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DISTURBANCES IN FETAL HOMEOSTASIS
WITH SPECIAL REFERENCE TO THE CONSEQUENCES ON PERINATAL
MORTALITY AND CHILD HEALTH

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**DISTURBANCES IN FETAL HOMEOSTASIS WITH SPECIAL REFERENCE
TO THE CONSEQUENCES ON PERINATAL MORTALITY AND CHILD HEALTH.**

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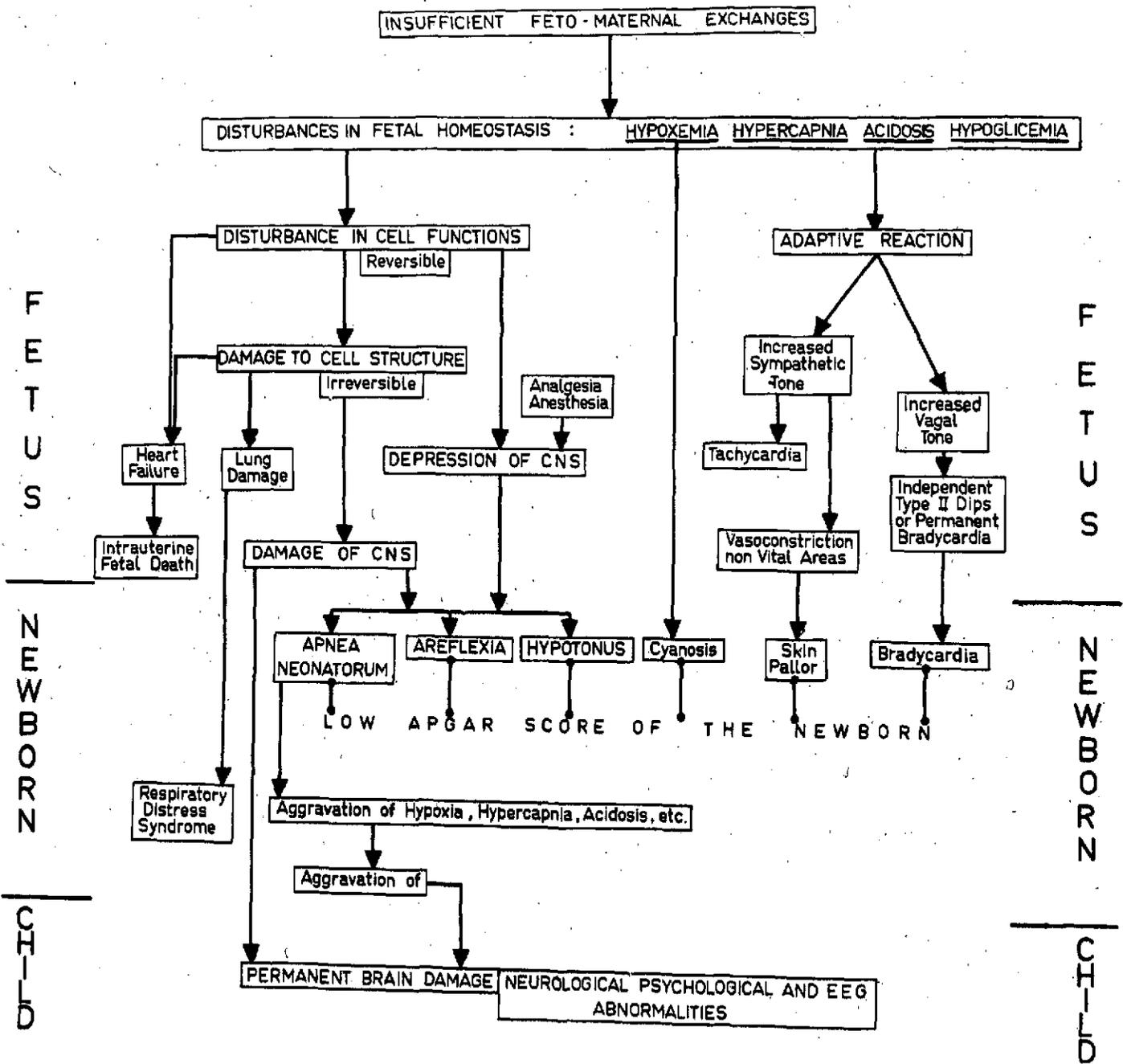


Figure 1. Diagram showing the factors studied in the present report and their interrelations.

A COMPREHENSIVE APPROACH (Figure 1)

When the exchange of nutrients between fetus and mother becomes insufficient to fulfill the metabolic needs of the conceptus, fetal homeostasis is disturbed and the composition of fetal blood becomes abnormal (hypoxemia, hypercapnia, acidemia, hypoglycemia, etc.).

Cell functions are first disturbed in a reversible manner; then at more severe stages cellular alterations become irreversible and associated with structural damage leading to death of the cells.

The depression of or damage to the Central Nervous System explains the apnea neonatorum, areflexia, and hypotonus of a newborn with low Apgar score. (Similar signs may be produced by overdosage of analgesics or anesthetics given to the mother). The damage to the CNS is irreversible and usually becomes evident later in the life of the child as neurological, psychological and EEG abnormalities.

Apnea neonatorum, if not corrected promptly, aggravates the hypoxia, hypercapnia and acidosis in the neonate and thus increases the brain damage.

Lesions caused to the fetal lung in utero may be responsible for the appearance of the Respiratory Distress Syndrome in the newborn.

The fetal myocardium receives preferential protection from the adaptive response of the fetus which accounts for fetal survival with little myocardial impairment despite important damage to the CNS, lungs and other organs. Only after these protective reactions have been overcome does the myocardium fail and intrauterine fetal death occur.

On the other hand, homeostatic disturbances elicit adaptive, defensive reactions of the fetus. Prominent among these are the cardiovascular reactions which include vasoconstriction in the non vital areas (skin, muscles, etc.) and increased circulation in the more important areas (myocardium, brain, placenta). The adaptive reactions also include characteristic changes in heart rate, which are very useful for the clinical diagnosis of intrapartum fetal distress.

The low Apgar score of the newborn is made up of signs which indicate depression of the CNS (apnea, areflexia, hypotonus) combined with other signs (bradycardia and skin pallor) resulting from strong defensive reactions. Both groups of signs are the consequence of severe disturbances of fetal homeostasis.

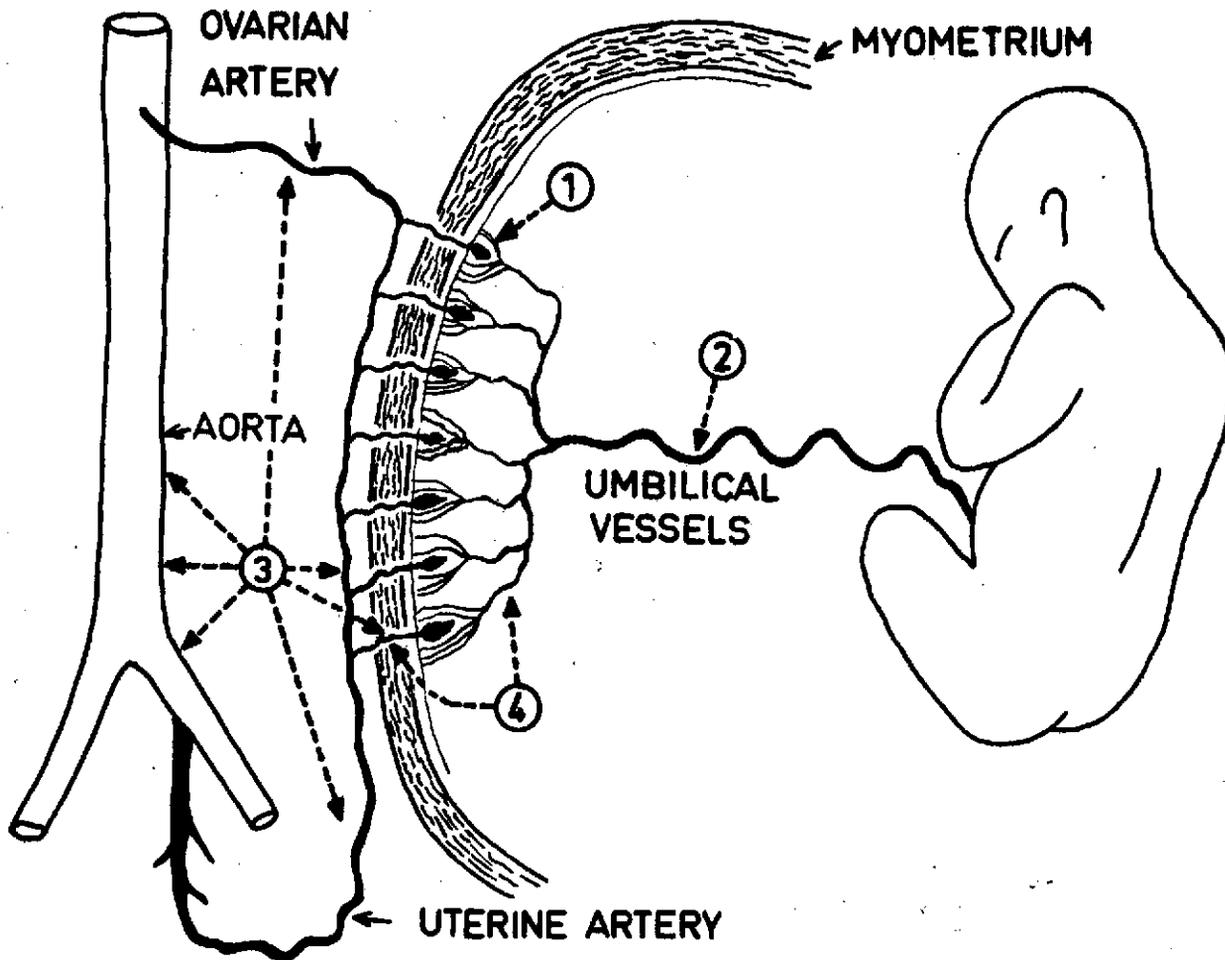


Figure 2. Location of the basic pathogenic mechanisms which may reduce metabolic exchange between mother and fetus. The numbers correspond to the text in the opposite page.

I. STUDIES IN THE FETUS

A) Pathogenesis of disturbances in fetal homeostasis

The maintenance of a normal homeostasis is a basic requisite for the proper functioning of fetal cells and the growth of the fetus. Fetal homeostasis is largely dependent on metabolic exchanges with the mother through the placenta.

The abnormal reduction of these exchanges causes a diminution in the supply of anabolites to the fetus and a retention of catabolites. Complex alterations occur in the composition of fetal blood.

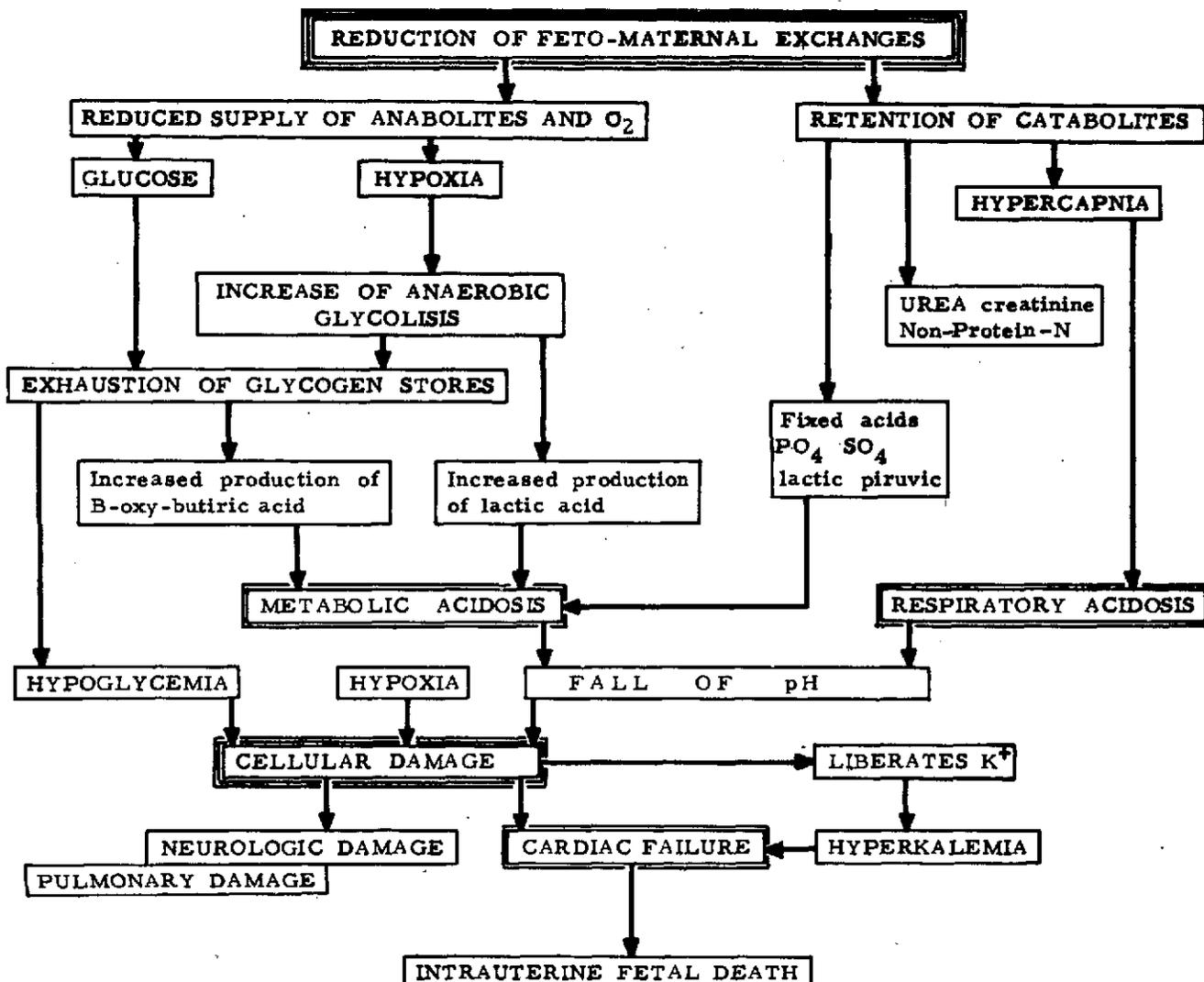
Insufficiency of feto-maternal exchanges may be produced by several mechanisms (70) such as: (Fig.2)

