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Intravenous Thiobarbiturate Anesthesia for Cesarean Section

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A strictly controlled thiobarbiturate–succinylcholine–oxygen sequence, with thiobarbiturate dosage 4–7 mg/kg, seems safe for elective cesarean section. Two hundred and forty-eight patients were divided into four groups, which received 4, 5½, 6½ or 8 mg/kg of thiobarbiturate, respectively. Blood samples for barbiturate analysis were drawn at birth from the maternal antecubital vein and the umbilical artery and vein. Apgar scores were good (7–10) in 75–90 per cent, and fair (4–6) in 6–19 per cent, of infants in the first three groups, but only 60 per cent good, 34 per cent fair, after 8 mg/kg. Amniotic or other fluid had accumulated in the oropharynxes of most infants with low scores. Factors combining to protect the fetal brain against massive invasion by thiobarbiturate from the mother include: swift decline of drug concentrations in maternal blood; nonhomogeneity of blood in the intervillous space; absence of a maternal–fetal capillary bed; hepatic extraction of drug from umbilical venous blood; progressive dilution; extensive shunting in the fetal circulation. (Key words: Cesarean section; Intravenous anesthesia; Thiobarbiturates; Thiamylal; Thiopental; Placental transfer of thiobarbiturates.)

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FEW PROCEDURES in anesthesiology have elicited such prompt and widespread acceptance by patients as the intravenous method of induction of general anesthesia. Concerning the use of this technique in obstetrics, it has been written that "barbiturates are undoubtedly popular because they: (1) produce prompt, pleasant induction of anesthesia, and an emergence which is also pleasant; (2) are associated with less nausea and vomiting than any other group of general anesthetics; (3) have no effect on uterine contractions; (4) require minimal apparatus; (5) are nonirritating to the respiratory tract, thus do not provoke formation of secretions; and (6) are nonexplosive." [1] To this list could be added that they (7) shorten the time lag between start of anesthesia and start of operation, decreasing the duration of fetal exposure to depressant drugs prior to delivery.

The anesthetic barbiturates consist of highly lipid-soluble molecules, which pass freely through lipoid membranes such as the blood–brain and other blood–tissue barriers.[2] There is abundant evidence that they also cross the placenta readily and appear in significant concentrations in umbilical venous blood.[3–7] Consequently, legitimate concern over the

possibility of fetal and neonatal depression has limited the use of these drugs in obstetric anesthesia.

The purpose of the present studies was to devise a method and define limits for the safe use of intravenous anesthesia for cesarean section.

Methods and Material

General Considerations

All but six of the 234 patients undergoing cesarean section at the Hiroshima Prefectural Hospital from October 1964 to July 1968 received general anesthesia, administered primarily intravenously as described below. When time permitted, the patients received Pethilorphan (meperidine hydrochloride, 50 mg, and levallorphan tartrate, 0.625 mg) and atropine sulfate, 0.5 mg, by intramuscular injection an hour before induction of anesthesia; urgent cases received atropine sulfate alone, 0.3 mg given slowly intravenously. Many patients were already in active labor. For greater uniformity in the series, labor was induced in the others by means of intravenous infusion of Atonin O (oxytocin), 10 units in 500 ml of glucose 5 per cent in water at a rate of 50 to 60 drops per minute, starting an hour prior to the induction of anesthesia. When effective labor had been instituted, with rhythmic uterine contractions at 2-to-3-minute intervals, the infusion was terminated. After all surgical preparations had been completed, including scrubbing and gowning of personnel and cleansing and draping of the operative field, anesthesia was induced by intravenous injection of thiobarbiturate. As the study evolved, each patient was assigned to one of four categories, according to dosage and method of injection, as follows:

Group I. Single-injection Method (4 mg/kg)

The main group of 140 patients received thiamylal sodium, 2.5 per cent, 4 mg/kg intravenously via the maternal antecubital vein in 20 seconds. In another ten patients the dose was increased to 6 mg/kg. The barbiturate was followed immediately by succinylcholine chloride, 1 mg/kg intravenously, to facilitate endotracheal intubation; the operation was begun immediately. Controlled respiration was then instituted with oxygen, 5 l/min, in a semiclosed anesthesia system; when spontaneous respiratory efforts resumed, they were assisted manually as needed until ligation of the umbilical cord. (Because of shortness of time until delivery planned in part of the series, anesthesia was induced with nitrous oxide and halothane via face mask in 21 patients. In each case, the trachea was intubated after intravenous injection of succinylcholine chloride, 1 mg/kg, and inhalation anesthesia continued for a period totalling less than four minutes. This was followed by three minutes of washout with oxygen, 100 per cent, prior to barbiturate injection as above.) Subsequent uterine and wound closures were accomplished with inhalation anesthesia using a mixture of halothane and nitrous oxide. Time of delivery was recorded as the moment of clamping the umbilical cord. In 47 of the 143 cases, blood samples for barbiturate measurement were obtained at birth from the maternal antecubital vein and from the umbilical artery and vein in a doubly clamped segment of cord. The chemical procedure used was a modification of the method of Brodie *et al.*[8] Apgar scores were determined one minute after birth,[10] but for infants requiring resuscitation the lowest score obtained during the period was recorded.

Group II. Supplementary Method: Two Injections

Five minutes after the initial injection of thiamylal, in addition to the above procedure, 34 other patients received a second injection of the drug, amounting to 1½ mg/kg, *i.e.*, a third of the first dose, also given intravenously into the antecubital vein over a 20-second period. Other details of management were unchanged.

