

REVIEW ARTICLE

THE EFFECT OF PAIN RELIEF FOR LABOR AND DELIVERY ON THE FETUS AND NEWBORN

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ATTEMPTS to relieve the pain of childbirth have been made from the earliest times. The ancient Egyptians advocated rubbing the abdomen with beer and oil of saffron, or vinegar and marble dust, or the skin was intricately tattooed to frighten away the powerful demons responsible for more fearful pain. Herbs with hypnotic or analgesic properties such as henbane, juice of the poppy, hemp and mandragora, were also known and were probably in use before 2000 B.C. But in the Middle Ages, with the growing belief that pain was a divine punishment, pains of childbirth being natural and inevitable, little was done to relieve the sufferings of women in labor.¹

Nevertheless, anesthesia had been the dream of mankind since the beginning of time and chemists of the Renaissance continued the search for some agent that would completely relieve pain. In 1846, ether publicly administered by William Morton was used successfully for surgery in Boston, and a year later Sir James Simpson, of Edinburgh, reported the use of chloroform in 30 painless deliveries. This advance was strenuously opposed by the Church in Scotland, ministers arguing that it was sacrilege to prevent pain which was divinely ordained. Similar resistance was encountered in the United States in 1848, when Walter Channing advocated the use of ether in obstetrics.² The anesthetic victory was finally won in 1853, when John Snow administered chloroform to Queen Victoria for the birth of her eighth child.¹

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Although Snow died five years later, he lived long enough to discover the dangers of chloroform. His book, "On Chloroform and Other Anaesthetics,"³ clearly shows that it is a more toxic and potent agent than ether. A provocative paper read in London in 1872, by Joy Jeffries, of Boston,⁴ led to the gradual substitution of ether for chloroform in general surgery in Great Britain; another American, Horatio Wood was responsible for bringing about a general revival of ether in Germany, in 1890.⁵ Discussing anesthesia deaths, Wood states, "I think it can be asserted that the probable ratio of deaths from chloroform is four or five times that of deaths from ether." Despite this knowledge, widespread use of chloroform in obstetrics was continued until well into the twentieth century, because of its ease of administration and rapid action.

Twilight sleep (morphine and scopolamine) was tried in 1902,⁶ and within a short time was being used extensively. While it was relatively safe for the mother, this combination of drugs produced many severely depressed infants. The proceedings of the Royal Society of Medicine (1917)⁷ describes apnea or white asphyxia in 16 of 19 liveborn infants, respiration being delayed for 10 to 20 minutes, and although it was noted that "the view that morphine is the cause of delayed respiration in the child is slightly supported by the results of these cases" the concluding remarks of the president firmly warned of the dangers to the baby. "When twilight sleep was first introduced, I used it in a certain number of my private cases, but I soon abandoned the method and do not intend to use it . . . it tends to produce uterine inertia . . . increasing morbidity rate. This fact has been proved beyond any question by various observers, and in itself

is a condemnation of the general adoption of so-called 'twilight sleep.'" However, twilight sleep continued to be popular, and some years later DeLee⁸ cryptically remarked that "the patient must be willing to pay the price of occasional loss or injury to the child as the cost for her relief from suffering."

Barbiturates in labor were reported in 1924⁹ and 1925¹⁰ and were used in combination with various other drugs in the years immediately following. Increasing doses of medication were employed as the goal of complete pain relief or amnesia seemed within reach.

However, there still remained a hard core of cautious and astute observers who maintained that heavy medication was associated with prolonged labor and more stillbirths.^{7,8} A significant study by Irving and associates was published in 1934.¹¹ The use of pantopon, morphine or any of its derivatives in labor was condemned since it prolonged labor in primiparae, increased operative interference and blood loss, and delayed the onset of respiration in 67 per cent of babies. Barbiturates produced a delayed onset in respiration in 35 per cent of cases, while in a control series (no medication) the incidence of apnea was only 1.9 per cent.

The progress to 1940 is well summarized by Waters and Harris.¹² "We have indulged too much in the hope for a possible drug or combination of drugs which may be expected to abolish safely all pain in connection with childbirth. We have looked upon new and untried drugs as the solution to our difficulty."

The regional approach to the control of pain was first employed in 1909, by von Stoeckel,¹³ but it was not until 1933, when Cleland¹⁴ first identified the pathway of uterine pain, that this method achieved any prominence. In the last 15 years, caudal anesthesia has gained widespread popularity due largely to Hingson's enthusiastic championing of the technique.^{15, 16}

And lastly, Grantly Dick Read.¹⁷ He first presented his ideas early in 1933. Although his method has been much criticized (more by the medical profession than the public) and does seem to require a special type of practitioner—possibly even a special type of patient—his is nevertheless a great contribution. He was the first person to point out that labor

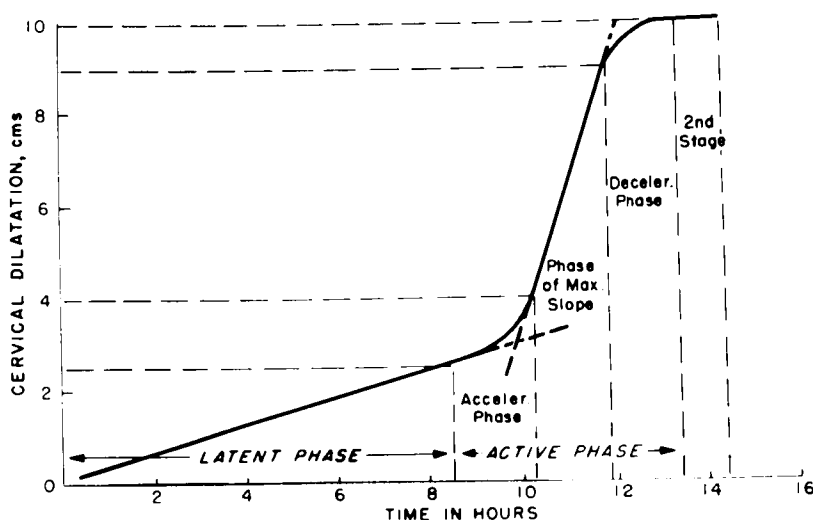
pains were not necessarily painful, suggesting that the pain was largely the result of fear and a tense "strung-up" body. He has stressed that labor is a natural process. The method has served an important function in making many obstetricians more conscious of the need to secure the full cooperation of their patients and the value of education in this respect. He has paved the way for smaller doses of medication. Eastman has aptly stated, "The proper psychologic management of the patient throughout antepartal care and labor is an indispensable basic sedative."¹⁸ And it might be added—medication is not a satisfactory substitute.

THE EFFECT OF ANESTHESIA AND ANALGESIA ON THE COURSE OF LABOR

In evaluating narcotics or hypnotics in obstetrics not only must pain relief be considered, but also the effect of the drug on the course of labor. An adverse effect is frequently denied. At best, however, it is possible only to have a vague clinical impression, unless an objective method of measurement is employed. Such a method has been introduced by Friedman.¹⁹⁻²² By plotting cervical dilatation against time, mean labor curves which are sigmoid in shape, have been obtained for primiparas and multiparas. By this method specific rate of change can be measured and moment to moment changes accurately observed. Eighteen hundred labors have been studied and mean labor curves defined (fig. 1). The first stage consists of a latent phase and an active phase, the latter being divided into three parts, an acceleration phase, phase of maximum slope and deceleration phase.

Effect of Sedation. These studies show that sedation has a profound influence on the course, incidence of complications and the outcome of labors. Heavy sedation slows cervical dilatation and is associated with a high incidence of inertia, necessitating stimulation by oxytocic agents and frequent operative deliveries. This applied to both primiparas and multiparas. Thus the earlier impressions^{7, 11, 23} on the effect of narcotics are confirmed. It is of interest that meperidine and scopolamine, too, had a significant delaying action, contrary to the clinical impression reported by some observers.^{24, 25} In a recent study²⁶ up to 1,600 mg. of meperidine were used in labor, and nalor-

FIG. 1. The mean labor curve, cervical dilatation versus time, based on the study of 500 primigravidas at term. The phases are defined in the text (ref. 19).



phine was given to the mother just prior to delivery. The published data show a direct correlation between the length of labor and the dose of the drug. In addition, the incidence of instrumental deliveries and cesarean section was as high as 50 per cent and 22 per cent respectively, in those receiving over 1,000 mg. of drug. Contrary to the opinion expressed by the authors, it would seem that there was good evidence that meperidine definitely decreased uterine contractions and slowed the progress of labor.

Effect of Caudal Anesthesia. Caudal anesthesia was found to produce an essentially normal cervimetric pattern in primigravidas¹⁹ but decided prolongation of the deceleration phase as well as slight lengthening of the active phase and second stage in multigravidas.²¹ Cervical dilatation was slowed by too premature application of the caudal or excessive preanesthetic medication.

Psychological Preparation. Those primigravidas receiving no medication were noteworthy.¹⁹ Although the mean curve was not significantly different from the "ideal" labor (with the exception of the short mean deceleration phase) comparison with the entire series revealed that all except the second stage were markedly shortened, and the slope markedly steepened. Of particular interest was the effect of good psychological preparation for labor. There was a significant reduction in the latent and active phases, the foreshortening

of the active phase reflecting a significant decrease in the duration of the acceleration phase.

EFFECT OF ANESTHESIA AND ANALGESIA ON THE FETUS

In the past, our basic understanding of physiology has been derived from animals, and since it is difficult to obtain direct information on the physiology of the human fetus, we must to a certain extent rely on this time-honored method until newer techniques are available. Although this method has limitations it is important to come to some conclusions and not merely to assume that the human fetus might be different.

The internal environment of the fetus is controlled largely by the placenta. Therefore, it depends indirectly on the efficiency of the maternal respiratory exchange, cardiac output, kidney function and the stability of her internal environment. Any drugs which effect these functions or alter the maternal environment will also indirectly affect the fetus. In addition, drugs which have a specific toxic action on the mother and pass the placenta are likely to be equally toxic to the fetus.