- 1) Placental lesions (infarcts, edema, etc.), which reduce the exchange capacity of the organ (69,150).
- 2) Diminished flow of fetal blood through the chorionic villi, which may be caused by:
 - a) compression of umbilical vessels by the contracting uterus (10,31,33,34,44);
 - b) vasoconstriction of umbilical vessels and their branches (11,112,151);
 - c) failure of fetal circulation.
- 3) Diminished flow of maternal blood through the IVS of the placenta, which may be caused by:
 - a) uterine contractions of labor which reduce maternal blood flow through the placenta by compressing the intramyometrial part of the vessels supplying the IVS (6,7,19,22,23,24,29,30,33,34,47,120,128,129); in addition, when the woman is in the supine position, also by compressing the abdominal aorta and common iliac arteries against the spine (19,98,121,122).
 - b) Reduction of lumen of uterine arteries and their branches, (arcuate, spirals) as in toxemia of pregnancy, chronic hypertensive disease, arteriosclerosis, etc. (18,47,58,59,65,100,105). Lack of arterial blood supply from the ovarian artery which normally anastomoses with the uterine artery.
 - c) Maternal arterial hypotension, which reduces the pressure of the blood perfusing utero-placental vessels, and facilitates their compression by uterine contractions (13,14,15,16,60,68,77).
- 4) Lack of correlation between the maternal and fetal blood flow in their respective distribution between the several cotyledons of the placenta (91,92,123,124,130).

B) Alterations occurring in the composition of fetal blood (Figure 3)

Although the concentration of all components of fetal blood may be altered, up to date only a few of them have been studied in the human fetus "in utero". Attention has been focused on some of the compounds which are related to the process of energy liberation in the cells, and also to the acid-base balance. The variables usually measured in human fetal blood ("in utero") (135, 136, 138) are Hb saturation, pO_2 , O_2 contents, pCO_2 , pH, Base Deficit, Buffer Base, Standard Bicarbonate, glucose, lactate, pyruvate, potassium ion, etc. (25, 89, 115, 116, 141).

Reduction in feto-maternal exchanges results always in one-way alterations of each component of fetal blood, namely those changes resulting from reduction in the supply of anabolites and from retention of catabolites (70). Examples of such alterations are a fall in Hb saturation, O_2 contents, pH, glucose, a rise in CO_2 , urea, creatinine, non-proteic Nitrogen, fixed acids (lactate, pyruvate) and increased Base Deficit.



C) Tissue damage resulting from disturbed homeostasis (Figure 3)

1) Mechanism. Although any change in blood composition may potentially disturb cell function, some variations have more important consequences than others. For example, a rise in the concentration of urea has little noxious effect "per se", whereas a fall in pH markedly affects several enzymatic systems of the cells (54, 82). Hypoglycemia may reduce the supply of the most suitable source of energy for tissues. Severe hypoxemia may lead to tissue hypoxia: the resultant increase in anaerobic glycolysis maintains energy liberation in the cells (and life) during hypoxia, but has two undesirable side effects: a) metabolic acidosis (57, 90, 93, 96); b) waste of glucose and exhaustion of glycogen stores (49, 56, 107).

When fetomaternal exchanges are insufficient for the metabolic needs of the fetus, hypoxemia, hypercapnia, acidosis, hypoglycemia, etc. occur simultaneously and probably add, (or even mutually enhance) their noxious effects on the cells; this is the biological substratum of the condition clinically known as "fetal distress" (36, 37, 38, 70).

2) Functional disturbance leads to structural damage. In early stages the disturbances in cell function are reversible. When they become too marked and excessively long-lasting, they lead to irreversible structural damage to the cells, tissues and organs. An example is the permanent brain damage which may be produced in the fetus by marked and prolonged disturbances in homeostasis (55, 153). (Fig.1).

It follows that disturbances in fetal homeostasis should be recognized and corrected before irreversible damage has occurred. There are signs which enable the clinician to make the early diagnosis of fetal distress; the most useful among them are the changes in FHR and in the pH of fetal blood (33, 36, 89, 135) which will be described below.

Once diagnosed, disturbances in fetal homeostasis should be corrected as soon as possible in order to prevent further damage. If this correction is not possible, the fetus should be delivered with the minimum delay and the composition of the blood of the newborn restored to normal as soon as possible (by pulmonary ventilation, i.v. injection of glucose and base).

D) Defensive reactions of the fetus (Figure 4)

Disturbed homeostasis damages fetal cells by the mechanisms explained above. If no defense reactions were present, fetal death would occur within a relative short time because of myocardial failure due to the combined effects of hypoxemia, hypercapnia, acidemia, hyperkalemia and exhaustion of glycogen stores in the myocardium. (Fig.3)

Disturbances of fetal homeostasis elicit defensive responses (Fig.1) which tend to minimize the cell damage in the vital organs and to prolong the survival of the fetus under these adverse conditions (36, 40, 141). Cardiovascular reactions are prominent and will receive special attention in this paper. Most of the responses are integrated by the CNS and they include:

A) Long-lasting, prolonged stimulation of the sympathetic system (Fig.4) which is responsible for the tachycardia and for the vasoconstriction occurring in the non-vital areas of the fetus.

B) Transient stimulations of the vagus nerve, occurring after each uterine contraction. Each of these vagal stimulations causes a transient fall of fetal heart rate (Type II dip).

We shall analyze first the vasomotor changes and the resulting redistribution of blood flow and second, the changes in fetal heart rate.

1) Vasomotor reactions - Cardiovascular defensive mechanism include:

A) Vasoconstriction of the non vital areas of the fetus i.e. those which are not indispensable for the immediate survival of the fetus such as the skin, skeletal muscle, lungs, abdominal viscera, etc. Blood flow is greatly reduced through these areas and so is oxygen consumption. (Oxygen saving mechanism - described by Saling).

The ischemic organs may be damaged since they survive by increasing anaerobic metabolism with augmented production of lactic acid. The resultant metabolic acidosis is more marked in the ischemic organs but it reflects also on the circulating blood. For example, pulmonary ischemia damages cells in the fetal lung facilitating the subsequent appearance of the Respiratory Distress Syndrome in the newborn.

B) Vasodilatation and increased blood flow in the vital areas: placenta, myocardium, CNS.

Umbilical vessels have no vasomotor nerve supply and are dilated by the direct effect (on the vascular wall) of hypoxia.

Since arterial pressure is normal or high (at least in the early stages of fetal homeostatic disturbance) the flow of fetal blood through the umbilical vessels and chorionic villi of the placenta is increased (56). This defensive reaction tends to augment fetomaternal exchanges and thus to restore normal fetal homeostasis. (At this early "defensive" stage of fetal distress the heart rate is usually tachycardic.)

At very advanced stages of fetal distress this defensive mechanism is no longer present and umbilical blood flow diminishes because of failure of fetal circulation; the umbilical vessels are closed (79) and the heart rate shows the "pre-mortem" bradycardia.

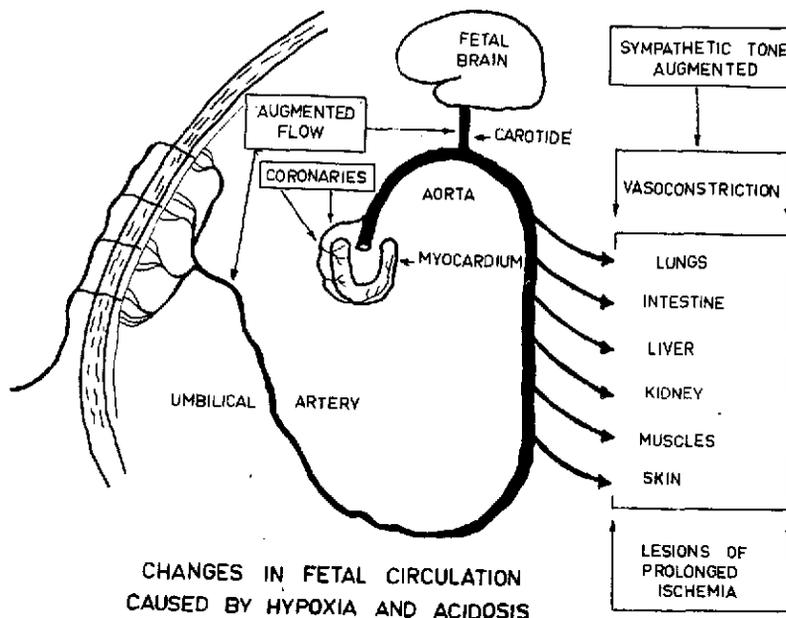
Coronary vasodilatation is probably due to increased sympathetic tone, and to the direct vasodilator effect of hypoxemia on the vascular wall.

Coronary blood flow increases and the resultant protection of the myocardium explains why the fetal heart continues to beat almost undamaged (as shown by the normal ECG) at a time when many severe lesions are already present in other less privileged areas of the fetus (17, 148).

Abnormal changes in the ECG appear very late, usually in the pre-mortem phases of "fetal distress" at the time of terminal cardiac failure (with bradycardia) preceding fetal death.

Cerebral blood flow increases, at least in early stages of fetal asphyxia, (56) probably because of the rise in arterial pressure. Cerebral flow declines in more advanced stages of fetal distress.

Protection to the brain is less efficient than defense of the myocardium; after a period of intense asphyxia lasting more than 12 minutes the full term monkey fetus may survive and the heart is apparently undamaged, whereas the brain has severe lesions.



D) Defensive Reactions of the fetus (continuation)

2) Changes in Fetal Heart Rate (FHR). The cardiovascular defense reactions of the fetus to disturbance in homeostasis include two characteristic changes in heart rate:

2-1) A rise in the Baseline: Tachycardia. In normal condition the mean Baseline FHR is 143 beats/min (S.D. 11 beats/mean). In intrapartum fetal distress the mean Baseline FHR is 165 beats/min. (S.D. 12 beats/min) (36,37,38,39,40).

2-2) Each uterine contraction causes a type II dip, i.e. a transient fall in FHR which occurs after the contraction in such a way that the bottom of the dip is recorded 30 to 60 seconds after the peak of the contraction. (Fig.5).

