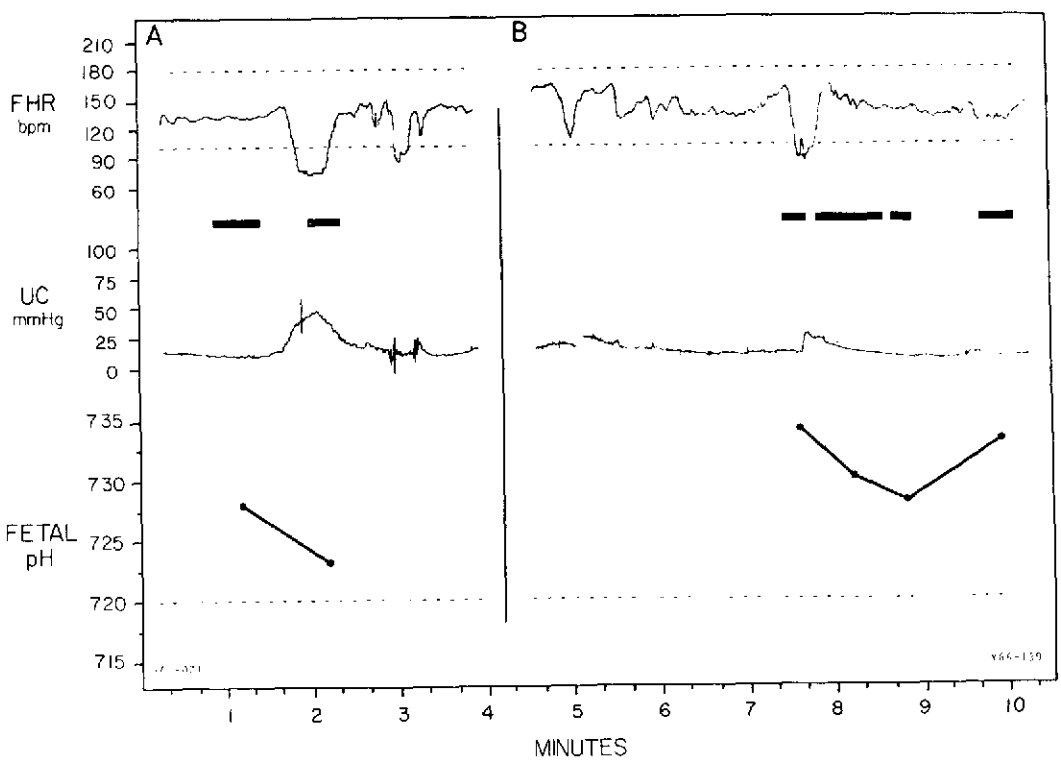

FIGURE 8. A, marked abrupt drop in fetal pH with variable deceleration. B, similar marked drop in fetal pH with umbilical cord compression and rapid return to pre-deceleration levels. (Reproduced from E. H. Hon and A. F. Khazin, *Obst. & Gynec.* 33:219, 1969, with permission of publishers, Harper & Row, New York.)

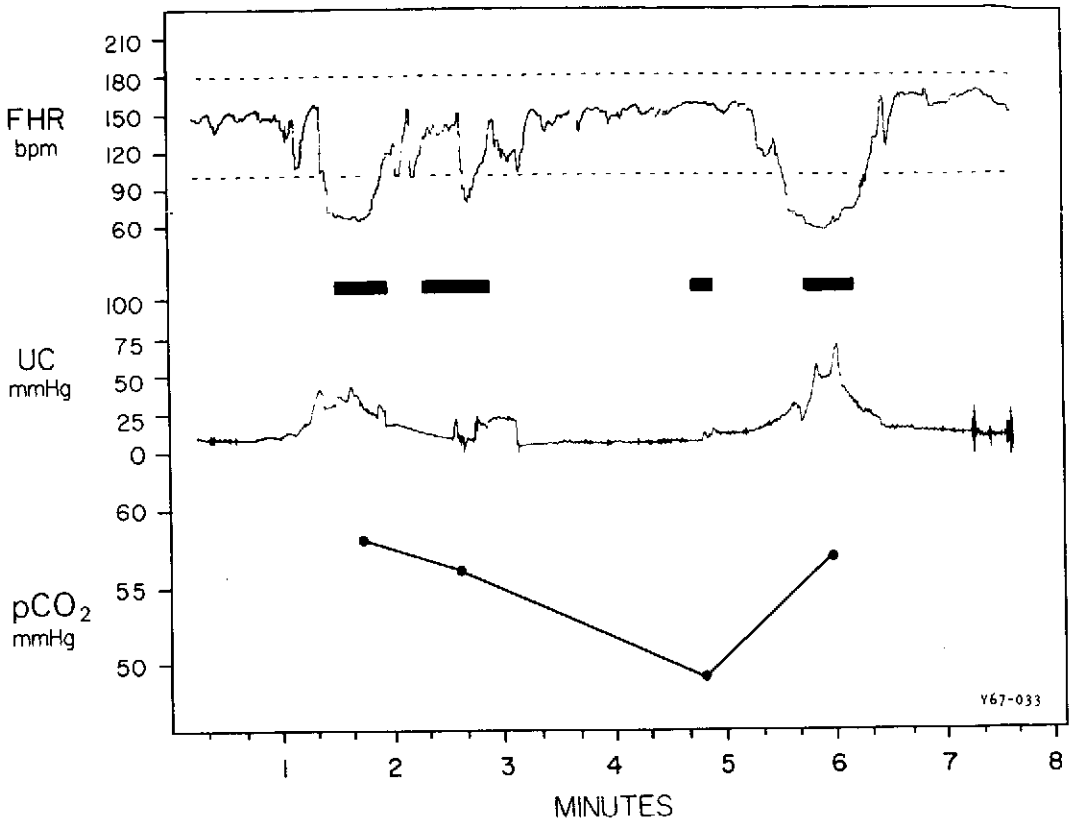

FIGURE 9. Rapid changes in pCO_2 of fetal scalp blood associated with FHR pattern of variable deceleration.

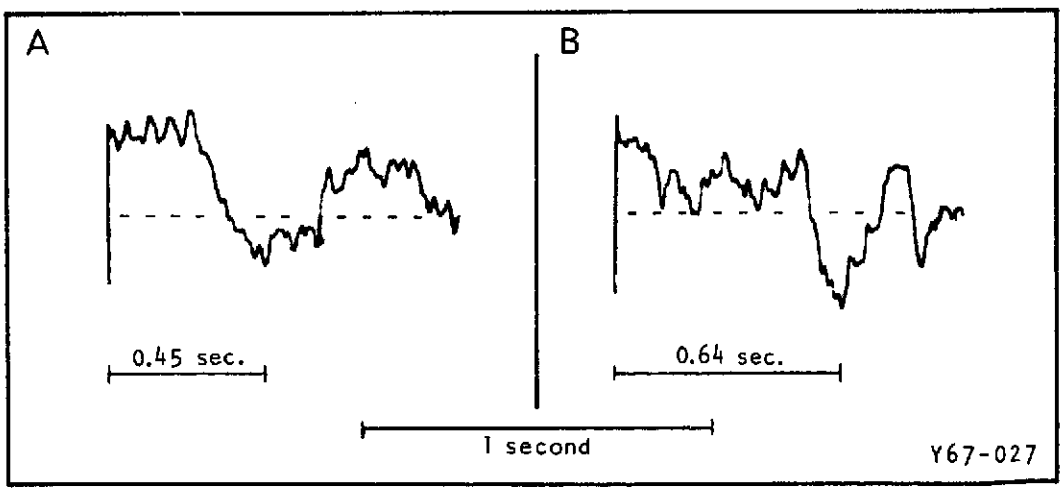

FIGURE 10. Recordings of group averages of 75 auditory evoked potentials obtained from fetal scalp. A was recorded when baseline FHR was normal except for moderate FHR irregularity; B, when FHR pattern of variable deceleration was present. Note difference in evoked potential waveform and latent interval when variable deceleration was present. (Reproduced with permission of publisher from *Diagnosis and Treatment of Fetal Disorders*, Springer-Verlag New York Inc., 1969, p. 185.)

Comments

Studies of human FHR patterns indicate that there are specific FHR patterns associated with umbilical cord compression that are strikingly similar to those observed by Barcroft and other workers in fetal animals. Concomitant FECG and biochemical studies of the fetus before, during, and after variable FHR deceleration support Barcroft's observation that the initial abrupt drop in FHR is largely reflex in origin and due to vagal stimulation. The rapid transitory changes in fetal pH and pCO_2 also indicate that short-lived umbilical cord compression has the biochemical characteristics of an acute respiratory acidosis and is relatively innocuous if not prolonged. With prolonged compression a degree of fetal asphyxia is introduced that is reflected in P wave and S-T segment changes and in fetal acidosis.

Clinically, short-lived variable deceleration is not, in our experience, usually associated with depressed infants. In most instances this FHR pattern can be corrected by maternal position change. However, with severe, prolonged, persistent variable deceleration there is neonatal depression and acidosis.

From a clinical standpoint it is important to recognize that umbilical cord compression is largely an accident of labor. Severe degrees of compression may occur without prior warning, although in many instances it develops over an extended period of time. It is probably an important cause of sudden death during the course of labor and delivery, since it may be associated with cardiac arrest.

While the changes in auditory evoked potentials associated with umbilical cord compression are clearly defined and quite evident, their significance is not known at the present time.

Summary

Specific FHR patterns indicative of umbilical cord compression, similar to those in the animal fetus, have been identified in the human fetus. Transitory cord compression causes a fetal respiratory acidosis that is usually innocuous; with prolonged compression, fetal asphyxia develops. Cord compression is largely an accident of labor which sometimes may lead to fetal cardiac arrest. While specific changes in fetal auditory evoked potentials are associated with cord compression, their significance is not known at the present time.

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CARDIOVASCULAR ADJUSTMENT OF THE FETUS DURING ASPHYXIA: THE AORTIC CHEMORECEPTORS

G. S. Dawes

The object of this paper is to discuss the mechanisms that operate to readjust the circulation and preserve the fetus during asphyxia. The experimental work has been done in sheep, and I shall confine myself first to consideration of mechanisms in this species, in which normal fetal arterial pO_2 is $\sim$23 and $pCO_2 \sim 47$ mm Hg. I shall distinguish between moderate asphyxia ($pO_2 > 12$ mm Hg, $pCO_2 < 60$ mm Hg) and severe asphyxia ($pO_2 < 12$ mm Hg, $pCO_2 > 60$ mm Hg).

Hypoxemia and the aortic bodies

In the fetal lamb the *local* circulatory effects of hypoxemia or hypercapnia are similar to those in the adult, with vasodilatation in the cerebral, coronary, limb, and (probably) mesenteric vessels and vasoconstriction in the pulmonary vessels. Superimposed on this there is, from 0.7 of term onwards, reflex control (*3*). Consequently, moderate asphyxia or hypoxemia causes tachycardia; a rise of arterial pressure; an increase of blood flow to the brain, heart, and placenta; and a decrease to the lung, kidneys, limbs, and (probably) mesenteric circulation, skin, and skeletal muscle (*1*). It is doubtful whether this is associated with an increase in cardiac output. The methods so far used do not show an increase of more than 10 to 15 per cent, which is within the limits of experimental error. This is not surprising, since fetal cardiac output is already high in the absence of asphyxia (*2*). It is uncertain whether the relative outputs of right and left hearts alter with moderate asphyxia.

It has been recognized for many years that the baroreceptors of both the aortic arch and the carotid sinus are normally operative in the fetal lamb during the last third of gestation. In the adult the systemic arterial chemoreceptors (both the aortic and the carotid bodies) play a major part in readjusting the circulation and breathing during hypoxemia and hypercapnia. But in the fetal lamb only the aortic bodies respond to moderate hypoxemia (*3*), as judged by the following evidence. When the fetal carotid pO_2 was raised over the range 40 down to 10 mm Hg (at a mean pCO_2 of 48 mm Hg) there was a rise of arterial pressure and hind-limb vasoconstriction, unaffected by section of the carotid nerves but abolished by cutting the cervical vagi or aortic nerves. Indeed, after the aortic nerves were cut, moderate hypoxemia caused a fall of blood pressure and femoral vasodilatation and, usually, the rapid onset of nonrespiratory acidosis. It was concluded that aortic chemoreceptor function contributed to fetal blood gas homeostasis near term, and that this system was tonically active at normal fetal blood gas values. Stimulation of the aortic bodies in adult dogs has a large effect upon the circulation and but little effect on breathing; this system is thus well suited to regulate the cardiovascular (and indirectly the respiratory) system in the fetus, in which maintenance of blood flow to the heart, brain, and organ of

gaseous exchange is essential to survival, but respiratory movements serve no useful purpose.

The failure of the carotid bodies to respond, even at pO_2 15–10 mm Hg, is not due to block in the central nervous system, since they can be excited by local injection of sodium cyanide. Within a few hours after birth they respond normally, and indeed are then mainly responsible for the hyperpnea of hypoxemia. Thus we suppose that after birth their threshold is reset, by a mechanism at present unknown.

Variation of fetal arterial pCO_2

A great deal of attention has been paid to oxygen supply to the fetus. The relationship between maternal and fetal pO_2 is complex, is dependent upon the integrated operation of many different factors (maternal uterine and umbilical blood flows, and the local perfusion: perfusion ratio in the placenta; on the shapes of the HbO_2 dissociation curves; on the magnitude of the Bohr and Haldane effects, and on O_2 consumption within the placenta) and has been the subject of intensive study. In contrast, the problems of pCO_2 adjustment between maternal and fetal bloods has been relatively neglected, possibly because it has been assumed that, since CO_2 is readily diffusible, the relationship is largely independent of any hypothetical barrier to gaseous diffusion in the placenta and hence simpler. Yet the same factors (including placental CO_2 production) must apply.

The relation was re-examined in sheep as a preliminary to investigating the interaction of pCO_2 and pO_2 on the aortic bodies (Baillie, Dawes, Merlet, and Richards, unpublished observations). The simplest system for study is that in which there is no fetal CO_2 production, one that can be contrived by replacing the fetus with a reservoir and pump that circulates warm fetal blood through the intact placenta *in situ*. In this preparation there is close correlation between umbilical vascular pCO_2 and maternal pCO_2 (over the range 15–45 mm Hg). Presumably because of placental CO_2 production, the pCO_2 of umbilical blood is on average 6 mm Hg higher than that of maternal arterial blood, and the slope of the line relating the two is not significantly different from unity.

With the fetus intact at 0.61–0.77 of term, the fetal carotid pCO_2 is 14 mm Hg higher than that of maternal arterial blood, and once again the slope of the line relating the two is close to unity. But with intact fetuses at >0.9 of term the slope of the line relating fetal carotid and maternal arterial pCO_2 is only 0.59, significantly different from unity ($p<0.001$).[1] The slope of this line is such as to minimize changes of fetal p_aCO_2. For instance, when the latter is altered by 30 mm Hg over the range 20–50 mm Hg (an extreme maternal variation from hypo- to hypercapnia) the former varies only by 17 mm Hg from 39–56 mm Hg. This represents a considerable homeostasis by the feto-placental system near term. It may be due in part to changes in the placenta and in part to changes in the fetus. So far only the latter have been examined.

Interaction of pO_2 and pCO_2 on the aortic bodies of the fetus

To test this possibility, fetal lambs near term were made hypocapnic (mean pH 7.39, p_aCO_2 37.5; pO_2 maintained at 23) and were then exposed to hypoxemia. In the presence of hypocapnia, hypoxemia (a fall in pO_2 of 10 mm Hg) caused no significant rise of arterial pressure or femoral vasoconstriction, while in its absence there was a normal response. This demonstrates an interaction in regulation of the fetal circulation by pO_2 and pCO_2, which (from other evidence) is likely to be exerted through the aortic chemoreceptors. This, then, is a mechanism—and probably the main mechanism—by which the fetal circulation is adjusted to blood gas changes and by which it attempts to regulate its internal environment. It is operative tonically over the normal physiological range of blood gas variations and determines the initial responses of the fetus to moderate asphyxia.

In severe asphyxia ($pO_2<10$ mm Hg) other factors come into operation. There is a fall in

[1] There was no evidence of nonrespiratory acidosis in these experiments.

fetal O_2 consumption and development of progressive nonrespiratory acidosis. There is a fall in heart rate (part reflex and part independent of vagal cardiac efferent nerves) and the onset of cardiac failure (in spite of liberation of catecholamines from the adrenal medulla). There is ultimately central nervous block of respiratory reflexes, and therefore almost certainly of cardiovascular reflexes. There is eventually a progressive fall of blood pressure to the point where even rapid reoxygenation is ineffective and cardiac massage becomes necessary for resuscitation. To the physiologist these are late, terminal signs of impending death. I would emphasize that before this stage is reached there is a wide range ("moderate asphyxia") within which life can be supported through the existence of the natural safety margin in O_2 supply, through the natural homeostatic mechanisms of the fetus, of which aortic chemoreceptor function is a cardinal part. It seems reasonable to suggest that the first warning system that operates during fetal asphyxia in man, the early tachycardia that precedes the full development of fetal distress, is a sign of aortic chemoreceptor function.

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DISCUSSION

Poseiro: I have some questions for Dr. Hon. First, what percentage of cord complications did he find in his series? As far as I know, this is a very common complication. Second, as I have argued with many physicians, the position of the cord at the moment of delivery does not indicate the position of the cord inside the uterus. In other words, a cord compression may exist (in the absence of cord around the neck) between part of the body of the fetus and the uterine wall, and the position of the cord at the moment of delivery indicates nothing.

Hon: So far as the first question is concerned, we find the cord compression pattern to be present in about 90 per cent of our series of high-risk patients in whom we diagnose clinical fetal distress for which cesarean section is indicated. This is in a population of higher socioeconomic status, in which toxemia is not seen often. With a different population the percentage may be lower. For obstetrics in general, this is about as high as it would come.

The position of cord at delivery is always a question of controversy to some extent. Early in our work we tried to relate the position of the cord at delivery to the compression patterns. We did this rather blindly, and I think we found that on about 60 per cent of the occasions on which cord compression patterns were present, the cord was physically around the baby somewhere. I think, therefore, that it is important to recognize that, even with severe umbilical cord compressions, the cord may not necessarily be around the baby at the time of delivery.

It does not take much reflection to recognize that the most severe types of cord compression have to do with prolapse of the cord. Certainly, with incipient prolapse of the cord one may deliver the baby and find the cord completely entangled.

Adamsons: I should like to comment about the clinical significance of this late deceleration or type II dips. In rhesus monkeys with indwelling catheters in which membranes could be considered intact because they had been sutured and no cord complications apparently existed, we have not been able to document late deceleration unless the fetus was asphyxiated.

I wonder whether it is safe to infer that a certain number of dips II or frequency of late deceleration over some period of time is compatible with optimal condition of the fetus. No doubt many of the fetuses will be resuscitated adequately, and perhaps they will go through processes in which some of the original disturbances will be corrected. But I want to stress the great significance, in our opinion, of dips II as indicators of significant departure from normality in fetal acid-base composition.

Dawes: The fetus was not removed in these experiments. We did not touch the placenta and did not remove the fetus from the uterus. So there was no reason to suppose, under those conditions, that maternal-placental blood flow would be altered. On the fetal side the blood was continuously circulated at about 300 ml/min.

Windle: I am pleased to note that at long last it is recognized that the supine position is not the normal one for delivery of the human fetus. I have been chided by my obstetrical friends for a long time about unphysiological practices, of which this is a notable one. As far as I know, man is the only animal forced to undergo delivery in the supine position. But this is not by any means the only unphysiological factor that enters into the delivery of the human fetus. It may be worthwhile to put on record here that there appears to be, at least in this country, lamentable ignorance regarding the physiology of birth and of the fetus. In fact, there are few medical schools in this country that teach any of these parameters of physiology any longer; when they are taught, they are taught in departments

of obstetrics by obstetricians who may know relatively little about the subject.

It is time the matter came to the attention of a body such as this. Perhaps something can be done.