Group III. Supplementary Method: Three Injections

In another 28 patients the two-injection procedure was followed by a third injection 15 minutes after the first and amounting to 1 mg/kg, *i.e.*, a fourth of the initial dose, again intravenously in 20 seconds. With the cooperation of the obstetrician, the deliveries were all accomplished within the next 15 minutes. Some of these patients received a small

TABLE 1. Results, Cesarean Section Group I, Single-injection Method (4 mg/kg)

Case	Body Weight (kg)	Injection–Delivery Interval	Thiobarbiturate Level			Apgar Score	Amniotic Fluid in Pharynx	Resuscitation
			Maternal Vein (mg./l)	Umbilical Vein (mg./l)	Umbilical Artery (mg./l)			
37	74.0	†32″	48.2	0.0	0.0	10	(±)	
14	50.0	†40″	33.7	2.1	0.0	10	(−)	
27	58.0	†42″	31.9	0.9	0.0	10	(−)	
35*	68.0	†50″	29.8	7.8	0.0	10	(±)	
36	59.0	†50″	31.0	4.8	0.6	8	(±)	
15	56.0	†1′10″	24.8	13.6	1.3	10	(−)	
28	51.0	†1′15″	23.0	6.9	0.4	10	(−)	
38	62.0	†1′25″	24.4	7.0	1.3	10	(±)	
26	58.5	†1′35″	17.8	13.8	3.6	10	(−)	
35*	68.0	†1′50″	14.2	8.8	4.1	10	(+)	
16	60.0	†1′25″	8.1	8.0	7.1	10	(−)	
29	60.0	†2′00″	7.8	9.6	4.3	10	(±)	
25	50.0	†2′07″	10.6	13.4	2.4	10	(−)	
21	65.0	†2′21″	8.0	10.8	3.2	10	(−)	
30	58.5	†2′30″	8.9	7.6	3.9	9	(±)	
17	53.5	†2′30″	9.8	6.4	4.1	10	(−)	
9	63.0	2′40″	12.0	8.9	2.8	10	(−)	
22	56.0	†2′57″	7.6	7.6	4.7	10	(±)	
10	65.0	3′00″	6.8	9.5	4.8	10	(−)	
34	59.0	†3′00″	10.5	8.1	5.4	10	(±)	
31	59.0	†3′25″	7.4	6.1	7.8	10	(−)	
33	52.0	†3′25″	14.0	6.1	5.6	6	(+)	O_2, 3 min
156	66.0	3′28″	12.2	4.6	6.3	10	(+)	
7	59.0	3′33″	7.8	7.6	7.3	10	(−)	
6	58.0	3′35″	6.8	4.6	4.3	10	(−)	
39	62.0	†4′00″	8.8	8.1	4.6	10	(−)	
2	62.0	4′15″	6.5	4.3	6.3	10	(−)	
115	52.0	4′15″	6.9	5.4	4.3	10	(±)	
114	58.0	4′18″	7.1	6.3	6.2	10	(−)	
18	59.5	4′25″	8.0	6.8	7.2	5	(±)	O_2, 1 min
8	60.0	4′35″	9.0	6.2	4.0	10	(−)	
4	46.0	4′45″	4.6	7.6	3.9	9	(±)	
11	56.0	4′50″	5.1	3.6	2.0	10	(+)	
1	52.5	5′00″	8.3	7.4	6.1	10	(−)	
118	53.0	5′00″	4.4	2.1	2.0	10	(±)	
5	48.0	5′09″	4.5	5.8	5.1	10	(−)	
87	78.0	5′10″	6.1	4.3	3.6	7	(−)	
102	54.0	5′10″	10.4	9.2	3.1	10	(+)	
13	65.0	5′20″	6.8	7.8	6.0	10	(−)	
12	54.0	6′00″	6.1	6.0	5.8	10	(−)	
24	54.0	6′55″	7.4	5.1	5.5	10	(+)	
3	56.0	7′25″	4.7	0.4	3.6	10	(−)	
116	52.0	7′30″	4.7	3.6	3.1	10	(±)	
23	78.0	8′00″	4.7	4.9	4.3	10	(+)	
32	56.5	8′30″	4.8	2.4	2.0	5	(+)	O_2, 3 min
19	64.0	9′10″	5.5	3.0	1.1	10	(−)	
113	49.0	10′25″	5.1	3.0	2.0	9	(+)	

* Twins.
† Induction with nitrous oxide–halothane.

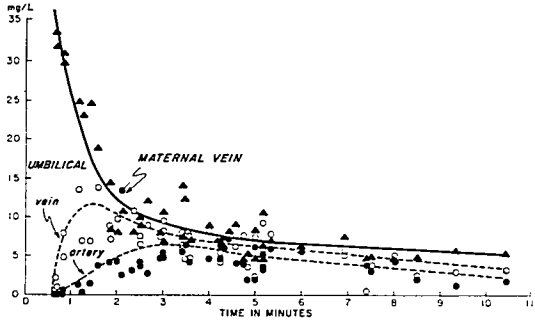

FIG. 1. Cesarean section group I. Single-injection method (4 mg/kg). Thiamylal concentrations in maternal vein (▲----▲), umbilical vein (○----○), umbilical artery (●----●). Curves drawn by inspection.

supplementary dose of succinylcholine chloride immediately prior to the intentionally delayed skin incision.

GROUP IV. SINGLE-INJECTION METHOD (8 MG/KG)

Another 35 patients received the same anesthetic management as in group I, but at double the dose of thiobarbiturate, *i.e.*, 8 mg/kg injected into the maternal antecubital vein in 45 seconds. (One additional patient inadvertently was given 10 mg/kg.) A second, but lesser, difference was that in 16 of the 35 patients thiopental sodium, 2.5 per cent, was used instead of thiamylal sodium. (As before, because of short time requirements, some (15) patients received nitrous oxide and halothane for less than four minutes, followed by three minutes of washout with oxygen, 100 per cent, prior to barbiturate injection.) Following tracheal intubation, pulmonary ventilation with oxygen was assisted or controlled, depending on whether respiratory efforts were present or not.