In mild fetal distress tachycardia may be the only change in FHR. In severe distress the high Baseline FHR is usually associated with type II dips (Figs.5 and 6B). In very severe conditions type II dips overlap with each other and the tachycardia may be masked

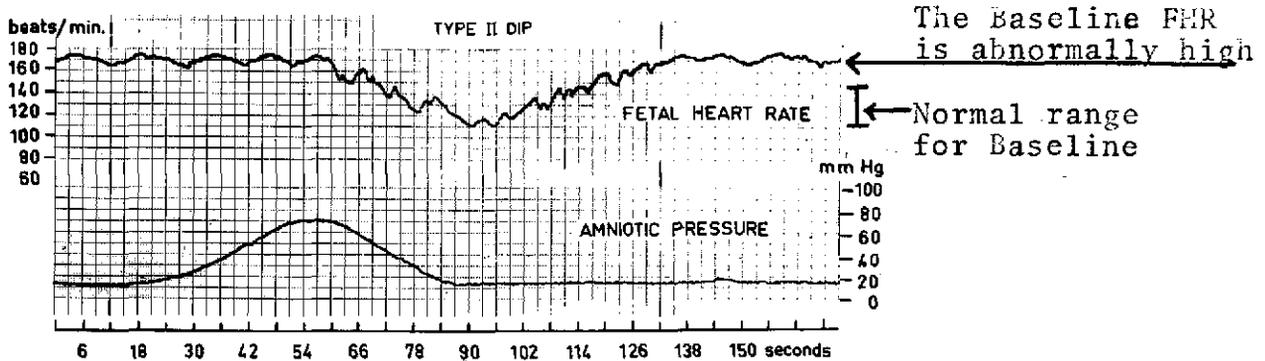


Figure 5. Typical pattern of FHR in severe fetal distress during labor. High Baseline combined with type II dip.

Recording paper at high velocity (10 cm per minute) for showing better the chronological relation between the uterine contractions and the type II dip.

In Figure 6B a similar record is shown with the recording paper at a much lower velocity.

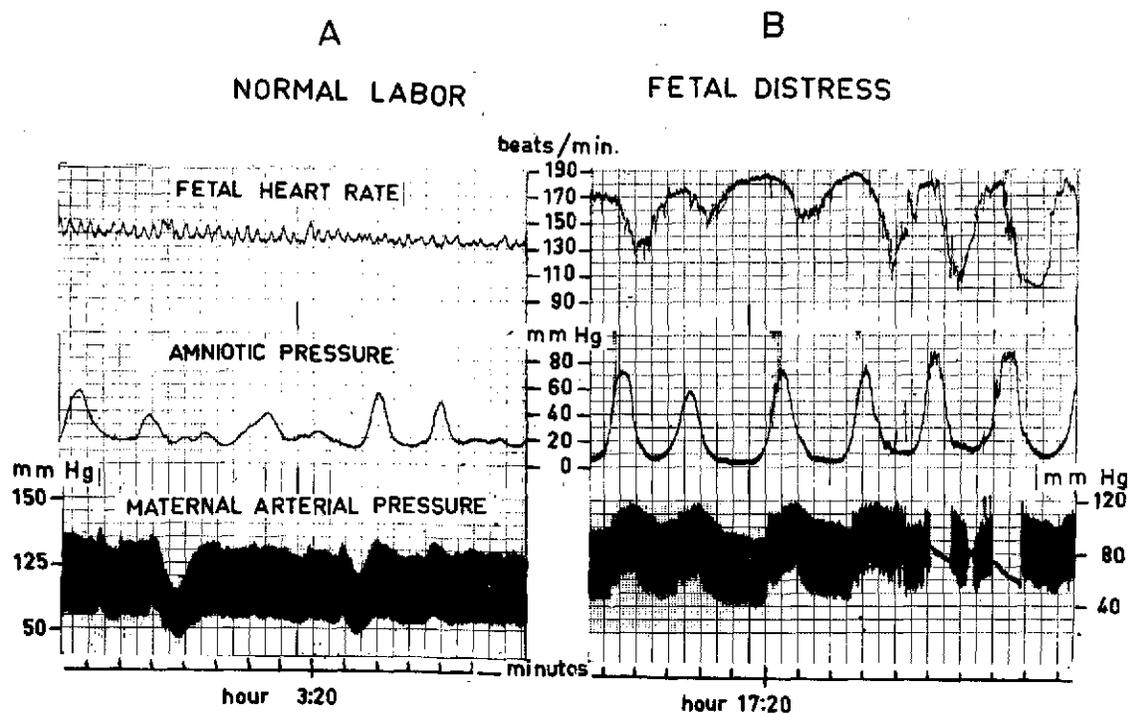


Fig. 6 A Typical normal pattern of FHR during labor.

The Baseline FHR is within the normal range.

Uterine contractions have normal intensity and do not produce type II dips in FHR.

The small oscillations present in the FHR tracing are a normal feature.

Fetal blood had normal oxygen content and pH.

At delivery Apgar score was 10.

Fig. 6 B Typical pattern of FHR in severe fetal distress during labor.

The Baseline is abnormally high.

Each uterine contraction causes a type II dip.

Uterine contractions are very strong (this is one factor causing fetal distress).

A microsample of fetal blood obtained from the fetal scalp showed hypoxemia and acidemia.

At delivery, 30 minutes later Apgar score was 1.

At one year of age, the child showed neurological abnormalities.

Both tracings were obtained with the recording paper at low velocity (1 cm per minute).

E) Correlation between intrapartum changes in FHR and those occurring simultaneously in the composition of fetal blood.

As a working hypothesis we have postulated (1, 36, 40, 102) that in "fetal distress" the stimulation of the vagal and sympathetic systems (responsible for the type II dips and the rise in Basal FHR) is caused by the changes in the composition of fetal blood (hypoxemia, hypercapnia, acidosis).

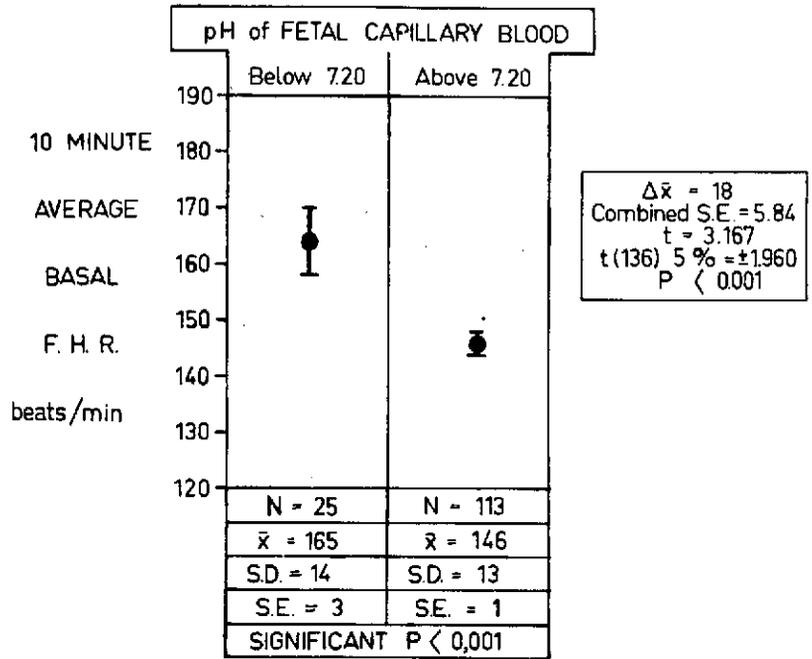
In order to test this hypothesis FHR is correlated with values of pO₂, pH, pCO₂ and Base Deficit in fetal blood.

1) Baseline FHR and pH of fetal blood. During labor several microsamples of fetal capillary blood are obtained from the fetal scalp, according to the technique developed by Saling, (134, 138, 140, 141). The pH of blood is measured by means of the Astrup micro-electrode (8).

For each fetal blood sample, the average value of Baseline FHR is measured in the FHR record during the 10 minutes, which precede sampling. The values of Baseline FHR thus obtained were divided into two groups, according to the pH of the corresponding blood sample (pH below or above 7.20).

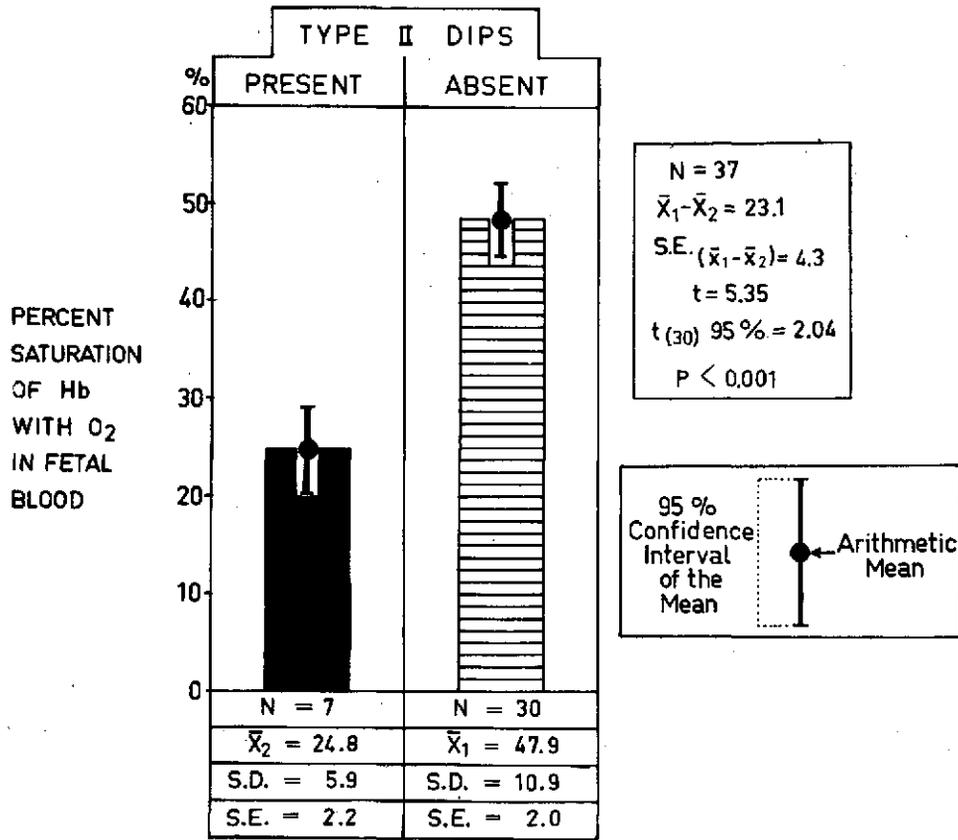
The mean Baseline FHR (165 beats/min.) of the group of blood samples with pH below 7.20 is significantly higher ($p < 0.001$) than the mean Baseline FHR (146 beats/min.) corresponding to the group with pH above 7.20 (Fig.12).

It follows that when fetal blood was acidotic Baseline FHR was abnormally high (tachycardia).



2) Type II dips and composition of fetal blood

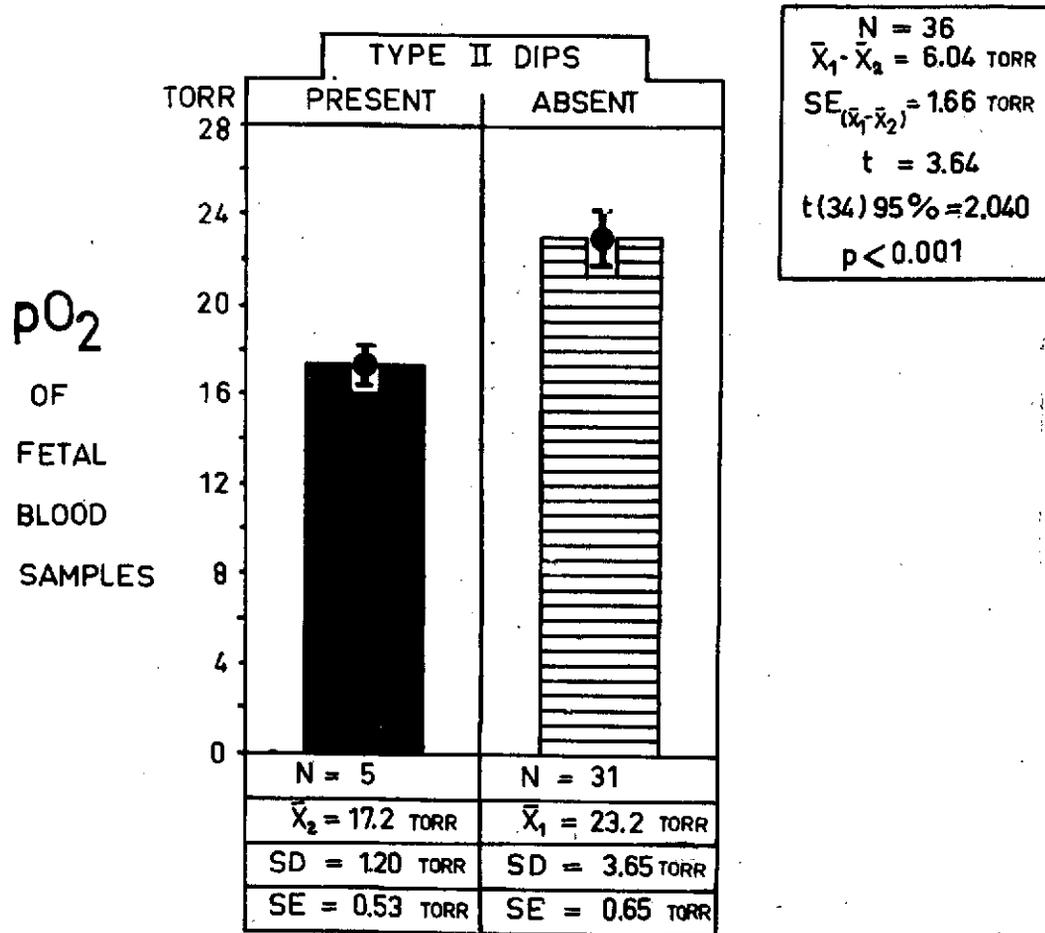
The composition of fetal blood samples obtained when type II dips are present in the FHR tracing was compared against that of blood samples withdrawn in the absence of type II dips. The following factors were studied in fetal blood. 1) Hb saturation with oxygen; 2) pO₂; 3) pH; 4) pCO₂; 5) Base Deficit.