Maternal Respiratory Exchange. Narcotics, barbiturates and other nonvolatile drugs, as well as inhalation agents in sufficient dosage all cause depression of the maternal respiratory center. Waters and Harris¹² have shown that the respiratory exchange may be lowered 23

per cent by as little as $4\frac{1}{2}$ grains of sodium pentobarbital given orally. They state that rarely can doses of more volatile agents, adequate for pain relief, be administered without measurable decrease in minute volume pulmonary ventilation. Of equal importance is the effect on reflex responses from the pharynx and larynx. If at the same time the vomiting center is stimulated, a potentially dangerous situation exists, and this is well attested to by maternal deaths from aspiration. Depression of the cough reflex promotes the chance of later chronic obstructive phenomena, and depression of ciliary activity of the respiratory tract is now a recognized effect of pain relieving drugs. Waters and Harris have further stressed that even the most experienced anesthetist cannot prophesy whether reflex disturbances will take place in a given patient from a particular drug and dosage, and has difficulty by observation alone, in recognizing respiratory obstruction of a degree to cause anoxia. They warn of the temptation to permit mothers to inhale oxygen-deficient atmospheres during the administration of inhalation agents of slight potency, such as nitrous oxide.

Maternal Cardiac Output. During pregnancy the blood volume increases approximately 30 per cent.²⁷ Eastman¹⁸ considers this the greatest single alteration which the gravid organism undergoes. The blood viscosity decreases about 12 per cent²⁷ while cardiac output increases by approximately 30 per cent.^{28, 29} Uterine flow accounts for 8 to 12 per cent of the cardiac output.³¹ Burwell^{32, 33} has observed the similarity between the changes in circulation in arteriovenous fistulas and certain circulatory alterations in pregnancy and has postulated that the placenta acts as an arteriovenous shunt. At present there are no studies to indicate that sedation or anesthesia alters the cardiac output of women in labor, and because of the muscular effort during contraction this will not be an easy phenomenon to investigate.

However, reduction in the maternal blood pressure during spinal or caudal anesthesia, or from postural hypotension due to pressure of the uterus on the inferior vena cava, is likely to have a profound effect. Barcroft³⁴ knew of the importance of posture and the dangers of shock from postural hypotension at term, and

consequently performed his experiments with the ewe suspended by slings on her side in a saline bath. Further, although he used spinal anesthesia, he was aware that this, too, could change the normal physiological conditions, and was "never very happy about results obtained in the last few days." Dawes³⁶ has demonstrated that the cord oxygen levels are considerably higher when pentobarbital is used rather than spinal anesthesia. Low values have also been obtained with basal sedation and local anesthesia.³⁷ This is presumably due to increased tension and straining on the part of the ewe.

These studies are well supported by data from babies delivered at elective cesarean section under spinal anesthesia (see Asphyxia of the Newborn) and low levels have been found in the absence of significant changes in maternal blood pressure. It is difficult to give a spinal anesthetic without any change in blood pressure, and even if pressure is restored by the use of vasopressors, there is no assurance that regional circulation through the uterus remains normal. In an effort to prevent a fall in blood pressure, vasopressors have been administered before the spinal. Here, too, the regional circulation might be altered without evidence of any change in the mother's brachial blood pressure.

The pale appearance of the uterus at cesarean section under spinal anesthesia, compared to the appearance when cyclopropane is used, and the great difficulty experienced in intrauterine manipulations under caudal anesthesia, has led to the clinical impression that these forms of anesthesia increase uterine tonus. This impression has been reinforced by observations that uterine contractions appear as a "release" phenomenon under spinal anesthesia.³⁸ However, recent studies by Kretchmer and associates³⁹ indicate that increased tonus is unlikely, so that the low oxygen values observed are probably due to posture and changes in the maternal blood pressure.

There is another possible explanation for low oxygen levels and this relies on changes in maternal blood pressure during the uterine contraction. Just as exercise raises blood pressure, so considerable increases have been observed in laboring mothers.^{40a, b} During contractions the pressure within the uterine cavity

increases 40 to 80 mm. of mercury and in the second stage may rise to 260 mm. of mercury with strong bearing down efforts of the mother. Caldeyro-Barcia⁴¹ has shown that the pressure within the uterine wall is twice or three times as high as the pressure within the uterine cavity. The result of this pressure rise will be to compress the veins, and if the pressure increases sufficiently, the arteries. This will lead to venous congestion in the intervillous space, and during the more intense contractions possibly to actual stagnation. Concomitant elevation of the maternal blood pressure will to a certain extent maintain arterial flow. It is not known whether the maternal arterial pressure rises during contractions under caudal anesthesia. This subject deserves further study.

Stability of the Mother's Internal Environment. The higher fetal mortality and morbidity in diabetes and toxemia of pregnancy have received considerable attention. Prolonged labor, too, carries an increased mortality^{18, 42} and the tragic consequences to both mother and baby are no better documented than in the descriptive letter written by Dr. John Sims in 1817,¹ about the labor of Princess Charlotte which lasted for 52 hours. "The child was born without artificial assistance at nine o'clock in the evening. Attempts were made for a good while to reanimate it by inflating the lungs, friction, hot baths, etc., without effect; the heart could not be made to beat even once. . . . About half-past twelve o'clock she complained of severe pain in her chest, became extremely restless, with rapid, weak and irregular pulse. . . ." Two hours later, "She was quieter: the death rattle continued, she turned several times upon her face, drew up her legs, the hands grew cold, and she was no more."

Whether the higher infant mortality is the result of prolonged labor alone, operative delivery, or infection is still not clear. There is no doubt that if the mother becomes exhausted, dehydrated and acidotic, the strength of her uterine contractions diminishes and her expulsive efforts become ineffectual. But there are likely to be additional effects. Experimental work recently has shown that in acidosis, cardiac output is reduced.⁴³ Both the maternal acidosis (which will be reflected in the fetus⁴⁴)

and a reduction in cardiac output could endanger the infant's survival.

While it may appear unduly speculative to equate this situation with that encountered when excessive sedation is employed, it is nevertheless important to consider the possible consequences of injudicious medication and a prolonged labor.

EFFECTS OF ANESTHESIA AND ANALGESIA ON THE NEWBORN INFANT

Evaluation at Birth. A standard method of evaluation, while it does have limitations, forms a basis whereby drug dose response or clinical material from different centers can be compared. Several methods are currently in use. It should be stressed at the outset that none of these is a substitute for a careful physical examination, and recording the changing status of the infant as he recovers or deteriorates. In retrospective studies of infants who have subsequently revealed signs of mental retardation or cerebral palsy, a great deficiency has been lack of worthwhile clinical information for the first few minutes or hours of life. A scoring system partly remedies this deficit—but it is no substitute. Because the clinical status of the infant may rapidly change for better or worse, the method of evaluation should be simple, taking into account readily observable signs, and should be related to time.

Determining the presence or absence of breathing, or breathing and crying time, is the simplest method in use. This allows little room for error of judgment, but it neglects other important vital signs and the infant who gasps once or twice as soon as he is delivered, and subsequently makes no effort, will be incorrectly evaluated. Nevertheless, an infant who is breathing well by one minute is undoubtedly minimally asphyxiated and is in good condition.

APGAR SCORE: The scoring system introduced by Apgar, in 1953,^{45, 46} (table 1) takes into account heart rate, respiration, tone, reflex response and color. A score of 2 for each sign is given if all these signs are good; heart rate over 100, vigorous crying or rhythmical respiration, full muscle tone, prompt response to stimulation and the body entirely pink—a total of 10. A score of 1 for each sign is given for a heart rate less than 100, occasional respirations,

TABLE 1
EVALUATION OF NEWBORN INFANT

Sign	0	1	2
Heart rate	Absent	Slow (below 100)	Over 100
Respiratory effort	Absent	Slow Irregular	Good Crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex response to tangential slap on sole of foot	No response	Grimace	Vigorous cry
Color	Blue Pale	Body pink Extremities blue	Completely pink

Method of scoring: 60 seconds after complete birth of infant (disregarding cord and placenta), these five objective signs are evaluated and each given a score of 0, 1, or 2. A score of 10 indicates an infant in the best possible condition (ref. 17).

diminished tone, poor reflex response and cyanosis of extremities. A score of 0 is given if all signs are absent. All the signs are not of equal value—nor are they mutually independent. Nevertheless, over the past eight years useful correlations have been obtained with mortality^{45, 46, 47} and biochemical status at birth.⁴⁸

With little experience, the obstetrician, pediatrician, or anesthesiologist can learn to make a rapid mental record of the five signs. Color and respiration can be observed; tone can be felt; reflex response to a slap on the sole of the foot is part of the initial resuscitation; and heart rate can either be observed from the cord pulsation or listened for with a stethoscope. The score should be decided upon at one minute and recorded.

Vigorous infants score 7, 8, 9 or 10, crying within a minute of birth, the score to a large extent depending upon how soon and how vigorously they cry. Mildly depressed infants

score 4, 5 or 6. These are usually the medicated babies. Once respiration is established, they rapidly pass to the high score group. They require minimal resuscitation. Usually gentle stimuli are sufficient. The depressed infants score 0, 1, 2 or 3. These are limp and pale; they may make occasional gasps but usually there is no respiratory effort. The only sign of life is a heart beat and occasionally a grimace to a slap on the sole of the foot. The infants thus fall into three broad clinical groups: vigorous, mildly depressed and severely depressed.

Heart rate is the most important sign, and the last to be absent. Color is the least important and the first to change. Respiration, tone and reflex response are absent, roughly in that order. Between individual observers there is occasionally a difference of 1 or 2. After a little experience there is rarely failure to agree in the evaluation between observers.