STUDIES IN NONPREGNANT WOMEN

The techniques of barbiturate administration utilized in the above four groups of patients were simulated in four otherwise healthy women undergoing gynecologic operations for removal of ovarian cyst, uterine myomata or carcinoma of the cervix. As with those maternity patients whose deliveries were planned very soon after barbiturate injection, the preliminary preparations were completed during endotracheal anesthesia with halothane and

TABLE 2. Technique of Administration and Apgar Score

	Group I				Group II		Group III		Group IV				Total	
	4 mg/kg		6 mg/kg						8 mg/kg		10 mg/kg			
No. of cases No. of babies	140 143		10 10		34 34		28 28		35 35		1 1		248 251	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Apgar score														
7–10	130	90.9	8	80	25	73.5	22	78.6	20	57.1	1	100	206	82.1
4–6	9	6.3	2	20	7	20.6	5	17.9	12	34.3			35	13.9
0–3	4	2.8			2	5.9	1	3.5	3	8.6			10	4.0

TABLE 3. Injection–Delivery Interval and Apgar Score

Time (min)	Group I (4 mg/kg)		Group II		Group III		Group IV (8 mg/kg)		
	No.	Mean Score	No.	Mean Score	No.	Mean Score	No.	Mean Score	Subgroup Mean Score
1	5	9.6					2	10	
2	7	10.0					3	7.3	8.2 ± 2.3*
3	8	9.9					4	8.0	
4	10	9.5					5	7.0	
5	34	9.0					7	6.7	
6	38	8.9	5	7.2			4	5.5	6.4 ± 1.7*
7	24	8.8	8	9.2			3	5.7	
8	18	9.4	8	7.5					
9–10			7	7.9			5	9.2	
10–15	1	9.0	6	8.7			2	8.0	8.9 ± 1.1*
16					5	8.8			
17					6	8.3			
18					3	6.3			
19					3	8.7			
20					3	8.7			
21–23					4	10.0			
23–25					4	8.8			

* Relative deviation from the mean.

nitrous oxide. After catheters for sampling of blood had been inserted into a femoral artery and an antecubital vein, the anesthetic agents were turned off and oxygen only was administered by the semiclosed method for three minutes at a flow rate of 5 l/min. The subjects then received thiobarbiturate intravenously in the same dosage and sequence used in the cesarean section groups. Blood samples were obtained at appropriate intervals

TABLE 4. Thiobarbiturates in Umbilical Vessels and Apgar Score

	Group I		Group II		Group III		Group IV	
	No.	Mean Score	No.	Mean Score	No.	Mean Score	No.	Mean Score
Thiobarbiturate in umbilical vein (mg/l)								
0–4	10	9.4	3	2.7	3	4.7	5	8.4
4.1–6	25	9.0	12	8.6	8	8.8	12	6.7
6.1–8			9	8.3	14	9.1		
8.1–12	9	10.0	9	8.9	3	9.3	9	6.8
over 12	3	10.0					8	8.4
Thiobarbiturate in umbilical artery (mg/l)								
0–2	13	9.4	3	2.7	2	6	4	8
2.1–4	11	9.5	9	9.3	4	7.8	4	8
4.1–6	15	9.7	18	8.4	17	8.8	14	7.1
6.1–8	8	9.4	2	9.5	4	9.5	10	7
8.1–10			1	5	1	9	2	8.5

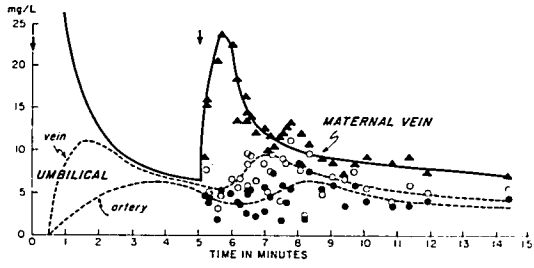

FIG. 2. Cesarean section group II. Supplementary method: two injections. Legend as in fig. 1.

TABLE 5. Results, Cesarean Section Group II, Supplementary Method: Two Injections

Case	Body Weight (kg)	Injection–Delivery Interval	Thiobarbiturate Level			Apgar Score	Amniotic Fluid in Pharynx	Resuscitation
			Maternal Vein (mg/l)	Umbilical Vein (mg/l)	Umbilical Artery (mg/l)			
50	66.5	5'15"	9.2	7.7	4.9	10	(±)	
60	74.0	5'20"	15.5	4.8	4.4	10	(±)	
75	47.0	5'20"	15.9	4.6	4.4	4	( )	O_2, 2 min
61	58.0	5'35"	20.4	3.1	1.8	2	(−)	O_2, 3 min
42	78.5	5'42"	23.5	4.6	5.4	10	(−)	
76	46.5	6'00"	22.3	6.6	4.8	8	(+)	O_2, 20 sec
43	62.0	6'11"	18.4	5.8	3.9	10	(−)	
41	59.5	6'15"	13.7	6.6	3.4	10	(−)	
40	63.5	6'28"	17.4	5.8	2.5	8	( )	O_2, 2 min
54	58.0	6'30"	13.7	9.6	4.8	10	(±)	
69	57.0	6'30"	14.8	8.5	5.1	10	(−)	
47	57.0	6'35"	14.0	9.5	5.6	8	(−)	
70	46.0	6'45"	12.2	6.6	2.2	10	(−)	
72	51.5	7'00"	12.7	8.4	5.7	10	(−)	
71	59.0	7'05"	10.0	5.0	2.7	10	(−)	
73	57.5	7'10"	11.8	7.4	4.5	7	(+)	
56	70.5	7'15"	10.4	9.7	7.5	9	(−)	intubation
67	78.0	7'30"	11.6	4.0	1.8	1	(−)	O_2, 5 min
74	62.0	7'35"	11.9	9.0	5.8	7	(+)	
51	52.5	7'40"	12.5	8.5	4.0	6	(+)	O_2, 2.5 min
50	61.0	7'47"	13.1	11.1	5.6	10	(−)	
55	57.0	8'07"	11.9	7.8	8.5	5	(+)	O_2, 3 min
44	61.5	8'14"	7.9	2.2	2.0	5	(±)	O_2, 3 min
52	58.0	8'20"	10.7	9.7	6.6	10	(−)	
63	53.5	8'45"	9.0	5.0	5.6	10	(−)	
57	61.0	9'03"	8.5	7.0	6.0	10	(−)	
62	60.5	9'25"	7.3	6.8	3.5	10	(−)	intubation
58	70.5	9'42"	9.5	7.6	6.0	5	( )	O_2, 5 min
64	55.5	10'03"	9.4	5.5	4.0	10	(−)	
46	58.0	10'50"	8.6	5.1	4.5	6	(±)	O_2, 2 min
65	65.0	11'20"	9.4	6.0	3.5	10	(−)	
66	61.0	12'55"	7.5	5.0	4.2	10	(−)	
53	67.0	14'20"	7.1	5.6	4.6	6	(±)	
82	58.0	18'15"	—	—	—	10	(−)	