Type II dips and Hb saturation with oxygen in fetal blood (Figure 13)

Hb saturation was measured in 37 samples of fetal blood obtained during labor. Thirty of these samples were withdrawn when type II dips were absent from the FHR tracing. The mean value of Hb saturation for this group (47.9%) is much higher than that (24.8%) corresponding to the 7 blood samples withdrawn while type II dips were present. The difference between the two means is highly significant (p < 0.001).

Conclusion: The mean Hb saturation of fetal blood samples is significantly lower when type II dips are present than when they are absent from the FHR tracing.



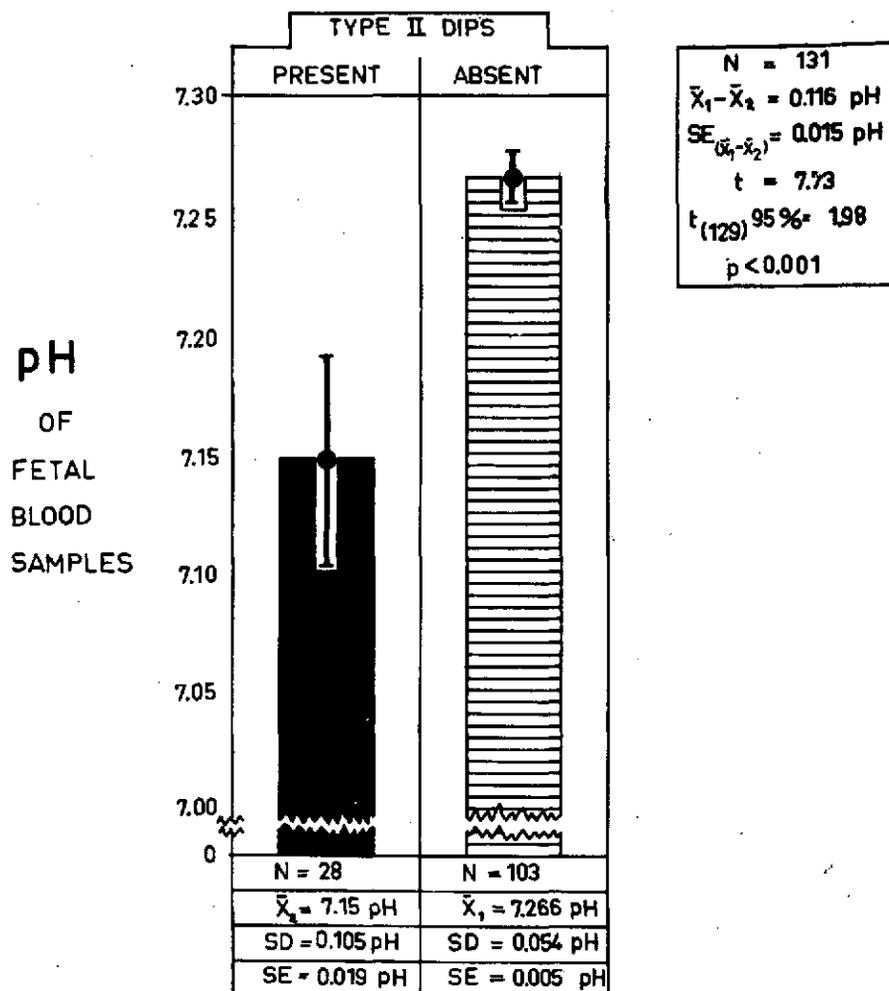
Type II dips and pO₂ in fetal blood (Figure 14)

In the group of 31 blood samples obtained when type II dips were absent, the mean value of pO₂ (23.2 mm Hg) is higher than the mean value of pO₂ (17.2 mm Hg) corresponding to the group of five samples withdrawn when type II dips were present. The difference between the two means is highly significant (p < 0.001).

Conclusion: The mean pO₂ of fetal blood samples was significantly lower when type II dips were present than when they were absent.

Comment: Type II dips and fetal oxygen. We have postulated that the factor directly involved in the pathogenesis of each type II dip is the transient fall of fetal pO₂ caused by each uterine contraction (1, 31, 32). When fetal pO₂ falls below a critical level (18-20 mm Hg) vagal stimulation occurs and the type II dip is produced (Figs.17 and 18).

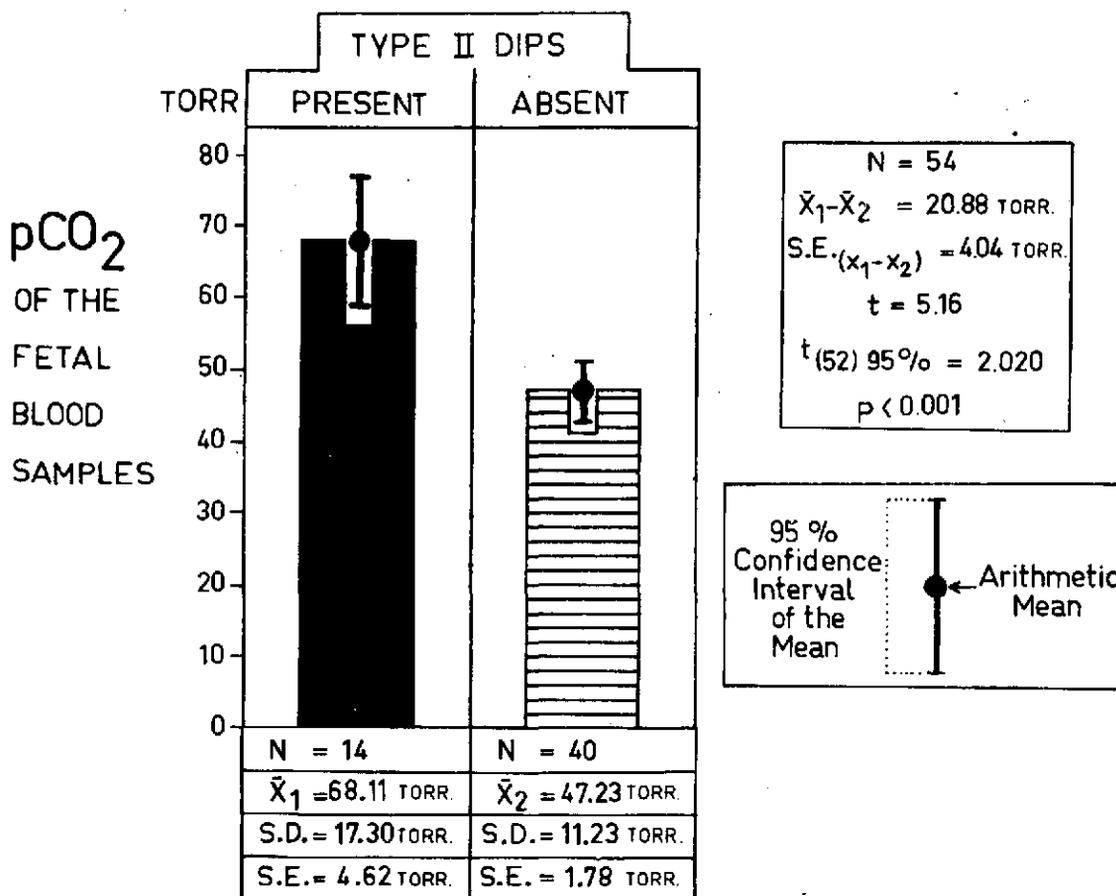
It follows that the occurrence of type II dips should be greatly facilitated when the transient pO₂ falls caused by the contractions of the uterus are superimposed on a pre-existing low pO₂ baseline due to chronic placental insufficiency (Fig.18, right column). This assumption is in agreement with the results reported above (Figs.13 and 14).



Type II dips and pH in fetal blood (Figure 15)

The pH was measured in 131 samples of fetal blood obtained during labor. A first group is made up of 103 blood samples withdrawn when type II dips were absent from the FHR tracing (Figure 15). The mean pH of this group (pH = 7.26) is significantly higher ($p < 0.001$) than the mean pH (7.15) of the second group made up of 28 samples withdrawn when type II dips were present in the FHR tracing.

Conclusion: The mean pH of fetal blood samples was significantly lower when type II dips were present than when they were absent from the FHR tracing.



Type II dips and pCO₂ in fetal blood (Figure 16)

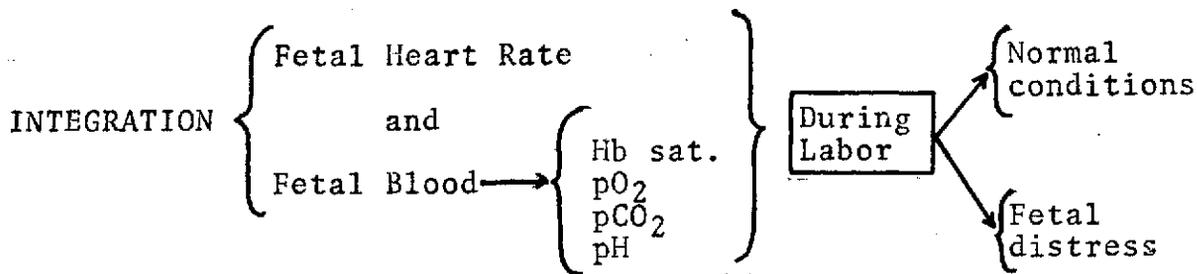
The pCO₂ was measured in 54 samples of fetal blood obtained during labor. Group #1 consists of 40 samples withdrawn in the absence of type II dips. The mean pCO₂ (47.2 mm Hg) of group #1 is significantly lower (p < 0.001) than the mean pCO₂ (68.1 mm Hg) of group #2, made up of 14 samples obtained when type II dips were present in FHR tracing.

Conclusion: The mean pCO₂ of fetal blood samples was significantly higher when type II dips were present than when they were absent from the FHR tracing.

Comment: The correlation of type II dips with fetal hypercapnia and acidosis is less sharp than the correlation with fetal hypoxemia.

A critical level beyond which type II dips would be present is much more poorly defined for pH and pCO₂ than it is for oxygen. This result agrees with the hypothesis that changes in pH and pCO₂ are not directly involved in the production of type II dips as it is the case for pO₂.

The rise in fetal pCO₂ and the resultant fall in fetal pH are produced by the same cause that produces the fall in fetal oxygen. Thus, fetal hypercapnia and ("respiratory") acidosis appear in association with fetal hypoxemia, and both with presence of type II dips.



The results presented in this paper show that when type II dips are present, fetal blood has a significantly lower Hb saturation, lower pO₂, lower pH and a higher pCO₂ than when type II dips are absent from the FHR record.

Furthermore the differences in pH and in pCO₂ between fetal and maternal blood are also greater in the presence than in the absence of type II dips.

These results agree with our working hypothesis (1,36,39,102) in which we postulate that the primary factor in fetal distress is a reduction in metabolic exchanges between mother and fetus.

A chronic "placental insufficiency" causes a chronic reduction of metabolic exchanges between fetus and mother. The consequence is, among other changes, a persistent lowering of the baseline of pO₂ and pH, and a persistent rise in the baseline of pCO₂ (Figs.17 and 18).

Each uterine contraction reduces maternal blood flow through the placenta and causes a transient episode of "acute placental insufficiency" even if the structure of the placenta is absolutely normal. The consequence is an acute reduction of feto-maternal exchanges which produces a transient fall in pO₂ and in pH and a transient rise in pCO₂ (Figs. 17 and 18).