This scoring system has been used for a number of years in Winnipeg and Helsinki and published reports on mortality^{49, 50} show a close agreement (fig. 2). It is now being widely employed on the Child Development Project sponsored by the National Institute of Health. Scores are being recorded at 1, 3, 5 and 10 minutes in an effort to determine whether the clinical signs are of any prognostic value regarding subsequent mental development.

One group of investigators⁵¹ found that the newborn infants' color, cry and muscle tone were too dependent on variable subjective opinion to be of value. Color may be difficult to assess, but there is little doubt when muscle tone is completely absent or when it is fully present as in a vigorously crying child. Cry is

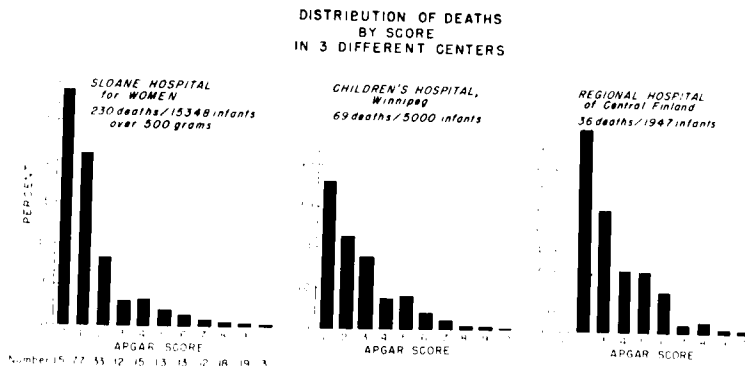


FIGURE 2.

certainly more variable than respiration, and is less useful as an index of vigor.

Another report²⁶ found the scoring system too complex. In this study severely depressed infants required intensive resuscitation for 15 minutes or more, moderately depressed for five to 15 minutes, and mild for up to five minutes. It is not noted whether the infants remained apneic over this period, nor what forms of resuscitation were used. Such a gross method of evaluation would only be of use in a clinic where massive doses of sedation were employed. It would accept as normal, severely asphyxiated infants delivered with minimal or no medication who made spontaneous gasps shortly after birth.

The preliminary finding of one study quoted by Reid⁵² suggested that Apgar scoring failed to offer an immediate prognosis as to survival or death. These observations are at variance with others noted above.^{45-47, 49b, 50} One can only state that the majority of low score infants recover, but of the infants who die, the greater proportion will be in the low score group.

ASPHYXIA

This word has an interesting origin, and Eastman¹⁸ states that few words have undergone such radical changes in meaning. It is of Greek derivation, and originally indicated lack of pulse. During the nineteenth century, the word was used to describe suffocation. Eastman further states that "obstetricians have taken further liberties with it, and customarily refer to any baby who does not breathe at birth as 'asphyxiated.'" He suggests that apnea neonatorum be substituted for this term.

Asphyxia now carries a rather precise physiological connotation, related to suffocation. It is defined as anoxia plus hypercapnia. Other derangements which result from this state, such as a metabolic acidosis and electrolyte imbalance, can also logically be included. Since these biochemical changes are found in depressed and apneic newborn infants, the term asphyxia remains useful but it should be used only as physiologically defined. Anoxia and hypoxia relate only to absent or low oxygen levels and are not terms which can be substituted for asphyxia.

Asphyxia Livida and Pallida. These are among the oldest terms used to describe the

condition of depressed newborns, livida being a milder form. They depend primarily on the color of the infant. Color, as has been noted earlier, is the most subjective and least valuable sign. Probably this is the reason for the terms falling into disuse.

Flagg's Classification. Flagg⁵³ has described the physical signs accompanying stages of asphyxia of the newborn as (1) stage of depression; (2) stage of spasticity; and (3) stage of flaccidity.

These categories led to some misunderstanding since the spastic stage introduced the idea of increased tone and obstetricians, in following Flagg's indications for resuscitation, were inclined to wait for tone to become marked assuming the infant was in the stage of depression when indeed the infant was in the stage of flaccidity. The flaccid group as defined by Flagg is as follows:

Respiration occurs at long intervals, or cannot be demonstrated.

Cyanosis or pallor.

Complete flaccidity with relaxed jaw.

No resistance to suction or exposure of the pharynx.

Fluid in the hypopharynx.

Apex beat may not be demonstrable.

This corresponds well with the low score group in the Apgar rating.

CONDITION AT BIRTH IN RELATION TO MATERNAL ANALGESIA AND ANESTHESIA

One of the enigmas in the responsiveness of the newborn has been the reported lack of correlation between the dose of a particular drug to the mother, and the ability of the baby to breathe spontaneously. Mengert⁵⁴ reports "an infant who breathed and cried immediately, and showed no sign of any difficulty after the hypodermic injection to the mother of ½ grain of morphine two hours and fifty minutes before delivery" and another mother "received 2 grains of morphine in ¼-grain doses during the 20 hours preceding her delivery . . . the child breathed spontaneously." Shute and Davis⁵⁵ have pointed out that "it is interesting to note that a large number of infants born under optimum conditions for the production of narcosis showed no trace of the effects of the drug." A similar disparity may be ob-

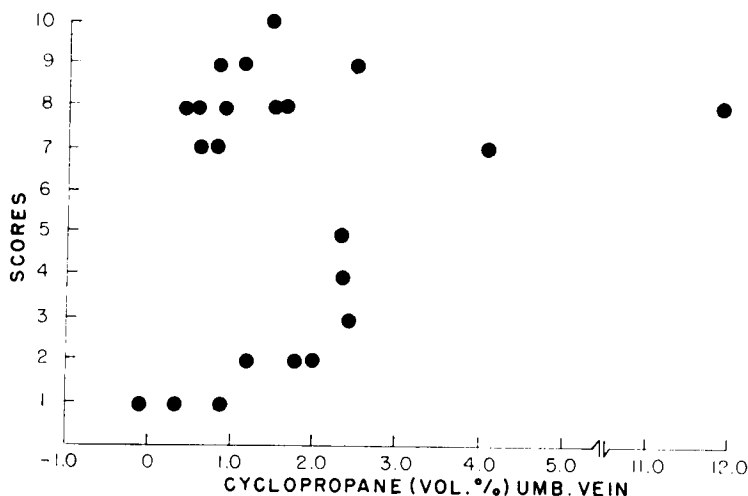


FIG. 3. Relation of scores to concentration of cyclopropane in umbilical vein.

served with barbiturates,⁵⁶⁻⁵⁷ meperidine,⁵⁸ gas, oxygen and ether⁵⁹ and cyclopropane.^{46, 60}

Nowhere in medicine can the recollection of clinical impressions be more deceptive. It is essential to remember not only the vigorous but also the depressed infants and to contrast these with the reaction of infants delivered without sedation or anesthesia. Undoubtedly the "alertness" and vigor of the infant at birth may on occasion contrast sharply with the sleepy or unconscious state of the mother; the important question is "in what proportion?" Irving and associates¹¹ showed that while less than two per cent of infants delivered of mothers having no sedation had a delayed onset of respiration, 35 to 67 per cent had delayed respiration if sedation was used. Hellman and Hingson⁶¹ have shown that there is a significant difference in the reaction of both term and premature infants, as determined by the breathing and crying times according to whether or not the anesthetic used crossed the placenta in appreciable amounts. Further, in a study of over 3,000 full term infants,⁴⁶ Apgar scores were significantly better ($p < 0.001$) for both vaginal vertex and elective cesarean section deliveries if only regional anesthesia was used. From these data it must be concluded that systemic analgesia and anesthesia to the mother affects the infant.

Nevertheless, the intriguing question remains "Why does sedation seem to affect some infants so minimally?" Two possible explanations immediately come to mind: the placenta

might act as a partial or complete barrier to the transfer of certain drugs; there might be an additional factor accounting for apnea of depression.

THE PLACENTA AS A BARRIER: The placenta is readily permeable to ether and cyclopropane^{46, 59, 60, 62, 63} and to barbiturates,^{57, 64, 65, 66, 67} These drugs pass rapidly into the fetus, cyclopropane being found in fetal blood within three minutes of inhalation by the mother⁴⁶ and thiopental also within three minutes.^{65, 67} Meperidine, too, has been shown to be present in fetal blood⁶⁸ in concentrations 60 to 70 per cent of those in maternal blood. Absence of drug in the fetal tissues is apparently not the explanation.

When the actual levels of cyclopropane and barbiturates in the fetal blood are measured, it is of further interest that blood levels and infant response show no correlation^{46, 57} (fig. 3). In adults, depth of anesthesia cannot be gauged by blood levels of barbiturates⁶⁹ so that some variation between blood level and response in the case of infants would not be surprising. However, arterial concentration of cyclopropane and depth of anesthesia bear a close relationship in adults, so that the lack of correlation in the infant is unexpected.

Flowers⁵⁷ has suggested three possible explanations in the case of barbiturates: (1) Differences in water and lipid content of infant brain compared to the maternal. This difference would not explain the lack of correlation in the case of cyclopropane. (2) A fall in

P_{CO_2} in the infant at birth producing a rise in pH; his studies show the well recognized elevated levels of P_{CO_2} in cord blood. However, there is not a sudden rise in pH at the moment of birth as the author assumes. This adjustment takes one or more hours, and immediately after delivery the pH actually falls further (see below). The persisting or increasing acidosis would be unlikely to reduce the hypnotic effect of the drug. (3) Variation in the infants "adaptability response": If by this is meant a reflex response, the only way drugs could improve it would be by peripheral or central stimulation.