of 15 to 60 seconds for periods of five, ten or 25 minutes after the initial injection of barbiturate. A uniform sampling time of five seconds per specimen was used. As before, barbiturate concentrations were measured by a modification of the method of Brodie et al.[9]

Results

Group I. Single-injection Method (4 mg/kg)

The interval (I.D.I.)* from barbiturate injection to delivery of the infant varied from 30 seconds to ten and a half minutes. Thiobarbiturate concentrations in the 47 samples of maternal venous blood obtained at the time of delivery ranged rapidly downward from 48.2 to 15 mg/l within two minutes, then continued to decline much more gradually, generally varying inversely with I.D.I. (table 1 and fig. 1). To a lesser extent, random variations were also introduced by individual differences in body composition. Beyond three and a half minutes, all values were below 15 mg/l. Drug concentrations in umbilical venous blood rose from 0.0 mg/l at 30 seconds to a peak value of 13.8 mg/l about one and a half minutes after injection, then fell gradually. Thiamylal was not detected in the umbilical artery until about 50 seconds after administration to the mother. Thereafter, there was a gradual rise to a peak value of 7.8 mg/l at about three and a half minutes, followed by slow decline. Beyond the peak concentrations, because of wide scattering of the values obtained, there was little correlation between time of delivery and drug levels in either umbilical vein or umbilical artery.

Most (130, or 90.9 per cent) of the 143 infants were vigorous at birth, scoring 7 or higher; nine, or 6.3 per cent, were classed as fair (scores 4–6); while only four, or 2.8 per cent, had poor scores (0–3)† (table 2). The lower Apgar scores could not be correlated with duration of anesthesia (table 3), barbiturate concentration in the umbilical vessels (table 4), fetal position, degree of urgency of cesarean section or the presence or absence of spontaneous labor. Accumulation of amniotic fluid in the oropharynx, however, was present in most of the infants with low scores.

Group II. Supplementary Method: Two Injections (at 0 and 5 min)

With I.D.I. varying from 5¼ to 18¼ minutes, thiamylal concentration in maternal venous blood rose swiftly to a second peak of 23.5 mg/l at five and three fourths minutes, declining thereafter as expected, first sharply, then more gradually (table 5 and fig. 2). A peak value of 11.1 mg/l was obtained in the umbilical vein at seven and three fourths minutes, although near-peak values were observed over a minute earlier. In the umbilical artery, the maximum drug level (8.5 mg/l) was obtained at eight minutes.

Twenty-five (73.5 per cent) of these 34 babies were evaluated as good, with Apgar scores of 7–10; seven (20.6 per cent) scored 4–6 and two (5.9 per cent), 0–3 (table 2).

Group III. Supplementary Method: Three Injections (at 0, 5 and 15 min)

I.D.I. in this group ranged from 15 to 25 minutes following the initial injection of barbiturate. Thiamylal levels in maternal venous blood rose steeply to another peak of 28.2 mg/l at 15¾ minutes, followed by the accustomed biphasic decline (table 6 and fig. 3). Although the maximum drug level (8.5 mg/l) was observed in the umbilical vein at 18½ minutes, values of 8.4 mg/l were obtained at both 16 and 19 minutes. In the umbilical artery, the highest concentration (8.2 mg/l) was found at 19¾ minutes.

Apgar scores were good (7–10) in 22 (78.6 per cent) of the 28 infants, fair (4–6) in five (17.9 per cent), poor (0–3) in one (3.5 per cent) (table 2).

Group IV. Single-injection Method (8 mg/kg)

With I.D.I. varying from three fourths to 13 minutes thiobarbiturate concentrations in

* "I.D.I.," as introduced by Hodges *et al.*,[9] signified "induction–delivery interval," induction being synonymous with the injection of barbiturate. In the present work, I.D.I. is taken to signify "injection–delivery interval," since anesthesia was actually induced by inhalation of nitrous oxide and halothane in some patients in group I and some in group IV as described above.

† As originally proposed, the categories of "good," "fair" and "poor" included infants whose Apgar scores were 8–10, 3–7 and 0–2, respectively,[10, 11] but as a result of biochemical studies,[12, 13] infants scoring 7 now rank in the "good" group and those scoring 3 are classed as "poor."[14]

TABLE 6. Results, Cesarean Section Group III, Supplementary Method: Three Injections