Waterlow: I have a general comment on that. Sometimes the question is asked, What is the purpose of these special sessions of this meeting? I find it very satisfying to see the basic physiology brought into practical use. I was a pupil of Barcroft, and indeed Don Barron was the most stimulating teacher in my time in Cambridge, so Dr. Hon's paper was very welcome to me. This is a very good example of the way in which these meetings are making us aware of the practical implications for clinical medicine of basic studies of this sort, particularly nowadays when most physiologists are biophysicists.

Hon: I should like to comment on what Dr. Adamsons has said about the dips II, or late deceleration patterns. I certainly agree with the idea that it is very difficult to quantitate late deceleration. My feeling, after having studied the biochemistry of the fetus and followed a few babies over the years, is that it will be very difficult, looking at fetal heart rate patterns as we understand them at present, to come up with a hard number which separates normality from minimal damage from death. Perhaps it is asking too much to expect the obstetrician to define a condition in which such-and-such a baby will live *x* hours or suffer such-and-such damage; I am not sure that we can ever hope for this kind of answer.

Now, applying this to clinical medicine, and considering all the things we can do with an infant or an adult in our hands, most of us would be very hesitant about prognosticating the degree of damage he will suffer if he survives or how quickly he will die if he is going to.

It seems to me that the fetal electrocardiogram is a better predictor of the neonatal biochemical status than anything else we have. One of our major problems, I think, is that we do not have a good reference point for success. That is, we do not know what is a "good" newborn in terms of later infant growth and development. Without this reference point it is going to be difficult for the fetal physiologist to quantitate in a real way what are the instances of fetal distress.

Cohen: Dr. Dawes can tell me whether anything is known about the carbonic anhydrase level in either the placenta or fetal tissues during pregnancy. I should think this would be a critical factor in determining the ratio of CO_2 to bicarbonate, considering that the mother will have a large excess of sulphonamides and the infant a limited amount. Certain drugs could have a determinating effect on the disposition of CO_2/bicarbonate ratios.

Dawes: I believe that in animals near term the levels are less than in the mother. The figure I recall is about 1/10. I came to the conclusion that there was an adequate safety margin at that level. But I agree that this is something that ought to be looked into.

Perhaps I should say also how well I agree with what Dr. Hon has said. We are dealing with an extremely complex system. No physiologist likes to be asked what controls the heart rate, because of the number of variables that influence it. What is clear from animal studies, and perhaps the human studies too, is that by the time severe bradycardia occurs the reserves are exhausted.

Méndez-Bauer: With respect to Dr. Adamsons' question, what we showed are essentially the facts. We did see that if less than 10 per cent of the uterine contractions produce dips II the newborn is in good condition. We found also that fewer than 20 dips recorded during labor were followed by a healthy newborn.

Now, what you are really asking for is an explanation of these facts. I wonder whether what is really happening is that in cases of low incidence of dips II they may be due to causes that do not act systematically during labor—for instance, cord compressions which may produce dips II occasionally but not frequently and without causing a basal poor situation of the fetus. This is the only explanation I have to offer.

James: I should just like to make a comment about the definition of dips I and II and to add a word of caution.

I think that schemata of this type are useful in the initial sorting out of information. But, as

Dr. Dawes has mentioned, the responses of the fetal heart rate are complex and occur in response to a number of influences. Recently we have had an opportunity to question whether cord compression gives one type of heart rate change and uteroplacental insufficiency another. We have observed repeated dips II or late decelerations in the experimental preparation, where it is possible to sample from the umbilical vein and artery. Rather than seeing a decrease in the A-V difference, which would indicate uteroplacental insufficiency, we have seen a huge increase, indicating cord compression. Thus, dips II may in point of fact indicate not uteroplacental insufficiency but cord compression. I think it is necessary to review the whole problem of heart rate change and keep an open mind about whether it is caused by cord compression in one instance and uteroplacental insufficiency in other.

Méndez-Bauer: Let me remind you of something we have found in human beings: When the umbilical cord is compressed around the neck of the human fetus, you may find the appearance of overlapping dips I and II. We have been able to separate the two by giving atropine to the mother and the fetus.

Caldeyro-Barcia: The work in primates may be very useful in clarifying this point, because it provides continuous information, particularly on blood composition, that is not possible to have in the human being.

FETAL ASPHYXIA AND PERINATAL BRAIN DAMAGE

Ronald E. Myers

A significant proportion of the cases of perinatal brain injury in the human has been thought due to episodes of asphyxia occurring during pregnancy or at the time of birth (*1, 7, 20*).[1] Indeed, an association of brain injury with placenta previa, placental abruption, precipitate labor, umbilical cord prolapse, and other abnormalities is occasionally seen in examining the records of damaged children (*5, 6, 8, 21*). Only too frequently, however, retrospective study of medical records in individual cases has failed to exhibit such correlations.

Evidence has accumulated suggesting that brain abnormalities may develop in relation to events or circumstances taking place during pregnancy but not necessarily of a sudden catastrophic nature well marked by clinically apparent signs or symptoms. For example, extensive softening of the hemispheral white matter has occasionally been described in low-birth-weight infants whose mothers have suffered from severe anemia during pregnancy (*18, 22*).

Recent statistical studies on the contribution of fetal growth retardation or prematurity to the incidence of cerebral abnormalities (*2, 3*) have revealed a definite predisposition among these dysmature and premature populations toward the development of brain abnormalities leading to impaired performances in psychological and neurological tests carried out in later life. Indeed, such an association between a higher incidence of brain damage and prematurity was suggested as early as the time of Little, who found that 22 out of 24 cases of severe perinatal brain damage under study had occurred in low-birth-weight individuals (*10*).

Postnatal events in the newborn nursery may also contribute to the occurrence of cerebral palsy. For example, a relationship has been suggested between respiratory disturbances and/or cyanotic episodes in the newborn period and later spastic diplegia (*13*). These diverse facts point up the complexity of the problem of perinatal brain damage and of the influences contributing to its occurrence.

Only in recent times have studies been established to investigate, using experimental animals, the influences that may affect nervous system integrity in the perinatal period. Windle and his co-workers have made pioneering efforts in this area, subjecting term monkey fetuses to brief episodes of total asphyxia. In these studies the fetuses were delivered surgically still within their intact amniotic sacs, the moment of placental separation marking the onset of asphyxia. The asphyctic episode was terminated by opening the sac and removing the fetus, inserting an endotracheal tube, and instituting positive pressure oxygen ventilation.

Such episodes of total asphyxia resulted in patterns of pathological change largely restricted to the brain stem (Figures 1, 2, and 3). Structural alterations were regularly demonstrable in the inferior colliculi, the trigeminal sensory nuclei, the superior olives, the posterior and

[1] The terms *perinatal* and *perinatal period*, for the purpose of this paper and as properly defined, refer to the span of time occupied by the latter half of pregnancy (20 weeks in the human), the process of birth, and the newborn period (4 weeks in the human).

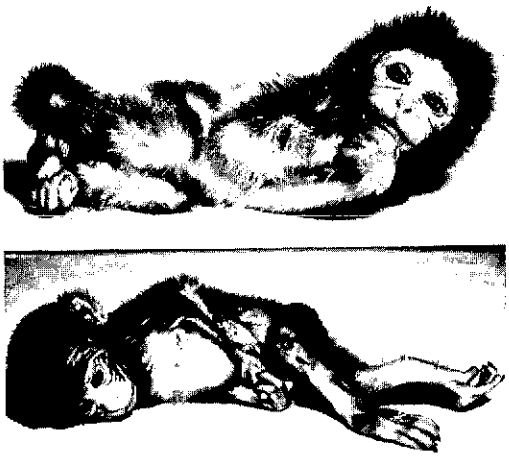

FIGURE 1. Palsied states produced in rhesus monkey infants by episodes of acute total asphyxia delivered at time of birth. Animal above exhibits severe flexor hypertonus with contractures in all extremities; animal below manifests some extensor hypertonus associated with severe amyotrophy. Amyotrophic changes in muscles result from severe damage to spinal cord with destruction of anterior horn cells. Though these clinical states resemble those exhibited by humans with cerebral palsy, they result from lesions in a nervous system distribution rarely occurring in relation to human perinatal injury.

lateral ventral nuclei of the thalamus, and so on, the specific nuclei affected depending upon the length of asphyxia and the physiological state of the animal at the time of insult (*19*; see also *15, 16*).

Windle suggests that the brain-stem pattern of pathological change produced by episodes of total asphyxia in the experimental animal constitutes a reliable and accurate model of perinatal injury as it occurs in the human (*23, 25*). In point of fact, however, this pattern of pathology fails in all particulars to coincide with the patterns of pathology commonly associated with perinatal injury in the human.

Malamud portrays as typical of perinatal brain damage in the human, patterns of pathology predominantly hemispheral in distribution. These patterns include ulegyria, diffuse white-matter sclerosis, and status marmoratus of the basal ganglia. In 17 sample cases of human perinatal injury, ulegyria was found in 12, diffuse white matter sclerosis in 15, and status

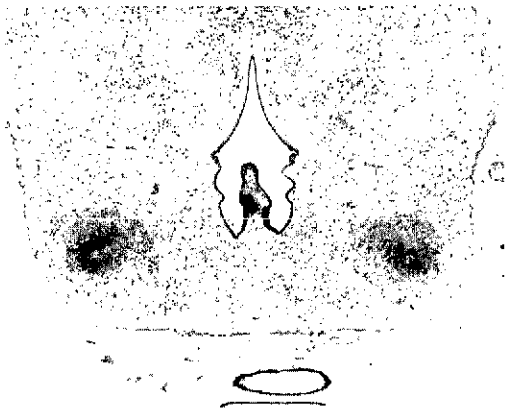

FIGURE 2. Destructive changes in central nucleus of inferior colliculus of term monkey fetus subjected to total asphyxia for 14½ minutes. Such lesions appear bilaterally and are largely restricted to brain stem loci. After acute total asphyxia, a regularly occurring rank order of involvement of different structures in brain stem may be seen; numbers of structures affected depend on severity of insult.

marmoratus in all. These three hemispheral lesion types, aside from being the most commonly encountered, were frequently combined in various combinations and to various degrees (*11*). In an earlier study, Malamud found that 85 per cent of over 100 cases of perinatal in-

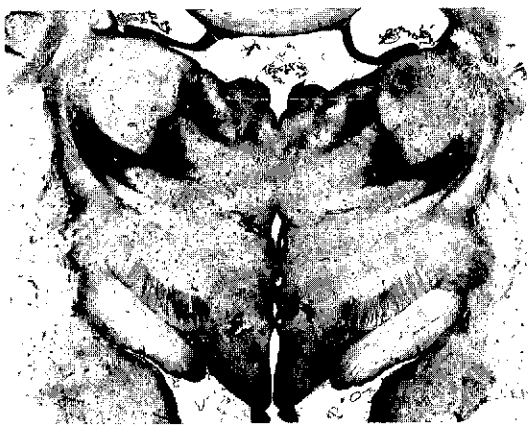

FIGURE 3. Distribution of lesions in thalamus and subthalamus of rhesus monkey infant six months after 14-minute episode of acute total asphyxia administered at surgical delivery under barbiturate anesthesia (Holzer stain). This distribution of damage is part of brain-stem pattern of pathology repetitively seen after episodes of total asphyxia (see text).

jury exhibited one or the other or some combination of these three lesion types (*12*). Among these cases, pathological involvement of the lower brain stem was exceptional. When brainstem changes did occur, they did not resemble the changes found in the experimental animal and were largely overshadowed by the more extensive and prominent involvement of the hemispheres.

From time to time, instances have been reported of a pattern of damage in the human brain stem resembling that produced by episodes of acute total asphyxia in the monkey infant. Instead of an association with asphyxia, however, this pattern of damage in the human is described as occurring primarily following temporary arrest of circulation in the infant or young child (*4, 9*).

More recently, Myers and co-workers have investigated the effects of stressing the term monkey fetus with a quite different type of asphyctic insult—that of prolonged partial asphyxia. In contrast to earlier studies in which interference with respiratory gas exchange between mother and fetus was abrupt and total (acute total asphyxia), in the more recent studies the interruption of gas exchange was only partial but lasted a longer time (prolonged partial asphyxia or fetal asphyctic compromise).

In utero term monkey fetuses were subjected to episodes of prolonged partial asphyxia (*17*), produced by increasing uterine irritability and the frequency of uterine contractions through the use of intravenous oxytocic agents. Among these animals, brain swelling occurred in 7 out of 10 cases, as evidenced by herniation of the cerebellar tonsils and vermis and by varying degrees of cerebral convolutional flattening (Figure 4).

Brain swelling, common among these fetuses subjected to prolonged periods of partial asphyxia, regularly failed to occur among fetuses enduring episodes of total asphyxia in our laboratory. This remained true even when the length of total asphyxia was sufficient to produce severe brain damage (14 to 18 minutes). This remarkable difference in outcome according to the type of asphyxia sustained already suggested a basic dissimilarity between the circumstances of partial and total asphyxia.

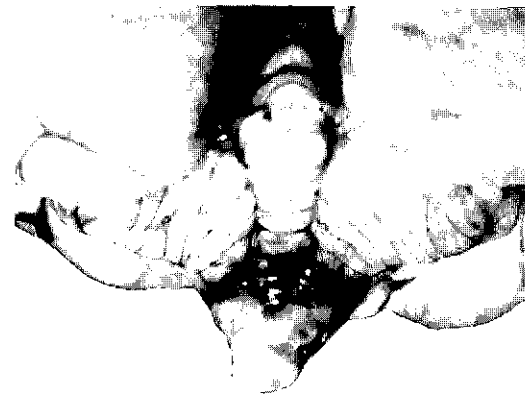

FIGURE 4. Deformation of cerebellar tonsils and vermis due to herniation through foramen magnum. Herniated, compressed cerebellar tissue exhibits capillary hemorrhage into its substance. Such swelling of brain with cerebellar tonsilar herniation occurred in large proportion of animals subjected to prolonged partial asphyxia *in utero*. By contrast, brain swelling, as indicated by such gross criteria, never occurred after acute total asphyxia.

During investigations of the effects of acute total asphyxia, a remarkable animal was observed that throws light on the causation of perinatal injury in the human (*14*). After surgical delivery, this animal (No. 796) was subjected to a 15-minute episode of total asphyxia in a routine fashion. Afterwards, along with several other animals of the series, he was allowed to survive in the colony for six months. During this survival period he exhibited, like all the other animals, an essentially unchanging neurological status.

Examination of this animal's brain after sacrifice revealed an entirely unexpected pattern of pathology consisting of a triad of ulegyria, hemispheral white-matter sclerosis, and status marmortaus of the basal ganglia (see Figures 5, 6, and 7). Contrasting with the prominent hemispheral involvement, the pattern of damage to the lower brain stem typical of acute total asphyxia was largely suppressed in this animal.

The clinical chemical and laboratory findings

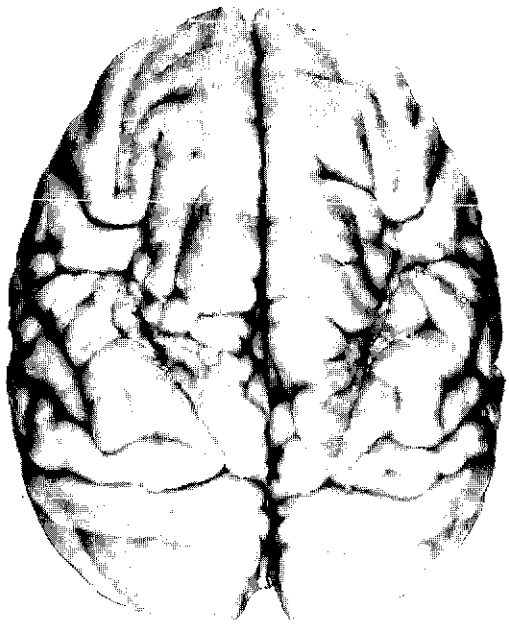

FIGURE 5. Brain of monkey 796 exhibiting extensive bilateral sclerotic microgyria involving convolutions in paracentral regions following acute total asphyxia superimposed on incidentally occurring state of asphyxial compromise *in utero*. Pattern closely resembles ulegyria in man and differs in all respects from that occurring after acute total asphyxia alone.

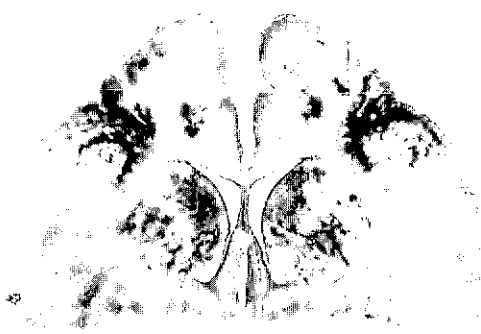

FIGURE 6. Coronal microscopic section through brain of monkey 796 stained with Holzer technique. Astrocytic fibrosis with sclerosis extensively involves white matter underlying area of cortical atrophic destruction. Both cortex and basal ganglia also exhibit reticulated pattern of astrocytic scarring associated with complete destruction of neurons within zones of fibrosis. Process in basal ganglia closely resembles status marmoratus in human, a common pattern after perinatal injury.

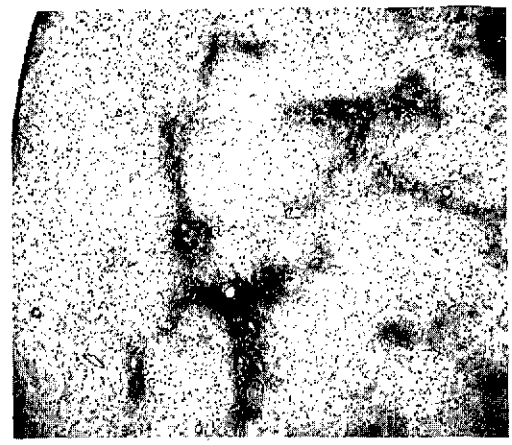

FIGURE 7. Section through head of caudate nucleus stained with Holzer technique, showing in greater detail reticulated zones of astrocytic fibrosis. Note strong tendency to perivenular distribution of process. Astrocytic scarring is associated with concomitant, coextensive neuronal destruction.

on monkey 796 at the time of his delivery and acute total asphyctic insult were evaluated to determine the possible bases for the divergence of his brain pathological pattern from that typical of reaction to acute total asphyxia. He was found to differ from others in the acute total asphyxia series in incidentally exhibiting some degree of asphyctic compromise (partial asphyxia with acidosis) at surgical delivery, just before being subjected to a further episode of acute total asphyxia.

Careful study of this animal was of particular concern since the patterns of pathology in his brain, afflicting as they did the hemispheres rather than the brain stem, mimicked closely the pathology of perinatal injury in the human as depicted by Malamud (see above). This case suggested that *in utero* fetal compromise may play an important role in the development of perinatal injury in the human.

The frequent occurrence of brain swelling in animals subjected to episodes of prolonged partial asphyxia *in utero,* as described above, and the appearance in animal No. 796, who had incidentally sustained an episode of asphyctic compromise *in utero* prior to delivery, of the very patterns of brain pathology that typify human

perinatal injury led us to investigate further the effects of prolonged partial asphyxia on the fetal rhesus monkey.

In collaboration with Dr. Alfred Brann, a series of term monkey fetuses was subjected to fetal compromise *in utero* by inducing a lowering of the blood pressure in the mother by means of .5 to 1.5 per cent fluothane carried in an oxygen vehicle. Hypotension in the maternal arterial circuit results in an impairment in perfusion of the intervillous spaces of the placenta. This inadequate maternal intervillous perfusion results in an inadequate volume exchange of respiratory gases between the mother and the fetus. This produces a lowered partial pressure of oxygen in the fetal blood; at the same time, carbon dioxide builds up in the fetus because of the diminished exchange from the fetus to the mother. As the hypoxic and hypercarbic state endures, the fetus tends to undergo deterioration because of a developing failure in its own cardiovascular compensations. The degrees of deterioration or of compromise of the fetus under these circumstances of partial asphyxia can be regulated to some degree by regulating the levels of the maternal blood pressure.

A series of newborns were delivered after being subjected to three-to-five-hour episodes of partial asphyxia *in utero* as described above. These animals exhibited one of three brain pathological outcomes, depending on the severity and duration of asphyctic compromise: (1) no apparent pathological changes in the brain; (2) mild to moderate swelling of the brain; or (3) patterns of acute cerebral necrosis. These changes refer to the condition of the brain when the animals are sacrificed or themselves die in the first few hours or days after the delivery of the insult.