		FETAL BLOOD		
Reduction of feto-maternal exchange		pO ₂	pCO ₂	pH
Chronic placental insufficiency	→ chronic →	low	high	low
Uterine contraction	→ acute →	fall	ascent	fall
		↓ below the critical level ↓ vagal stimulation ↓ type II dip		

Figure 17

The transient variations produced by uterine contractions may be superimposed on a normal baseline when the exchange functions of the placenta were normal before the onset of labor (Fig.18, left column).

Or they may be superimposed on an abnormal baseline (low for pH and pO₂, high for pCO₂) when a chronic placental insufficiency pre-existed to the onset of labor (Fig.18, right column).

The acute effects of each uterine contraction transiently aggravate the pre-existing alterations caused by a chronic placental insufficiency.

When fetal pO₂ falls below a given "critical level" (assumed to be 18 mm Hg in figure 18) hypoxia stimulates the vagus and a type II dips occurs. The lower the baseline of pO₂ the higher the chances that uterine contractions would cause type II dips in the FHR tracing.

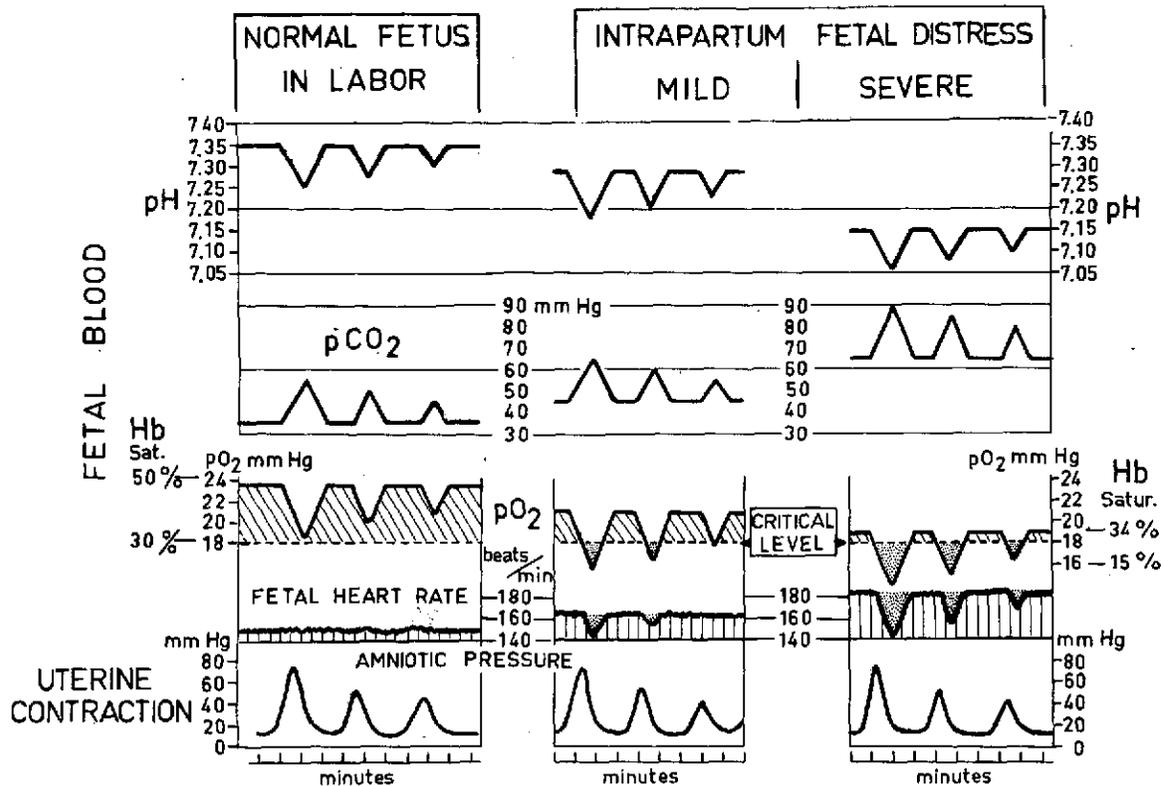
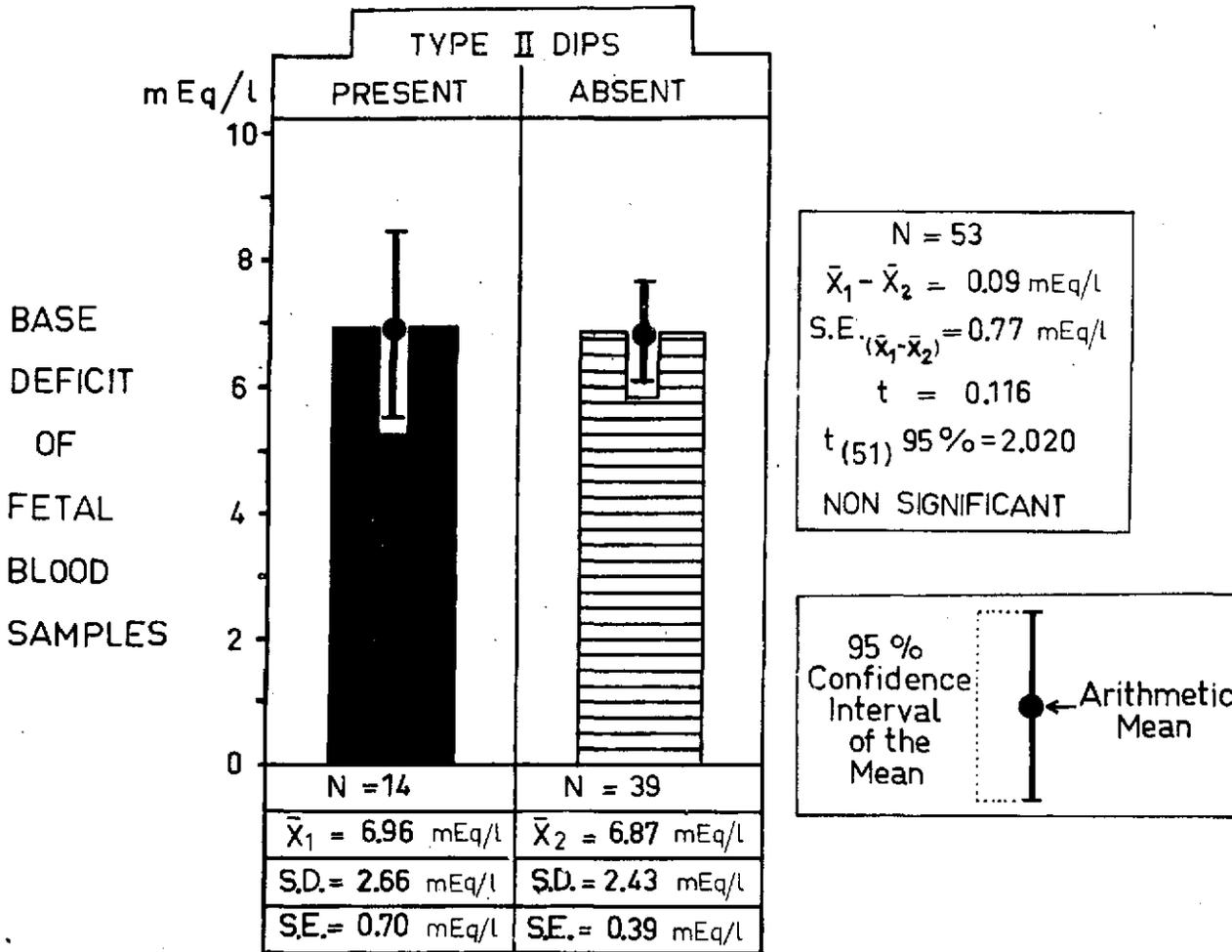


Figure 18. Diagrammatic representation of the several variables studied in the fetus, drawn according to the authors' interpretation. To the left the conditions in normal labor. To the right the conditions in fetal distress due to chronic placental insufficiency. The effects of uterine contractions are superimposed.



Base Deficit in fetal blood (Fig.19)

Base Deficit was measured in 53 samples of fetal blood. Group #1 consists of 39 samples obtained in the absence of type II dips. Group #2 is made up of 14 samples withdrawn when type II dips were present in the FHR tracing. The mean values of Base Deficit in Group #1 and #2 are 6.87 and 6.96 mEq/l respectively.

Obviously the very small difference between the two means is not significant. The S.D. of both groups are very similar (Fig.19) and there is a complete overlapping in the individual Base Deficit values of both groups, as if they belonged to the same population.

Conclusion: the presence or absence of type II dips was not correlated with the Base Deficit value in fetal blood.

Since Base Deficit is a measure of Metabolic Acidosis we may state that in the fetus studied the presence of type II dips was not associated with increased metabolic acidosis.

Comments: Type II dips and metabolic acidosis in fetal blood

The absence of correlation between presence and absence of type II dips and the value of Base Deficit in fetal blood (or the gradient in Base Deficit between mother and fetus) poses an interesting problem. Many authors consider that "metabolic" acidosis (measured by Base Deficit) is the most important humoral factor for the diagnosis of "fetal distress".

A rise in Base Deficit of fetal blood may be produced by two mechanisms:

(1) A rise in maternal Base Deficit (maternal "metabolic" acidosis, which is frequently found in labor). This rise is reflected on the Base Deficit of fetal blood. This mechanism seems to be the most important source of variation of Base Deficit of fetal blood in our series of cases. The exchanges between mother and fetus may be normal.

(2) Fetal hypoxia and increased production of lactic acid. This condition is caused by a severe and prolonged reduction of exchange between mother and fetus: the insufficient supply of oxygen to the fetus increases fetal anaerobic metabolism and the production of lactic acid by fetal tissues. Base Deficit rises in fetal blood.

In addition, there is an obstacle to the elimination of lactic acid from fetus to mother. In these conditions, the feto-maternal gradient of Base Deficit should be greatly increased.

In the present series, only one patient had a feto-maternal gradient higher than 4 mEq/l (reaching up to 10 mEq/l). This is the only patient in which mechanism #2 may have played a significant role.

In all other cases of our series, the feto-maternal gradient was smaller than 4 mEq/l, suggesting that there was no significant "metabolic" acidosis of fetal origin, i.e. caused by severe and prolonged reduction of feto-maternal exchange.

The development of such severe condition was probably prevented thanks to the early diagnosis of fetal distress. Thus, proper therapy was instituted before metabolic acidosis could develop in the fetus.

This may be the reason why, in our series, the presence of type II dips was not correlated with increased value of fetal Base Deficit or of the gradient in Base Deficit between mother and fetus.

The early diagnosis was based on the presence of type II dips and high Baseline in FHR an also in a low pH, high pCO₂, low Hb saturation and low pO₂ in fetal blood.

Relative importance of fetal pCO₂ and Base Deficit as causes of pH variations in the present series of fetuses.

The range of variation of fetal Base Deficit in our series (extreme values 3 and 12 mEq/l) can only account for a small part of the changes observed in pH of fetal blood.

If we assume that pCO₂ remained constant, such variations of Base Deficit could only account for a change of 0.1 pH units.

In contrast, the range of variations observed in fetal pCO₂ (extreme values 30 and 95 mm Hg) may account for changes of 0.3 pH units, assuming that the Base Deficit remained constant.

It follows that in our series of fetal blood samples, the changes in pH were caused mainly by variations in pCO₂ and to a much lesser extent by changes in Base Deficit.

This statement is supported by the high linear correlation ($r = 0.90$) observed between pH and pCO₂ in the fetal blood samples in which both variables were measured (Fig.20).

The determination coefficient ($r^2 = 0.81$) indicates that 81% of the changes in pH are explained by pCO₂ changes.

On the other hand, pH shows no correlation with Base Deficit (Fig.21) in the same series of blood samples.