Case	Body Weight (kg)	Injection-Delivery Interval	Thiamylal Level			Apgar Score	Amniotic Fluid in Pharynx	Resuscitation
			Maternal Vein (mg./l)	Umbilical Vein (mg./l)	Umbilical Artery (mg./l)			
83	62.5	15'05"	6.8	5.5	5.4	10	(−)	
100	56.2	15'35"	6.9	6.1	5.1	10	(−)	
103	58.0	15'40"	28.2	4.6	3.2	8	(+)	O_2, 1 min
97	66.5	15'45"	21.3	2.5	2.7	6	(+)	O_2, 1 min
99	64.5	15'52"	11.3	5.1	5.1	10	(±)	
90	58.0	16'00"	16.6	8.4	6.7	10	(−)	
86	65.0	16'05"	16.4	7.7	5.8	8	(−)	O_2, 1 min
92	59.0	16'15"	13.8	6.3	1.5	10	(−)	
98	59.0	16'20"	13.2	6.7	4.1	10	(−)	
96	66.0	16'30"	11.4	1.3	1.1	2	(−)	O_2, 3 min
94	57.0	16'45"	12.2	7.1	5.1	10	(−)	
77	63.0	17'05"	7.9	5.9	5.4	7	(+)	O_2, 1 min
93	55.5	17'28"	10.8	7.8	5.1	6	(+)	O_2, 1 min
95	44.0	17'45"	10.5	3.9	2.7	6	(+)	O_2, 2 min
88	47.0	17'07"	8.0	7.3	5.7	8	(+)	O_2, 2 min
104	70.00	18'30"	11.4	8.5	7.1	8	(+)	
106	73.5	18'45"	12.4	7.6	8.2	9	(−)	
79	51.0	19'09"	7.3	8.4	4.6	10	(−)	
107	55.5	19'30"	9.0	7.2	4.9	6	(+)	O_2, 2 min
109	57.0	19'45"	8.3	6.1	5.1	10	(−)	
78	68.0	20'03"	8.1	6.1	4.3	10	(±)	
89	60.0	21'15"	6.7	6.5	6.6	10	(−)	
80	67.5	21'25"	8.4	6.1	5.0	10	(−)	
84	61.0	22'19"	7.5	4.8	5.5	10	(−)	
108	59.0	23'12"	5.6	5.3	4.1	9	(+)	
81	56.5	23'17"	7.8	4.3	2.9	10	(+)	
85	67.0	24'21"	7.0	5.8	5.7	6	(+)	O_2, 2 min
101	55.0	25'00"	7.5	7.3	6.5	10	(±)	

maternal venous blood reached a peak of 83.6 mg/l at one minute, and thereafter declined as in group I (4 mg/kg) but at expectedly higher levels (table 7 and fig. 4). Only after eight minutes were all values consistently below 15 mg/l. Drug levels in umbilical venous blood rose to a maximum of 17.7 mg/l at three minutes and then fell gradually. In the umbilical artery, the first detectable concentration (1.3 mg/l) of thiobarbiturate appeared one and a half minutes after injection. The levels rose steadily to a value of 8.1 mg/l at three minutes following which there was, in general, a gently downward slope, with interspersed high values of 8.0 and 8.3 mg/l about five minutes and 7.8 about eight minutes, after injection.

The trend of Apgar scores of the 35 infants in this group was distinctly lower than in any of the other groups studied (table 2). Only 20 babies (57.1 per cent) were rated as good, with scores of 7–10, while 12, or 34.3 per cent, were classed as fair (4–6) and three (8.6 per cent) as poor (0–3). Nevertheless, there was still no discernible correlation between condition of the baby at birth and drug concentration in either umbilical vein or umbilical artery (table 4), fetal position, degree of urgency of cesarean section or the presence or absence of spontaneous labor. Nor

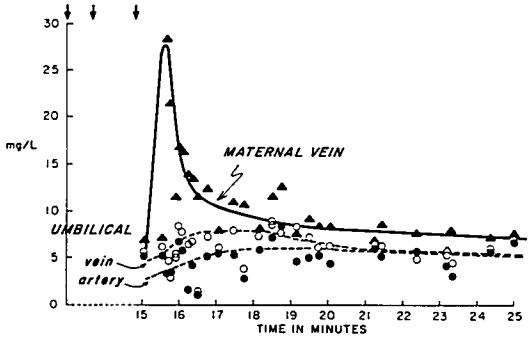

FIG. 3. Cesarean section group III. Supplementary method: three injections. Legend as in fig. 1.

was it possible to differentiate between the 16 patients who received thiopental and the 19 who received thiamylal.

On the other hand the impression was gained that low Apgar scores were most frequently encountered in infants delivered between three and seven minutes after thiobarbiturate injection (table 3). Nine of the 19 infants in this subgroup were sleepy and depressed, in contrast to their fellows delivered before three or after seven minutes. Despite these clinical observations, however, the subgroup did not differ statistically (table 3).

Resuscitation of the newborn was required in 16 cases. This usually consisted of suctioning of amniotic fluid from the oropharynx and inhalation of oxygen via face mask for two to three minutes, but three severely-depressed infants did require endotracheal intubation as well. All 16 were resuscitated successfully. Their subsequent development was normal and indistinguishable from that of infants delivered vaginally from unanesthetized mothers, according to usual obstetric practice in Japan.

STUDIES IN NONPREGNANT WOMEN

Figures 5–8 show thiobarbiturate concentrations in blood from the femoral artery and the antecubital vein of each of the four nonpregnant women who received thiamylal or thiopental in the same dosage and sequence employed with patients in cesarean section groups I–IV. After each injection, the anticipated rises in both arterial and venous concentration were observed, with subsequent biphasic decline; arteriovenous differences disappeared within one and a half to three or four minutes.

Discussion

An acceptable method of anesthesia for cesarean section must provide safety for the newborn infant despite obstetric and other causes of fetal distress which may necessitate resuscitation. To these should not be added the further burden of neonatal depression from anesthetic drugs. Since the anesthetic sequence described above avoids the use of inhalation anesthetics, all of which are potentially depressant to the fetus, and utilizes relatively small doses (1 mg/kg) of the muscle relaxant succinylcholine, which does not begin to cross the placenta except after large single intravenous doses of 300 mg or more,[15] these two potential causes of neonatal depression and/or respiratory impairment have been eliminated. The anesthesiologist's responsibility for iatrogenic depression of the newborn must then be assessed in terms of the amount of thiobarbiturate able to reach the fetus *in utero*. In this regard an Apgar score in the "good" category (7–10) is mute evidence of successful prophylaxis.

