THE ROLE OF DRUGS IN FOETAL MORTALITY*

NEIL A. STEWART, M.D.**

IT HAS BEEN SAID that the most dangerous day of our life is the day on which we are born. There is no doubt that this statement is true, and while there have been great advances in our modern age in pre-partum care, antisepsis, method of delivery and infant care, there have been added during the past one hundred years additional hazards attendant upon the use of obstetrical analgesia and anaesthesia

Since Queen Victoria received chloroform in 1853 at the birth of Prince Leopold, the use of pain-relieving drugs has become an established procedure. It is only during the present century that the use of analgesic drugs in the first and second stages of labour has become popular. In 1902 Von Steinbuchel added scopolamine to morphine and so the famous era of "Twilight Sleep" was born. This combination was used very extensively for about twenty years and was followed by many other drugs, such as large doses of paraldehyde by rectum, tremendous doses of barbiturates by mouth, and a number of others. Many of these drugs have been discontinued because of their obvious effects on the foetus, and we are now in the stage where we are using not only a few of the old and trusted drugs but also certain new drugs and combinations of drugs which are felt to be safer for the infant

It is extremely difficult to evaluate the effects of analgesia and anaesthesia on the foetus in a scientific manner, and it is necessary to rely to a great extent on clinical impressions at the time of delivery, the history of the baby following delivery, or autopsy findings in the case of the stillborn or those dying soon after birth. However, a great deal of experimental work has been done involving the use of animals during the past twenty years, and while it is always dangerous to assume that animals react in the same way as human beings nevertheless this work can at least give us a lead as to what is happening in the case of humans

In order to estimate the effects of drugs on the foetus, it has been necessary to find some way of assessing these effects without the other complications of labour. This has been found to be possible in the case of the rabbit, which comes to full term at thirty days (1). By the administration of corpus luteum material, the gestation period can be prolonged to at least thirty-two days. During this time the foetus can be observed under both normal and abnormal conditions. For instance, the uterus can be opened under conduction anaesthesia in a saline bath and the litter watched under direct vision with the placental circulation intact. A number of very interesting things can be observed by this method, and it can be definitely proved that the foetus breathes amniotic fluid, not only by watching the breathing but by introducing various dyes into the fluid and later finding the dyes in the lungs of the foetus. The effects on the foetus of drugs and anaesthetics administered to the mother can also be observed, and it has been

*Presented at a meeting of the Western Divisions, Canadian Anaesthetists' Society, Vancouver, B C, April 5-7, 1956

**St Vincent's Hospital, Vancouver, B C.

shown that some drugs slow the breathing and others completely arrest it. It has also been demonstrated by this method that there are numerous cases of foetal pneumonia and asphyxia neonatorum that are not related to analgesia and anaesthesia but are present for a considerable time before birth, and that therefore the use of such drugs cannot be held accountable in all cases where there seems to be no logical explanation for the birth of a dead baby.

A great deal has been said and written about sensitivity of the foetal respiratory system to drugs and anoxia. While there is no doubt that this partly exists, the most amazing thing about a foetus is its ability to withstand trauma, narcosis, and anoxia. Every day healthy, lusty babies are born by narcotized, anaesthetized mothers. It is a matter of record that the cord blood at birth shows much less oxygen concentration than that of the mother and that some babies can live for a period of thirty minutes following birth without drawing a breath, which would indicate a resistance to lack of oxygen at least ten times that of an adult.

In order to have an understanding of the effects of drugs on the foetus it is necessary not only to study the direct effects on the foetus but also to study their influence on the mother; whether they tend to increase or decrease the force and frequency of the contractions, whether labour is prolonged or modified by the agent used, the transmissibility of the drug through the placental membrane; the mode of such transmission and the variations in oxygen tension in the mother's blood, all of which factors have a place in determining the final outcome for the foetus. It has been shown, as previously mentioned, that certain drugs and anaesthetics inhibit the respiration of the foetus *in utero* and it has also been shown that babies born in advanced anoxic condition owing to depression of their respiratory activity directly by drugs, or owing to the action of these drugs in prolonging labour, even though resuscitated often remain in a lethargic or deeply depressed condition for days, and in many cases die in the first week of life. It consequently becomes important to know, not only from a standpoint of foetal mortality but also of foetal morbidity just what action the various agents we use have both on mother and foetus and also the best time during labour for administration of these drugs.