No brain pathological changes. In many instances no evidence was seen of swelling or of other morphological changes in the brain, whether it was examined at the time of the insult or during the first days of post-insult survival.

Where no pathological changes were noted, the prolonged episodes of *in utero* partial asphyxia were generally of mild degree. In such instances the fetal blood, sampled throughout the course of the insult, usually exhibited less severe changes in hydrogen ion concentration, the fetal abdominal aorta blood pH values being in the range of or greater than 7.0–7.1. The partial pressures of carbon dioxide in the fetal arterial blood samples under these circumstances were usually less than 70–80 mm Hg. Oxygen saturations in the fetal blood were generally greater than 30 per cent, while base deficits remained less than 10 to 13.

In evaluating these levels of blood chemical changes in relation to their long-term effects on the *in utero* fetus, it is important to appreciate that the brain pathological outcome is a function not only of the degree of the asphyctic compromise but of its duration as well. Thus, insult duration plays an important role in defining the occurrence and the nature of the damage to the fetal brain and must be taken into account in any evaluation of the correlation between blood changes and brain damage.

Swelling of the brain. Gross morphological indicators of brain swelling were used. Swelling was described as present when evidence existed for flattening of the cerebral convolutions or for herniation of the cerebellar tonsils or vermis into the foramen magnum (see Figure 4).

Brain swelling was generally observed when the fetal acid-base and respiratory gas values in the blood had deteriorated beyond those described above in relation to "no brain pathological changes." This was true only when they were maintained at such lower levels throughout the greater length of the period of compromise. Generally speaking, swelling of the brain occurred when the fetal blood values were maintained in the range in which the pH = 6.9–7.0; pO_2 = 15–18; pCO_2 = 80–90 mm Hg; O_2 saturation = 15–17%, and base deficit = 13–18.

Acute cerebral necrosis. Early lesions of acute cerebral necrosis began to appear already in animals exhibiting acid-base and blood gas

changes in the lower portions of the range described above as producing brain swelling. More severe and extensive necrosis of the hemispheres was generally associated with more deteriorated chemical values in the blood or with more prolonged periods of compromise.

The lesions of acute cerebral necrosis were spectacular. The process involved the entirety of the two hemispheres in some instances, producing severe softening and friability of the tissue throughout, as illustrated in Figures 8 and 9. In other instances, the cerebral tissue necrosis with softening was confined to more restricted regions of the brain leaving other areas relatively intact in consistency and gross appearance (Figure 10). The necrotic process was nonhemorrhagic in some instances; in others the areas of necrosis were peppered with petechial hemorrhages or suffused with diffuse extravasation of blood. In no instances were hematomas observed in relation to the acute cerebral necrosis.

When highly focal in distribution, the areas of necrosis tended to involve the paracentral regions or the junction zone between the parietal and occipital lobes (Figure 11). In many cases the necrotic lesions were bilateral in distribution and symmetrical in extent. In a significant number of cases, however, the process involved only one hemisphere.

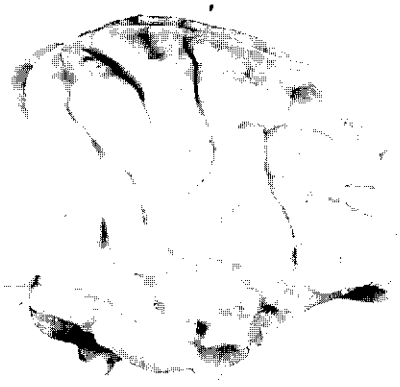

FIGURE 8. Acute cerebral necrosis extensively involving both hemispheres expressed as remarkable tissue friability readily manifest from photograph. This appearance of brain was clearly apparent immediately on removal after death and did not represent post-mortem change.

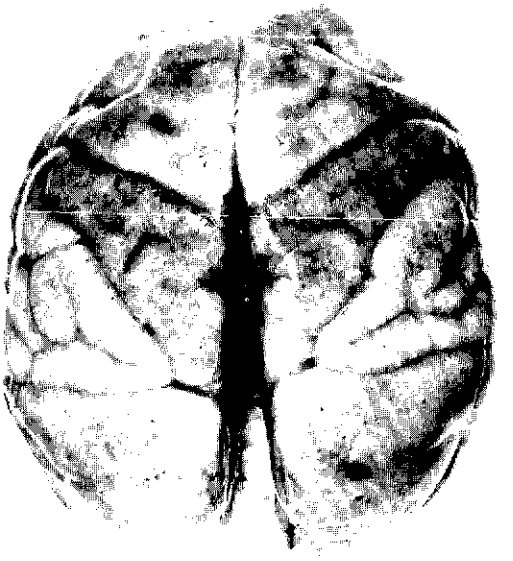

FIGURE 9. Acute cerebral necrosis involving both hemispheres but with greater involvement of postcentral gyri and occipital lobes. More severely involved areas exhibited greater degrees of softening, tissues suffused with petechial hemorrhages. Areas of lesser involvement preserved more normal consistency. Such animals commonly failed to survive for more than a few hours in nursery because respiratory problems (respiratory distress syndrome) developed.

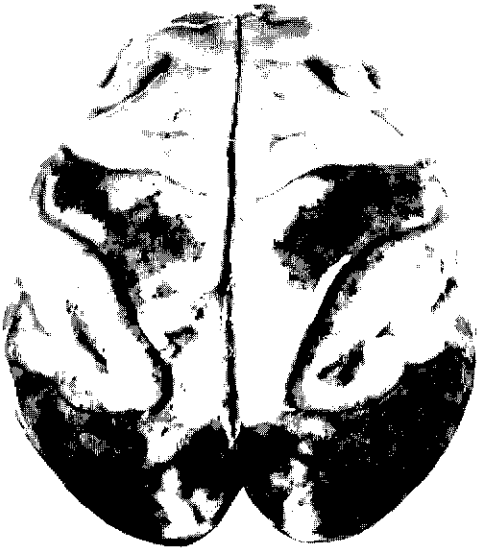

FIGURE 10. Acute cerebral necrosis involving both hemispheres but with focal lesion distribution. Process tended to be symmetrical in distribution and more often than not was hemorrhagic.

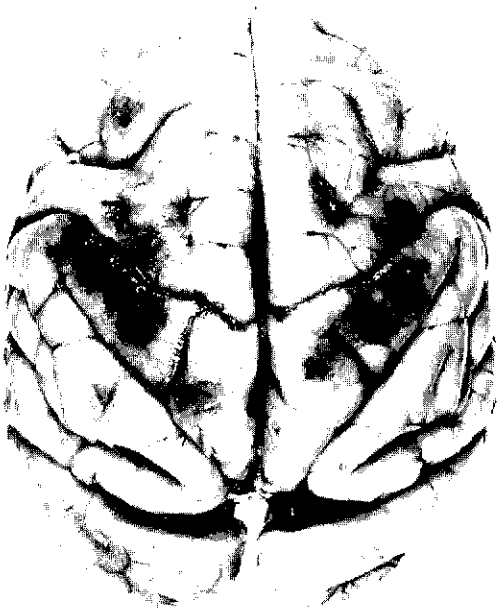

FIGURE 11. Acute cerebral necrosis limited in distribution to paracentral region bilaterally. Note similarity in distribution to that of sclerotic microgyria in Figure 3. Generally, less extensive necrotic lesions occurred in relation to less severe or less prolonged periods of asphyctic compromise. Such lesions may occur in absence of brain swelling.

FIGURE 12. Coronal section through brain of animal exhibiting acute hemorrhagic cerebral necrosis, with tendency toward greater involvement of depths of sulci than of crowns of gyri. Tendency for involvement of dorsal third to half of hemispheres is also seen (see Figures 4 and 11).

Several additional features of the process of acute cerebral necrosis became evident on coronal sectioning of the brains. First, the necrotic process tended to be more severe in the depths of sulci than in the crowns of gyri (Figures 12 and 13). Second, it was most severe in or was entirely restricted to the superior one-half to one-third of the cross-section of the cerebrum. Third, the process, including its hemorrhagic aspects, frequently extended to involve the basal ganglia bilaterally, including the caudate nucleus, the putamen, and occasionally the globus pallidus (Figure 13). It is important to note that these characteristics of lesion distribution in relation to acute cerebral necrosis resemble the geographic distribution of the destructive process in the perinatally damaged human as exemplified in the old static lesions of cerebral palsy.

This last group of cases reveals that asphyctic compromise of the term monkey fetus in the uterus may produce patterns of acute cerebral necrosis of a range of types and distribution.

The animals exhibiting more severe degrees of acute cerebral necrosis failed to survive the immediate newborn period despite close care and surveillance in the nursery. To a considerable extent this difficulty in survival related to persistent post-insult respiratory problems, in which

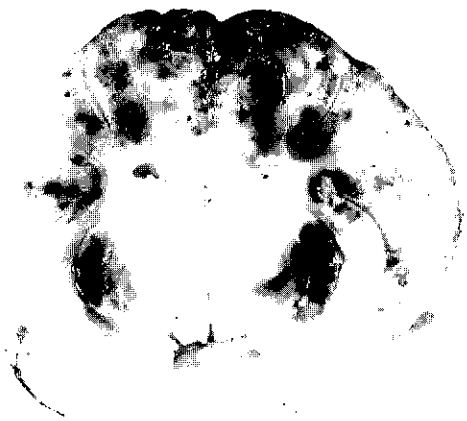

FIGURE 13. Coronal brain section exhibiting severe involvement of the hemispheres in focal hemorrhagic cerebral necrosis. Note greater involvement in depths of sulci, more extensive involvement of dorsal half of brain, and inclusion of basal ganglia in acute hemorrhagic necrosis.

increasing difficulty was encountered in maintaining an adequate respiratory gas status of the blood of the fetus despite oxygen therapy. This failure of longer-term fetal survival limited the possibility of determining the patterns of pathology that might ultimately have developed in the brains of these animals. Not enough time had elapsed to permit the resorption of the necrotic tissue and the expression of the gross and histopathological changes of the long-term static lesions.

Severer degrees of prolonged partial asphyxia have led to death early in the newborn period. To clarify the late neuropathological effects of *in utero* asphyctic compromise, it was necessary to expose the term fetuses to lesser degrees of compromise. Such animals did indeed survive past the newborn period in large proportion. The levels of hypoxia and hypercarbia required during asphyctic compromise to produce this lesser damage with survival corresponded approximately to those levels described above as resulting in brain swelling or early cerebral necrosis.

When these animals were allowed to survive for two to four weeks, distinct changes in appearance and texture occurred in the areas involved in cerebral necrosis (Figure 14). The affected tissue, instead of remaining soft and friable, began to exhibit toughness and resilience to the touch. At the same time the damaged convolutions began to collapse and to exhibit an unusual flabbiness associated with wrinkling. The damaged zones also exhibited some chalk-white cloudiness or opaqueness compared to adjoining normal tissue. The regions involved in these semichronic morphological changes corresponded in location to the zones exhibiting acute cerebral necrosis in animals dying early.

This alteration of toughening, collapse, and clouding of the convolutions failed to correspond in appearance to the well-known changes in appearance that characterize the old static lesions of perinatally damaged humans. However, when survival lengths of up to six months beyond the period of insult were allowed, the tissue alterations observed began to approach in appearances those typical for humans.

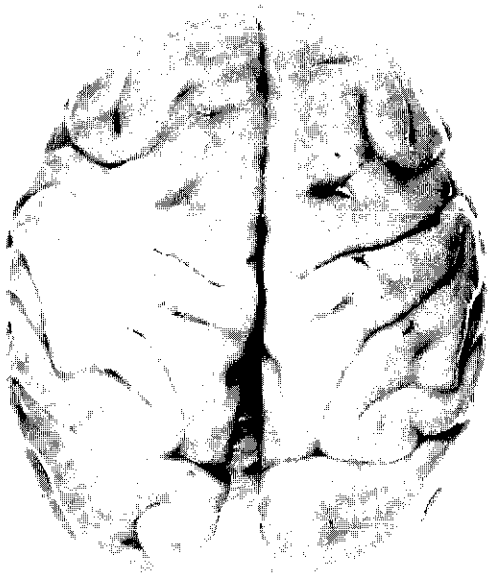

FIGURE 14. Monkey brain appearance 2 weeks after episode of prolonged partial asphyxia delivered just prior to birth. Inferior parietal and prelunate convolutions and inferior portions of pre- and postcentral gyri on left exhibited flabbiness and partial collapse along with chalk-white cloudy appearance. Pial surfaces of involved convolutions were toughened in consistency. These alterations were intermediate between softened, friable tissues of acute cerebral necrosis and atrophic, hardened, knobby ones of convolutions in ulegyria.

The unequivocal changes of sclerotic microgyria or atrophic cortical sclerosis in the brain of such an animal may be seen in Figure 15. Associated with the atrophic destructive changes in the cortex were varying degrees of damage to the underlying white matter characterized by glial scarring and sclerosis. Among brain specimens thus far studied, status marmoratus of the basal ganglia has been less frequent.

In summary, the studies described focus upon experimental fetal compromise. With severe and prolonged partial asphyxia *in utero,* the ability of the fetus to survive past the newborn period is put in jeopardy. When such infants expire

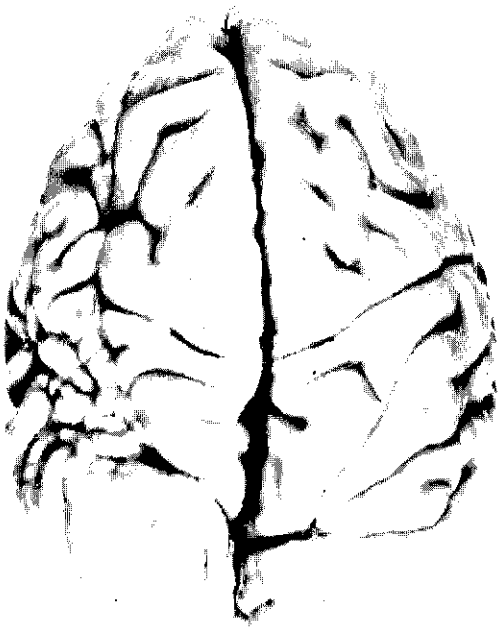

FIGURE 15. Experimental reproduction of sclerotic microgyria or ulegyria in monkey. This appearance represents end stages of tissue transformations occurring after acute cerebral necrosis on long-term survival. These lesions produced under controlled conditions closely resemble those of perinatal injury in human. When involvement is unilateral, marked atrophy of corresponding hemisphere occurs. Distribution of atrophic cortical sclerosis in this brain coincides closely with subacute changes exhibited by that in Figure 14.

or are sacrificed within the first few hours or days of the post-insult period, an examination of their brains reveals brain swelling associated with greater or lesser degrees of hemispheral necrosis. In some instances, the necrotic process is focal in distribution and symmetrical in its involvement of both hemispheres. The cerebral necrosis may be hemorrhagic or non-hemorrhagic in nature.

When less-damaged infants are allowed to survive for one to two months, the pattern of necrosis with tissue softness and friability is transformed into one of tissue collapse associated with shriveling and toughening of the involved convolutions. With still-longer survival, these foci of alteration undergo further conversion into a nodular, sclerotic microgyria. This latter appearance is typical of atrophic cortical sclerosis. Thus, it has proved possible to reproduce in the experimental animal under highly controlled conditions the patterns of brain pathology typifying human perinatal injury.

The process ultimately leading to these patterns of pathology is that of a sustained partial asphyxiation *in utero* consisting of an impaired exchange of respiratory gases between the maternal and fetal blood streams. This impairment in exchange results in the accumulation of carbon dioxide in the fetal blood associated with a deficiency in oxygen partial pressures. At the same time, a mixed respiratory and metabolic acidosis develops, leading to a severe base deficit. These changes in the status of the blood must reach critical levels and endure for substantial periods of time before fetal damage occurs.

The circumstance of prolonged partial asphyxia differs in many ways from that of acute total asphyxia. Of particular importance is the recognition that these two types of insult result in two quite distinct patterns of pathology in the brain. An episode of acute total asphyxia, when of sufficient length, results in a pattern of pathology restricted to the brain stem and bearing little resemblance to the more common patterns of brain change in perinatal injury in the human. Episodes of prolonged partial asphyxia, on the other hand, lead to patterns of hemispheral damage closely mimicking the pathology of human cerebral plasy.

Acknowledgments

The author expresses his gratitude to Mr. William Rodríguez and Mr. Luis González for their assistance during the surgical procedures and to Mr. Esteban Monell Torrens and Mrs. Carmen Freixas for their aid in clinical chemistry. Mr. Pedro Solá Amadeo is responsible for the photographic reproductions. Dr. Alfred W. Brann, Jr., collaborated in the studies on prolonged partial asphyxia.

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ASPHYXIAL BRAIN DAMAGE AT BIRTH, WITH REFERENCE TO THE MINIMALLY AFFECTED CHILD[1]

William F. Windle

I shall talk about the minimally brain-damaged infant—the rhesus monkey infant, to be sure, but by inference the human too. It is not possible to determine how many children have minimal brain damage caused by mishaps in the perinatal period, but it is becoming increasingly clear that the number may be greater than we like to believe.

It has been estimated that once an hour an infant with cerebral palsy is being born in the United States; once every five minutes, one with demonstrable mental retardation. The recognized rate of crippling from these two is about 3 per cent of live births (*3*). Besides these severely brain-damaged infants, there are many more with less obvious neurological deficits. The Collaborative Perinatal Study program of the National Institutes of Health brought to light statistics indicating that approximately 1.5 per cent of the one-year-old infants in a prospective study showed neurological abnormalities (*1*). If these findings, collected in 14 of our foremost medical institutions, are representative of the nation at large (and they surely must be), they tell us that nearly half a million children are born each year with neurological deficits. Had the evaluations been made earlier than at one year, the number found to be defective probably would have been even higher. No great alarm has been expressed because by four years of age the majority of these children showed no clinical neurological signs (*1*). Of course, one cannot adequately evaluate their neuropathological status.

Experimental model

The need to have an animal model is clear. My remarks will be confined to results of asphyxia neonatorum of the monkey *Macaca mulatta*.[2] By the term *asphyxia neonatorum*, I mean the condition of a fetus deprived of oxygen before or during birth, whose respiratory mechanism is affected and often rendered incapable of functioning. Not only is he anoxic, his blood is acidotic, his heart rate is slow, and his blood pressure has fallen.

Asphyxia was induced in monkey fetuses near term while delivering them by cesarean section under local anesthesia. Either the contents of the uterus were removed intact at hysterotomy, or the fetal head was delivered, a condom filled with saline solution slipped over it, and the umbilical cord clamped. Thus, asphyxiation was instituted. It could be terminated electively by freeing the fetal head and, when necessary, passing a tracheal cannula to resuscitate by insufflation of the lungs with oxygen (*5*).

Many of the infant monkeys asphyxiated dur-

[1] Research receiving current support from grant HD 03407 of the National Institute of Child Health and Human Development and from grant RT–1 of the Social Rehabilitation Service.

[2] Many colleagues engaged in these studies. Their publications are listed in the bibliographies of the several articles to which reference is made in this report.

ing or after birth and resuscitated were reared in nursery cages and given tests and examinations periodically to reveal their neurological status. They were compared with nonasphyxiated control monkeys delivered and reared similarly. A few of them are still alive, having completed about one third of their expected life span of 30 years. Others were killed at intervals so that histological studies of their brains could be made to ascertain what damage had been produced by asphyxia neonatorum and what changes might have occurred with time (*4*).

Minimum brain damage from asphyxia at birth

It is generally believed that human infants with low initial Apgar scores who present indications of birth asphyxia and perhaps require resuscitation but then recover and display no persisting neurological deficits are normal. Our experiments in newborn monkeys do not support this view. Although asphyxiation of the fetus for less than six minutes was not followed by detectable deficits, asphyxiation for eight minutes or more invariably produced at least transient neurological signs and permanent structural brain damage. This was true whether or not resuscitation had been required to initiate breathing. (Spontaneous gasping persisted for more than eight minutes, as a rule.)