Such success was apparent in the 90 per cent of infants scoring 7–10 following delivery

TABLE 7. Results, Cesarean Section Group IV, Single-injection Method (8 mg/kg)

Case	Body Weight (kg)	Injection–Delivery Interval	Drug*	Thiobarbiturate Level			Apgar Score	Amniotic Fluid in Pharynx	Resuscitation
				Maternal Vein (mg %)	Umbilical Vein (mg %)	Umbilical Artery (mg %)			
136	62.5	† 43″	a	51.0	2.6	0.0	10	(−)	
137	58.5	† 60″	a	82.3	1.3	0.0	10	(−)	
130	51.0	† 1′10″	a	83.6	2.0	0.0	9	(−)	
139	57.0	† 1′33″	b	31.0	2.2	1.3	3	(+++)	intubation
143	62.0	† 1′40″	b	28.4	7.6	2.2	10	(±)	
142	53.0	† 2′02″	b	25.2	5.6	3.2	3	(±)	intubation
131	59.0	† 2′30″	a	23.5	15.4	5.1	10	(−)	
135	6.50	† 2′44″	a	25.2	17.4	5.8	10	(−)	
138	57.5	† 3′00″	b	24.3	17.7	8.1	9	(±)	
154	55.5	† 3′20″	b	30.0	15.4	5.8	6	(+)	O_2, 3 min
145	60.5	† 3′23″	b	18.6	12.5	4.0	10	(−)	
153	63.0	3′28″	b	—	—	—	7	(±)	O_2, 2 min
133	58.5	† 3′40″	a	24.0	13.4	7.6	6	(±)	O_2, 3 min
141	57.7	† 3′58″	b	12.5	13.1	5.1	6	(++)	O_2, 5 min
144	58.5	4′02″	b	13.6	5.6	6.0	6	(+)	O_2, 5 min
151	53.0	† 4′10″	b	16.1	7.01	2.2	9	(±)	
140	77.4	† 4′30″	b	13.7	9.2	7.1	9	(−)	
121	54.0	4′50″	a	16.4	13.2	8.0	10	(−)	
156	56.5	4′53″	b	21.8	10.0	7.5	4	(+)	O_2, 2 min
117	74.0	5′00″	b	13.6	7.8	8.3	8	(+)	
119	53.0	5′00″	a	15.7	4.6	6.1	1	(+++)	intubation
132	66.5	† 5′05″	a	17.3	8.3	5.9	6	(++)	O_2, 5 min
122	59.0	5′09″	a	18.4	7.7	5.0	6	(±)	O_2, 2 min
128	56.0	5′35″	a	19.4	11.1	7.1	4	(−)	O_2, 3 min
152	60.0	5′52″	b	12.5	8.6	5.3	6	(+)	O_2, 3 min
134	57.0	6′02″	a	15.8	8.5	5.8	4	(+)	O_2, 5 min
129	68.0	6′03″	b	11.9	10.8	6.6	8	(+)	
149	57.0	6′42″	a	16.9	7.3	4.7	5	(+)	O_2, 3 min
150	60.0	7′18″	b	9.2	7.6	4.7	10	(+)	
126	53.0	7′48″	a	11.3	8.3	6.8	10	(−)	
124	66.0	8′08″	a	12.2	5.5	5.5	8	(+)	
125	63.0	8′11″	a	15.3	9.3	7.8	10	(−)	
148	63.0	9′44″	b	11.9	7.8	6.9	8	(±)	
146	58.5	11′23″	b	7.1	5.6	5.3	6	(+++)	O_2, 3 min
147	58.7	12′55″	b	9.2	3.6	4.8	10	(−)	

* a = thiopental; b = thiamylal.
† Induction with nitrous oxide-halothane.

by cesarean section from mothers anesthetized with thiamylal, 4 mg/kg (table 2). The results in the small group of ten patients receiving thiamylal, 6 mg/kg, were almost as satisfactory (80 per cent of the infants were classified as good, 20 per cent as fair), with similar findings in the groups receiving one or two supplementary doses (approximately 75 per cent of the babies rated good, 19 per cent fair) (table 2). In sharp contrast, after administration of 8 mg/kg of thiobarbiturate to the mother, less than 60 per cent

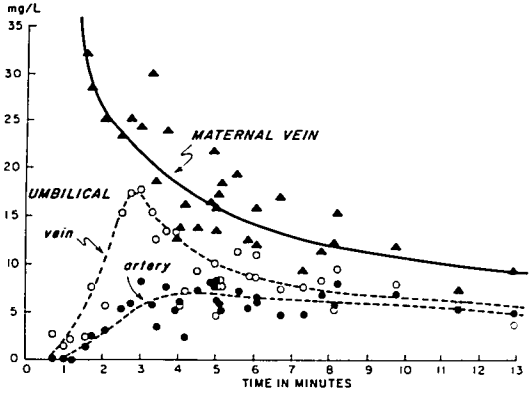

FIG. 4. Cesarean section group IV. Single-injection method (8 mg/kg). Legend as in fig. 1.

of the infants were appraised as good, with 34 per cent fair (table 2). The occasionally observed combination of low Apgar score and low drug concentration in umbilical vessels would seem to indicate a circulatory abnormality of the placenta or cord.

Close scrutiny of the differences in experimental findings between the groups at the two extremes, receiving 4 and 8 mg/kg of thiobarbiturate, respectively, may be useful in defining the limits of safety of the anesthetic technique being proposed. Although the purist may object to the seemingly indiscriminate comparison of two different drugs, thiamylal and thiopental, the two are indistinguishable for all practical purposes.[16, 17] They were consequently considered interchangeably as "thiobarbiturates" in the present studies and in the conclusions reached, although in fact thiamylal was used in the majority of cases.