AN ADDITIONAL FACTOR ACCOUNTING FOR DEPRESSION: The explanation might well reside in the changes in pH and the blood gases, but relate more to the changes before and during delivery rather than after. Waters and Harris¹² have published a striking example to illustrate this point in the records of two elective cesarean sections, 27 months apart on the same mother, both performed under cyclopropane, with the same premedication. In each instance the infant was delivered after the same length of time both as regards operation and anesthesia. However, one baby breathed immediately, and the other took 30 minutes. "Intense fear was present when the woman came to the operating room on each occasion and was the apparent cause of low blood pressure and small pulse pressure on each occasion. In the first instance, cyclopropane was administered with excess oxygen and a smooth induction occurred, with restoration of mother's normal circulatory condition as soon as she

was anesthetized. The baby cried spontaneously. In the second instance, cyclopropane in an atmosphere without excess oxygen was used. Induction was rough with severe respiratory obstruction. Mother's blood was cyanotic when the incision was made. Restoration of a free airway, good oxygenation and probably of normal maternal blood pressure relations was not accomplished until eight minutes after the cord had been severed. Strenuous efforts were necessary over a period of a half hour before the baby's respiration was established."

A similar relationship was found in a later study by Apgar and co-workers⁴⁶ when the degree of anoxia and asphyxia were considered. Infants with high levels of cyclopropane were only vigorous if minimally asphyxiated, while moderate degrees of asphyxia even with low levels of cyclopropane produced severe depression. It has therefore been proposed that one unknown factor causing a variable response to drugs, is birth asphyxia.

Oxygenation at Birth and Birth Asphyxia. In recent years oxygen levels in the newborn infant at delivery have been intensively studied, blood being obtained from the umbilical cord.^{48, 63, 70-76} A wide range of values has been revealed. Eastman⁷⁰ was responsible for some of the earliest pioneering work. He reported oxygen saturations in the umbilical artery from 6 to 27 per cent, and in the vein 38 to 58 per cent, in 15 babies delivered vaginally. In one elective cesarean section a value of 30 per cent was obtained from the umbilical artery and 63 per cent from the vein.

TABLE 2
COMPARISON OF OXYGEN SATURATION IN UMBILICAL CORD VESSELS

Author	Average Oxygen Saturation, %		No. Cases		Range		Delivery
	Artery	Vein	Artery	Vein	Artery	Vein	
Eastman ⁷⁰	16	50	15	15	6-27	38-58	Vaginal vertex
	30	63		1			Cesarean section
Smith ⁶³	16	51	37	40	2-48	16-81	Vaginal vertex
Clemetson and Churchman ⁷¹	31	63	10	12	2-50	35-84	Spontaneous vaginal vertex
Walker ⁷⁵	20	48	9	10	1-28	13-60	Spontaneous vaginal vertex
Rooth and Sjøstedt ⁷³	32	61	69	98	0-62	9-83	Spontaneous vaginal vertex
Author's Series ⁴⁸	23	51	304	360	0-67	9-96	Cesarean section and vaginal vertex; all vigorous at birth

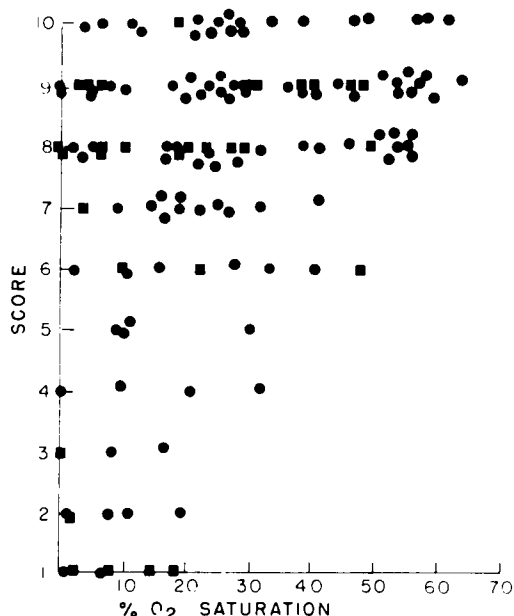


FIG. 4. Relation of oxygen saturation in the umbilical artery to condition at birth, as measured by the Apgar Score.

Table 2 demonstrates that the larger the series, the wider has been the range. The author's series show 0 to 67 in the artery and 9 to 96 in the vein. A few samples from the umbilical vein have been almost identical to maternal arterial blood. It was further observed that even at elective cesarean section the same wide range was obtained.

Some investigators have taken an average of these values to be an indication of the normal intra-uterine environment; others have ignored the lower values and taken an average of the remaining ones. Treatment of data in this way is responsible for the current idea that the intra-uterine environment is, by adult standards, a grossly anoxic one.

However, this method of analysis is valid only when sampling conditions are stable, and the subject is in a steady state. These criteria hardly apply when the baby is being squeezed through the vagina; the cord may be compressed and the strong expulsive contractions of the uterus are likely to interfere with normal circulation through the intervillous space.

In addition, some conclusions have been made, assuming that the umbilical vein blood represents babies arterial blood and the um-

bilical artery contains venous blood. This view of the fetal circulation is open to question, since Dawes⁷⁷ has demonstrated that the blood in the umbilical artery represents the arterial blood of the fetal lambs, and the blood going to the head is little different from that going to the lower part of the body in the rhesus monkey fetus.⁷⁸ If the birth oxygenation data are reviewed in the light of this knowledge, it is even more difficult to concede that the cord blood at birth represents the intra-uterine environment; otherwise some infants would have to thrive on almost no oxygen.

By correlating the clinical condition of the infant at birth with oxygen saturation in the umbilical artery several interesting relationships are seen (fig. 4). Clinical status has been graded according to the Apgar score (table 1).^{45, 47} Vigorous infants demonstrate a wide range of oxygenation, some crying lustily with no measurable oxygen in their arterial blood. On the other hand, higher values are not seen in the depressed group. The occurrence of no measurable oxygen in a proportion of vigorous infants, is probably the most weighty evidence against cord blood reflecting the normal intra-uterine environment.

An alternative method of analysis is to consider the wide range of values obtained as reflecting various degrees of interference with exchange of oxygen between mother and baby during the delivery process. This provides a rather different picture. It suggests that the highest values of oxygen in the cord blood more nearly represent the normal *in utero* environment. It suggests further, that the large number of low values at birth indicate that the baby is born with his oxygen reserves exhausted.

The question now arises as to just how long the infant has been anoxic. Serial determinations in apneic newborn babies give little information about the rate of fall of oxygen saturation since levels are already so low. However, the rate of change after revival of newborn puppies delivered by cesarean section demonstrates that oxygen saturation falls from over 90 per cent to less than 10 per cent in approximately two minutes (fig. 5). This rapid change has been obtained in human adults,⁷⁹ dogs⁸⁰ and puppies,⁸¹ by other investigators. This figure also demonstrates that

if exchange of oxygen is prevented, there are changes in addition to the fall in oxygen saturation. Carbon dioxide accumulates and *pH* falls rapidly, averaging 0.1 of a *pH* unit/minute for the first five minutes and then approximately 0.1 of a *pH* unit every three minutes. These results are similar to those observed by Dawes in newborn lambs.⁷⁸ It will be demonstrated later that the human infant behaves in a similar fashion. A horizontal line has been drawn at a level of *pH* 7.0 and zero oxygen. This is the point where adult animals develop ventricular fibrillation and die. However, puppies continue to have a good heart beat and blood pressure, and the *pH* continues to fall to levels which are not seen in the adult.

The *pH* change occurs not only as a result of the accumulation of carbon dioxide, but also of fixed acid radicals such as phosphate and lactate. Carbon dioxide tension rises at the rate of 5 to 10 mm of mercury per minute and the buffer base initially falls about two milliequivalents per liter per minute. Therefore, in the absence of respiration, not only does the oxygen level fall precipitously, but a profound acidosis also occurs, which is contributed to by carbon dioxide and other metabolic acid products. These collective changes have been defined physiologically, as asphyxia (see above).

Appreciation of the rate at which oxygen saturation and *pH* can change, emphasizes how

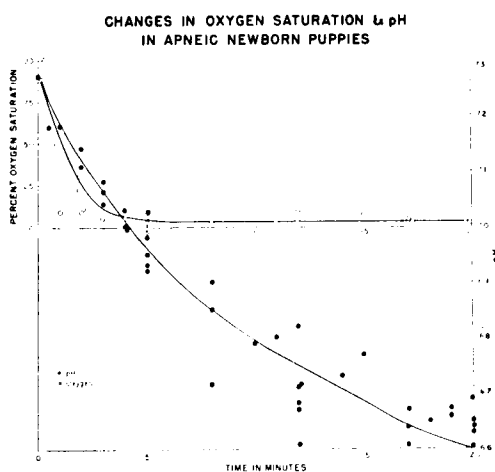


FIGURE 5.

a brief period of cord compression, or alteration in the uterine circulation could change these factors, and offers an explanation for the low levels of oxygen which are found in many vigorous newborn infants. If the low levels of oxygen in the newborn baby reflect a period of deprivation or reduced exchange of oxygen with the mother, changes in carbon dioxide tension, *pH* and buffer base should also be present. This concurrent changes do occur. While the average value for oxygen in the vigorous newborn is in the region of 25 per cent saturation, the average P_{CO_2} is 55 mm. of

TABLE 3
STATISTICAL COMPARISON OF VIGOROUS AND DEPRESSED INFANTS*

	Vigorous Infants (Score† 8-10) Samples from Umbilical Artery			Depressed Infants (Score 0-4) Umbilical Artery or Portal Vein‡			
	Number Studied	Mean	S.D.	Number Studied	Mean	S.D.	<i>p</i>
<i>pH</i>	30	7.26	0.085	10	7.04	0.142	.01
P_{CO_2} (mm. Hg)	27	55.3	10.25	9	82.0	19.93	.01
Buffer base**	27	41.5	3.68	10	31.4	6.93	.01

* From James, L. S., *et al.*³⁸

† Appgar, V., *et al.*^{35,37}

‡ To determine the biochemical status of the depressed group, samples from either the umbilical artery, the portal vein area in the liver, or from the right or left atria have been used. In this group, frequently the cord is collapsed and bloodless or the blood is present in loculated sections between areas of complete occlusion. Consequently, a sample of the circulating blood from the infant, either arterial or venous, if obtained before the onset of respiration, will give a more reliable indication of the condition of the infant.