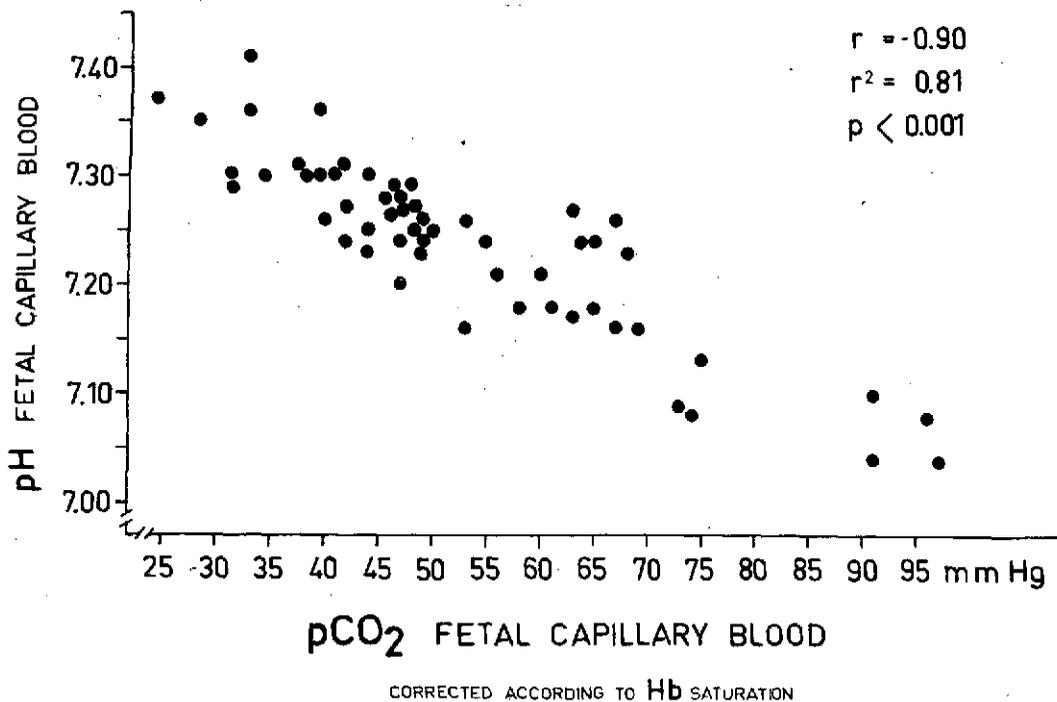


Figure 20. High linear correlation between pH and pCO₂ in fetal blood samples.

Importance of hypercapnia in fetal distress and depression of the newborn. Most of our fetuses having low pH and high pCO_2 showed intrapartum and postpartum signs of fetal distress (independently of the Base Deficit values) (36).

We consider that "respiratory acidosis" (due to high pCO_2) is an important factor in intrapartum fetal distress which may lead to neonatal depression as shown by a low Apgar score, specially in the first minute of life (38).

This statement is in partial disagreement with Saling (141), which considers high pCO_2 and respiratory acidosis as being of less importance and concentrates his efforts on the measurement of "metabolic acidosis".

Saling's approach may be correct if only severe fetal distress is taken into account; but in mild distress or in early stages of the condition, when the diagnosis should be made in order to act in due time to prevent fetal damage the "respiratory acidosis" (high pCO_2) is an important factor which should also be recognized and measured.

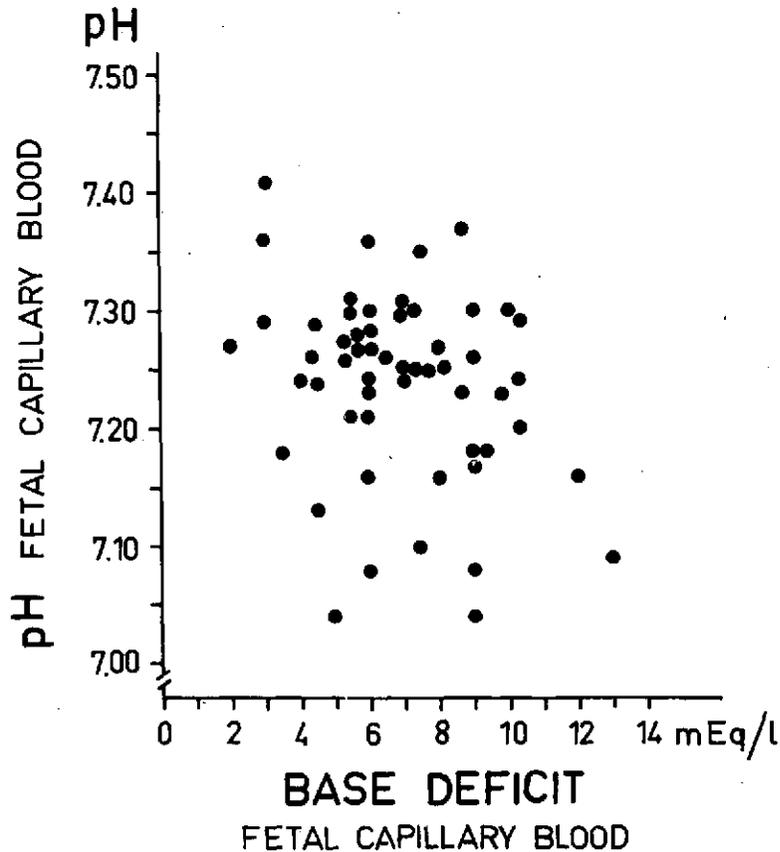


Figure 21. Lack of correlation between pH and Base Deficit in fetal blood samples (same group as that shown in Fig.21).

II. STUDIES IN THE NEWBORN

A) Homeostatic disturbances cause low Apgar score

Intrapartum acidemia, hypoxemia, hypercapnia and other related homeostatic disturbances in the fetus cause a low Apgar score at birth (11,48,62,79,87,89,97,99,114) by the following mechanisms (Fig.1):

1) Depression of the CNS and resultant muscular hypotonus, absence of reflexes, and apnea (46,81) (i.e. three components of a low Apgar score).

2) Stimulation of vagus and bradycardia (fourth component of a low Apgar score).

3) Stimulation of the sympathetic system, skin vasoconstriction and pallor (fifth component of a low Apgar score).

4) Cyanosis is the direct result of a low Hb saturation of fetal blood. When skin vasoconstriction is present, cyanosis is not perceived even if Hb saturation is very low (the skin is pale).

When the baby is born with disturbed homeostasis, the establishment of an adequate pulmonary ventilation will result in marked improvement in blood composition, heart rate and other functions of the newborn, with the consequent rise in the serial Apgar score indicating the recovery of the infant (79,82,83).

If no adequate pulmonary ventilation is obtained, aggravation of hypoxemia and respiratory acidosis may occur. Damage to the cells of several organs will continue to be produced and the prognosis for the child becomes even more somber.

B) Pharmacologic depression also causes low Apgar score

The CNS of the newborn may also be depressed (but not damaged) by an entirely different mechanism, namely the inhibitory effects of analgesic and anesthetic drugs administered to the mother during labor.

This pharmacological depression of the newborn may be a source of error when evaluating CNS disturbances in the newborn by means of the Apgar score (4, 46, 81). To minimize this cause of error, we always give the same moderate dose of analgesia to all our patients. No anesthesia is given.

Pharmacologic depression of the newborn (CNS) causes apnea, hypotonus and absence of reflexes, but does not cause cyanosis, skin pallor or bradycardia, at least in the first minute of life.

C) Correlation between the Apgar score (first minute) and the pH of fetal blood sampled during labor.

The hypothesis behind this correlation is that alterations of fetal blood composition are the cause which depresses CNS and stimulates the vagus and the sympathetic system, all of which will result in a low Apgar score (1st. minute) (36).

Figure 22 shows the first minute Apgar score of each of 21 infants plotted against the mean value of the pH of all the samples of fetal capillary blood obtained from the same infant during the 30 minutes preceding delivery. A direct linear correlation is found between the two variables (the lower the fetal pH, the lower the Apgar score of the newborn).

The correlation coefficient is high ($r = 0.84$) and significantly different from zero ($p < 0.001$). Similar though less definite correlations have been found between Apgar score and pH of blood from the umbilical artery (or vein) measured at birth.

These results support the ominous prognostic significance (for the condition of the newborn) attributed by Saling (135, 139) to a low pH value repeatedly measured in fetal blood during labor.

Fetuses with pH higher than 7.20 were "vigorous" at birth (Apgar score 7 to 10). Those with pH values between 7.10 and 7.20 were "mildly depressed" (Apgar score 4 to 6 at the 1st. minute). Fetuses with pH values lower than 7.10 were "very depressed" at birth (Apgar score 3 or lower).

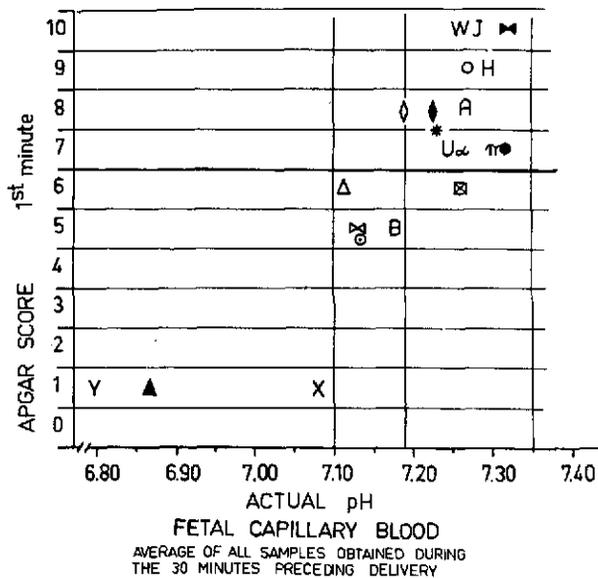


Figure 22. Direct linear relation between the first minute Apgar score and the average pH of all the blood samples obtained in each fetus during the 30 minutes preceding delivery.

D) Correlation between the Apgar score and the intra-partum changes in FHR

The rationale behind this correlation is the following:

Certain abnormal changes of fetal blood during labor (low pH, low Hb saturation, etc.) cause two types of effects:

(1) In FHR during labor: type II dips and abnormal rise of Baseline FHR.

(2) In the newborn: depression at birth (1st. minute Apgar score 6 or lower).

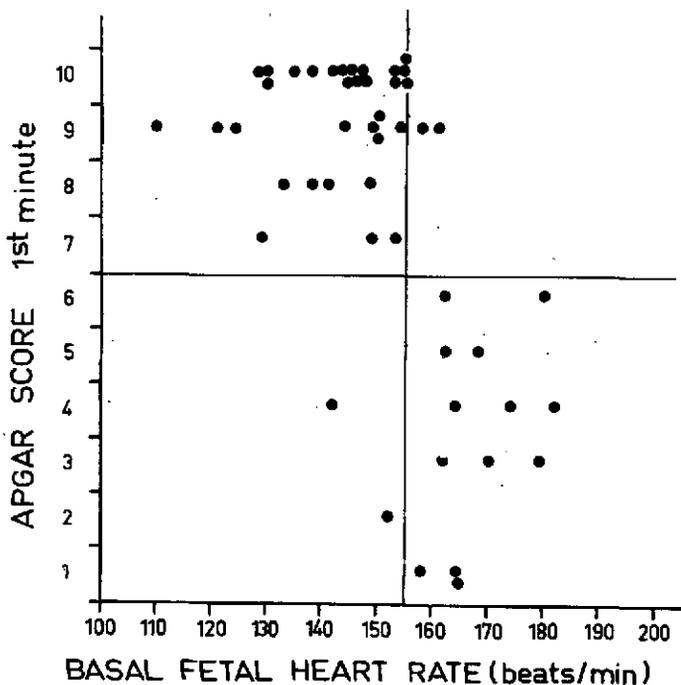
If (1) and (2) are effects resulting from a common cause, a correlation between them might be expected.

The statistical analysis of the results obtained in 49 infants (see below) demonstrates a significant correlation between (1) and (2).

These results are the basis for conferring an ominous prognostic value (for the condition of the newborn) to the above changes in FHR detected during labor, which enables early diagnosis of fetal distress (39).

In contrast, no correlation with the Apgar score has been found for other FHR variations occurring during labor such as "type I dips", "spikes", "transient ascents", "small rapid oscillations", etc., which seem to have no diagnostic value for "fetal distress" or prognostic value for the condition of the newborn (36,37,38).

Figure 23



Apgar score and Basal FHR (Baseline). The first minute Apgar score of each of the 49 infants is plotted against the "average Basal FHR" during labor.

In 32 out of the 34 vigorous newborn, Basal FHR is above 155 beats/min.

In 13 out of the 15 depressed newborns the Basal FHR is above 155 beats/min.

1) Apgar score and Basal FHR (Baseline). This study was made in 49 labors in which FHR was graphically recorded with the cardi tachometer from the onset of labor without interruption until delivery.

The average value of Basal FHR was calculated for each fetus as follows. The Baseline was measured in the graphic record of FHR by the method previously described (36, 101). In each record several hundreds of readings were made, one reading before each uterine contraction. The arithmetic mean of all the values obtained in each record was adopted as the "average Basal FHR" of that fetus during labor.

The condition of the newborn was evaluated by the Apgar score (3, 5) which was determined in all the infants by the same pediatrician.

In Figure 23 the "average Basal FHR" of each fetus is plotted against the Apgar score (1st. minute) of the corresponding newborn.