The minimum neuropathology was limited to certain brain-stem centers associated with general body sensation and hearing, but not with those of vision. The most vulnerable centers were the inferior colliculus and the ventrolateral group of thalamic nuclei. Nerve cells in these were destroyed. The lesions were nonhemorrhagic, sharply circumscribed, and bilaterally symmetrical, and the surrounding brain tissue was normal (*7, 12*).

The lesson from these experiments is that one cannot safely assume the fetus to be so resistant to oxygen deficiency that no harm will come to it from a short exposure to asphyxia neonatorum. If the human infant responds like the monkey—and there is evidence that it does (*2*)—its brain will certainly have been damaged by asphyxia severe enough to have

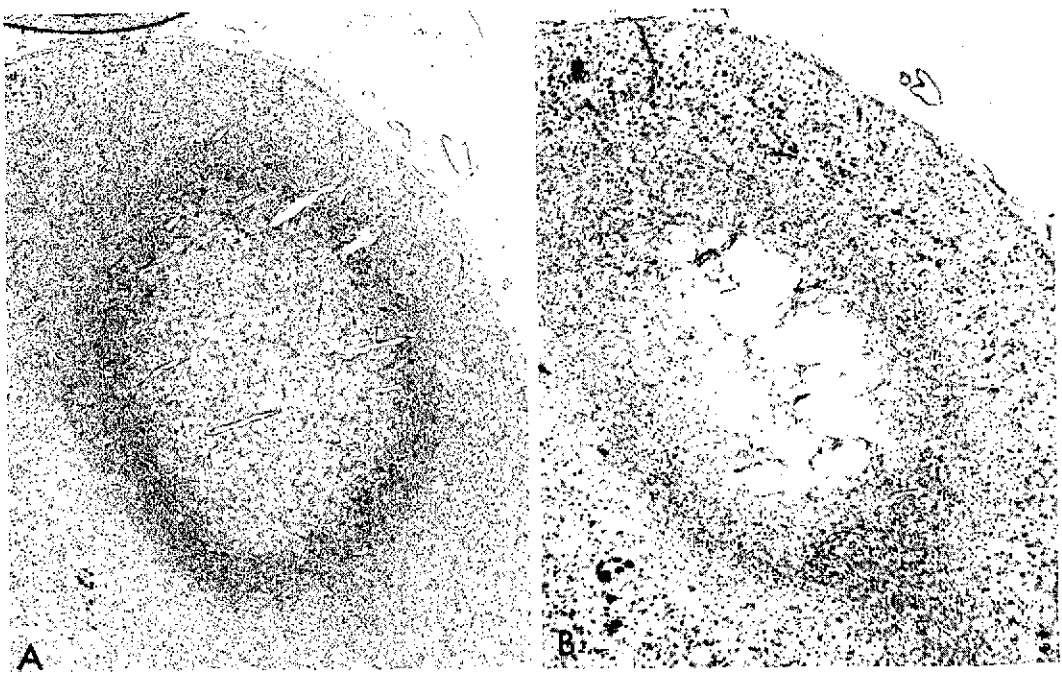

FIGURE 1. Lesion in inferior colliculus. A, nine days after 16¾ minutes' asphyxiation (*7*); B, four years, nine months after 14¼ minutes' asphyxiation (*4*). (Reproduced with permission of Academic Press, the copyright holder.)

required resuscitation. This damage will be permanent, even though it may not register symptomatically or may be noticeable clinically for only a little while. The effect of this on the human offspring as he matures is unknown, but I submit that his mentality may not be as good as it would have been if he were undamaged.

Severe neurological deficits of asphyxia

More prolonged asphyxiation at birth resulted in extensive and persistent symptoms of brain damage. Twelve to 17 minutes of placental separation or umbilical cord clamping always produced monkeys that failed to breathe and required resuscitation. The neuropathology was more extensive than that following brief asphyxial episodes. Figure 1 shows the inferior collicular lesion nine days (A) and four years and nine months (B) after birth. It involved additional groups of nerve cells, as in the cerebellum illustrated in Figure 2. Asphyxiation for longer times—up to 21 minutes—produced comotose monkey infants with extreme neural damage in the brain stem but relatively less involvement of cerebral cortex (unpublished observation).

Time does not permit consideration of com-

TABLE 1. Subjects in study of changes in neurological status with time

MONKEY NO.	SEX	GESTATION AGE (DAYS)	BIRTH WEIGHT (G)	DURATION ASPHYXIA (MIN:SEC)	TERMINAL AGE (YR:MO)
Principal series					
65	M	157	486	11:33	4.11
57	F	157	390	12:00	0.10
66	M	157	423	13:15	4:10
136	M	158	426	13:56	3:10
162	M	158	unk	14:00	3:06
130	M	156	471	14:00	3:11
60	F	157	588	14:05	8:09
76	M	157	461	14:15	4:09
208	M	157	470	15:00	2:08
144	M	157	398	15:15	3:08
31	M	162	472	17:00	5:06
34	F	172	478	[a]	1:03
Supplementary series					
13	F	159	463	4:35	2:05
56	F	157	462	6:05	7:11
11	F	157	390	6:08	2:05
7B	M	163	442	6:55	2:06
MA	F	unk	590	13:25	0:06
181	F	156	423	15:00	0:08
182	M	156	490	15:00	0:08
154	M	159	559	15:45	0:06
Animals living					
63	F	157	359	13:25	10:07 [b]
69	M	157	417	16:00	10:05 [b]
128	F	156	443	16:00	9:05 [b]
150	F	156	432	15:00	9:01 [b]

[a] This infant was delivered spontaneously by breech, head extracted manually, duration of asphyxia impossible to determine.

[b] Age in June 1969.

FIGURE 2. Lesion in the central vermis of cerebellum, nine months after birth asphyxia (*14*). (Reproduced with permission of Association for Research in Nervous and Mental Diseases.)

plicating factors that affect the brain damage of asphyxia neonatorum, notably prematurity, respiratory distress of the neonate, kernicterus, cerebral hemorrhages, and induction of labor with drugs. The extent of brain damage was modified adversely when such conditions occurred (*6, 10, 13, 14*).

Modifications of brain damage with time

The functional and structural modifications of asphyxial brain damage can best be illustrated in a selected group of asphyxiated monkeys that were permitted to live, most of them for three years or more. The asphyxiated monkeys are listed in Table 1.

The experiments in which asphyxia was produced were recorded at birth and periodically thereafter in motion pictures. Neurological examinations were made from time to time throughout life. Some of the monkeys were given psychological tests. Finally, the brains were serially sectioned for histological studies.

These monkeys presented functional neurological deficits after resuscitation, and some of them resembled human children with cerebral palsy. None could right itself, but lay on its side and when stimulated made random uncoordinated movements of the extremities. In contrast, normal monkeys right themselves and creep in a sprawling fashion a few hours after birth.

At one week, the erect posture had not been achieved. The extremities were often spastic. The helpless monkey infants slept most of the time. Their crying was weak and usually occurred only when they were handled. A few had seizures.

As the monkey infants matured, some of the early neurological deficits disappeared, and from then on the animals seemed to adjust

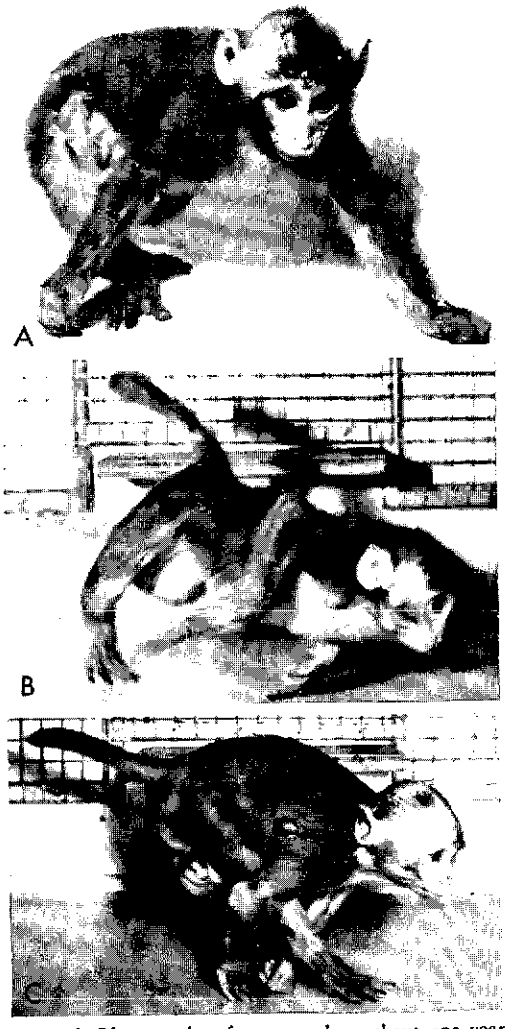

FIGURE 3. Photographs of two monkeys about one year old, each asphyxiated at birth for 15 minutes (*15*). A and B are same monkey. (Reproduced with permission of *Revue Neurologique*.)

gradually to their handicaps. Normal monkeys one month old are alert, emotional, and active; they run, jump, and climb with considerable facility. The month-old monkey asphyxiates, on the other hand, found locomotion difficult. Their activity level was low, their facial expression was dull, and they lacked curiosity about strange objects or new surroundings (*8*). The three photographs of monkeys about one year old shown in Figure 3 illustrate abnormal posture, falling when the monkey tried to run, and marked forelimb spasticity.

By one to three years of age they still lacked manual dexterity. Seizures disappeared and most of them had an essentially normal electroencephalogram. They were docile, friendly, unemotional monkeys, not easily disturbed and rarely exhibiting tantrums. Their adjustment to the neurological deficits of infancy reached a plateau in three or four years.

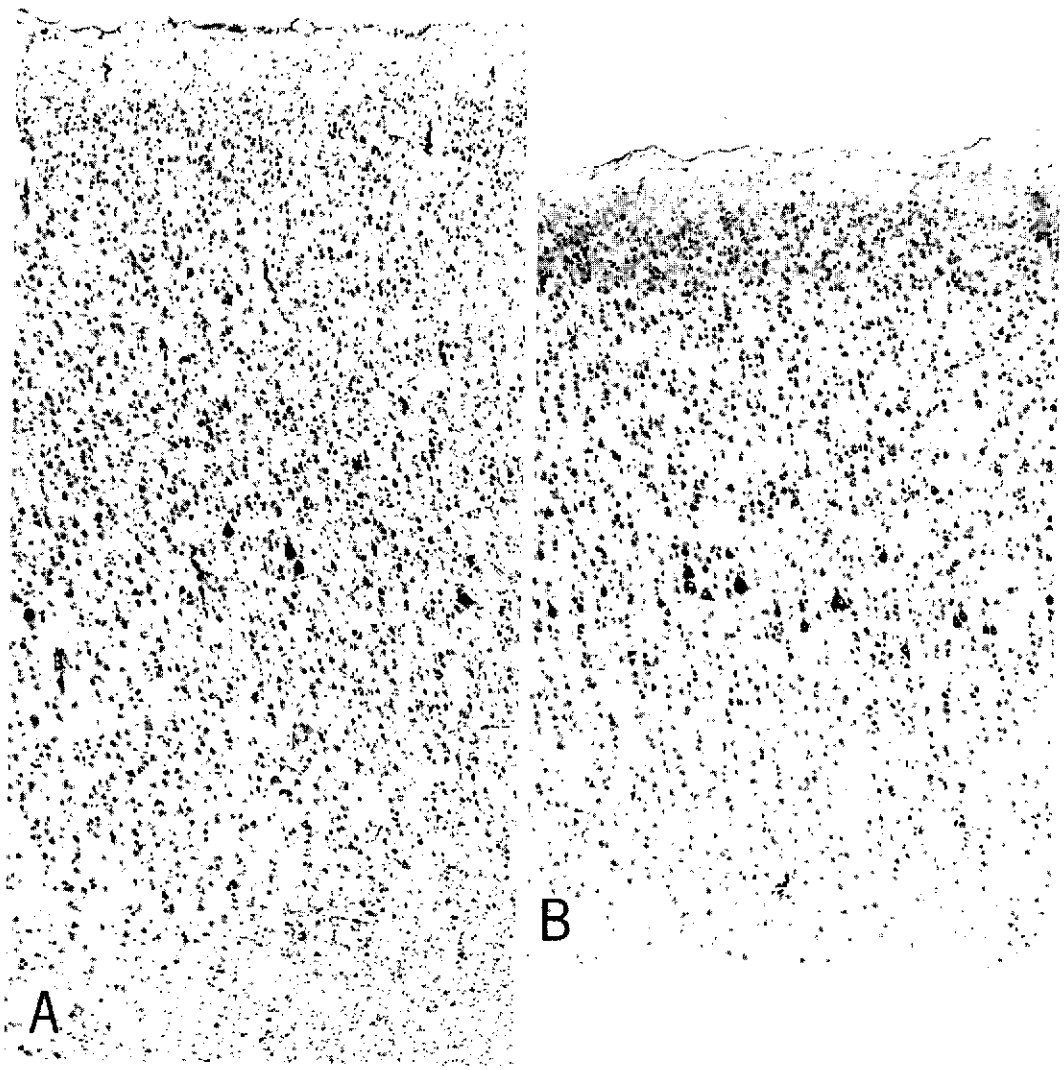

FIGURE 4. Postcentral gyrus of the cerebral cortex of (A) nonasphyxiated control and (B) 5.5-year-old monkey asphyxiated for 17 minutes at birth (*4*). (Reproduced with permission of Academic Press, the copyright holder.)

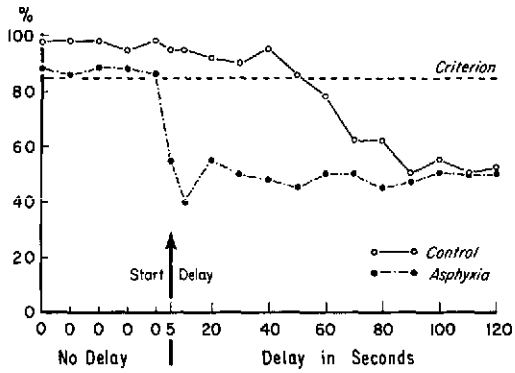

FIGURE 5. Comparison of performances on delayed-response test of two groups of asphyxiated monkeys 9–10 years old (*9*). The asphyxiates are listed in Table 1 (living). (Reproduced with permission of Academic Press, the copyright holder.)

The brains of the monkeys that appeared to have recovered contained scars of the primary focal lesions that had been caused by the asphyxia. The pattern was the same as that of acute preparations, but there was a great difference between the brains of monkeys allowed to survive for several years and those of recently asphyxiated monkeys. In spite of marked behavioral improvement, there was no evidence of structural "repair" in the brain tissues. Quite the contrary. Extensive widespread depletion of nerve-cell populations had occurred in regions unaffected by the initial asphyxia (*4, 11*).

This depletion of cells was most clearly seen in some regions of the cerebral cortex but also in portions of the thalamus, brain-stem reticular formation, and elsewhere. It was not associated with scar formation, as had been the case in the primary focal lesions. Nerve cells simply had disappeared, probably as the result of a transneuronal degeneration (*4*), leaving these initially intact portions of the nervous system atrophic. Compare the normal cortex with the atrophic cortex in the two photographs in Figure 4.

The remarkable finding in our experiments was that time alone (without planned therapy) generated considerable improvement in physical and behavioral characteristics but was associated with progressive deterioration of brain structure. These monkeys clearly were retarded. In psychological tests at nine to ten years of age, animals in this category were able to retain simple information for only a fraction of the time their nonasphyxiated controls could (*9*). Figure 5 compares the performance of asphyxiates and controls on a delayed-response test.

What does this mean in terms of the human infant who survives asphyxia neonatorum and initially presents signs of neurological deficits? The Collaborative Perinatal Study demonstrated that most infants with deficits persisting for one year lost them by four years of age (*1*). The brain-damaged monkeys at roughly comparable stages in development likewise lost most of their neurological deficits. The difference is that we know that the brains of the "recovered" monkeys are histologically abnormal, while we only assume on clinical grounds that the brains of "recovered" human infants are normal. I do not doubt that they, too, are riddled with lesions.

Parents and physicians are relieved and pleased when a child has weathered a distressful infancy and escapes overt signs of cerebral palsy. Our experiments in the monkey caution us that we should not be complacent, for the child is likely to be affected in subtle ways and, like our monkeys, grow up to be mentally retarded.

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THE APGAR SCORES AND FOUR-YEAR PSYCHOLOGICAL EXAMINATION PERFORMANCE[1]

Joseph S. Drage, Heinz W. Berendes, and Pearl D. Fisher[2]

This report will present some preliminary findings of the Collaborative Study data relating Apgar scores observed at five minutes after birth to measures of psychological performance as judged by a battery of psychological examinations administered to Study children at four years of age.

Table 1 reviews the Apgar scoring technique designed in 1952 as a practical method for evaluating the condition of the newborn infant at one minute after birth. Five items are evaluated: heart rate, respiratory effort, muscle tone, reflex irritability, and color. Each of the five items evaluated is given a numerical score of 0, 1, or 2, and the total of the subscores is the Apgar score. A high score would describe the optimal newborn condition; a low score, a newborn in poor condition. Studies by Apgar and James reveal biochemical evidence that infants scoring 3 or less are severely asphyxiated. Initially, Dr. Apgar devised the system to be used one minute after birth to focus attention on the newborn infant and identify those in need of resuscitation. Her observations included the association of low one-minute scores to increased neonatal mortality. In the Collaborative Study her work has been documented and the increased ability of the five-minute Apgar score to predict neonatal mortality, especially mortality during the first 24 hours of life, has been shown. Other work done within the Study suggests that the five-minute Apgar score is useful in predicting infant morbidity, which is defined as neurological abnormality detected on examination at one year of age. This report relates findings on a battery of psychological examinations administered at four years to children with high and low five-minute Apgar scores, controlling on race, maternal education, and birth weight.

Table 2 reports the mean four-year IQ for white children by high and low five-minute Apgar scores, birth weight, and maternal edu-

[1] A report from the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood, supported by the National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland, U.S.A.

[2] Presented by Dr. Drage.

TABLE 1. Evaluation of the newborn infant: the Apgar method of scoring

SIGN	SCORE 0	SCORE 1	SCORE 2
Heart rate	Absent	Slow (below 100)	Over 100
Respiratory effort	Absent	Weak cry, hypoventilation	Good effort, strong cry
Muscle tone	Limp	Some flexion of extremities	Well flexed
Reflex irritability (response of skin stimulation to feet)	No response	Some motion	Crying active
Color	Blue, pale	Body pink, extremities blue	Completely pink

TABLE 2. Mean four-year IQ for white children by high (8–10) and low (0–6) five-minute Apgar scores, birth weight, and maternal education

MATERNAL EDUCATION	6 YEARS OR LESS		7–9 YEARS		10–12 YEARS		13 YEARS OR MORE		TOTAL	
APGAR	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10
2,500 grams or less										
Mean IQ	—	84.0	101.4	97.8	96.4	104.1	118.0	107.0	100.1	102.1
N	0	16	16	104	25	254	4	40	45	414
T	—		0.884		2.392		—		0.764	
p	—		n.s.		.05–.01		—		n.s.	
Over 2,500 grams										
Mean IQ	90.5	96.9	96.6	99.4	101.5	104.9	119.0	114.8	101.8	105.2
N	10	228	59	1,368	182	4,964	29	1,204	280	7,764
T	1.224		1.543		3.171		1.420		3.629	
p	n.s.		n.s.		<.001		n.s.		<.001	

cation. Children with malformations of the central nervous system, mongolism, hypothyroidism, and other syndromes associated with MR have been excluded. The IQ is determined by administration of the Stanford-Binet test (Form L-M). Birth weight has been divided into 2,500 grams or less and over 2,500 grams. Maternal education is classified as 6 years or less, 7–9 years, 10–12 years, and 13 years or more. The five-minute scores have been grouped as low (0–6) and high (8–10).