** Buffer base indicates total available buffer and includes both the bicarbonate (or alkali reserve), the protein, and the hemoglobin. A depression from the normal is a measure of metabolic acidosis.

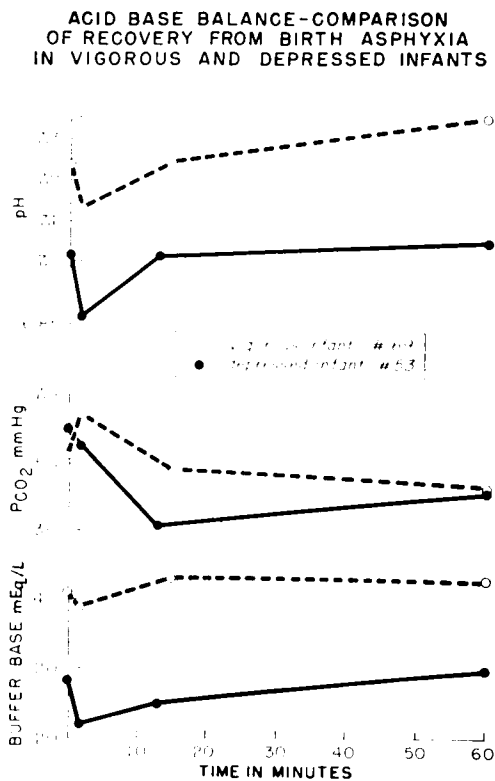


FIG. 6. The pattern of change in pH, P_{CO_2} and buffer base in a vigorous infant (dotted lines), delivered after an easy and uncomplicated labor of a multiparous mother who had required neither analgesia nor anesthesia. This is compared with a severely asphyxiated infant (continuous line), who was born under regional anesthesia following signs of fetal distress, bathed in thick meconium, and with the umbilical cord wrapped 3 times round his neck. At delivery he was limp and unresponsive. Following prompt resuscitation, the first breath occurred at 3½ minutes, and deep well sustained respirations continued thereafter. The P_{CO_2} fell rapidly, but the metabolic acidosis showed a much slower rate of recovery.

mercury and pH 7.25—similar wide ranges being seen in all three⁴⁸ (table 3). The acid-base balance in the low score infants was significantly different (table 3), the P_{CO_2} averaging 82.0 mm. of mercury the pH averaging 7.04, while the BB averaged 31.4 mEq./l. Immediately following delivery a fall in pH is seen in both vigorous and depressed infants (figs. 6, 7, 8, 9), the fall being greater in the depressed group, particularly if resuscitation is delayed. The fall in the vigorous group occurs uniformly and was unexpected, taking place even though the onset of respiration was

prompt, *i.e.*, within seconds of delivery. The subsequent rise in pH and buffer base appears to depend primarily on the effectiveness of respiration. By one hour, levels which are similar to the maternal level before labor began are attained, the average rate of recovery being similar in vigorous and depressed infants.⁸²

A similar pattern of change occurs in the tension of carbon dioxide and in the levels of lactic acid, but these mirror the changes in buffering capacity (there was a brief rise in P_{CO_2} and lactic acid, and then a subsequent fall). The lactic acid levels account for approximately one-half to two-thirds of the change in buffer base.

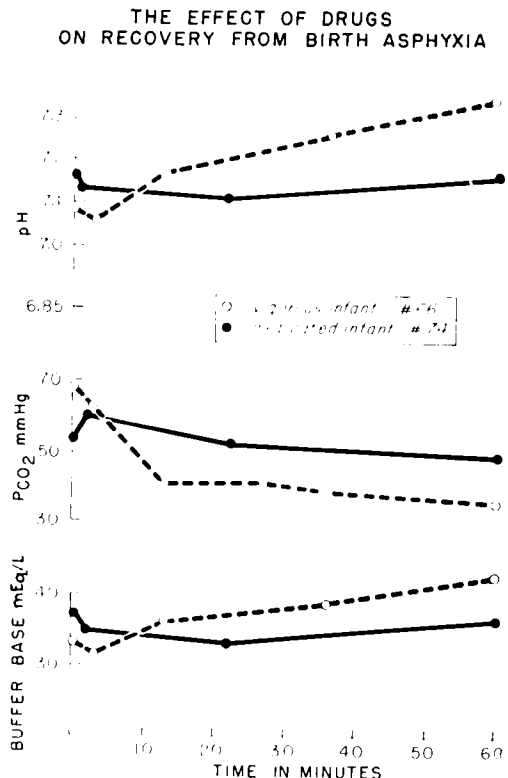


FIG. 7. Comparison of an infant delivered with no sedation or anesthesia (dotted line) with an infant whose mother was given 200 mg. of barbiturate and 100 mg. of meperidine over three hours prior to delivery (continuous line). Both infants were in the vigorous group and breathed spontaneously within seconds of delivery. The difference in rate of recovery is unmistakable, the continued elevated P_{CO_2} being evidence of hypoventilation in the medicated infant.

These data demonstrate that an increase in acidosis following delivery takes place even though vigorous respirations start immediately after the baby is born. This is unlikely to be due to muscular movement since a greater rise is seen in the limp unresponsive infants who require resuscitation. It is probably due to several factors: first, re-establishment of blood flow in areas that have been poorly circulated; second, an unloading of acid products of metabolism, accumulating during a period of oxygen deprivation; third, possible cord compression, the fall in pH actually occurring before birth, the cord blood therefore not truly representing conditions within the baby at the

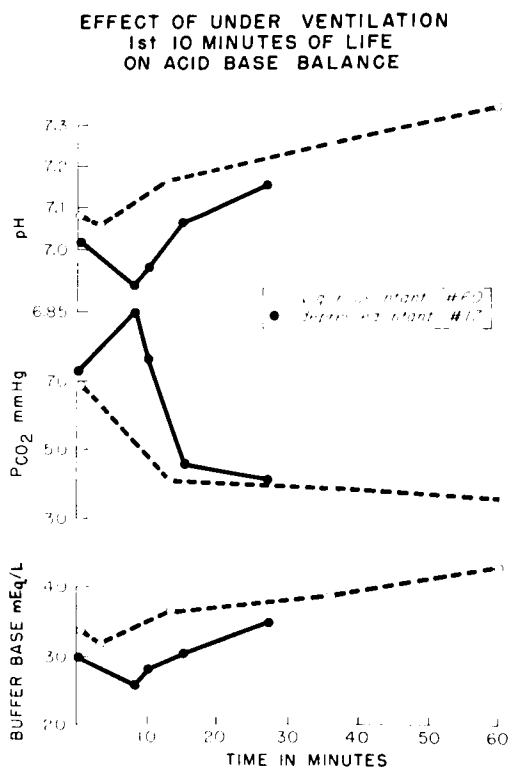


Fig. 8. An infant whose mother received a variety of drugs, meperidine 100 mg., seconal 200 mg. and chlorpromazine (continuous line) compared with a nonmedicated infant (dotted line). At birth the medicated infant was mildly depressed, being given a score of 6. Although he breathed spontaneously within 20 seconds, the respirations were not regular, and he remained cyanotic and somewhat limp. The pH fell rapidly. With gentle stimulation and assisted respiration with positive pressure oxygen the changes were readily reversed.

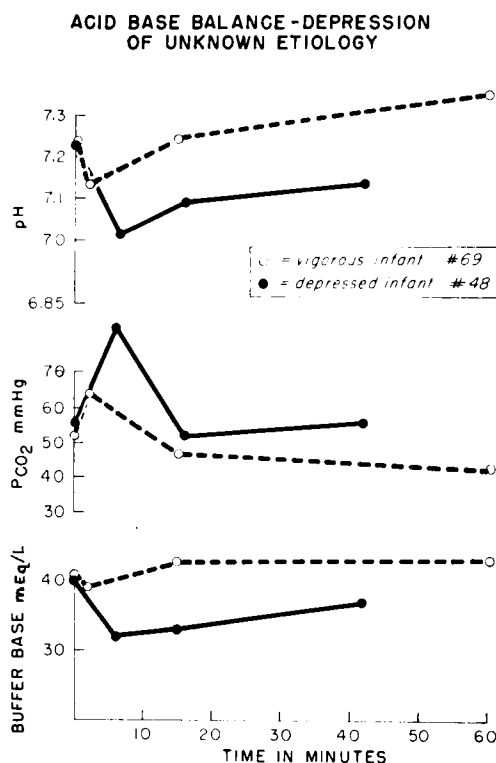


Fig. 9. The acid-base changes in an infant delivered after a precipitous labor are represented by a continuous line. In this instance the cervix dilated fully within 30 minutes of the onset of labor. The mother received no medication or anesthesia. At delivery this infant appeared to be in a satisfactory condition (score 8), but comparison of his recovery pattern with an infant delivered after an easy labor (dotted line) shows a difference.

moment of birth. A similar rise is seen in seals when they surface after diving. Thus, this brief increase in acidosis following birth, is added evidence of an anoxic period during the final stages of delivery.

ASPHYXIA AND ELECTROLYTE CHANGES: Acidosis is reflected in the potassium levels. Here the depressed infants have values which average one milliequivalent higher than the vigorous group.⁸² Over the first hour, with recovery from birth asphyxia, the values fall by approximately one milliequivalent per liter, the vigorous infants reaching the mean maternal arterial levels by this time. Occasionally potassium levels in the cord blood may be as high as ten milliequivalents per liter. In the author's study such values have accompanied severe asphyxia associated with some

form of cord occlusion. Three infants studied have had abnormally elevated levels at one hour. One of these was an edematous infant of a diabetic mother, in respiratory distress, the others were severely asphyxiated due to diaphragmatic hernias and hypoplastic lungs.

