

as brain concentrations were not included in the anencephalic tissue levels measured, and spinal cord levels are not relevant because of differences in the origins of the perfusing blood. On the other hand, there is clinical evidence from the same laboratory<sup>2</sup> of depression not due to asphyxia following thiopental for elective cesarean section. This would indicate that the drug does indeed cause neonatal depression when circumstances are favorable.

From the guinea-pig experiments an approximate liver:blood partition coefficient of 6:1 or 7:1 can be calculated for the fetus. Thus, retention in the fetal liver is likely to be much longer than it is in the adult, where it has been shown that three minutes may elapse after injection before detectable levels appear in the hepatic vein blood.<sup>1</sup>

The delay-line theory postulates that the hepatic sinusoid from its portal to its hepatic-vein end functions for diffusible molecules in a manner analogous to a gas chromatography column. Entering blood is purged of thiopental which is moved along the sinusoid at a much slower rate than the blood flow itself. The retention time is proportional to the tissue:blood partition coefficient and can be calculated theoretically.

It is important to realize that the "liver chromatograph" can function perfectly only for substances which pass without hindrance across cell membranes. This would not include any fat-soluble drug, pentobarbital or lidocaine for example, which does not equilibrate completely during a single passage through a capillary bed. Again, the same laboratory has demonstrated this.<sup>2</sup> Lidocaine traverses the liver rapidly and is found at high concentration in fetal heart blood as early as one minute after the end of maternal injection.

The experiments in which thiopental was injected into the guinea-pig umbilical vein showed that the liver held on to nearly all the injected dose for a full 2-3 minutes after presentation to it. This cannot be explained purely on the basis of a high tissue:blood partition coefficient and rapid equilibration if the normal model of exponential tissue filling is applied. The behavior of lidocaine disproved the authors' theory of venous congestion of the liver to explain this (and, in fact, at birth the reverse actually occurs: blood leaves the liver<sup>4</sup>). Their only other explanation, that uptake by unidentified special pro-

teins might occur, would necessitate the drug's later release again by some unknown mechanism to explain its subsequent reappearance in the general circulation. On the other hand, the delay-line theory fits all the observations, but does raise the question of how rapidly systemic levels may increase when the liver finally releases its store.

Because the umbilical vein blood is separated into three parts (ductus venosus blood, right-lobe blood diluted with portal-vein blood before entering the sinusoids, and left lobe blood not diluted this way), it does after all seem likely that in general the brain levels will rise slowly, to peak at a clinically safe level. However, I wish to make a plea that this may not always be so, that so far there is not nearly enough evidence to say that it is, even in the "normal" case, and in fact that in at least one circumstance, elective cesarean section, there is good evidence to suggest that central depression of the fetus due to thiopental can and does occur.

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*To the Editor:*—For a number of years we have been interested in the strategic position of the fetal liver, relevant to the uptake of anesthetic agents which cross the placenta,<sup>1-4</sup> and in the possibility that late release of drugs from the liver might cause a secondary depression of the newborn. However, to date there

has been neither clinical nor laboratory evidence to support this possibility in relation to thiopental.

Our first clinical study,<sup>3</sup> quoted by Dr. Robinson, showed that infants delivered by cesarean section were more depressed than those delivered vaginally, although the doses of thiopental administered to the mothers were the same. While we originally attributed the depression to thiopental, subsequent studies<sup>5,6</sup> have indicated that it was probably caused by nitrous oxide, since the incidence of depression was related both to duration of nitrous oxide administration and to nitrous oxide levels in the umbilical artery. When nitrous oxide was not used for maintenance of anesthesia during elective cesarean sections (thiopental-succinylcholine-oxygen sequence), the dose of the barbiturate was found to be the only determinant of neonatal condition.<sup>7</sup> When less than 7 mg/kg of thiopental was given to the mother as a single induction dose, there was no neonatal depression, irrespective of the length of the interval between injection and delivery. When the dose was 8 mg/kg and the infant was delivered between 3 and 7 minutes later, there was a significant incidence of depression. This particular interval of 3 to 7 minutes was too close to the maternal injection to be consistent with the "delay-line" theory, and was also accompanied by higher drug levels in the umbilical artery and vein blood.

Thus, the depressed infants in our study cannot be used as evidence supporting the "delay-line" theory. Neither can our data on placental transfer of lidocaine,<sup>8</sup> also quoted by Dr. Robinson, be interpreted as showing limited uptake of drugs other than thiopental by the fetal liver. Concentrations of lidocaine in the liver were much higher than in any other fetal organ studied. As a result, drug concentration in the heart blood of the fetus was only approximately 25 per cent of that in the maternal blood one minute after injection.

On the other hand, we share Dr. Robinson's concern about the limited ability of the fetal

liver to protect other fetal organs from many drugs and anesthetic agents administered to the mother in high doses and for prolonged periods.

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