In general, the drugs and anaesthetics used during labour act in two ways (i) they raise the pain threshold, and (ii) they produce a feeling of sleepiness, euphoria and well-being.

Most of the drugs can be classified under the following headings:

(1) Narcotic drugs such as morphine, codeine, pantapone, Demerol and heroin, which act mainly by raising the pain threshold but also produce euphoria.

(2) Barbiturates such as Nembutal, Seconal, sodium pentobarbital, and Pentothal, which act mainly by producing euphoria, drowsiness, and sleep.

(3) Drugs such as scopolamine which produces amnesia.

(4) The anti-histamine group such as Largactil, Phenergan, which produce drowsiness and tend to potentiate the action of other drugs.

(5) Inhalation anaesthetics such as ether, chloroform, nitrous oxide, tri-chlorethylene, and cyclopropane.

(6) Conduction anaesthetics—Procaine, Pontocaine, Nupercaine, etc.

While it is not possible at this time to discuss each drug separately, an effort will be made to discuss them as groups and to indicate the advantages and disadvantages of each group.

As has been mentioned previously, morphine and its derivatives, particularly in combination with scopolamine, were very popular for many years. There is no doubt that this combination has been one of the most effective in easing the pain of the pre-delivery period of child birth. However use of it has been largely discontinued as it has been found clinically to cause too much depression to the foetus, and more particularly so if administered between the second and third hour before delivery.

The practice of using large doses of barbiturates has also been largely discontinued, and these drugs have been blamed for causing lethargic depressed babies who do not breathe well or nurse readily. However, the interest in Sodium Pentothal has recently been revived and there are some anaesthesiologists who are using Pentothal as an anaesthetic for delivery (2). Levis of London has been using this drug for many years (3) His method is to give $\frac{1}{4}$ gr. Pentothal about twenty minutes before delivery, and he states that while the concentration of Pentothal in the mother's blood and the cord blood is the same at the time of birth, nevertheless he has never noticed any depression of the baby which he felt could be attributed to the anaesthetic. In support of this observation, work done during the past year on humans by McKechnie and Converse of Albany indicates that the foetal blood reaches equilibrium with the maternal blood three minutes after the injection of Sodium Pentothal. They also state that the reason for their favourable findings on the use of Pentothal for obstetrics is that this drug administered intravenously is distributed throughout the body through a fat phase and a water phase, the latter consisting of blood and organ tissue, and that the concentration in blood and organ tissue passes into fat. They therefore think that a large portion of the initial Pentothal injection is removed by the tissues and that not enough is transferred via the umbilical cord to reach a level in the brain of the foetus adequate to produce depression. If these observations are correct, it would appear that a single dose of Pentothal would not be injurious to the foetus but that repeated injections would be, owing to storage of the drug in fat.

Of the volatile anaesthetics and gases in use, ether, nitrous oxide, and cyclopropane are the most common. In work done by Snyder on animals with ether it was found that foetal respiration was completely abolished when the level of surgical anaesthesia was reached in the mother. However ether is nevertheless an excellent anaesthetic for delivery provided it is not administered for too long a time or to the level of surgical anaesthesia, and its safety can be attested by the fact that it is widely used throughout the country, particularly where trained anaesthetists are not available.

Nitrous oxide is a remarkably safe anaesthetic provided that a ratio of 80 per cent nitrous oxide and 20 per cent oxygen is not exceeded. It has very little effect on the foetus, provides satisfactory analgesia for the mother, and is rapidly eliminated.