Among the children whose birth weights were 2,500 grams or less, the 414 with five-minute Apgar scores of 8–10 had a mean IQ of 102, and the 45 with five-minute Apgar scores of 0–6 had a mean IQ of 100. There is no statistical significance by T-test between these means. In the group of children whose mothers had 10 to 12 years of education, there was a mean difference between the high and low Apgar groups of about 8 IQ points, with significance at the level of .05–.01.

Among the children who had weighed more than 2,500 grams at birth, the 7,764 with five-minute scores of 8–10 had a mean IQ of 105.2; the 280 with 5-minute scores of 0–6 had a mean IQ of 101.8. This 3.4-point difference among the large number of cases involved represents a probability of less than .001. The findings are similar for the 10-to-12-year maternal education group. Indeed, in three of the four levels of maternal education—all except 13 years or more—a higher mean IQ is associated with the higher Apgar score group.

It is of interest that for both birth-weight groups, the mean IQ increases with increasing maternal education. This shows the marked importance of assessing maternal education, or some other indicator of the socioeconomic-educational status of the family, in discussing and reporting data on IQ. Also to be noted is the consistently lower mean IQ of the lower-birth-weight group within each education level.

Table 3 reports the mean four-year IQ for Negro children by high and low five-minute score, maternal education, and birth weight. The total group of infants weighing 2,500 grams or less shows a mean difference of 2.5 IQ points between high and low Apgar-score groups. At each level of maternal education, there are differences in the mean IQ between the high and low Apgar-score group, with the low-score group consistently having the lower mean IQ. However, the differences are not enough to show statistical significance by the T-test. For the children weighing more than 2,500 grams at

TABLE 3. Mean four-year IQ for Negro children by high (8–10) and low (0–6) five-minute Apgar scores, birth weight, and maternal education

MATERNAL EDUCATION	6 YEARS OR LESS		7–9 YEARS		10–12 YEARS		13 YEARS OR MORE		TOTAL	
APGAR	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10
2,500 grams or less										
Mean IQ	76.2	83.6	83.9	85.1	89.2	91.5	90.4	97.0	87.1	89.6
N	12	51	39	248	95	593	7	38	153	930
T	1.660		0.475		1.540		—		2.001	
p	n.s.		n.s.		n.s.		—		<.05	
Over 2,500 grams										
Mean IQ	87.4	87.7	87.9	89.0	92.8	93.4	93.7	99.3	91.3	92.3
N	25	385	83	2037	242	5243	15	422	365	8087
T	0.137		0.781		0.658		1.548		1.360	
p	n.s.		n.s.		n.s.		n.s.		n.s.	

birth, we see no statistically significant difference between the high and low Apgar-score groups. In general, the mean IQ is slightly lower for the low Apgar group. Again, it is seen that the mean IQ rises with increasing maternal education for both birth-weight groups and that the infants weighing more than 2,500 grams have consistently higher mean IQs than the lower-weight infants within any given maternal education level.

Table 4 gives the mean four-year Graham-Ernhart Block Sort score for white children by high and low five-minute Apgar scores, birth weight, and maternal education. This is a test of concept formation. The child is given a set of 26 blocks in an assortment of three colors, three shapes, and three sizes and is asked to sort them by various criteria of similarity. The differences in the mean Graham Block score among the children who had weighed 2,500

TABLE 4. Mean four-year Graham Block score for white children by high (8–10) and low (0–6) five-minute Apgar scores, birth weight, and maternal education

MATERNAL EDUCATION	6 YEARS OR LESS		7–9 YEARS		10–12 YEARS		13 YEARS OR MORE		TOTAL	
APGAR	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10
2,500 grams or less										
Mean GBS	—	30.0	28.4	33.8	34.7	34.2	37.5	39.0	32.7	34.0
N	0	16	16	104	25	254	4	40	45	414
T	—		2.515		0.285		—		1.020	
p	—		.01–.001		n.s.		—		n.s.	
Over 2,500 grams										
Mean GBS	27.2	32.4	32.3	34.2	33.9	35.4	38.6	37.4	33.8	35.4
N	10	228	59	1,368	182	4,964	29	1,204	280	7,764
T	1.839		1.868		2.823		1.120		3.682	
p	n.s.		n.s.		.01–.001		n.s.		<.001	

grams or less showed significance only among those with a maternal education level of 7 to 9 years. Among those weighing more than 2,500 grams, differences between the mean Graham Block scores are significant for the total group and for the group with maternal education of 10 to 12 years. As with the IQ scores, when the maternal education level rises so does the mean Graham Block score. In general, for any given educational level, the higher-birth-weight group has the higher mean score.

Table 5 shows the mean four-year Graham Block score for Negro children by high and low Apgar scores, birth weight, and maternal education. Here there is some significance for the total group among those weighing 2,500 grams or less at birth, but no significance between the high and the low score for the heavier infants. However, the mean scores are consistently lower for the low Apgar scores.

Several other assessments are made on the four-year psychological examination: fine motor performance, gross motor performance, a behavioral profile, and an over-all impression. The fine motor evaluation consists of four subtests: (1) a Wallin Peg Board Test, in which the child is given 30 seconds to put as many pegs into the board as possible, using only one hand at a time; (2) reproduction of a circle, a cross, and a square; (3) the number of beads strung in two minutes; and (4) a Porteus maze, on which the child is asked to do a pencil tracing between lines. "Normal" fine motor performance is reported when three or more of the subtests are passed, "suspect" when only one or two are passed, and "abnormal" when none are passed. In the gross motor evaluation, three tests are given to the child: (1) walking at least three feet along a ten-foot straight line without stepping off, (2) hopping on one foot in place, and (3) ball catching. Normal gross motor performance is passing two or more of the tests, suspect passing only one, and abnormal passing none. The behavioral profile is an attempt by the psychologist to evaluate the qualitative and quantitative aspects of the child's behavior as it is observed during the psychological testing and in psychological observation with a view to detecting possible brain damage. A number of items are evaluated on a 5-point scale: emotional reactivity, degree of irritability, degree of cooperation, degree of dependence, duration of attention span, goal orientation, response to direction, level of activity, nature of activity, and nature of communication. The assumption underlying the scales is that the

TABLE 5. Mean four-year Graham Block score for Negro children by high (8–10) and low (0–6) five-minute Apgar scores, birth weight, and maternal education

MATERNAL EDUCATION	6 YEARS OR LESS		7–9 YEARS		10–12 YEARS		13 YEARS OR MORE		TOTAL	
APGAR	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10	0–6	8–10
2,500 grams or less										
Mean GBS	24.4	29.4	26.8	28.8	29.9	31.0	32.0	33.0	28.7	30.4
N	12	51	39	248	95	593	7	38	153	930
T	1.482		1.110		1.064		—		1.992	
p	n.s.		n.s.		n.s.		—		.05–.01	
Over 2,500 grams										
Mean GBS	28.2	29.5	29.6	30.4	31.3	31.8	28.6	32.8	30.6	31.4
N	25	385	83	2,037	242	5,243	15	422	365	8,087
T	0.701		0.727		0.951		1.877		1.723	
p	n.s.		n.s.		n.s.		n.s.		n.s.	

child with brain injury will manifest an atypical and demonstrable behavioral syndrome when compared with his peers of normal development. The last item reported, the over-all impression, is based on the five tests given: intelligence, fine motor evaluation, gross motor evaluation, concept formation as measured by Graham-Ernhart Block Sort, and behavioral profile. Birth weight is divided into 2,500 grams or less and over 2,500 grams.

Table 6 gives the results for white children. For birth weight less than 2,500 grams, there is an insufficient number of children in the low five-minute Apgar-score group for statistical testing, except for the over-all impression, in which there are more than the expected number of suspect and abnormal children in the low-Apgar group. Significance is at the level of .005 to .001. For white infants weighing more than 2,500 grams, the number suspect and abnormal among the group of infant with 0–6 Apgar scores is significantly greater for each of the tests than those found suspect and abnormal with 8–10 Apgar scores. For fine motor, the χ^2 is 12.2 with a resulting probability between .005 and .001. For the gross motor evaluation, the χ^2 is slightly less, with a probability of .005–.001. For the behavioral profile, the χ^2 is 14.1 with a probability of less than .001. For the over-all impression, the χ^2 is 18.3, with a probability of less than .001.

Table 7 reports the fine motor, gross motor, behavioral profile, and over-all impression for Negro children with birth weight above and below 2,500 grams and by high and low Apgar scores. For the lower-weight infants, fine and gross motor abnormalities are significantly higher among those with low Apgar scores, with the association stronger for fine motor abnormality. Increased abnormality associated with low Apgar scores approaches significance for the behavioral profile, and the over-all impression is significant, with a probability between .05 and .025. For the Negro infants heavier than 2,500

TABLE 6. Results of four-year fine and gross motor tests, behavioral profile, and over-all impression of white children, by birth weight and Apgar score

	BIRTH WEIGHT 2,500 GRAMS OR LESS				BIRTH WEIGHT OVER 2,500 GRAMS			
	5-MINUTE APGAR				5-MINUTE APGAR			
	0–6	8–10	χ^2	p	0–6	8–10	χ^2	p
Fine motor								
Normal	31	327			233	6775		
Suspect	12	80	—	—	41	944	12.287	.005–.001
Abnormal	2	7			6	45		
Gross motor								
Normal	33	364			249	7165		
Suspect	9	41	—	—	24	535	10.026	.01–.005
Abnormal	3	9			7	64		
Behavioral profile								
Normal	37	336			219	6660		
Suspect	7	67	—	—	50	957	14.121	<.001
Abnormal	1	11			11	147		
Over-all impression								
Normal	31	334			227	6795		
Suspect	7	63	10.887	.005–.001	38	815	18.336	<.001
Abnormal	7	17			15	154		

TABLE 7. Results of fine and gross motor tests, behavioral profile, and over-all impression of Negro children, by birth weight and Apgar score

	BIRTH WEIGHT 2,500 GRAMS OR LESS				BIRTH WEIGHT OVER 2,500 GRAMS			
	5-MINUTE APGAR				5-MINUTE APGAR			
	0–6	8–10	χ^2	p	0–6	8–10	χ^2	p
Fine Motor								
Normal	72	556			236	5412		
Suspect	71	353	14.464	<.001	121	2584	3.816	n.s.
Abnormal	10	21			8	91		
Gross Motor								
Normal	121	819			335	7475		
Suspect	22	87	11.063	.005–.001	22	524	3.871	n.s.
Abnormal	10	24			8	88		
Behavioral profile								
Normal	121	752			321	6990		
Suspect	24	159	5.554	n.s.	42	1008	—	—
Abnormal	8	19			2	89		
Over-all impression								
Normal	99	674			280	6519		
Suspect	36	195	6.395	.05–.025	65	1284	5.234	n.s.
Abnormal	18	61			20	284		

grams, none of the tests show significant differences. To be noted, however, is the very large number of Negro children classified as having suspect fine motor performance, compared to the whites; the rate is almost three times that for the white children, and the fact that so many have been thus classified would interfere with differences that might be detected between the low and high Apgar scoring groups. For the over-all impression, the abnormal and the suspect rate among Negro children is almost twice that of white children.

In brief, from a *preliminary* look at these data, there is no consistently significant mean IQ-score difference between children with high and low five-minute Apgar scores except in isolated instances, when controlled by maternal education, birth weight, and race. However, in any given instance, the lower mean IQ is generally associated with the lower Apgar-score group. These same observations hold true for the Graham Block Sort associations. When four-year psychological data are available on the entire sample of 45,000 Study children, these differences may become significant if the mean differences should persist. The consistent relationships of maternal education and birth weight to the IQ and Graham Block Sort scores suggest that finer increments of maternal education and birth weight would be desirable in future studies when the total population available would support such an analysis.

In summarizing the relationship between Apgar scores and fine and gross motor assessments, fine motor deficiencies seem most strongly related to low scores, followed to a lesser degree by gross motor findings. When numbers permit, more and finer control groupings may make possible a more precise definition of these differences.

FETAL DISTRESS: ITS SIGNIFICANCE IN NEUROLOGICAL AND MENTAL IMPAIRMENT OF CHILDHOOD

Heinz W. Berendes

As indicators of fetal distress, the obstetrician has relied for some time on alterations of the fetal heart rate (FHR) observed during labor—in particular, FHR below 100—and/or the presence of meconium in the absence of breech presentation. These crude but clinically useful indicators identify children at risk and are associated with an increase in neonatal mortality and neonatal morbidity as expressed by low one-minute and five-minute Apgar scores. In an attempt to study the association between lowering of the FHR and neurological or mental deficits in surviving children, the following approach was used, drawing on information collected as part of the Collaborative Perinatal Study. Children were identified who had been born during the first three years of this program, were therefore at least four years old, and were derived from pregnancies in which at least one observation of an FHR below 80 was made during labor. Data from the neurological and psychological examinations of these children through the first four years of their lives were then compared with the population of children from which this sample was drawn.

Table 1 compares the mean IQ of children who had at least one FHR observation under 80 during the first stage of labor with that

TABLE 1. Mean IQ of children with low FHR during first stage of labor, by race and institution

	WHITE			NEGRO		
		IQ			IQ	
INSTITUTION	NO. CASES	OBSERVED	EXPECTED	NO. CASES	OBSERVED	EXPECTED
05	40	105.6	107.6	4	101	104
10	2	107	112.4	—	—	—
15	—	—	—	6	84.8	85.7
31	10	94.2	103	20	97.4	96.2
37	1	99	97	11	96.6	93.2
45	1	96	92.7	6	85	88.2
50	11	103	104.8	—	—	—
60	11	93.6	97.1	9	90.3	89.2
66	2	116	97	36	90.5	92.4
71	3	122.7	102.7	—	—	—
82	—	—	—	12	88.7	87.8
All institutions		102.9	104.1		92	91.5

TABLE 2. Mean IQ of children with low FHR during second stage of labor, by race and institution

	WHITE			NEGRO		
		IQ			IQ	
INSTITUTION	NO. CASES	OBSERVED	EXPECTED	NO. CASES	OBSERVED	EXPECTED
05	82	105.2	107.6	12	99.1	104.2
10	4	109	112.4	—	—	—
15	—	—	—	1	92	85.7
31	6	115.3	103	11	99.7	96.2
37	1	107	97	5	86.8	93.2
45	—	—	—	3	97.3	88.2
50	17	111.1	104.8	—	—	—
55	—	—	—	2	79	94.3
60	19	95.1	97.1	6	83.3	89.3
66	1	88	97	17	86.1	92.4
71	9	107	102.3	3	91.7	96.9
82	—	—	—	12	88	87.8
All institutions		105.1	104.1		91.1	91.5

of the rest of the population. The mean IQ of whites with low FHR during the first stage is 102.9, compared to an expected 104.1. In Negroes the difference is even smaller, with a mean IQ of 92 in the low-FHR children, compared to an expected 91.5. Because of the population differences of the various institutions contributing to this program, the data are arranged by institution. For the most part we see only small differences in mean IQ where we have at least 10 children, and the direction of the difference is not consistent.

Table 2 shows the same comparisons by low FHR observed only during the second stage of labor. Here, for white children, the mean IQ observed was 105.1, compared to an expected 104.1. In Negroes the observed IQ was 91.1, compared to an expected 91.5. The data by institution reveal inconsistent differences. Some instances show a slightly higher mean IQ for children with low FHR and others the opposite.

The socioeconomic characteristics of the population are strongly associated with intelligence as measured. Table 3 displays the mean IQ of children with low FHR during the first stage of labor by maternal education and race. For neither ethnic group do we observe a consistent pattern. Only small IQ differences are seen

TABLE 3. Mean IQ of children with low FHR during first stage of labor, by maternal education and race

	WHITE			NEGRO		
		IQ			IQ	
MATERNAL EDUCATION	NO. CASES	OBSERVED	EXPECTED	NO. CASES	OBSERVED	EXPECTED
Grade 6 or lower	2	107.5	95	13	88.7	86.5
Grades 7–9	16	102.3	99.6	26	86.3	88.2
Grades 10–12	45	103.3	104.1	56	95.0	92.3
1–4 years college; Grade 12 with some college	13	108.8	113.6	3	102	98.8
Graduate work	—	—	126.9	2	106	101

TABLE 4. Mean IQ of children with low FHR during second stage of labor, by maternal education and race

MATERNAL EDUCATION	WHITES NO. CASES	WHITES IQ OBSERVED	WHITES IQ EXPECTED	NEGROES NO. CASES	NEGROES IQ OBSERVED	NEGROES IQ EXPECTED
Grade 6 or lower	2	88	95	1	78	86.5
Grades 7–9	22	96.2	99.6	12	87.3	88.2
Grades 10–12	82	103.3	104.1	53	91.1	92.3
1–4 years college; Grade 12, some college	28	117.1	113.6	3	104	98.8
Graduate work			126.9	2	105	101

between the low FHR group and the control population, and these differences are not consistent. Table 4 shows the mean IQ of children by maternal education and race for low FHR during the second stage of labor. Again the differences are minor between the groups we are comparing. In order to increase the number of observations, we combine in Table 5 the data on all low-FHR children, irrespective of the stage of labor when the observation was made, again arranged by maternal education and race. For all maternal education groups with 10 cases or more, the mean IQ differences of low-FHR and control groups are less than 3 points—that is, essentially identical. These data were also grouped by number of low-FHR observations and by the duration of the observed episodes. No consistent differences in IQ distribution or mean IQ were seen.

Table 6 reports the proportion of children with low FHR by stage of labor who had a four-year IQ under 70. For the second stage of labor, the observed rate was identical to the expected one. There are slight differences for the first-stage group, going in different directions, for whites and Negroes. The preliminary conclusion that might be drawn from these

TABLE 6. Low-FHR children with IQ under 70 at four years of age, by stage of labor and race

RACE	FIRST STAGE OF LABOR OBSERVED NO.	FIRST STAGE OF LABOR OBSERVED %	FIRST STAGE OF LABOR % EXPECTED	SECOND STAGE OF LABOR OBSERVED NO.	SECOND STAGE OF LABOR OBSERVED %	SECOND STAGE OF LABOR % EXPECTED
White	2/85	2.3	1.4	2/140	1.4	1.4
Negro	4/101	4.0	5.6	4/71	5.6	5.6

TABLE 5. Mean IQ of children with low FHR during first and/or second stage of labor, by maternal education and race

MATERNAL EDUCATION	WHITES NO. CASES	WHITES IQ OBSERVED	WHITES IQ EXPECTED	NEGROES NO. CASES	NEGROES IQ OBSERVED	NEGROES IQ EXPECTED
Grade 6 or lower	4	97.6	95	14	88	86.5
Grades 7–9	38	98.8	99.6	38	86.6	88.2
Grades 10–12	127	103.3	104.1	109	93.1	92.3
1–4 years college; Grade 12, some college	41	114.5	113.6	6	103	98.8
Graduate work	—	—	126.9	4	105.5	101

data is that the clinical rating of low FHR does not correlate with IQ in four-year-old children, nor does it appear to correlate with mental retardation as measured by the Stanford-Binet test at four years. There is a possibility that small differences might exist, which we were unable to detect because of sample size limitations.

We then looked at neurological manifestations in these groups of children. Table 7 indicates neurological findings in surviving children with low FHR observed during the first stage of labor. We limited this tabulation to children with birth weights above 2,500 grams, in view of the complexity of the association in prematures. Of children with low heart rates during the first stage of labor, six had abnormal neurological findings that were rather definite. These include two with hypotonia and deep tendon reflexes, two with complex diplegia, one with a small head and increased deep tendon reflexes, and one who was grossly brain-damaged and institutionalized. This gives an abnormality rate of around 2.8 per cent. In the control population the abnormality rate is 1.2 per cent. In addition, in five children convulsions—in three cases febrile—were reported; this is somewhat higher than expected.

Table 8 reports the neurological status of children with low FHR during the second stage of labor. The abnormality rate is almost identical in the two groups except for a slight increase in convulsions, febrile or other, in the low FHR group.

TABLE 7. Neurological status of children with low FHR during first stage of labor weighing more than 2,500 grams at birth

STATUS	NO. CASES	% FOUND	% EXPECTED
Normal	193		
Abnormal [a]	6	2.85	1.25
Convulsions			
Febrile	3	1.42	.44
Other	2	.95	.36
Suspect findings	6		
Total	210		

[a] 2 hypotonia with DTR; 2 complex diplegia; 1 small head with increased DTR; 1 grossly brain-damaged.