In 32 out of the 34 "vigorous" newborns (Apgar score 7-10) the "average Basal FHR" during labor was lower than 155 beats/min. (the lowest value recorded was 112 beats/min.). The "average Basal FHR" was higher than 155 beats/min. in only two vigorous infants.

In 13 of the 15 infants which were depressed at birth (Apgar score 1-6) the "average Basal FHR" during labor was higher than 155 beats/min. (the highest value recorded was 185 beats/min.). In only two out of the 15 depressed infants the "average Basal FHR" was lower than 155 beats/min.

One of these two infants is case No.1658, an example of pharmacologic depression of the newborn without intrapartum fetal distress.

During labor the mother received an excessive dosage of Demerol 660mg in 12 hours.

Prognostic significance of Basal FHR. For practical purposes a tentative limit can be set at 155 beats/min. The rise of the Basal FHR above this value is considered as a sign of fetal distress. The higher the level of the Baseline in the FHR tracing and the longer the time during which it remains above 155 beats/min, the worse will be the prognosis for the newborn and for the child (35, 78).

Results of other investigators. Our findings agree with those of Fitzgerald and McFarlane (64), Brady et al. (26,28), who found that tachycardia preceded the delivery of a depressed newborn, Steer (149) and Walker (151) found that the perinatal mortality was higher in fetuses with intrapartum tachycardia.

Our results disagree with those of Lund (94,95), Fenton and Steer (63) and Ginsburg et al. (66,67) who reported no association between intrapartum tachycardia and the condition of the newborn.

2) Apgar score and type II dips. This study was made in 48 cases in which FHR was recorded electronically without interruption from the onset of labor until delivery.

The amplitude of each type II dip is the difference in FHR between the Baseline FHR preceding the dip and the FHR at the bottom of the dip. For example, the first type II dip illustrated in Figure 6B has an amplitude of (170 Beats/min.) less (135 beats/min.) =35 beats/min. or "amplitude units". To avoid confusion, in the future we shall indicate the amplitude of dips in "amplitude units" instead of beats/min.

In each FHR tracing the amplitudes of all the type II dips recorded during labor are measured and added. The resulting value is known as "sum of amplitudes" of type II dips of that case. It is also expressed in "amplitude units". The "sum of amplitudes" of each labor depends on the total number of type II dips recorded in that labor as well as on their individual amplitude.

In Figure 24 the "sum of amplitudes" of each labor has been plotted against the corresponding Apgar score of the newborn. In 32 out of the 34 vigorous infants (Apgar score 7 or higher) the "sum of amplitudes" was lower than 600 "amplitude units". Only two vigorous newborns had a "sum of amplitudes" greater than 600 "amplitude units".

In these two cases the type II dips were produced only in the early first stage of labor (several hours before delivery), when a cause of fetal distress was acting for a limited period of time. Later, fetal distress was corrected, and type II dips disappeared. No type II dips were recorded during the last 4 hours of labor during which FHR had a normal pattern. The fetuses had been restored to normal conditions and the infants were vigorous at birth.

In 13 out of the 14 depressed newborns (Apgar score 6 or lower), the "sum of amplitudes" is greater than 600 "amplitude units" (the highest value recorded was 5500 "amplitude units"). There is only one depressed newborn with a "sum of amplitudes" smaller than 600 "amplitude units".

This Case #1658, an example of pharmacologic depression of the newborn, caused by excessive dosage of Demerol (660mg in 12 hours given to the mother during labor).

Conclusion: The infant has a very high probability of having a low Apgar score at birth when the "sum of amplitudes" of type II dips recorded during labor is greater than 600 "amplitude units".

E) Recapitulation on the prognostic significance of type II dips.

The preceding paragraphs demonstrate that type II dips should be considered as a sign of intrapartum fetal distress and as having an ominous prognostic connotation for the newborn.

A depressed newborn should be expected when during labor more than 20 type II dips have been produced, and the sum of their amplitudes is greater than 600 "amplitude units".

The preceding statement has the following limitation: if type II dips are produced early in labor, and if they disappear at least two hours before delivery, the newborn may be vigorous.

When type II dips appear the obstetrician should investigate the causes of fetal distress, and, if possible, correct them before irreversible damage is produced in the fetus. If this correction is not possible the fetus should be delivered soon.

In the absence of type II dips the prognosis for the newborn is good. However, pharmacologic depression may be present in the absence of intrapartum distress (and of type II dips) if high doses of anesthetic or analgesics have been given to the mother during labor. Pure pharmacologic depression can be easily managed after birth, and, if corrected, leaves no permanent damage to the infant.

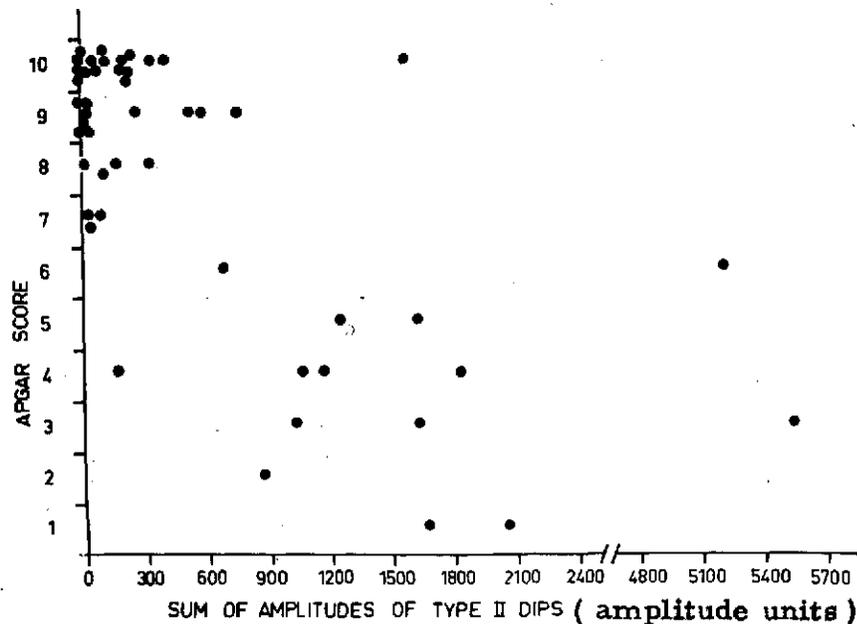


Figure 24. In 32 out of the 34 infants which were vigorous at birth, the "sum of amplitudes" of type II dips during labor is smaller than 600 "amplitude units". In 13 out of the 14 depressed newborns the "sum of amplitudes" is greater than 600 "amplitude units".

III. STUDIES IN THE CHILD

Irreversible damage caused to the infant either during pregnancy, labor or neonatal period will become evident later in the life of the child.

Damage to the cells of the lungs may favor the appearance of the Respiratory Distress Syndrome in the newborn.

Damage to the Brain will be revealed by abnormalities found in neurologic and psychologic tests or in the EEG tracings.

A) The Respiratory Distress Syndrome (RDS)

The pulmonary lesions found at autopsy of newborn infants dying of Respiratory Distress Syndrome (RDS) (i.e. atelectasis, hyaline membrane) have been attributed to vaso-constriction of the pulmonary arterioles of the fetus in response to fetal distress (43). All the disturbances observed in RDS infants may be accounted for by ischemia of the fetal lung as the initial local pathological event.

This hypothesis maintains that fetal lung hypoperfusion is a consequence of fetal blood redistribution during difficult labor (56). This hypoperfusion will damage the great alveolar cells which are presumably concerned with the production and maintenance of the surfactant lining layer.

Consequently, pulmonary function comes impaired in subsequent extrauterine life. There is clinical evidence to suggest that intrauterine fetal asphyxia may predispose to respiratory distress (45,80).

Experimental RDS having clinical and anatomical aspects similar to the human syndrome (including hyaline membranes) has been produced in the lamb by causing hypoxia in the ewe before delivery (132).

Analysis of our series of RDS. In a total of 59 infants weighing more than 2500 g., born to non-diabetic mothers, we have found 5 instances (8.4%) of RDS. One of the infants died on the third day and the autopsy disclosed widespread bilateral atelectasis. The other four recovered.

The diagnosis of the syndrome was based on the clinical criteria proposed by Miller (103) who also reported that the incidence of RDS in 500 infants born vaginally and weighing more than 2500 g. at birth was 8.8%.

1) RDS prevalence in relation to Apgar score. It has been reported that a low Apgar score at birth is a frequent herald of RDS in premature infants (133) and also in term infants (104).

In a group of 16 infants of our series scoring 1-6 at the 1st. minute, 5 cases (31.25%) of RDS were found.

In a group of 43 infants scoring 7-10, none presented the syndrome.

Of the low score group, 4 had scores of 1-3 and required resuscitation. Two of them were born by cesarean section performed because of intrapartum fetal distress. These findings are illustrated in Figure 25.

The above preliminary results agree with the hypothesis that neonatal distress is associated with the RDS.

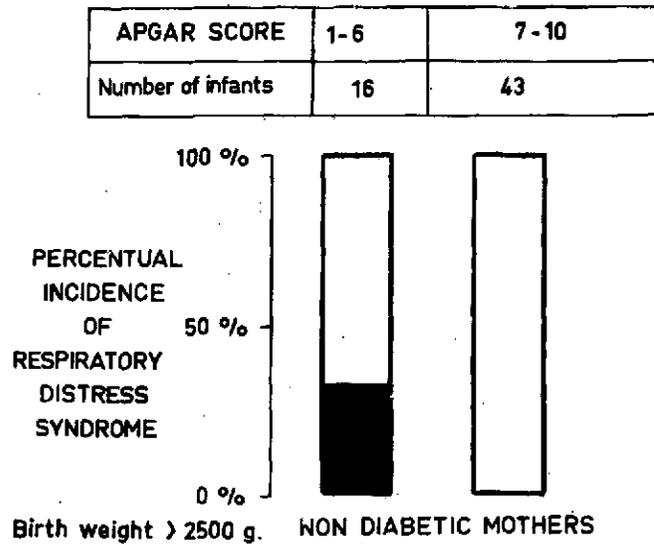


Figure 25. Comparative percentual incidence of Respiratory Distress Syndrome in relation to Apgar score at birth (first minute) in 59 term infants born of non-diabetic mothers.

2) RDS prevalence and intrapartum Mean Baseline FHR (Fig.26). Thirty nine infants were divided into two groups: in one, consisting of 9 cases having a Mean Baseline FHR higher than 160 beats/min, 4 cases of RDS were found (44.44%); in the other, comprising 30 cases that had Mean Baseline FHR lower than 160 beats/min, there was no instance of RDS. These findings suggest a correlation between intrapartum fetal tachycardia and appearance of RDS.

3) RDS prevalence and intrapartum type II dips (Fig.27). We shall now consider the "sum of amplitudes" of all the type II dips recorded during each labor. The group in which this sum is higher than 600 amplitude units consists of 8 subjects; in 3 cases (37.50%) RDS occurred.

In the group made up of the infants having a sum of amplitudes lower than 600 amplitude units (24 subjects) there was only one case (4.16%) of RDS.

4) RDS prevalence and the combination of type II dips with tachycardia (Fig.28). In the group of infants which during labor presented Mean Baseline FHR higher than 160 beats/min, combined with a "sum of amplitudes" of type II dips higher than 600 amplitude units, 3 out of 6 newborns (50%) exhibited RDS.

On the other hand, from a group of 15 subjects in whom these two parameters were under the safe limits just stated, none presented RDS. These findings agree with the previously mentioned view that intrapartum fetal distress plays an important role in the pathogenesis of RDS.

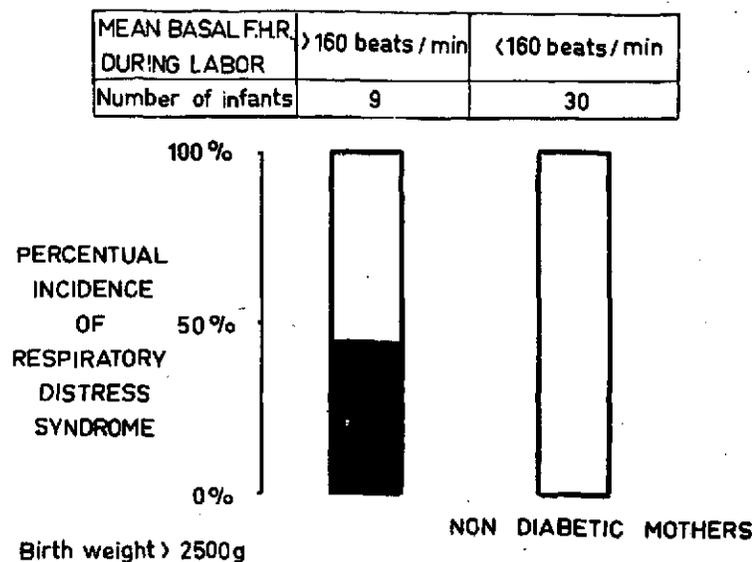


Figure 26. Comparative percentual incidence of Respiratory Distress Syndrome in relation to Mean Baseline FHR during labor in 39 term infants born of non-diabetic mothers.