These high values stimulated a study of the rate of rise of potassium in the placenta after the birth of the baby. This appears to occur quite rapidly and correlates with a fall in pH. The rise in potassium was due to a transfer from within the cells and not hemolysis since the plasma hemoglobin was not elevated in any of the samples accepted for analysis. In obtaining these results, care was taken to remove a large volume of blood from the placental vessels, in order that blood from within the villi could be obtained and not just a sample from the superficial veins.

These studies have demonstrated that potassium levels in vigorous infants, who achieve a relatively normal acid-base balance by one hour, are little different from those of the adult, irrespective of the gestational age. This confirms recent studies that potassium levels are not elevated in normal prematures.⁸³⁻⁸⁵ High values may be the result of acidosis or disturbances in acid-base balance; or because the samples were obtained from the placenta some time after birth.⁸⁶

Meschia, Battaglia and associates^{87, 88} have shed considerable light on the complex changes, and have shown that the total osmolarity may rise 10 to 45 mOsm/kg. H₂O above the normal level after a brief period of anoxia. In addition, raising the P_{CO₂} experimentally is associated with electrolyte shifts, and liberation of potassium from the intracellular stores.⁸⁹ The recovery phase from CO₂ retention is just as complex a phenomenon.^{90, 91} Much remains to be done before the total body reaction to asphyxia is completely understood.

In summary, the wide range of oxygen saturation values, the relationship between these and other variables which change with asphyxia, namely pH, P_{CO₂}, buffer base and potassium levels, and the pattern of recovery following birth, all suggest that during the delivery process there is a marked reduction in exchange of oxygen and carbon dioxide between mother and baby.

EFFECT OF OXYGEN TO THE MOTHER DURING

LABOR: If this circumstantial evidence is true there should be little difference in the oxygen saturation of the infant, when the mother is given added oxygen. A group of 40 infants delivered with the mothers breathing air, were compared to a group of 40 infants where the mother was given pure oxygen for up to one hour before delivery. There appeared to be no significant difference between the two groups.⁹² This is contrary to several published reports⁹²⁻⁹⁶ but these have been based on small numbers of cases—usually less than 15 and sometimes only five. When the normal range of variation is so great, conclusions can only be drawn if a larger number of babies are studied.

While there can be little question that increasing the oxygen tension gradient across the placenta will result in an increased transfer to the fetus, for this to occur the maternal-placental-fetal circulations must be intact and functioning efficiently. The result of this study in no way alters the rationale for giving oxygen to the mother, but emphasizes that the effectiveness of this procedure during delivery, or fetal distress, deserves further study, particularly in view of the experimental evidence that high oxygen tensions constrict the fetal vessels in the placenta.^{97, 98}

INTRA-UTERINE ENVIRONMENT: Up to the present time, the weight of evidence has indicated that the intra-uterine environment is grossly anoxic by adult standards. However, Sir Joseph Bancroft,³¹ who introduced the concept of "Everest in utero," was fully aware of the difficulties and limitations of experimental methods and of the ways in which anesthesia, posture, surgery and manipulation could change the physiological state. These difficulties have been stressed again by Assali³¹ and he concludes that "even under the best possible experimental conditions, measurement of the umbilical blood flow and umbilical blood oxygen, particularly in early gestation, are subject to a variety of errors, some of which are as yet insurmountable. . . . It is probable, therefore, that most of the figures, including ours, do not represent the true picture of oxygen supply of the fetus, *in utero*, in "basal" state. The fact that different investigators have obtained nearly similar values, particularly in regard to oxygen saturation in

the umbilical vessels, does not prove that these values represent the true picture, *in utero*."

The oxygen consumption of the human fetus and placenta, calculated from the oxygen consumption of uterus + placenta + fetus (the data being obtained with the uterus intact), is at least equal to that of the mother¹⁰¹ and according to Assali,³¹ actually greater. The more recent data agree well with the findings of Acheson, Dawes and Mott⁹⁹ in experiments on the newborn lambs. These experiments also showed that when the arterial oxygen saturation of the carotid arterial blood fell below 35 per cent there was a rapid fall in oxygen consumption. If the fetus behaves in a similar fashion—and there is reason to believe that it does—here then is further data inconsistent with the concept of "Everest in utero." If low oxygen values are normal, how can the fetus have an oxygen consumption similar to or higher than the mother?

Employing a new technique, whereby the umbilical vessels were bypassed, Dawes⁷⁸ recently has shown that under optimal conditions, where surgical procedures are minimal and of short duration, the oxygen saturation in the carotid artery of the Rhesus monkey fetus is 79 per cent and that in the femoral artery 74 per cent. Since femoral artery blood is the same as that returning to the placenta via the umbilical arteries, the blood flowing from the placenta to the fetus must have been considerably better oxygenated.

Assali and co-workers³¹ have gone even further, bypassing all surgery and introducing polarographic electrodes for measuring tissue oxygen tension, directly into the brain of the pregnant guinea pig and her fetus. Those studies have shown that the oxygen tensions of both mother and fetus, *in utero*, were equal.

This new information is of great importance. It confirms the indirect evidence in human babies, described earlier, for a higher oxygen environment, *in utero*, and shows that the concept of a low oxygen environment, *in utero*, has been based on a mistaken premise. From this it must be concluded that labor and delivery are primarily responsible for low oxygen levels and acidosis at birth. The great majority of infants recover from this episode of "physiological" asphyxia quite readily. With good pulmonary ventilation, a vigorous non-

medicated baby will have a relatively normal acid-base balance by one hour.

FACTORS WHICH MAY CONTRIBUTE TO THE ASPHYXIA

CORD COMPRESSION: Any reduction in the blood flow through the cord will lower arterial oxygenation since the blood in fetal veins will be passing directly into the arterial circulation with little or no mixing with oxygenated blood flowing from the placenta in the umbilical vein. The saturation in the umbilical vein will remain unchanged or may even be raised, since the fetal blood will remain in contact with blood in the intervillous space for a longer period; but with reduction in flow, little of this blood will reach the fetal circulation. The reduction in flow can be caused by kinking, prolapse, pressure between the fetus and the rim of the pelvis or vagina, or when the cord is wound tightly round the neck. Clemetson and Churchman⁷¹ have shown the large difference in saturation between the umbilical artery blood and that in the vein, which may be found in this last situation. Manipulation of the cord causes constriction of the umbilical arteries, which in turn slows the stream of blood through the placenta. Barcroft³⁴ has vividly described the acute sensitivity of these vessels, particularly at term.

Analyses of cord blood at birth indicate that approximately one-third of babies delivered vaginally have a wide difference in oxygen levels between the umbilical vein and artery.^{48, 76} Only a small proportion of these infants had visible evidence of cord obstruction, suggesting that some degree of cord occlusion occurs more frequently than is apparent clinically. Direct observations by Maxwell of occult prolapse of the cord at cesarean section support this idea.¹⁰⁰

Another possible cause for the wide A-V difference has been proposed; namely, that fetal tissues have a greater ability to extract oxygen.¹⁸ This is an assumption based in the first place on low oxygen levels in the umbilical artery and secondly on the high coefficient of oxygen utilization. These two factors are not independent and should be considered together. The ability to extract almost all of the oxygen from the circulating blood is not a property exclusive to fetal tis-

sues. During violent exercise blood returning from active muscles is almost completely free from oxygen. Without a knowledge of blood flow and oxygen consumption it is somewhat hazardous to draw conclusions from the difference in oxygen levels in the vessels of the umbilical cord. The infant may be extracting a greater proportion but actually be getting less oxygen. Reid⁵² recently has stressed that even though the umbilical vein oxygen may be normal, the fetus will be in oxygen deficit if the blood flow through the cord is impeded.

The oxygen coefficient of utilization is defined as follows:

$$\frac{\text{O}_2 \text{ taken up by the tissues}}{\text{O}_2 \text{ content of arterial blood}}$$

In employing this formula for the fetus, it has been transposed to

$$\frac{\text{O}_2 \text{ content of umbilical vein} - \text{O}_2 \text{ content of umbilical artery}}{\text{O}_2 \text{ content of umbilical vein}}$$

Since oxygen uptake by the tissues infers oxygen consumption, there is some question as to whether this is a valid transposition. Without a knowledge of the volume of blood flow per unit of time (flow rate), the UV oxygen-UA oxygen gives no information regarding the oxygen uptake by the fetus. Further, the umbilical artery blood is more representative of blood supplying the fetal tissues than blood in the umbilical vein.^{77, 78} If this fetal arterial blood is low in oxygen (below 35 per cent saturation) the oxygen consumption by the fetus is likely to be markedly decreased.⁹⁹ In consequence, if the coefficient is regarded as being directly related to the oxygen consumption, the calculation based on the second formula would be fallacious and misleading.

CHANGES IN UTERINE BLOOD FLOW: These may occur as discussed earlier, from several causes. The supine position has been shown to be associated with compression of the mother's inferior vena cava by the heavy gravid uterus. Howard and his associates³⁵ have demonstrated that the pressure in the femoral vein may be raised from 108 to 239 mm. of water by this mechanism. This rise will decrease the pressure gradient between the uterine artery and vein and will tend to reduce blood flow through the uterus. When

the obstruction to the inferior vena cava is more complete, sufficient to cause hypotension in the mother,¹⁰² an even greater reduction in flow will occur. This factor must be considered in cesarean section during which the mother may be flat on her back for 15 or 20 minutes before the baby is delivered. It is probable that the occasional very low oxygen value obtained in both cord vessels at cesarean section under local anesthesia is caused partly by this obstruction effect.⁷³

Maternal hypotension occurring during spinal or caudal anesthesia (see above) and strong uterine contractions, particularly in the expulsive phase^{40, 41} may also reduce uterine blood flow. The lower oxygen levels reported by Henderson¹⁰³ in infants born by cesarean section under spinal anesthesia compared to the levels when inhalation techniques were used is similar to experimental observations when spinal anesthesia was compared with thiopental.³⁶

When uterine blood flow is reduced, the oxygen tension gradient between the maternal arterial and fetal blood will increase, while the oxygen levels in both the umbilical vein and artery will fall, the content in the vein approaching that of the artery (reduction of the A-V difference). On occasion the oxygen levels in both vessels may be almost identical.^{48, 101}

PLACENTAL INFARCTION OR PARTIAL SEPARATION: Both conditions will lead to a reduction in the effective area of diffusion and if extensive, will lead to a lower oxygen level in the fetus. Although the placenta has been regarded as having a large "functional reserve," there is reason to question this belief, particularly in the infant at term. Little^{104, 105} has recently observed that the fetus died in eight instances before labor or in the early stages of labor with the placenta 30 per cent infarcted. He has further shown that as the degree of infarction increases, the incidence of fetal distress also increases significantly. If the placenta was more than five per cent infarcted, the incidence of fetal distress was ten per cent.