TABLE 8. Neurological status of children with low FHR during second stage of labor weighing more than 2,500 grams at birth

STATUS	NO. CASES	% FOUND	% EXPECTED
Normal	241		
Abnormal [a]	4	1.6	1.25
Convulsions			
Febrile	3	1.2	.44
Other	2	.78	.36
Suspect findings	8		
Total	258		

[a] 1 brachial plexus palsy; 2 hypotonia with DTR; 1 multiple neurological findings with facial palsy.

In order to see whether low FHR or meconium staining are associated with various types of cerebral palsy, another study design was used. Children were identified from the Study population who had typical symptoms and signs of cerebral palsy at one year of age. We removed from this group those in whom the neurological defect was clearly the result of a post-neonatal insult, such as meningitis or head injury, or of some prenatal factor, such as congenital rubella. This analysis includes about one third of the children with cerebral palsy from the Collaborative Perinatal Project. The cerebral palsy group was then matched by institution of birth, race, maternal age, parity, sex of child, and birth weight to obtain a control group. The frequencies of one or more FHR observations of 100 or lower and meconium staining were then tabulated for the two groups.

Table 9 compares children with complex diplegia (*1*) with controls. Fetal heart rates of 100 or below are present in 2 out of the 34 children with complex diplegia, compared to 0 of the controls. Meconium staining was observed in 6 out of the 34 complex diplegias, compared to 5 of the 34 controls. A comparison between groups of Apgar one- and five-minute ratings of 3 or below reveals some minor differences: low Apgar scores appear to be somewhat more frequent among the children with complex

TABLE 9. Comparison of low FHR, meconium staining, and low Apgar scores in children with complex diplegia and controls

SIGN	COMPLEX DIPLEGIA (34)	CONTROLS (34)
FHR 100 or lower	2	0
Meconium staining	6	5
1-minute Apgar score 3 or below	3	1
5-minute Apgar score 3 or below	1	0
Any of above	9	6

diplegia. Any of the four findings were observed in 9 of 34 children with complex diplegia compared to 6 of the 34 controls.

In this sample there were 13 children with spastic diplegia (Table 10). Essentially there are no differences here in the frequency of low FHR and meconium staining in the two groups. However, we note that 5 of the 13 spastic diplegias had very low one-minute Apgar scores compared to 0 out of 13 controls.

There were 11 cases of hemiplegia B (Table 11). Any of these four signs were present in 2 each of the subjects and of the 11 controls. Three children belonged to a mixed type.

If we consider all types, as is done in Table 12 with 61 cases and controls, we see that FHR of 100 and below are seen in 5 of the 61 cases with cerebral palsy, compared with 2 of the 61 controls. On the basis of the data from the total population one would have expected a

TABLE 10. Comparison of low FHR, meconium staining, and low Apgar scores in children with spastic diplegia and controls

SIGN	SPASTIC DIPLEGIA (13)	CONTROLS (13)
FHR 100 or below	1	0
Meconium staining	1	1
1-minute Apgar score 3 or below	5	0
5-minute Apgar score 3 or below	0	0
Any of above	5	1

TABLE 11. Comparison of low FHR, meconium staining, and low Apgar scores in children with hemiplegia and controls, and in those with mixed-type cerebral palsy and controls

SIGN	HEMIPLEGIA		MIXED TYPES	
	CASES (11)	CONTROLS (11)	CASES (3)	CONTROLS (3)
FHR 100 or below	0	1	2	1
Meconium staining	2	0	1	1
1-minute Apgar score 3 or below	1	1	1	1
5-minute Apgar score 3 or below	0	0	1	0
Any of above	2	2	2	1

frequency of around 4 per cent. The controls show a slightly lower 3.3 per cent; the 8.2 per cent for the cerebral palsy cases is somewhat higher. Meconium staining is seen in 10 out of 61 cerebral palsy cases compared to 7 of 61 controls.

The one- and five-minute Apgar-score data show larger differences. These low scores were seen more frequently in the cerebral palsy group than in the controls, with the controls matching closely the expected incidence in the total population. Any of the four findings occurred in 18 of the 61 cerebral palsy cases, compared to 10 of the 61 controls.

TABLE 12. Comparison of low FHR, meconium staining, and low Apgar scores in children with all types of cerebral palsy and controls

SIGN	CASES (61)			CONTROLS (61)	
	NO.	%	% EXPECTED	NO.	%
FHR 100 or below	5	8.2	4.4	2	3.3
Meconium staining	10			7	
1-min Apgar 3 or below	10	16.3	5.6	3	4.9
5-min Apgar 3 or below	3	4.9	1.0	0	0
Any of above	18	29.5		10	16.3

In summary, no differences in mean IQ or IQ under 70 were seen in children who had low FHR, as defined for purposes of this study, in the first or second stage of labor as compared to the population from which they were drawn. Small differences were observed in certain neurological findings, particularly in children with low FHR during the first stage of labor. More of these appeared to be abnormal than was expected.

Comparison of the frequencies of indicators of fetal distress—that is, low fetal heart rate, meconium staining, low one- and five-minute Apgar score—suggests a difference between children with various types of cerebral palsy and their controls. An increase was found in CP children.

Small differences in prenatal indicators of distress were observed among children with complex diplegia. Low Apgar scores were noted specifically among children with spastic diplegia.

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DISCUSSION

Caldwell: I have a brief comment on Dr. Windle's excellent, and I think very provocative, talk.

For the past several years I have been very much concerned, in our research on prenatal manipulation and postnatal behavior, with the possibility, at least in the rat, that after a prenatal insult the animal develops some sort of compensatory behavior, primarily in the period from birth to weaning, that results in giving the indication at the time behavior is measured—which is usually after weaning—that the animal is normal. As a result, we have been involved in a rather lengthy project to devise techniques for measuring learning in the rat immediately upon birth and then following the ontogeny of these behaviors throughout the growth process. We have in fact shown that after different degrees of birth insult compensatory behaviors do indeed develop; they would not show up if the animal's behavior as an adult could be measured, but closer inspection reveals that they frequently result in an impairment of later performance of complex tasks.

Therefore, I think his point is extremely well taken: that, although clinically the subject may look normal after different birth traumas, this need not be the case.

Windle: That is most interesting. I do not think I can add anything to that. I am not familiar with the structural picture of the rat brain after neonatal asphyxia.

May I ask a question of Dr. Berendes? This Collaborative Study has been going on a long time, and I know you have a great deal of data. It would be most instructive if you could compare the infants that had to be resuscitated at birth with those that were born with all their faculties—crying, and pink, and all the rest. Perhaps obstetricians do not like to put it down in their records when they have to resuscitate a baby, but you surely must have some information about the incidence of asphyxia requiring resuscitation. From the animal studies so far, it would seem to me that it is crucial to compare the neurological picture in such infants at birth, at one year, and at whatever terminal date you want to set.

Berendes: I do not have the exact answer that Dr. Windle would like to have. I looked into this some time ago; it is in the transcript of the 1964 Obstetrical Congress in Buenos Aires.

The problem is a difficult one in the sense that procedures like resuscitation are unfortunately used in a nonrandom fashion. That is, some institutions do a lot and others do little. If children with and without resuscitation are grouped by Apgar score,—and I did this because Dr. Apgar had introduced her score mainly in an attempt at early identification of children requiring resuscitation—those who have not been resuscitated will be found to be better off than those who have.

What really happens, of course, is that the one-minute Apgar score does not describe the situation precisely. Before the physician proceeds with resuscitation, some time has passed—seconds or a minute—and the child may have improved substantially so that no resuscitation is necessary, whereas the youngster with persistent depression is resuscitated.

We are talking again about groups of children who are not quite alike.

Myers: I should like to express admiration for the accomplishments of the Collaborative Perinatal Study. Listening to the papers from that effort during the last two days has been most provocative and informative.

There is a need for us to attend with great care to the points raised by these studies. The results seem to suggest that such indicators of fetal distress as fetal heart rate changes or meconium staining during labor or low five-minute Apgar scores after delivery are poorly

correlated with the later occurrence of neurological deficits or intellectual impairment. In reflecting on these conclusions, it should be emphasized that the performances evaluated in later life in these studies were not merely gross ones—as, for example, the occurrence of positive neurological signs—but also those having to do with more subtle measures, such as intelligence and the execution of fine skills.

These results agree with the findings of the Aberdeen studies described yesterday by Dr. Birch. In those studies, all neurologically and/or intellectually impaired individuals were identified from the population of children born in the community during roughly a two-year period, and the circumstances surrounding their gestation and birth were examined for possible positive correlations with their later impaired neurological statuses.

The findings, again, were remarkable. These neurologically damaged children tended as a group to have been prematurely born or to have been abnormally small at birth. As a group they also failed to thrive in the newborn period. Many were associated with abnormal pregnancies. At the same time, few were of normal weight at birth and few gave indications of complications at birth or signs of fetal distress with depression in the early hours following birth. These studies suggest that it may be wrong to believe that perinatal brain damage in the majority of cases is due to complications arising during labor or the delivery process.

If thinking with regard to perinatal brain damage and its causation were reviewed, it would be found that in early times virtually all such cases were thought to arise in relation to difficulties at birth. Then came a time when the question was raised whether a few such babies might not have been damaged during pregnancy itself rather than during delivery. Later the possibility was expressed that more than a few such babies might have received brain damage prior to delivery. Now the more appropriate question appears to be whether almost all such cases may not have received injury to their brains at a time prior to or following delivery. The latter alternative appears the most strongly suggested by both the Aberdeen studies and the studies of the Collaborative Perinatal Study Project.

One cannot help being impressed by the importance of these conclusions if they prove correct. If the great burden of human perinatal brain injury is caused by events occurring either during pregnancy itself or following birth, in the newborn nursery, this should be recognized. In such circumstances, it is probable that the amount of injury occurring in individual cases may be prevented or lessened by recognizing and treating the diseased states associated with the morbid process, whether they be medical conditions of the mother (anemia, cardiac or circulatory disturbances, eclampsia, nutritional deficiencies, and others) or distressed states of the newborn (respiratory distress syndrome, infection, hypoglycemia, jaundice, and so on).

Pathological brain patterns resembling human perinatal brain injury can be produced by subjecting monkey fetuses to prolonged partial asphyxia *at the time of birth,* as I pointed out in my paper. It is suggested by some that this experimental result conflicts in one way or another with the statistical results described above, which suggest that human perinatal injury tends to occur in association with circumstances or events obtaining *outside* the time of birth.

However, this suggestion is not sound. Several instances of brain injury in the monkey have resulted from spontaneous events taking place during pregnancy at some time prior to birth. One case, associated with an incomplete placental abruption, developed an estimated 50 days prior to delivery and exhibited severe cystic degeneration of the brain at the time of birth.[1] More recently, a second monkey infant was delivered after an episode of vaginal bleeding lasting up to six days. There was evidence that the damage might have occurred as early as five weeks before delivery. The brain changes encountered in this second animal closely resembled those produced by episodes of prolonged partial asphyxia as delivered to monkeys at the time of birth.

[1] Myers, R. E. Cystic brain alteration after incomplete placental abruption in monkey. *Arch. Neurol.* In press.

Thus, when fetuses undergo similar episodes of prolonged partial asphyxia either at earlier gestational ages or at the time of birth, similar pathological outcomes result. From this it is seen that the animal experimental data do not contradict the data of the Collaborative Perinatal Study in that similar human-type brain pathological outcomes may occur in relation to insults delivered either during later pregnancy or at the time of delivery.

A few comments should be made regarding the suggestion that the order of magnitude of changes in acid-base and blood gas values required to produce brain damage in the experimental animal are out of the range of values that may be expected to occur even in pathological states in the human. Human fetuses do die *in utero*. Human fetuses dying *in utero* may be expected to exhibit striking changes in acid-base and blood gas values along the way. Some of these fetuses may be expected to survive the period of severe compromise or threatened death. They also would be expected to exhibit striking changes in acid-base and blood gas values during their periods of compromise. However, no one thus far has been able to measure, and hence we do not know, what the blood values may be of such human fetuses threatened with severe compromise or death during middle or late pregnancy.

In the experimental procedures carried out thus far, monkey fetuses have been compromised *in utero* by subjecting the mothers to a variety of stressful states such as the administration of high doses of oxytocin, the production of maternal hypotension, or the induction of hypoxic hypoxia. These stresses have been relatively benign as regards the welfare of the mothers. However, the effects on the fetuses were catastrophic and often resulted in severe brain damage or death, depending on the degree of stress. In view of the mildness of the stresses applied to the mothers in these cases and the relatively naturally occurring mechanisms through which the fetuses sustained their compromise *in utero*, the burden of proof would appear to be on those who suggest that the human fetus is never subjected to such stresses and never experiences the degree of deterioration in acid-base and blood gas values I have described for the experimental animal.

Neel: I had been saving a few remarks, but this seems an appropriate time to introduce them. This is a symposium on perinatal factors affecting human development, so it is only natural the emphasis should be on the various insults that can overtake the pregnant mother or the child during the birth process and how these may have a lasting effect on the child. But as the sole representative of human genetics at this meeting, I should like to stress the etiological complexity of many of the end points we have been discussing as these are seen in man rather than in the experimental animal.

There is not the slightest doubt that there are noxious influences that can forever mark the child, but I submit that, genetically speaking, there are accident-prone mothers and fetuses. Not all mothers on low-protein diets will have children whose IQ is thereby lowered. Not all children with temporary fetal asphyxia develop signs of brain damage. I suggest the obvious—that in the case of a damaged child we are often concerned with the insult falling on prepared soil, which indeed is what Dr. Myers has just been speaking of. Both intrinsic and extrinsic factors are involved, both genetic and nongenetic factors are at work. Yesterday Dr. Birch almost suggested that the geneticist should wait until the environmental factors were all cleaned up and we could get a true picture of genetics. Apparently he expects the millenium before I do.

I suggest that we have to look at both at the same time. By the proper use of sibling and twin data in many of these studies, we can begin to disentangle the genetic from the nongenetic in human development.

Churchill: Perhaps by painting with a broadish brush I can help clear up the anoxic confusion.

To accent points, I shall be purposely a little dogmatic. Viewing the taxonomy of cerebral palsies, one sees that there are six species or more. Athetotic cerebral palsy (CP) of the type that may derive from asphyxia neonatorum is rela-

tively rare, constituting about 6 per cent of the total CP population.

Some years ago, in a study of the athetotic cerebral palsies, I defined two athetotic groups: one with cortical spinal tract signs, the other without such signs but with either deafness or loss of supraversion of gaze. The history of these two groups differed markedly, the associations being quite strong. The former group was associated with fetal distress, the babies requiring resuscitation; the latter was associated with neonatal jaundice, usually from Rh incompatibility.

Apropos of Dr. Windle's work on the combined effect of hyperbilirubinemia and asphyxia on newborn monkey brain, the observations on hybrid athetotic CP cases may be of interest. Several patients had cortico-spinal tract signs combined with deafness or loss of supraversion of gaze, and these patients had both neonatal jaundice and asphyxia.

Neurologists equate athetotic movements with damage to the basal ganglia, especially the corpus striatum. This long-held neurological view has been hard to confirm; experimental lesions placed in the stratum have failed to induce athetosis. However, recently Liles and Davis produced sustained choreic and athetoid movements in cats by placing discrete lesions in the anterior ventral portions of the caudatum in a region stimulation of which inhibits cortically induced movement.

I should like to ask Drs. Windle and Myers whether they observed lesions at this location in their animals, and also how consistently they find signs suggesting athetosis or other signatures of basal gangliar dysfunction in their asphyxiated animals.

Some, myself included, have thought that the lesion responsible for athetotic CP with cortico-spinal tract deficit was perhaps etat marbre, as described by the Vogts years ago, but we have no pathological confirmation. Do chronic lesions in asphyxiated monkeys resemble this?

Plüm in Denmark reported on athetotic CP with findings very similar to those I have described.

Both of us suffer from the possibilities of bias inherent in retrospective studies and also the tyranny of small case numbers, but as yet no one else has come forth with prospectively collected data with which to prove or disprove our hypothesis on the etiology of this particular type of cerebral palsy.

Windle: In our series of monkeys that were asphyxiated and resuscitated at birth, the incidence of athetosis was extremely low and appeared late. I have a motion picture of one very typical athetoid, and that is one of only three seen in a rather large series. I certainly would not hold to the view that cerebral palsy of the athetoid type is the only type related to asphyxia neonatorum. That is an erroneous concept.

All our animals with athetosis had lesions in the putamen, but so did others. We commonly found lesions in the putamen of animals that had not shown athetosis but had other neurological deficits. We found lesions in the basal ganglia fairly commonly in the animals that had been asphyxiated 15 minutes or more. I mentioned an animal asphyxiated for no less than 21 minutes and possibly as long as 24 minutes that was resuscitated; the basal ganglia were entirely gone. It was comatose, of course.

Myers: Dr. Churchill has attempted to describe why the Collaborative Perinatal Study has not uncovered a more clear-cut association between birth complications and injury to the brain by referring to a retrospective study indicating that palsied children with athetosis exhibit an increased incidence of difficulties at birth. Basically, however, this reply does not answer the question but rather seems to highlight the apparent discrepancies that exist between a number of retrospective studies suggesting that such a correlation exists and the results of the Collaborative Study.

I think Dr. Berendes suggested in his presentation that athetosis fails to manifest itself clinically until later than the first year. Is he suggesting that the unexpectedly low correlation between indicators of fetal distress at birth and later brain damage may be due to the late, and hence unappreciated, appearance of signs of brain damage in such cases?

Berendes: We do not identify athetoid children at one year of age. This we expected, and many neuropediatricians felt the same way. We know that of all athetoid children only a small number are identified at one year. Neurological examinations are only done in this program at one and seven years, and not enough children have reached age seven.

It has occurred to me that perhaps we are not really so far apart, in the following sense: We are discussing not so much the sequel of fetal or neonatal asphyxia as the sequelae or natural history of fetal brain damage or of brain damage that presumably has its origin during the period surrounding birth. I do not believe that we really know what is happening to the experimental animals you have been working with and the long-range prognosis of their neurological abnormalities.

I thought that Dr. Windle's comments two years ago and again today were extremely interesting. He has reported marked improvement in these animals neurologically and yet he still observes profound changes in the brain when they are sacrificed.

One other point should be made. When we talk about neurological deficits in man, we have to keep in mind that at least some of them are highly associated with low-birth-weight or early-born children. I do not think that this problem has been approached experimentally in rhesus monkeys. Simple spastic diplegia is a condition that occurs almost exclusively in children weighing less than 1,500 grams.

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

L. Stanley James

Administration of oxygen to the mother

For a number of years there has been some question as to the effectiveness or even safety of administering high concentrations of oxygen to the mother. Doubts were first raised when we were performing nitrogen wash-outs in the mother and fetus by allowing the mother to breathe 100 per cent oxygen for up to 60 minutes prior to cesarean section. At delivery five infants were mildy depressed and had low oxygen saturations in their cord blood (*4*). Later we were unable to demonstrate that maternal breathing of 100 per cent oxygen prior to delivery per vaginam appreciably altered the oxygen level in cord blood (*19*) (Figure 1). Added to these observations, experiments of Nyberg and Westin (*21*) on the isolated placenta indicated that high levels of oxygen in cord blood might even cause the placental vessels to constrict.

However, controlled observations on both the exteriorized fetal lamb (*10, 13*) and the fetal lamb *in utero* (*7, 20*) have demonstrated that both fetal oxygen tension and saturation can be raised when maternal p_AO_2 is increased. Experiments on eight pregnant ewes by Battaglia and co-workers with the ewe under spinal anesthesia and sedated with nembutal showed an average increase in fetal UV pO_2 of 19 mm Hg and in UA of 7 mm Hg; the oxygen saturation increases were greater, averaging 26 per cent in the UV and 21 per cent in the UA (Figure 2). Our own observations with catheters chronically implanted in the fetal lamb have been made with the mother non-anesthetized. The magnitude of increase we have observed is considerably less: 12 mm Hg in the UV and 5 mm Hg in the UA. These differences in results may be due in part to higher control values in the latter study in both mother and fetus, the mother's oxygen levels being 100 per cent and the pO_2s between 95 and 100 mm Hg. Our animals were not anesthetized or sedated.