The so-called conduction type of anaesthetic is probably safest for the baby, with one reservation. It has been noted that if there is too much reduction in

blood pressure of the mother, the relative blood pressures of the mother and foetus are disturbed. This differential blood pressure has been loosely called the "placental blood pressure," and while other factors are involved there is no doubt that a lowering of maternal blood pressure could have a serious effect by altering the passage of gases through the placenta. However, the point is relatively academic and could be readily compensated for by the use of vasopressors and the administration of oxygen to the mother. In spite of the fact that conduction anaesthesia is safest for the baby in that it does not involve the use of narcotic or depressant drugs, it nevertheless enjoys limited popularity. Epidural and caudal blocks are the methods commonly used today. Many dangerous complications may ensue, such as arrest of labour, high or total spinal anaesthesia, or introduction into the spinal fluid of lethal doses due to congenital abnormalities or lack of skill on the part of the operator.

Recently a group of synthetic anti-histamine type drugs have appeared on the obstetrical horizon and have been subjected to extensive clinical tests. These drugs, of which Phenergan and Largactil (4) are an example, are often called "neuroplegic" drugs. They act by producing torpor and somnolence and by potentiating the action of other drugs and anaesthetics. These drugs also have certain side effects such as partial blockage of both sympathetic and para-sympathetic systems, and thus have an effect on maternal blood pressure which is rather unpredictable. Opinions vary regarding the use of these drugs. However one large obstetrical hospital in the city of Vancouver uses Phenergan with very good results and apparently with very little effect on the babies.

Before closing it should be stated that this paper has had to do with full-term babies. It is generally agreed among obstetricians and anaesthesiologists that the premature infant is particularly sensitive to alterations in its physiological functions attendant upon the use of drugs, and that the greatest care should be used in handling these cases. Recently a drug which bears the trade name of Nalline has come into extensive use as an antidote for narcotic over-dosage (5). Many obstetricians wish this drug to be administered either to the mother before delivery, or to the baby after delivery. This is an excellent drug when used in its proper place but it tends to intensify and prolong the action of barbiturates and general anaesthetic agents, and in obstetrics should only be used in those cases where these have not been administered.

CONCLUSIONS

1. The best combination of drugs in the medical armamentarium for the reduction of pain during labour has been that of morphine and scopolamine, but this combination has proved very dangerous to the baby.

2. The use of barbiturates is generally contra-indicated, but new work has been done with Sodium Pentothal, and possibly this anaesthetic may be used more extensively when more definite knowledge is obtained.

3. Constant and expert supervision is needed over the administration of all drugs pre-partum.

4. The ideal analgesic agent for maternity work has not yet been found.

RÉSUMÉ

En obstétrique, depuis l'usage de l'anesthésie par la Reine Victoria, il est fait un usage courant de l'analgésie et de l'anesthésie. Au cours des vingt dernières années, on a mis au point des appareils permettant d'observer la respiration du foetus dans l'utérus et il est maintenant possible d'observer "de visu" les effets, sur la respiration du foetus, des substances anesthésiques et des drogues employées. Au cours de la première partie du siècle, on employait fréquemment la morphine et la scopolamine; aujourd'hui, à cause des effets contraires de ces drogues sur le foetus, on a réduit de beaucoup leur usage et on les a remplacées par le Demerol et le Phenergan. Comme substances anesthésiques, le cyclopropane, le protoxyde d'azote, le trichloréthylène et l'anesthésie régionale ont remplacé l'éther et le chloroforme. Pour les prématurés, toutes les drogues sont dangereuses. Pour combattre la dépression causée par les drogues sur le foetus, on ne devrait pas employer la nalline en même temps que l'anesthésie générale ou en même temps que des barbituriques.

REFERENCES

- 1 SNYDER, F. F. *Obstetric Analgesia and Anesthesia. Their Effects Upon Labor and the Child*. Philadelphia: W. B. Saunders (1949).
- 2 McKECHNIE, F. B. & CONVERSE, J. G. Placental Transmission of Thiopental. *Am. J. Obst. & Gynec.* 43 (September 1955).
- 3 LEVIS, K. P. (London, England) Personal communication.
- 4 SAVAGE, DAVID. Chlorpromazine as an Analgesic in Labour. *Brit. J. Anaesth.* 27: 346 (July 1955).
- 5 GREEN, B. H. The Role of Nalline in the Prevention of Treatment of Narcotic Depression in the Newborn. *Am. J. Obst. & Gynec.* 70: 618 (September 1955).