REDUCTION IN MATERNAL EXCHANGE OF RESPIRATORY GASES: This will occur during breath holding, straining, poor anesthesia induction, and underventilation from overseda-

tion. Maternal exhaustion, associated with dehydration and a metabolic acidosis in a long and strenuous labor are also likely to contribute.

In view of these multiple factors, the important question arises as to whether or not the physiological data obtained at elective cesarean section are truly representative of the normal basal intra-uterine state. The answer is undoubtedly no.³¹ Supporting this opinion is the wide range in oxygen levels in the cord blood together with concurrent changes in acid-base balance, indicating interference with maternal and fetal gaseous exchange.⁴⁸ Not only must maternal posture, blood pressure changes and respiratory exchange be considered, but also alterations in the uterine circulation with manipulation, incision and the immediate contraction which occurs as the amniotic fluid gushes out. The time usually required from the moment the uterus is incised to extraction of the fetus and final clamping of the cord may be 60 seconds and often longer. This time interval should be considered in relation to the rate that oxygen levels have been shown to fall as indicated in figure 5. The oxygen levels in the cord may not fall as rapidly as this, but since there is no knowledge of the uterine blood flow at this time, one cannot assume that it is normal.

These arguments do not detract from the value of physiological studies, which have contributed greatly to our understanding,^{31, 70, 75, 101} but emphasize their limitations. While the degree of disturbance of gaseous exchange and asphyxia may in general be less at elective cesarean section performed under ideal circumstances, in all likelihood it will be present to some extent. It must be concluded, therefore, that the cord cannot be exposed without disturbing the normal condition of pregnancy, and studies of oxygen transfer from mother to fetus will become more meaningful if cognizance is taken of the acid-base status and P_{CO_2} .

ANALGESIA, ANESTHESIA AND ASPHYXIA

While mild asphyxia will stimulate respiration, profound degrees are depressant. This phenomenon has not been better demonstrated than in the early experiments of Schmidt.¹⁰⁶

A similar effect in the newborn is demonstrated by the response of two infants in figure 6. Even quite severely asphyxiated infants will respond rapidly if labor and delivery have been conducted with minimal or no sedation (fig. 7). Conversely, an infant who is only mildly asphyxiated will also respond rapidly in spite of anesthetics or heavy medication. The highest level of cyclopropane (fig. 3)⁴⁶ was in a vigorous infant (score 8) whose oxygen saturations in the umbilical vein and artery were 85 and 49 per cent, respectively, while the pH values were 7.35 and 7.30, respectively.

The potential danger lies in the possibility of asphyxia being superimposed upon a high level of depressant drugs or potent anesthetic agents. This is a likely explanation for the difference observed by Snyder in rabbit fetuses given large doses of morphine;²³ those delivered vaginally were less responsive and had a higher mortality. In the light of earlier discussion, this group was probably more asphyxiated.

Untoward reactions are rare with the potent inhalation agents, provided ventilation is maintained.¹⁰⁷⁻¹⁰⁹ Cardiac arrhythmias seem to be associated particularly with an elevated P_{CO_2} . The mean P_{CO_2} in the vigorous newborn is in the region of 55 mm. of mercury, and in the depressed infants, considerably higher. The combined effect of asphyxia with cyclopropane anesthesia is well demonstrated in the case reports of Waters and Harris¹² (see above).

Not only should the relationship of asphyxia to drug action be considered, but also the new evidence relating to the increased susceptibility of the newborn to depressant drugs. The opposite opinion is sometimes expressed by anesthesiologists based on their experience of difficult and long induction periods with ether in the newborn; this difficulty is, however, probably related to the fact that tidal volume, functional dead space and functional residual capacity are, by comparison with adults, relatively less, while the B.M.R. is higher.¹¹⁰ Dawes has noted the increased susceptibility in both lambs and puppies,¹¹¹ and inability to metabolize barbiturates has been reported in mice, guinea pigs¹¹² and rabbits.¹¹³ A hypersensitivity to *d*-tubocurarine chloride has also been proposed in human newborns,¹¹⁴ the

response resembling that of a myasthenic patient.

The presence of varying amounts of asphyxia and the possibility of increased susceptibility to drugs, are important factors to be taken into account, both in drug trials in obstetrics and in surgery in the newborn period.

Reference to figures 7 and 8 indicates the effects of underventilation at birth and shows how even small doses of analgesic or sedative drugs may slow the rate of recovery from birth asphyxia. These studies suggest that we should employ the drug antagonists¹¹⁵ more than is at present customary. Such an idea is supported by the studies of Roberts and co-workers.¹¹⁶ However, the introduction of antagonists should not be an excuse for the administration of massive doses of narcotics to the mother,²⁶ since these, of themselves, can alter the course of labor. Further, Eckenhoff and co-workers have doubted the efficacy of antagonists administered with clinical doses of narcotics.^{117a} This opinion is amplified in an excellent discussion by Eastman.^{117b}

EVALUATION OF DRUGS FROM THE CONDITION OF THE INFANT

The lack of correlation between the dose of a particular drug and the response of the infant has been mentioned earlier. This had tended to create a false sense of security in the minds of some obstetricians. Examination of figures 6, 7, 8 and 9 indicates that the clinical condition of the infant at birth and his biochemical readjustment are influenced not only by the dose of anesthetic agent, but also by the degree of biochemical change itself, and a third factor which is difficult to define, relating to the physical trauma of delivery. All three must be taken into account in evaluating the infant, and particularly his response to medication. The presence of two unknown variables, namely the biochemical changes of birth asphyxia and delivery trauma, undoubtedly account for the lack of correlation noted above.

EVALUATION OF DRUGS FROM INFANT MORTALITY

Today the over all perinatal mortality is extremely small and the problems arising from

analgesia and anesthesia are slight compared to those associated with the various complications of pregnancy. Hingson and Hellman state that consequently most investigations of the relationship of pain relief to fetal death have failed to yield conclusive answers.¹¹⁸

Because of the many obstetrical factors and the small perinatal mortality, one might be tempted to say that drugs played no role in the mortality. And in almost every death there is some other possible cause—including prematurity, hemorrhage and toxemia. Since mortality is too crude a measure, morbidity or the more subtle method of determining exactly how drugs affect the physiology of labor and neonatal adaptation may be chosen. At present our knowledge of this physiology is still in its infancy. It is hoped that as understanding of this subject increases, so will our ability to deal with the complications of labor without adding any potential hazard to the infant.

From time to time reports are published of prolonged apnea at birth and apparent complete recovery. Such a case history appeared in the *Lancet*, in 1958.¹¹⁹ A subsequent editorial comment¹²⁰ states "This is an exciting case history, full of drugging, blunder and woe, and of most evil portent for the baby." Endotracheal positive pressure resuscitation was instituted at ten minutes but the infant did not breathe satisfactorily for over eight hours. Even so, he won a baby prize at nine months.

It is important that such cases be carefully recorded for the purpose of future follow up. However, it is equally important that readers not be misled into thinking that the child will be completely normal if smiling, sitting up and walking all take place at expected times. Data developed by Pasamanick and Lilienfeld¹²¹ suggest that epilepsy, mental retardation and behavior disorders may be associated with difficulties during pregnancy and labor and the neonatal period. These disorders need not become apparent for three to five years.

ASPHYXIA AND ACIDOSIS PHYSIOLOGICAL EFFECTS

Following delivery and prompt lung expansion with crying, the oxygen saturation rises

rapidly. Within minutes after birth the blood is over 90 per cent saturated in a vigorous newborn and also in the depressed group if efficient resuscitation is given. However, the acidosis remains and disappears at a slower rate. These observations not only reveal the extreme lability of oxygen levels, but suggest that the degree of acidosis is a truer indication of a period of oxygen deprivation.

There is a growing volume of evidence¹¹⁰ indicating how asphyxia and acidosis may exert a profound effect on body functions. Not only is oxygen consumption markedly decreased when arterial oxygen levels fall below 35 per cent,⁹⁹ but it is also influenced by the tension of carbon dioxide.¹²² In addition, there are changes in blood osmolarity,^{87, 88} discussed earlier, cardiac, renal and hepatic function. Acidosis causes a reduction in cardiac output⁴³ and if asphyxia is prolonged, the blood pressure falls as a result of cardiovascular collapse and circulatory failure.^{110, 123-125} A diminution in urine output occurs when the arterial P_{CO_2} rises acutely^{126, 128} and the pH falls below 7.2.¹²⁹ There may be complete renal failure when pH reaches 7.0 or 7.1. Finally, raising the P_{CO_2} to 55 to 70 mm. of mercury reduces the bromsulphalein clearance significantly.^{130, 131}

Although the majority of infants survive the acidosis, it should not be concluded that asphyxia is completely safe, and evidence that disturbances of function occur in the asphyxiated newborn recently have been summarized.¹¹⁰ In this regard, the editorial comment in the obstetrical and gynecological survey (1957)¹³² on acidosis of the newborn is worthy of note. "Such extreme degrees of acidosis can be borne only for a very short time; it is common knowledge moreover that the fetus is especially vulnerable to acidosis as exemplified by the high fetal mortality whenever diabetic mothers develop acidosis."