With a pO_2 electrode implanted in the buttock

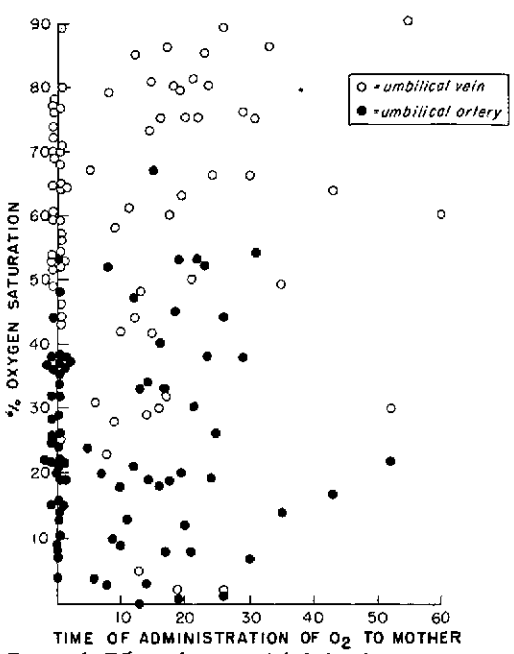


FIGURE 1. Effect of oxygen inhalation by mother upon birth oxygenation of infant.

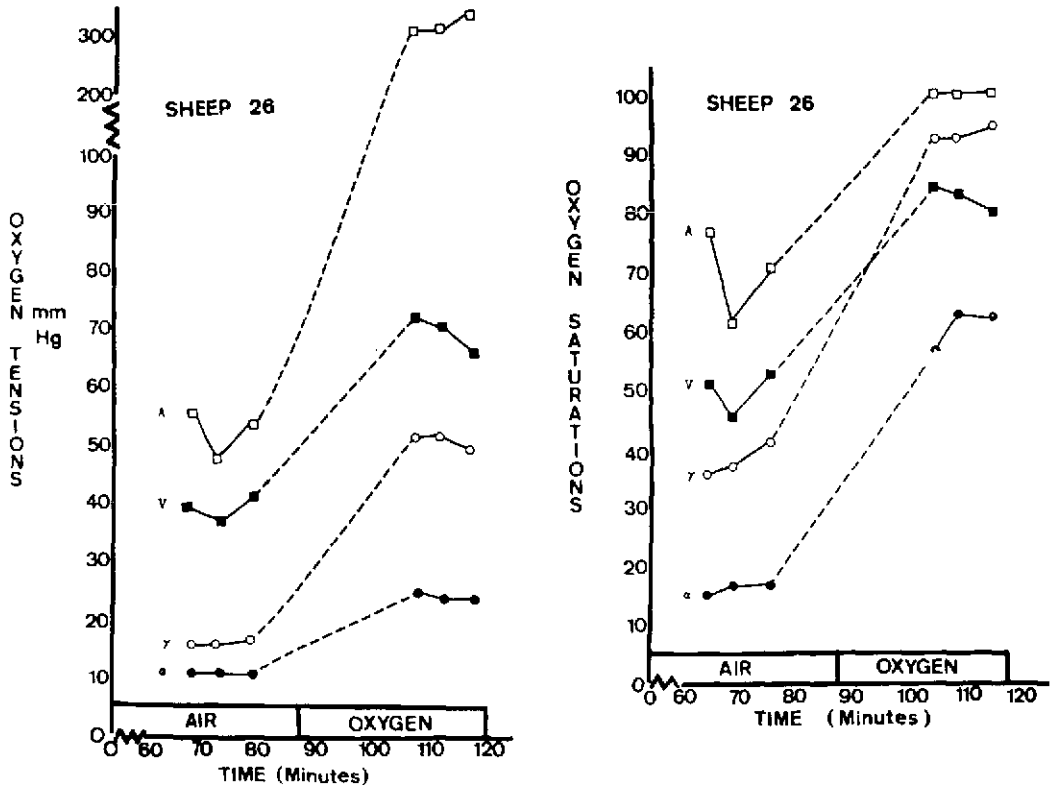


FIGURE 2. Oxygen tensions and saturations in maternal artery (A □), uterine vein (V ■), umbilical vein (γ ○), and umbilical artery (α ●) are presented during periods of air and oxygen inhalation (*7*).

of the human fetus, Caldeyro-Barcia and co-workers have demonstrated a rise in fetal tissue pO_2 with maternal oxygen administration (*11*), and also a reduction or abolition of the type II dips in fetal heart rate.

We have recently verified these observations in experiments on pregnant monkeys during labor; in these it has been possible to sample fetal carotid arterial blood for quantitative measurement of pO_2 and acid-base components. Raising the fetal pO_2 by 5 mm Hg may be sufficient to abolish the heart-rate abnormalities. However, if the uterine contractions are very strong and the fetal condition more compromised, it may not be possible to elevate fetal arterial pO_2 at all, even if the maternal arterial pO_2 is as high as 500 mm Hg. Fetal bradycardia, late deceleration, or type II dips were seen when the fetus was both hypoxic and acidotic. It was of interest, and of some concern, to note that fetal acidosis remained after oxygen administration and abolition of type II dips, and in some instances the acidosis increased when O_2 administration was stopped.

From these clinical and experimental observations several conclusions may be drawn:

1. It is safe to administer high concentrations of oxygen to the mother for the treatment of fetal distress.

2. Fetal oxygenation may be increased by this process and fetal heart rate abnormalities modified.

3. Fetal acidosis is not initially changed by maternal oxygen adminstration and under certain conditions may even become worse.

4. Maternal oxygen administration for the treatment of fetal distress can be considered as supplying temporary relief. The physician should not be lulled into a false sense of security because

fetal heart rate abnormalities have been reversed or modified.

Administration of glucose to the mother

It had been suggested that the intravenous administration of glucose to the mother is a rational treatment for fetal distress, in the belief that this will increase transfer of glucose of the fetus and provide additional substrate for anaerobic glycolysis during fetal hypoxia (*24*).

There are several fallacies in this argument. While it is true that glucose is the main substrate for fetal metabolism, particularly in the brain, and that it rapidly crosses the placenta, it is unlikely that it will cross more readily than oxygen, particularly if the utero-placental circulation is compromised. Furthermore, there is evidence that glucose transfer across the placenta involves active transport and in the human, at least, this process is oxygen-dependent (*22*). Finally, the anaerobic degradation of glucose to lactate is a pH-dependent process; the reaction is slow at a pH of 7.0 and virtually stops below a pH of 6.8 (*8*). Thus, if the fetus is hypoxic and acidotic he is not likely to be able to use his anaerobic mechanisms for energy. There are two circumstances in which glucose administration to the mother will benefit the fetus: (1) when the mother is dehydrated and ketotic or hypoglycemic, and (2) when the fetus is hypoglycemic as a result of placental dysfunction or intrauterine malnutrition. The first circumstance is encountered during prolonged labor, particularly if close attention has not been paid to maternal hydration and caloric requirements. Maternal dehydration acidosis, developing over a period of hours, is accompanied by fetal acidosis. Mild degrees of maternal acidosis do not appear to be associated with fetal distress; more severe degrees, probably associated with some compromise of the maternal intervillous space perfusion, may lead to fetal deterioration. Attention to the mother's caloric and fluid requirement can lead to quite prompt improvement in fetal condition.

The administration of sodium bicarbonate to the mother is also claimed to be of benefit. Evidence for this is less secure, since the bicarbonate ion crosses the placental barrier relatively slowly (*9*). In clinical observations the beneficial effects of fluid and calories have not been separated from the effects of alkali.

Phillips, Wood, and co-workers have recently described several cases of fetal hypoglycemia, two of which were stillborn (*22*). Under normal circumstances, fetal blood glucose determined from scalp samples is approximately 21 mg per cent lower than that of the mother. If it is less than 40 mg per cent (less than 2 standard deviations below the mean fetal level), the fetus may be considered to be hypoglycemic. There are at present no published data on the beneficial effects of administering glucose to the mother in these circumstances, but it is reasonable to assume that it would raise levels of fetal blood sugar. In our own experience we have found fetal hypoglycemia to be very rare (*25*), but in the majority of patients studied, the mothers have been receiving intravenous glucose. A systematic examination of fetal blood sugar in patients at risk is recommended.

Administration of alkali for fetal acidosis

If fetal acidosis is the result of fetal hypoxia and not secondary to derangements in maternal acid-base balance, the administration of alkali to the mother will not improve the fetal state and may be harmful if the mother is rendered alkalotic. As was noted earlier, bicarbonate transfer across the placenta is a slow process, as it is across the blood brain barrier.

The infusion of bicarbonate into the amniotic fluid has been suggested. Experiments in pregnant rhesus monkeys by Seeds and co-workers (*26*) have shown that this will result in elevation of fetal bicarbonate levels if the fetus is in good condition and presumably is able to swallow. Experiments in which the fetus was compromised or deteriorating showed no increase in fetal bicarbonate level. It should be noted that the hypoxic and acidotic fetus ceases to swallow. This is a useful diagnostic sign in erythroblastosis when hypaque is injected into the amniotic fluid to isolate the fetal gut.

Direct intravenous administration of alkali to the fetus has been tried in the fetal monkey by means of chronic catheter preparations (*3*). If the fetus is deteriorating because of hypoxia and acidosis, the infusion of alkali into the fetus can afford temporary relief. However, this again is only a temporary measure. It is not possible to provide sufficient alkali for more than a few minutes without overloading the fetal circulation if the hypoxia persists. When the alkali infusion is discontinued there is a rebound, and the fetus is invariably in a worse condition with regard to blood pressure, heart rate, and acid-base state than before.

Administration of oxygen, alkali, and glucose to the newborn

There is no technical problem in administering oxygen to the asphyxiated newborn except in cases of gross immaturity, obstruction from meconium, congenital anomalies of the lung or tracheo-bronchial tree, or intrauterine pneumonia. Standard resuscitative procedures with intubation and expansion of the lungs followed by artificial ventilation may be readily accomplished.

Correcting acid-base derangements that follow severe intrauterine asphyxia is a more complex problem.

The rationale for rapid correction of pH is based on experiments in newborn monkeys. The maintenance of a normal pH during asphyxia by rapid intravenous infusion of alkali together with glucose prolongs gasping and delays cardiovascular collapse (*1*). Resuscitation is also facilitated if alkali and glucose are infused at the same time as artificial ventilation is started (*2*); oxygen consumption is greater, and the time for establishing spontaneous breathing is shorter. Cardiac massage is less frequently necessary in the treated animals. The infusion of alkali and glucose alone may cause the blood pressure and heart rate to rise and spontaneous gasping to begin. It has been proposed that the beneficial effects of pH correction are derived from a prolongation and acceleration of anaerobic glycolysis, a restitution of the oxygen-carrying capacity of hemoglobin and the responsiveness of cardiovascular muscle to sympathomimetic amines, and a fall in pulmonary vascular resistance due to reduction and carbon dioxide tension.

The beneficial effects of alkali administration both to asphyxiated newborn monkeys and to adults with cardiac arrest suggest that a rapid correction of pH during resuscitation of severely asphyxiated newborn human infants would be of value.

Procedure for infant resuscitation

During resuscitation, every effort should be made to prevent heat loss. This is achieved by placing the infant under a radiant heat lamp. Three people should be available for emergency resuscitation—one for establishing an airway and ventilating the infant, one for cardiac massage and monitoring the heart rate, and one for umbilical catheterization and the administration of alkali. These three people should all be prepared as for a surgical operation with sterile gowns, gloves, and so on. All equipment, including laryngoscope, endotracheal tubes, and stethoscope, should be sterile. The resuscitation area, either a large open bassinet with a warming device or a table also with a warming pad, should be covered with a sterile sheet previously warmed from the overhead heat lamp.

It is of great importance, in resuscitating the severely asphyxiated newborn, that attention first be paid to the establishment of pulmonary ventilation. In brief, the steps should be as follows: establishment and maintenance of a clear airway; expansion of the lungs; continuance of ventilation with 100 per cent oxygen at a rate of 30 to 40 inflations per minute. Ventilation should be interrupted every six or seven breaths and alternated with periods of cardiac massage, the heart being massaged at a rate of 120 beats per minute. Both ventilation and cardiac massage may be carried out by one person; if two people are involved, it is important that they coordinate their actions so that cardiac massage and artificial ventilation are not given simultaneously. This can result in the

production of a pneumomediastinum or a pneumothorax, since ventilation will be done against a compressed tracheobronchial tree. While this has been proceeding, another physician can insert a catheter into the umbilical vein.

Administration of alkali

Ideally, the decision to administer alkali in conjunction with artificial ventilation should be made prior to delivery. Close clinical observation of the obstetric patient at high risk accompanied by electronic monitoring of the fetal heart rate and biochemical evaluation of the fetus by scalp sampling will provide the physician with the necessary information upon which he should plan his resuscitative procedures. Under such circumstances, it has been our experience that the need for emergency correction of deranged acid-base state is much less frequent, since the physician is warned of impending difficulties and is able to expedite delivery. However, there still exist a certain number of cases in which the newborn infant does need special attention at birth—prolapsed cord, severe maternal hypotension, antepartum hemorrhage, unsuspected meconium, and other circumstances. In principle, it is advisable initially to correct the metabolic component of the acid-base derangement only by one-half. The most severely asphyxiated infants—that is, those with an arterial pH below 7.0—will have a base deficit of 26 mEq/l or greater. By means of artificial ventilation alone, the base deficit can be reduced by approximately 10 mEq/l in a matter of five to ten minutes, provided that good alveolar ventilation is achieved and the infant does not remain in circulatory collapse. This change occurs as a result of bicarbonate shift (*14*) and should be taken into consideration in calculations for the initial base administration, in order to avoid overcorrection. In our own practice we aim first to *half-correct* this residual metabolic component of the acidosis. Thus a 3-kilogram infant would receive 8 mEq of base:

$$\frac{\text{base deficit } (26-10)}{2} \times \frac{\text{body weight 3 kg}}{\text{ECV } (3)}$$

This working formula is a gross approximation only, and assumes the ECV to be ⅓ body weight.

At present we recommend sodium bicarbonate rather than tris-hydroxy-aminomethane, because the latter solution, if given in too great a quantity, occasionally causes depression of the respiratory center and arrest of breathing. Sodium bicarbonate, as it is obtained from the ampule, contains nearly 1 mEq/ml (44.7 mEq in 50 ml, 0.9 molar solution). This solution has an osmolality of 1400 and a pH of 7.8. The solution is thus very hypertonic. It should be diluted in equal parts with distilled water to reduce its osmolality to 700 and infused at a rate not greater than 2 to 3 ml/min. If the heart rate is slow and irregular, the infusion should be accompanied by intermittent cardiac massage.

As soon as the infusion is completed, a second catheter should be inserted through the umbilical artery into the aorta and a blood sample taken for analysis of blood gases and acid-base state.

The optimal site for infusion is into the umbilical vein, the catheter being advanced to just beyond the ductus venosus. Our own experimental observations in newborn piglets asphyxiated to the point of circulatory collapse have indicated that this site is safer than the aorta for a relatively rapid administration of alkali (*18*).

Technique for umbilical catheterization

A completely straight, soft plastic feeding tube, if advanced to a distance of 10 cm from the skin surface of the umbilical vein, will lie just beyond the ductus venosus in the inferior vena cava. If the catheter is even slightly curved, it may catch on one of the radicals in the portal system. If there is any tendency for the catheter to bounce back as it is advanced, in all likelihood it is not passing through the ductus venosus. Rapid verification of the correct site can be obtained if the catheter has been previously attached to a strain gauge and a recording polygraph. The moment the ductus venosus is passed, the venous pulsations (a, c, and v waves) can be readily seen, unless there is cardiac arrest.

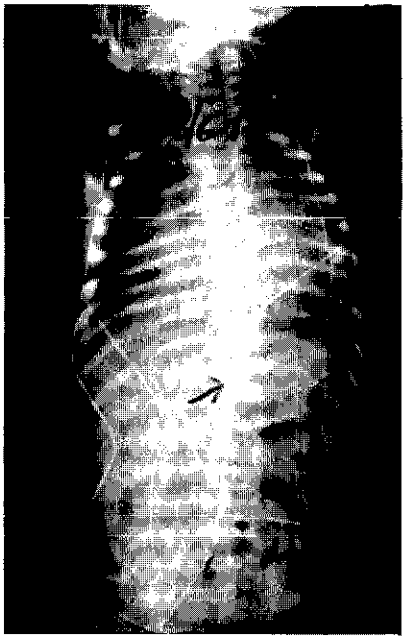
This means of verification of catheter position is more rapid and more suitable for delivery-room treatment than the use of an image-intensifier X-ray.

Technique of arterial catheterization

Only fine catheters should be used (3½ or 5 French). They should be as soft as possible, with a hole in the tip that is softly rounded. They should also be radio-opaque for radiologic localization. The lumen of the artery should be carefully identified after cutting the cord close to the abdominal wall with sharp scissors. Fine, curved nontoothed forceps should be gently placed in the pinpoint clot that usually marks the vessel opening. Pressure on the forceps is then gradually released to allow the natural spring to open the vessel gradually. This procedure is repeated four or five times, the forceps gradually being advanced to a depth of a quarter to a half inch. The catheter may then be introduced and will usually pass readily down to the region of the iliac artery. Occasionally some obstruction is met half an inch from the skin, but this rarely causes any difficulty. If resistance is felt at the entrance into the internal iliac artery, only moderate pressure should be applied. If the catheter will not advance, 0.5 ml of .5 per cent novocaine may be gently infused. This may be sufficient to release any spasm and permit further advancement of the catheter. If this maneuver is unsuccessful and resistance persists, the second umbilical artery should be catheterized. If damage to the vessels is to be avoided, resistance in the region of the internal iliac artery should not be treated aggressively. To avoid traumatic complications, efforts to catheterize should be discontinued if unsuccessful after three attempts.

Once the catheters are in place, a lateral film should be taken to verify position (*6*). The importance of a lateral film can readily be appreciated from Figure 3. In the PA view the catheter cannot be distinguished from the maze of wires attached to the thermistors.

A catheter introduced into the umbilical vein may reach a variety of positions. If advanced far enough, it will pass directly through the ductus



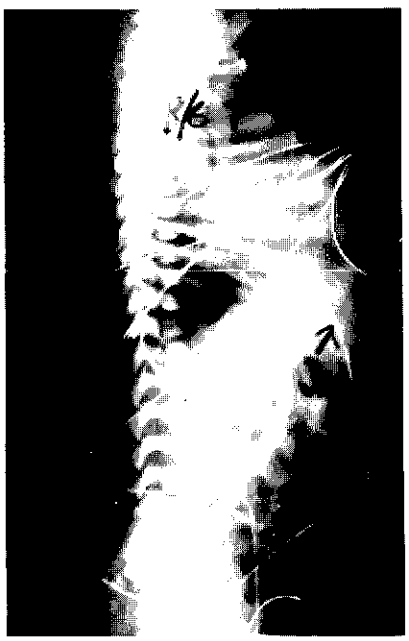


FIGURE 3. A (top), PA X-ray of infant with thermistors and an umbilical catheter in place; Note that maze of wires prevents identification of catheter position in this view. B (bottom), lateral with umbilical catheter in place and maze of thermistor wires attached to skin; this view clearly identifies that catheter has been inserted into an umbilical vein and is lying in portal system in liver.

venosus and foramen ovale into the left atrium (*19*). On the other hand, it may pass into the right or left branches of the portal vein, the superior or inferior mesenteric veins, or even the splenic vein (*6*). Lodged in these areas, catheters can be occlusive to blood flow, and would serve to localize any solutions infused. As was noted above, if the umbilical vein is to be used for the infusion of strong alkaline or hypertonic solutions, the ideal position is just beyond the ductus venosus in the inferior vena cava.

A catheter introduced into the umbilical artery will usually pass into the aorta from the internal iliac artery. Occasionally it will pass down the femoral or into the gluteal artery. The two latter sites are unsuitable for sampling and pressure measurements and also for the infusion of alkali. Either of two positions in the aorta is recommended for the catheter placement—in the lower abdomen below the renal arteries and inferior mesenteric artery or just above the diaphragm. If left in the internal iliac or the region of the aortic bifurcation, the chances of arterial spasm appear to be increased.