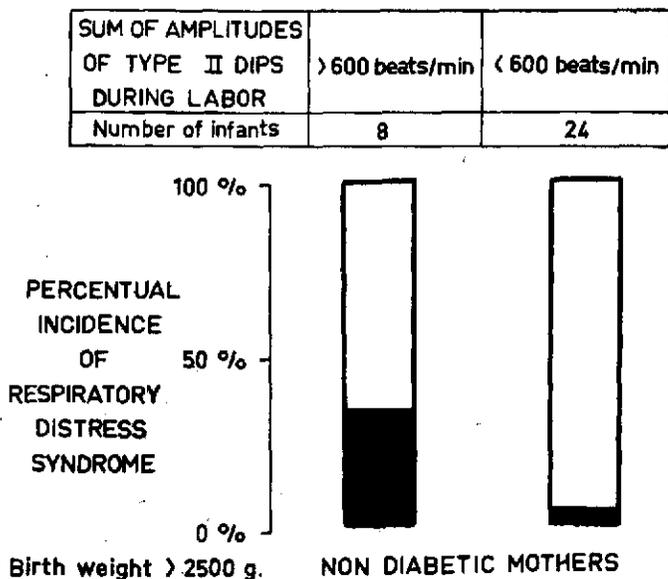


Figure 27. Comparative percentual incidence of Respiratory Distress Syndrome in relation to the sum of amplitudes of type II dips during labor in 32 term infants born of non-diabetic mothers.

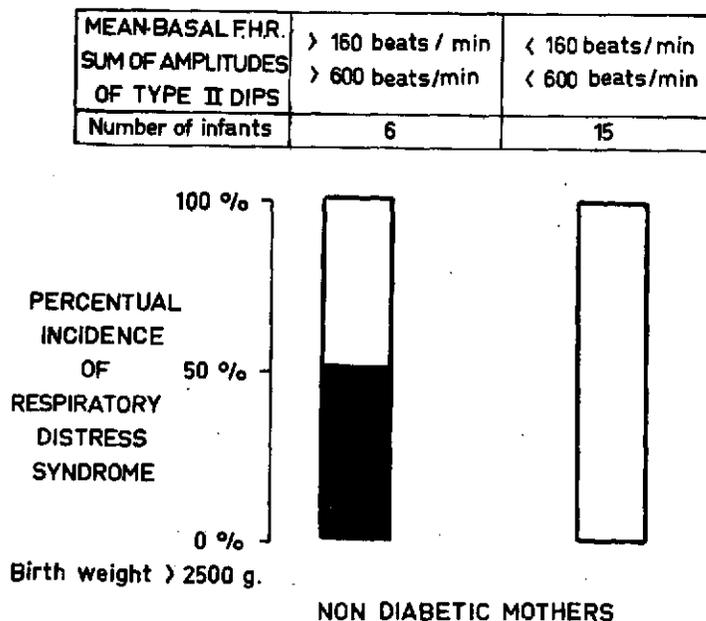


Figure 28. Comparative percentual incidence of Respiratory Distress Syndrome in relation to the association of two parameters: Mean Baseline FHR, and the sum of amplitudes of type II dips during labor, in 21 infants born of non-diabetic mothers.

B) EEG abnormalities in the child

The alterations of the EEG found in the children are presented here only as a finding that expresses a bio-electrical cerebral dysfunction and not as a manifestation of structural brain damage.

We are aware that the number of children studied is small, and that the EEGs have been obtained at different stages of development (from a few days of life to 5 years of age).

We have undertaken a follow up control of a group of infants who had been previously studied at labor, delivery, and birth.

EEG studies were made in 44 subjects, from whom a total of 74 EEGs were obtained. The tracings were evaluated without previous knowledge of the neonatal condition of the child.

Six abnormal tracings were found. Abnormalities consisted of: 1) focal epileptiform activity; 2) focal low voltage; 3) focal slow (1 - 1.5 c/s) waves.

1) EEG abnormalities in relation to Apgar score. Figure 29 shows the incidence of normal and abnormal EEGs according to the first minute Apgar score at birth.

Of a group of 17 subjects born with Apgar 1-6, 4 showed later EEG abnormalities. In a group of 27 subjects who scored 7-10 at birth, 2 showed EEG abnormalities later on.

These results, although preliminary, show a suggestive grouping of abnormal EEGs in children who had fetal distress, as expressed by their low Apgar score at birth.

2) EEG abnormalities and intrapartum Mean Baseline FHR-Figure 30. From a group of 35 subjects in whom the Mean Baseline FHR was recorded, in 9 subjects it was above 160 beats/min. Of these children, 3 showed abnormal EEGs.

Of 26 subjects in whom the Mean Baseline FHR was below 160 beats/min, 2 showed later abnormal EEGs.;

These results, although not conclusive, suggest that fetal distress, as expressed by fetal tachycardia during labor, is associated with higher incidence of EEG abnormalities than that found in the children which during labor had a normal Mean Baseline FHR.

FIRST MINUTE APGAR SCORE	(1-6)		(7-10)	
NUMBER OF CHILDREN	17		27	

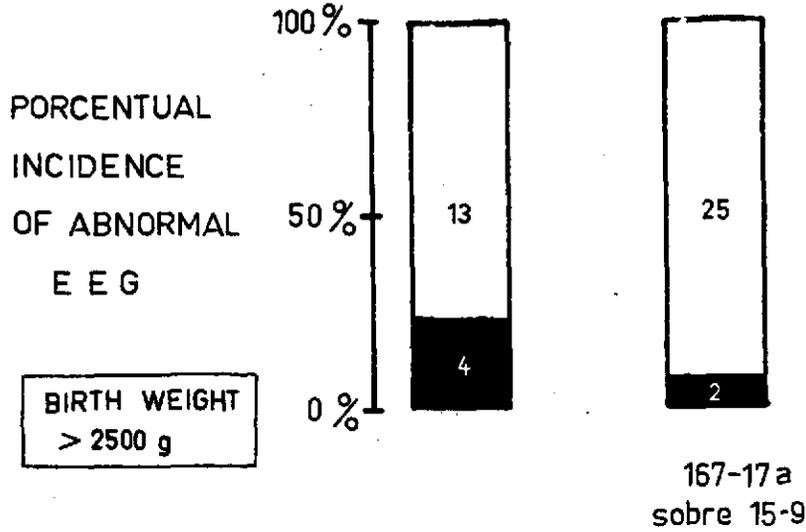


Fig.29

Incidence of abnormal EEG in the child according to the condition of the infant at birth

MEAN BASAL F.H.R. DURING LABOR	HIGHER THAN 160 $\frac{\text{beats}}{\text{min.}}$	LOWER THAN 160 $\frac{\text{beats}}{\text{min.}}$
NUMBER OF CHILDREN	(9)	(26)

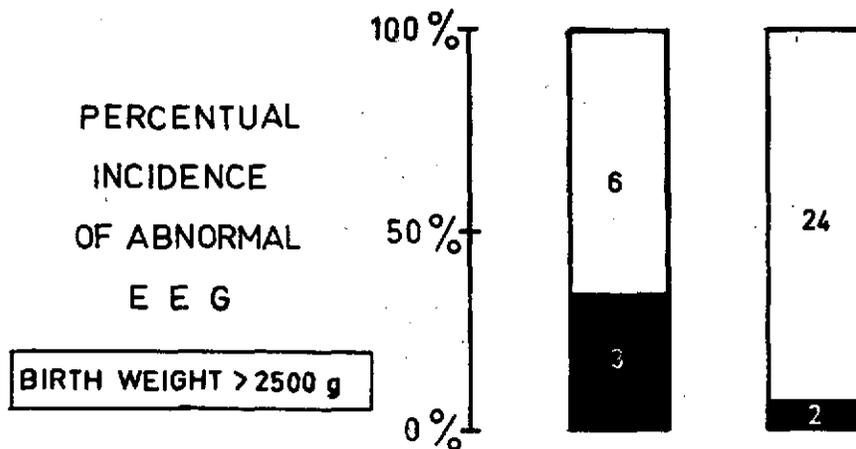


Fig.30

Incidence of abnormal EEG in the child according to the mean value of Baseline FHR during labor

3) EEG abnormalities and intrapartum type II dips (Figure 31). The sum of amplitudes of type II dips was obtained in 31 fetuses. In 9 subjects this sum was higher than 600 amplitude units, and abnormal EEGs were found in 3 of them. In 22 subjects in whom the sum of amplitudes of type II dips was lower than 600 amplitude units, there were only 2 abnormal EEGs.

These findings are in agreement with the view that fetal distress, as ascertained by the sum of amplitudes of type II dips, is associated with more than expected EEG abnormalities in later life.

4) EEG abnormalities and the combination of type II dips with tachycardia (Figure 32). The combination of the sum of amplitudes of type II dips higher than 600 amplitude units and a Mean Baseline FHR higher than 160 beats/min was found in 6 subjects. Of these, 2 presented abnormal EEGs.

In 15 subjects in whom both parameters were lower than these limits, 2 abnormal EEGs were disclosed.

These results further support the hypothesis of an association between intrapartum fetal distress (as ascertained by continuously recorded variations of fetal heart rate) and later alterations of the EEG in the child.

SUM OF AMPLITUDES OF TYPE II DIPS DURING LABOR	HIGHER THAN 600 Ampl. Units	LOWER THAN 600 Amplitude Units
NUMBER OF CHILDREN	(9)	(22)

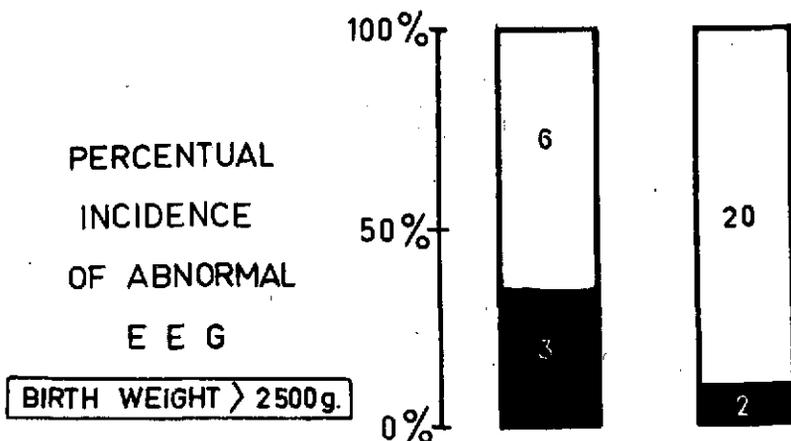


Fig.31

Incidence of abnormal EEG in the child according to the type II dips recorded during labor

MEAN BASAL F.H.R.	>160 beats/min	<160 beats/min
SUM OF AMPLITUDES OF TYPE II DIPS DURING LABOR	HIGHER THAN 600 Ampl. Units	LOWER THAN 600 Ampl. Units
NUMBER OF CHILDREN	(6)	(15)

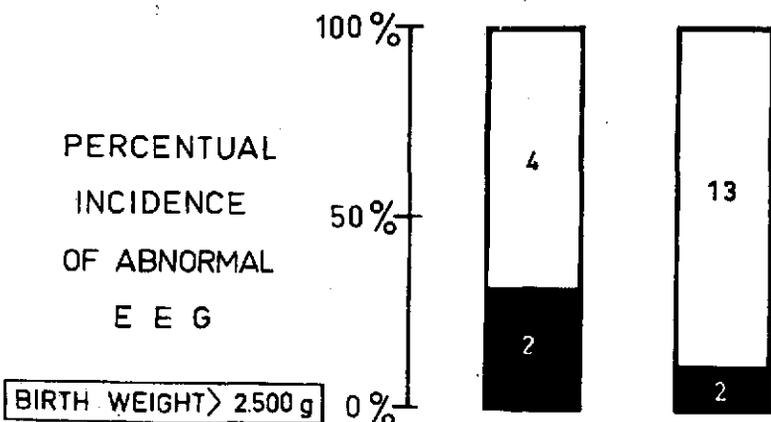


Fig.32

Incidence of abnormal EEG in the child according to the characteristics of FHR during labor

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