Recovery from the acidosis is primarily dependent on the prompt establishment and maintenance of good ventilation. John Snow was aware of the importance of resuscitation and ventilation and his astute clinical observations, published in the London Gazette,¹³³ in 1841, are so pertinent that they should be read by all caring for the newborn. "This artificial respiration should be persevered in for some

time, say an hour at least, before we give up in despair; and if our efforts be successful, we should still persevere until the child is completely revived, and capable of carrying on a full and effective respiration of its own: for the secondary asphyxia which so often comes on, arises, in my opinion, from an efficient respiration not having been established, whence the blood remains in a badly oxygenated state, and does not rouse the nervous system to its full sensibility, but allows it to remain in a condition, so to speak, of not truly appreciating its own want of respiration. I know an instance where the breathing of a child was accidentally interfered with just after birth; and although not to the extent of producing asphyxia, respiration was never properly performed, and the child died after a few hours." ("Secondary asphyxia" probably refers to the cyanosis and episodes of apnea seen in the condition known today as the respiratory distress syndrome or hyaline membrane disease.)

"IDEAL" ANALGESIA AND ANESTHESIA

As in general surgery there is no ideal analgesia or anesthesia for obstetrics. Of first importance is adequate preparation of the mother during pregnancy. The data of Friedman¹⁹ suggest that this may actually shorten labor. In addition, the patients will require appreciably smaller total amounts of analgesics and sedatives.¹³⁴ Hypnosis, for so long held in disrepute by medical men, should also be mentioned.¹³⁵ The benefits of this technique particularly in the rapid readjustment of the infant's acid-base balance have been studied by Moya and James.¹³⁶ Although the proponents of "natural childbirth" maintain that they do not use hypnosis, relaxation and suggestion are subtly used throughout the preparation period. Greenhill points out,¹³⁷ "This does not detract or add mystery to the Read method; quite the reverse. It makes order out of chaos because those familiar with the medical applications of hypnosis recognize the power and influence of suggestion and willingly use it as a valuable therapeutic adjunct."

Regional techniques are gaining in popularity but they are not without problems. The slowing of labor if the caudal or spinal is given too soon, maternal hypotension and in-

advertent high spinal anesthesia of overwhelming proportions (fortunately extremely rare) are disadvantages. As a result of maternal mortality from the last complication some centers strongly recommend against the use of spinal anesthesia. Greenhill¹³⁷ states that "it is the most dangerous type of anesthetic for pregnant women." On the other hand, Hingson and Hellman¹³⁸ report 78,000 obstetrical spinal anesthetics with only one maternal death. Complications from spinal anesthesia seem to be related to the increased lumbar lordosis of the pregnant woman and her vasomotor instability. For effective anesthesia the dose may be reduced from one-half to one-third of the usual amount. Despite some limitations, from the infant's point of view spinal anesthesia offers advantages over inhalation techniques for cesarean section. The infants are more vigorous, and a recent report¹³⁸ notes that since employing regional anesthesia rather than inhalation techniques the cesarean section syndrome (hyaline membrane disease) has almost disappeared.

Occasionally it is necessary to relax the uterus completely and rapidly—for example, for the delivery of a second twin when there is a sudden fall in the fetal heart rate. This is impossible with caudal or spinal techniques and can only be achieved with deep general anesthesia. Moya¹³⁹ has reported that halothane, when administered by means of a precision vaporizer, is the safest and most rapid agent; ether and chloroform are also effective. On the other hand, cyclopropane does not significantly depress uterine activity until plane three is reached, and even then it may be insufficient. This clinical experience is supported by the studies of Woodbury, Hamilton and Torpin¹⁰ showing that cyclopropane, in contrast to ether and chloroform causes small interference with uterine contractions.

The problems related to both regional and inhalation techniques are illustrated in an interesting analysis of second twin mortality, by Little and Friedman.¹⁴⁰ While over all mortality was lower with regional techniques, it was considerably higher if version-extraction was performed under regional anesthesia. On the other hand, the mortality with cyclopropane rose sharply if anesthesia was prolonged for longer than ten minutes. The number of

deaths involved is not sufficient for significant statistical analysis.

Theoretically, it would be ideal to have an agent which had a particular molecular configuration which prevented it from passing the placenta. Of the drugs used in anesthesia, curare and succinylcholine appear to have such properties. Moya and co-workers¹⁴¹ have recently shown that succinylcholine, when administered in usual doses, does not cross the placenta in demonstrable quantities. Curare was first reported for cesarean in conjunction with cyclopropane in 1945¹⁴² and shortly after in conjunction with a thiobarbiturate.¹⁴³

Emergency cesarean section for fetal distress can be one of the most challenging situations an anesthesiologist has to face, particularly if the mother has a full stomach and a severe antepartum hemorrhage. Not only must he have a thorough knowledge and experience of all available techniques, but also a thorough understanding of the physiology of pregnancy, labor and delivery. The more potent inhalation agents, ideal for the mother, are likely to prejudice the survival of the fetus. Because it crosses the placenta in such small quantities, succinylcholine in conjunction with light nitrous oxide anesthesia appears to offer special advantages, and these are at present under investigation.¹⁴⁴

As regards analgesia, there can be no question that the more powerful drugs not only depress the baby, but prolong labor. The problem has been excellently summarized by Waters and Harris.¹² "If complete safety and complete pain relief are to be our aims, we must admit that the two objects tend to be reciprocally incompatible—more safety, less pain relief; more pain relief, less safety." The authors also caution against the use of new drugs: "Taking up the use of a new drug or combination of drugs because some one else reports success with it, is a dangerous experiment, to be undertaken with care." These words of wisdom are even more important today when the physician is bombarded with an ever increasing number of new drugs under high pressure advertising. Once a drug is introduced, convenience may keep it in use, and many years are likely to elapse before there is evidence in the literature emphasizing disadvantages or dangers, even though there

are side effects which are detrimental to the welfare of both mother and child. The history of the use of chloroform and twilight sleep are excellent examples illustrating this point.

CONCLUSION

A historical survey of obstetrical anesthesia indicates that the pendulum is swinging from an era of excessive use of drugs, toward one of minimal medication. With a dramatic reduction in both maternal and infant mortality over the last 50 years, better antenatal care and greater education of the public, child-birth no longer conjurs up the traditional terrors of the past. Improvement in the mental attitude of mothers is one of the major factors contributing to this trend.

Hitherto great attention has been paid to pain relief and other pharmacological actions of various drugs were neglected. As a result we are only now beginning to appreciate how analgesic agents can prolong labor and indirectly exert a deleterious effect on the fetus.

Since the delivery process appears to reduce the exchange of oxygen and carbon dioxide between mother and baby, and the infant is born in a state of biochemical asphyxia, the physician must also be aware that the mildly depressant action of a particular drug may change to one of toxicity if asphyxia is superimposed.

The asphyxia partly accounts for the lack of correlation between the dose of a particular drug and the response of the baby at birth. To evaluate the newborn, not only must the amount of drug administered to the mother be considered, but also the degree of asphyxia and the trauma of delivery.

The degree of acidosis in the baby is a truer indication of a period of oxygen deprivation. Infants with a mild metabolic acidosis at birth may have either a relatively high or an extremely low oxygen saturation. In the absence of excessive medication of anesthesia, these infants are always vigorous. On the other hand, those infants with a profound metabolic acidosis always have low oxygen levels at birth and are invariably depressed.

Since oxygen levels are extremely labile, if exchange at the pulmonary or placental level is impeded, and the uterus or umbilical cord

cannot be exposed without to some extent disturbing the normal conditions of pregnancy, studies of oxygen transfer between mother and fetus will become more meaningful if cognizance is taken of the acid-base status and P_{CO_2} .

From adult and experimental physiology, acidosis may carry important implications. It increases the toxic action of potent anesthetic agents. Renal function is diminished with a pH of 7.2 and renal shutdown may occur when the pH reaches 7.0. Other effects relate to optimum pH for various enzyme functions. Finally, cardiovascular collapse is imminent when the pH falls below 6.9. For those actively engaged in the care of babies at birth, it is important to bear in mind how rapidly the pH will fall in the presence of apnea.

These factors all stress responsibilities of the anesthetist in the delivery room. Not only must he be skilled in the administration of anesthetics, but he must have a knowledge of pharmacology, and a thorough understanding of the physiology of pregnancy, labor and delivery, if he is to meet the challenging situations in obstetrical anesthesia successfully.

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POSTPARTUM HYPERTENSION A study of 8,000 deliveries performed under continuous caudal block analgesia indicated that the combined effect of a vasoconstrictor and an oxytocic drug in standard dosages, given three to six hours apart, led to severe hypertension in 34 (4.6 per cent of 741) patients. Headache was the most common symptom of these patients, occurring in about 80 per cent of cases. The rise in diastolic pressure is the more significant component and the one responsible for severe headache and rupture of cerebral blood vessels. Neither the headache nor the hypertension is relieved by routine therapy. However, chlorpromazine hydrochloride, 12.5 to 15 mg., given intravenously at the rate of 2.5 mg. every 15 seconds, will rapidly return the pressure to normal, apparently because of the adrenolytic action of the drug. Because of the severity of

this complication, the combination of a vasoconstrictor and an oxytocic drug should be eliminated if possible, and prophylactic administration of vasoconstrictor drugs should be omitted when regional block anesthesia is to be used for vaginal delivery. (*Casady, G. N., and others: Postpartum Hypertension After Use of Vasoconstrictor and Oxytocic Drugs, J. A M. A. 172: 1011 (March 5) 1960.*)

OXYTOCIN Synthetic oxytocin (Syntocinon) was administered to 3,342 patients for a wide range of indications. There was no synergistic action between the synthetic oxytocin and anesthesia with ethyl ether or cyclopropane by inhalation or with spinal anesthesia. (*Hibbard, L. T., and Andrews, A. V.: Synthetic Oxytocin, Calif. Medicine 92: 143 (Feb.) 1960.*)