The status of the circulation is obviously of great importance when hypertonic or strongly alkaline solutions are administered. For this reason, the relatively rapid-moving blood stream of the aorta is probably a safer site than the liver. From a clinical point of view, blood flow can be fairly reasonably assessed from blood pressure and, if low, can be supported by cardiac massage during injection (*18*). However, as was noted above, we favor administration through the umbilical vein, the catheter being advanced just beyond the ductus venosus.

Subsequent alkali administration

The infant's response to alkali administration will vary according to the degree of asphyxia, the effectiveness of ventilation, and the responsiveness of the cardiovascular system. It is important, therefore, to have a measurement of his acid-base state as soon as the initial dose of sodium bicarbonate has been given. This can usually be made by 15 minutes of age. The required amount of sodium bicarbonate for subsequent correction to a pH of 7.3 may then be calculated.

Complications from umbilical catheterization

Acute complications

False lumen and perforation. If the lumen of the constricted artery is not localized accurately it is possible to create a false lumen in the wall of the vessel. This may be erroneously interpreted as spasm when obstruction is met in the region of the internal iliac artery. If the catheter being inserted is rigid, the vessels may be perforated at this point, the catheter passing into the abdominal cavity. If undue force is exerted, even with a soft catheter, it may track extraperitoneally and result in retroperitoneal hemorrhage.

Blanching of the limb or alteration in pulse. This complication occurs in approximately 5 per cent of infants. It appears to be directly related to the relative size of the catheter in the aorta. The signs will usually disappear upon removal of the catheter. We do not advocate warming the contralateral limb in an effort to cause vasodilatation of the affected limb. If the limb blanches, the catheter should be removed promptly.

Accidental hemorrhage. This appears to be associated essentially with inexperience. The incidence is negligible when physicians and nursing personnel are accustomed to the use of stopcocks and connections.

Infection. The incidence of infection is difficult to evaluate, since most infants who have been catheterized have been placed on antibiotics.

Serious complications at necropsy

Table 1 summarizes the data on mortality and necropsy complications from five centers (*5, 12, 15, 17, 27*). The incidence of serious complications at necropsy is surprisingly low, ranging from 1.5 per cent to 7 per cent, and appeared as a significant cause of death in only 8 cases out of 478 infants.

The lesions include embolization, thrombosis of hepatic vein and liver necrosis, aortic thrombi, and infarcts. Of these, aortic thrombi were the

TABLE 1. Mortality and major complications from umbilical artery catheterization of sick infants in five medical centers (*23*)

INSTITUTION	NO. INFANTS	MORTALITY	MAJOR COMPLICATIONS (NECROPSY)	INCIDENCE (%)
Vanderbilt University (*15*)	317	103	6/92	2
Hammersmith Hospital (*17*)	335	148	5/144	1.5
Boston Lying-In Hospital (*12*)	387	93	18/86	4.5
Sick Children's Hospital, Toronto(*27*)	233	88	4/58	2
Babies Hospital, New York (*5*)	140	46	10/45	7

most common and were related in most cases to the duration of the catheterization. In the Boston series, 8 of 18 cases had thrombi, and all were catheterized for a prolonged period (average time 50 hours, the longest being 192 hours). The size of the catheter and the position in the aorta also appear to be related to the complication. A serious complication observed at Babies Hospital has been thrombosis of the renal arteries and renal shutdown leading to death. In newborn monkeys where the aorta is relatively small, occlusion of the inferior mesenteric arteries by the catheter with infarction of the bowel has been observed. The presenting sign for this complication has been bloody stool.

The tonicity and pH of solutions administered are additional contributing factors. Hemorrhagic necrosis of the liver has been observed in asphyxiated newborn infants (*16*) and newborn monkeys (*1*) treated with strong alkalis (sodium carbonate or THAM). It was found that if the pH of THAM was lowered from 10.4 to 8.6 by titration with HCl, the hypertonic solution could be administered safely. In relating liver necrosis to catheterization and the infusion of hypertonic solutions, it should be recalled that this complication also occurs following severe asphyxia alone.

Although catheterization of the umbilical vein and artery are relatively simple maneuvers and allow easy infusion of fluids or blood sampling, the procedures are not without hazard. Complications relate to trauma during insertion, the duration of catheterization, the size of the catheters used, the state of the circulation when solutions are being infused, and the pH or tonicity of the solutions infused. Although the incidence of complications is relatively low, the procedure is not recommended as an easy route for therapy and should only be used in very ill infants when monitoring is essential for diagnosis and therapeutic management.

Conclusion

While the administration of alkali during resuscitation may be a life-saving procedure for the most severely asphyxiated infant, it is not without hazard. By paying greater attention to clinical, electronic, and biochemical monitoring of the fetus during labor, the incidence of severe asphyxia at birth and the need for emergency resuscitative procedures will both be greatly reduced.

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A NEW APPROACH TO THE TREATMENT OF ACUTE INTRAPARTUM FETAL DISTRESS[1]

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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 (*4*). 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 (*3, 22*). Sometimes the contractions may also compress the umbilical vessels and reduce the flow of fetal blood through the chorionic villi (*14*). Both mechanisms lead to reduced feto-maternal exchanges and result in fetal hypoxia, hypercapnia, acidosis, and other homeostatic disturbances (*1, 19*). The measurement of pH, pO_2, and base deficit in fetal blood microsamples (Saling's method) (*25*) makes possible an early diagnosis of AIFD. This diagnosis can also be made by monitoring the appearance of dips II (*11, 19, 20, 21*), typical changes in fetal heart rate (FHR) equivalent to the "late decelerations" described by Hon (*15*).

Once the diagnosis of AIFD is made, the usual therapeutic approach is to administer oxygen (*2*) and glucose to the mother and, if no improvement is obtained, to deliver the fetus as soon as possible, either by cesarean section or by the vaginal route, according to the obstetrical conditions present. The results are not always good; in many instances the newborns are depressed, have a low Apgar score and a marked acidosis, and may require reanimation, tracheal intubation and artificial respiration, intravenous injections of bicarbonate, or TRIS. Many die despite all this treatment or, if they survive, show irreversible damage (*4, 7, 13*) particularly to the central nervous system.

The pathophysiology of the condition (*4, 5, 23*) has led to a new approach to the treatment of AIFD. Preliminary results of its application are reported in this paper. The bases of this new approach are (1) *the inhibition of uterine contractions,* which should augment the flow of blood through the placenta and increase the metabolic exchanges between the fetus and the mother, thus progressively correcting the disturbances in fetal homeostasis; and (2) *the postponement of delivery* until normal homeostasis has been restored, the expectation being that if the fetus has fully recovered *in utero* it will be born in vigorous condition, with a high Apgar score, and will not require resuscitation.

The drug employed for inhibiting uterine contractions is Orciprenaline (12, 17, 22);[3] the chemical formula is shown in Figure 1. It is a derivate of epinephrine in which an isopropyl radical has replaced one H of the amino group and the two hydroxyls in the phenyl group are in positions 3 and 5 instead of in positions 3

[1] Support received from grant PR/URU/4101 of the Pan American Health Organization/World Health Organization.

[2] Presented by Dr. Caldeyro-Barcia.

[3] Alupent®, manufactured by Boehringer Ingelheim.

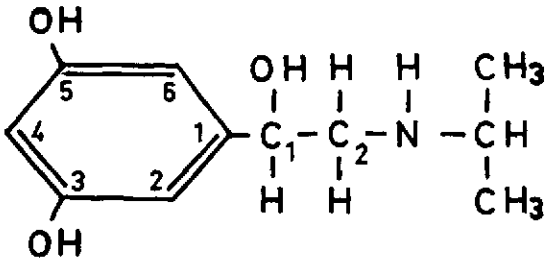

FIGURE 1. Chemical formula of Orciprenaline (Alupent®).

and 4. These structural changes enhance the stimulating effects on the beta adrenergic receptors.

Orciprenaline is administered by continuous intravenous infusion at rates of 20 to 30 μg a minute. Such dosages are usually sufficient to reduce uterine activity markedly in parturient women without producing undesirable side effects like arterial hypotension or severe tachycardia (*17, 24*), which may occur with higher dosages.

Figure 2 shows records of uterine contractions and FHR obtained in one case of very severe AIFD that was treated according to the approach described. The patient was a primigravida with 43 weeks of amenorrhea. Labor started spontaneously at hour 00:00. At hour 3:30, when cervical dilatation was 5 cm and the fetal head was in station –2, the membranes were artificially ruptured. At hour 3:55 a typical AIFD syndrome (*9, 10, 11*) developed in the FHR tracing, which showed a dip II following each uterine contraction. The pH of the fetal blood measured at hour 4:29 was 7.03—a very low value indicating severe fetal acidosis. The diagnosis of very severe AIFD was thus confirmed by two methods of assessing fetal condition. It should be noted that meconium was absent from the amniotic fluid, which shows the unreliability of this sign for the diagnosis of AIFD.

At hour 4:34 (Figure 2A) the intravenous infusion of Alupent was started, at the rate of 20 μg a minute; it was continued at the same rate for one hour. The uterine contractions were markedly inhibited; their average intensity, which had been 45 mm Hg before the infusion,

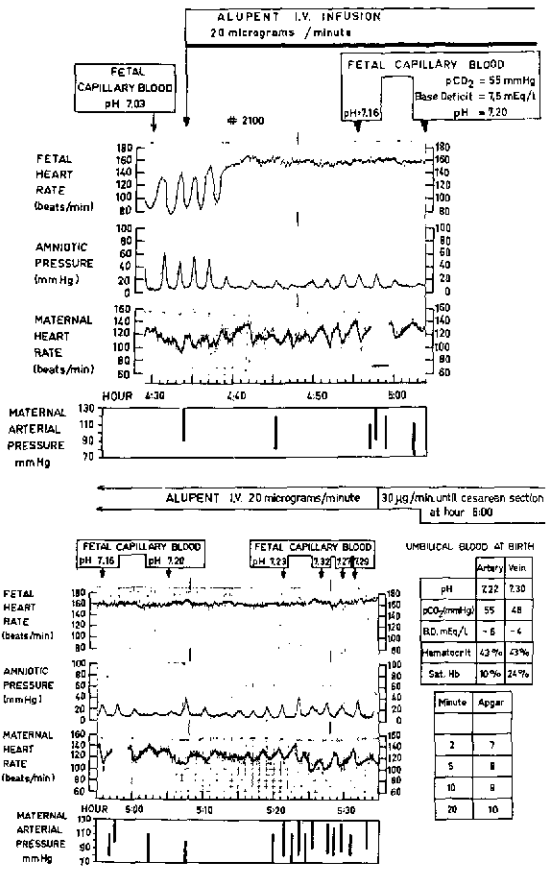

FIGURE 2. Records obtained in case of extremely severe AIFD, with marked acidosis (pH = 7.03) and dips II in FHR tracing. A (top): infusion of Alupent to mother inhibited uterine contractions and improved fetal conditions. B (bottom): Infusion was continued until cesarean section. Fetal pH recovered progressively to normal values. Records were discontinued at hour 5:35, to move patient to operating room. At right, umbilical-vessel blood samples obtained at birth and serial Apgar scores.

was reduced to 10 mm Hg during the first 30 minutes of administration of the drug. In the following 30 minutes uterine activity increased very gradually, indicating that the myometrium was partially escaping from the inhibitory influence of the drug (Figure 2B), but it remained well below the pre-infusion values at all times during the infusion.

Dips II disappeared from the FHR tracing as soon as the contractions became too weak to hinder maternal blood flow through the placenta.

The baseline FHR became slightly tachycardic (155–160 beats/min) during the first 30 minutes of the infusion and rose slowly to 165 beats/min during the next 30 minutes. This mild tachycardia is interpreted as a direct effect of Alupent on the fetal heart.

The pH of the fetal blood (Figures 2 and 3) increased progressively. It was 7.16 at hour 4:55, 20 minutes after the onset of the infusion, and 10 minutes later (hour 5:05) it had reached 7.20, which is the lowest limit of the normal range. It continued to rise, and in 20 minutes more (hour 5:25) had reached perfectly normal values (7.27 to 7.32), which were confirmed in three samples obtained between hours 5:25 and 5:32. Although no more samples were obtained between hour 5:32 and delivery at hour 6:00, it apparently remained within the normal range, since the blood sampled at birth from the umbilical artery and vein had normal pH values.

The remarkable improvement obtained in the pH of fetal blood is graphically illustrated in Figure 3. To the author's best knowledge, this is the first case reported of a complete recovery to a normal pH obtained *in utero* in a human fetus affected by severe acidosis during labor.

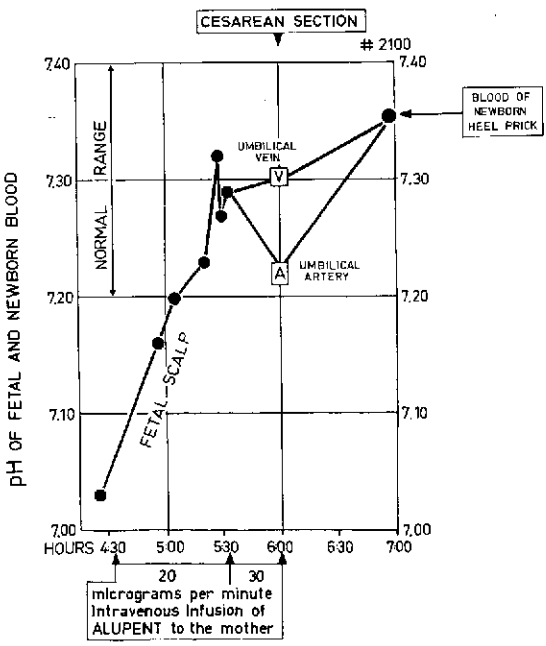

FIGURE 3. Values of fetal blood pH in same case illustrated in Figure 2. Initial extreme fetal acidosis was corrected by administration of Alupent to mother.

The infusion of Alupent at the rate of 20 μg a minute produced no significant changes in maternal arterial pressure, but it did cause a rise in maternal heart rate to 120 beats/min (Figure 2); this tachycardia caused no subjective symptoms in the mother, and the maternal ECG showed no other abnormal changes.

At hour 5:35 the recording of uterine contractions and of fetal and maternal heart rates was discontinued and the patient was transferred to another room for cesarean section. Alupent infusion was continued at the rate of 30 micrograms per minute until the moment of sectioning the uterus.[4] The infant was delivered at hour 6:00 in good condition, as is shown by the serial Apgar scores (7, 8, 9, and 10 at the second, fifth, tenth, and twentieth minutes of life) and by the composition of the blood obtained from the umbilical vessels clamped at the time of delivery.

The newborn weight was 3,400 grams and the crown-heel length 50 cm. The infant was thoroughly examined at birth and also at the first, third, and thirtieth days of life. EEGs were obtained at one, eight, and thirty days of life. All the examinations and EEGs were normal. The excellent outcome of this labor is much better than could have been expected if the classical approach had been employed for the treatment.

From previous work (*6, 8*) it can be predicted that if the conditions existing between hours 4:00 and 4:35 (dips II and severe fetal acidosis) had persisted uncorrected for more than 60 minutes, the fetus would have died *in utero,* from acute intrapartum asphyxia. If delivered alive, the newborn would have been severely depressed, requiring tracheal intubation and artificial respiration and intravenous injection of bicarbonate and glucose. If it had survived,

[4] Because of uterine relaxation and vasodilation caused by Alupent, severe maternal hemorrhage may occur after separation of the placenta. To prevent this complication the infusion should be discontinued before the uterus is sectioned and a potent oxytocic drug should be administered immediately after delivery of the fetus.

the likelihood of permanent brain damage and pulmonary complication would have been very high (8, 9, 13). Had an emergency cesarean section been performed, for example at hour 4:35, the infant would still have been severely depressed, although the damage would have been less because of the shorter period of intrauterine asphyxia.

Figure 4 illustrates another case of AIFD treated with Alupent. The records were obtained in a multipara with a prolonged pregnancy (43 weeks of amenorrhea), in whom labor started spontaneously at hour 00:00. Membranes were ruptured at hour 3:05. At hour 3:25 cervical dilatation was 7 cm and the station of the fetal head was –2. All uterine contractions in which the amniotic pressure at the peak was higher than 60 mm Hg produced dips II, indicating the presence of AIFD. A severe fetal bradycardia (80–90 beats/min) started at hour 3:49 and lasted four minutes. Treatment with an intravenous infusion of Alupent at the rate of 20 μg a minute was started at hour 3:52. The contractions were markedly inhibited, the full effect being obtained three minutes after the start of the infusion. The dips II disappeared as soon as the intensity of the contractions diminished. The baseline FHR, which was tachycardic (160 beats/min) before treatment, slowly descended toward normal levels and in 12 minutes was 140 beats/min. At hour 4:05 the recording of FHR, uterine contractions, and maternal arterial pressure was discontinued so that the patient could be transferred to the operating room. The administration of Alupent was continued.

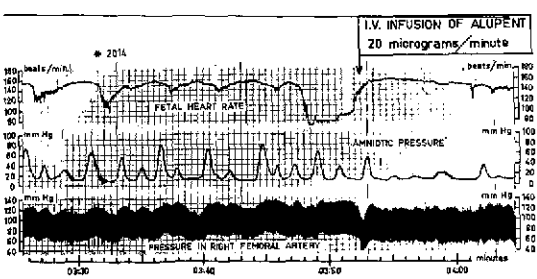

FIGURE 4. Records obtained in case of severe AIFD diagnosed by dips II and prolonged bradycardia at hours 3:48 to 3:52. Administration of Alupent to mother inhibited uterine contractions and FHR recovered normal pattern. Recording was discontinued at hour 4:05, to move patient to operating room. Alupent administration was continued until sectioning of uterus. Fetus was delivered at hour 4:42 in good condition.

The infant was delivered by cesarean section at hour 4:42 with Apgar scores of 9, 10, and 10 at the first, fifth, and tenth minutes of life. The newborn weight was 3,900 grams and the crown-heel length 52 cm. Thorough examination of the infant during the first 18 months of life showed no abnormalities whatsoever.

Discussion

From previous work (*6, 8, 18*) it is known that newborns are usually depressed and have a low Apgar score when signs of AIFD (dips II in the FHR tracing, pH of fetal blood below 7.20) have consistently been found during the hour preceding delivery. Both fetuses reported here, if delivered at the time when these signs were present, would most probably have been severely depressed. On the other hand, prolonging the period of AIFD without effective treatment leads to aggravation of the condition and eventually to intrapartum death.

In both cases reported here the excellent condition of the newborns was attributed to the recovery period of 50 to 80 minutes during which the uterine contractility was inhibited and the fetuses were able to restore normal homeostasis.

This approach to the treatment of AIFD has some advantages over other current therapeutic methods:

1. It suppresses a known factor in fetal asphyxia—the uterine contractions—and does so very rapidly, in two or three minutes after the Alupent infusion is started.

2. Normal homeostasis is restored by increasing feto-maternal metabolic exchanges through the placenta, which is the organ best suited to the purpose. In contrast, artificial pulmonary ventilation of a depressed newborn is very effective in correcting hypoxia and hypercapnia but is unable to modify, for example, metabolic acidosis or exhaustion of carbohydrate reserves. To correct such disturbances the newborn needs an

intravenous infusion of glucose, bicarbonate, or THAM or other treatment.

3. The other procedures—tracheal intubation of the newborn, positive pressure pulmonary ventilation, catheterization of the umbilical vein, injection of glucose and bicarbonate—all require skilled personnel and are not entirely innocuous (*16*).

Acknowledgment

The authors wish to acknowledge the technical cooperation of Doctors R. Portes, J. Molero, A. Fernández, A. Bal, B. Rodríguez, G. Delard (fellows of the Pan American Health Organization), R. López Canales and J. Barrios Amaya (fellows of the Second Latin American Course in Biology of Reproduction), S. Melander (fellow of the Population Council), L. Bermeo (fellow from the University of Guayaquil, Ecuador), and L. Novick (fellow from Evanston Hospital, Illinois, U.S.A.).

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