Despite the obvious quantitative and temporal differences observed in drug concentrations in maternal and fetal blood, described above under "Results" for cesarean section groups I and IV, receiving 4 and 8 mg/kg of thiobarbiturate, respectively, there was little or no correlation between any single measured value and the associated Apgar score (table 4). Nevertheless, the finding of consistently lower mean scores in the 8 mg kg group for any range of drug concentration in any of the three vessels (table 4) confirms the obvious: 8 mg kg to the mother is more deleterious to the infant than 4 mg/kg. To explain these results, we must examine events in the maternal blood stream, in the placenta, and in the fetus.

EVENTS IN THE MATERNAL BLOODSTREAM

A comparison of time–concentration curves in femoral arterial and antecubital venous blood in nonpregnant women after 4 mg/kg over a 20-second period and 8 mg kg over a 45-second period (figs. 5 and 8) is interesting. Doubtless because of the slower rate of administration of the larger doses, the peak concentrations achieved in arterial blood were practically identical. More important is the observation that, in each case, within one and a half to three or four minutes there was little discernible arteriovenous difference, where venous return from the forearm was concerned. In consequence, forearm venous blood samples obtained at these early times can be considered practically identical in drug content to arterial blood samples, whether femoral, brachial or even uterine.

To the uninitiate, the apparent disappearance of a concentration gradient between

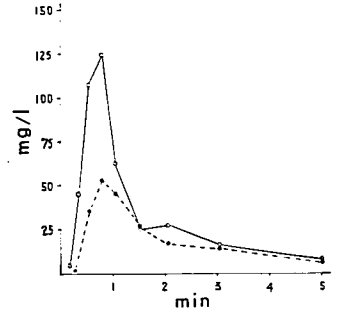

FIG. 5. Blood thiamylal concentrations. Single-injection method (4 mg/kg). Thiamylal concentrations in femoral artery (○-----○), antecubital vein (●-----●). Curves drawn by inspection.

brachial artery and antecubital vein would indicate the onset of equilibrium of drug diffusion across the forearm compartment. A moment's reflection reveals that this is not so. The forearm consists of poorly perfused tissues of the lean body mass (muscles, tendons, ligaments, connective tissue and bone) wrapped in skin and fascia. Because of their poor perfusion, these lean tissues require much more time, 15 to 30 minutes, for equilibration of thiobarbiturate content with the bloodstream.[2, 18] More logically, the early "equilibration" should be attributed to cutaneous vasodilatation and arteriovenous shunting following the induction of general anesthesia, while a barely perceptible arteriovenous difference, within the range of error of the chemical method,[8] enables the bulk of the forearm to continue to acquire thiobarbiturate slowly for many minutes longer.

It is essential to grasp this concept: despite the absence of blood–brain and other blood–tissue barriers to the highly lipid-soluble thiobarbiturates, speedy equilibration requires the rich perfusion seen only with viscera. It can be simulated, as in the forearm, by extensive shunting. As noted below, these comments apply importantly to the establishment of maternal–fetal and intrafetal equilibria.

Events in the Placenta

Despite obvious differences in circulation between the gravid and the nongravid uterus, within one to three minutes after thiobarbiturate injection for cesarean section drug concentrations measured in forearm venous blood samples may be assumed equivalent to those in arterial blood arriving at the same time at the uterus and placenta. If the utero-placental blood flow is also known, the actual amount of barbiturate available for exchange with the fetal circulation can be estimated.

The uterine blood flow at term amounts to about 500 to 700 ml/min (*i.e.*, about 10 per cent of the cardiac output), of which 400 to

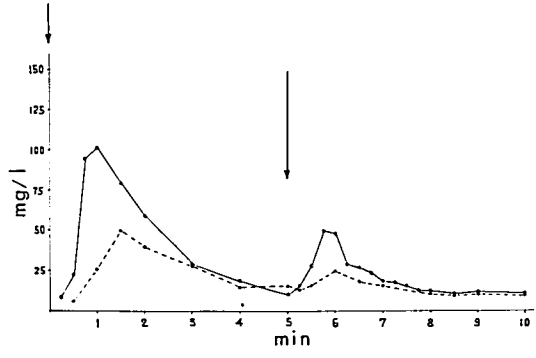

FIG. 6. Blood thiamylal concentrations. Supplementary method: two injections. Legend as in fig. 5.

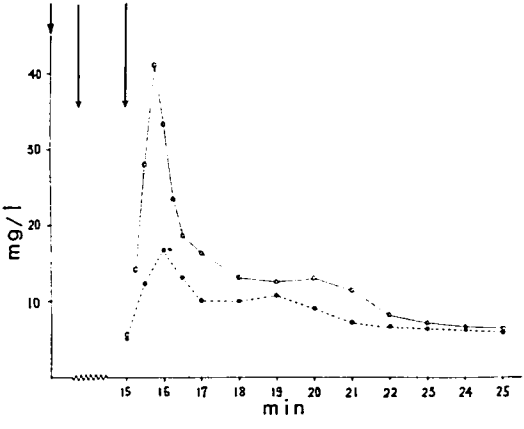

FIG. 7. Blood thiamylal concentrations. Supplementary method: three injections. Legend as in fig. 5.

600 ml/min reaches the placenta, the balance going to the myometrium.[1] A small part (about 50 ml/min) of the blood flow to the placenta does not enter the intervillous space, but provides for the nutritional needs of the placental tissue. The remaining 350 to 550 ml/min, amounting to some 75 per cent of the uterine blood flow, does reach the intervillous space for metabolic and other exchanges with the fetal circulation. In elegant cineradioangiographic studies of the primate placenta (which, like the human, is hemochorial), Ramsey and her colleagues observed that maternal blood enters the intervillous space from the endometrial spiral arterioles in discrete, relatively high-pressure, funnel-shaped spurts, the arterioles acting independently of each other so that not all are patent and discharging simultaneously.[19] They noted that blood flow into the intervillous space is also affected by intrauterine pressure, the uterine contractility pattern, and the contour of the individual contraction wave, as well as factors acting specifically on the arteriolar walls. The net result is a distinct nonhomogeneity of blood in the intervillous space. Drainage occurs via a corresponding system of veins without the interposition of a capillary network, in contrast to other organ tissues in the body.

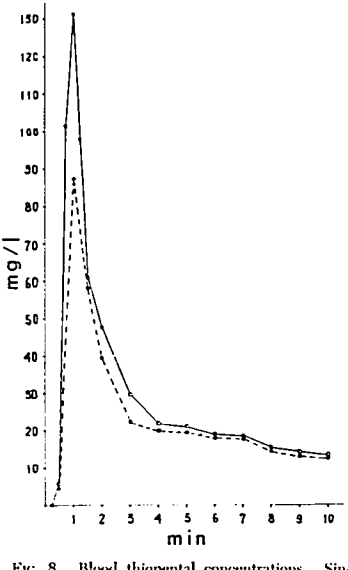

FIG. 8. Blood thiopental concentrations. Single-injection method (8 mg/kg). Legend as in fig. 5.

TABLE 8. Thiobarbiturate in the Intervillous Space

Minute	Mean Concentration (mg/l)	
	Dose: 4 mg/kg	Dose: 8 mg/kg
1	70	50
2	35	77.5
3	22.5	47.5
4	13.5	32.5
5	10	22.5
6		20
7		19
8		17
9		15
10		14

During anesthesia, thiobarbiturate molecules diffuse from the intervillous space across the syncytial epithelium of the chorionic villi, enter the villous capillaries, and proceed via the umbilical vein to the fetus. As shown in figures 1 and 4, measurable thiobarbiturate concentrations were detected in umbilical venous blood within 45 seconds after the start of drug administration to the mother, but did not reach peak values until one and a half to three minutes, depending on dose and duration of injection. Thus, despite the high lipid solubility of the anesthetic barbiturates, there is a brief but finite delay in their passage across the placental barrier. The lag is probably caused by the nonhomogeneous character of the blood in the intervillous space and the absence of a placental capillary bed for intimate contact and instantaneous exchange between mother and fetus.

EVENTS IN THE FETUS

The drug concentrations noted in the umbilical vein are, of course, not necessarily the concentrations arriving at the fetal brain. Indeed, a large part of the umbilical venous blood goes through the liver, which extracts substantial amounts of thiobarbiturate entering the fetus.[20-22]

There is also progressive dilution of thiobarbiturate en route to the arterial side of the fetal circulation. Although a certain amount of streaming takes place, blood in the umbilical vein becomes admixed with fetal venous blood from the gastrointestinal tract, from the lower extremities, from the head and upper extremities, and finally from the lungs, before returning to the placenta via the umbilical artery.[23] This would suggest that drug concentrations in the umbilical artery are much more nearly representative of those reaching the fetal brain than are concentrations in the umbilical vein.

In addition, aided by extensive shunting via the foramen ovale and the ductus arteriosus, an estimated 57 per cent of the combined cardiac output of the lamb fetus (and presumably a similar amount in the human) returns to the placenta without perfusing fetal tissues.[24] These three factors, hepatic extraction, dilution by admixture, and shunting via the ductus arteriosus, combine with the momentary placental barrier to protect the fetal brain from the full depressant effects of the thiobarbiturate injected into the maternal vein.

The protection offered by these mechanisms is, alas, only temporary. They provide a delaying action, which does not prevent continued mixing, distribution and ultimate equilibration of thiobarbiturate within the fetus. In this respect the fetus may be compared to the maternal forearm. As noted above, prompt disappearance of arteriovenous difference between the forearm vessels was a pseudo-equilibration due to vasodilation and shunting. Data from other sources enabled us to infer that uptake of thiobarbiturate by forearm tissues continued for many minutes before diffusion equilibrium of drug distribution in the forearm compartment was truly established.[2, 18] Unfortunately, there are no "data from other sources" elucidating the pharmacokinetics of thiobarbiturates in the human fetus. Let us, however, attempt an appraisal from the information available.

In the two groups receiving 4 and 8 mg/kg, respectively, a quick guess would lead to the conclusion that doubling the dose to the mother should double the amount of thiobarbiturate presented to the fetus at various times. The data seem to concur. Table 8 presents approximate values for mean drug concentration minute-by-minute in maternal arterial blood, obtained by visual inspection of the arterial blood curves in figures 5 and 8.

(As noted above, the uteroplacental blood flow at term accounts for about 10 per cent of the cardiac output, introducing a potential error in this attempt to transfer to the gravida data obtained from the nonpregnant woman. However, the similarity in contour between the thiobarbiturate time–concentration curves after 4 and after 8 mg/kg doses in antecubital venous blood in pregnant (figs. 1 and 4) and nonpregnant women (figs. 5 and 8) suggests that the differences in drug content may actually be small. It seems reasonable, therefore, to extrapolate to the gravida concentration data from femoral arterial blood in the nonpregnant woman.)

Ignoring the first minute, during which the drug was being administered to the mother, the mean concentration of barbiturate present in the intervillous space, hence available for transfer to the fetus, during each succeeding minute after the 8 mg/kg dose was more than double that after 4 mg/kg. (Failure to observe confirmatory differences in drug concentration in umbilical venous blood (*i.e.*, on the fetal side of the placenta) between the two groups (figs. 1 and 4) is not too surprising since the times chosen were much too early for diffusion equilibrium within the mother, within the fetus, or between mother and fetus to have been achieved.) Although obviously not all of the thiobarbiturate present in the blood flowing through the intervillous space crosses over into the fetal circulation, it is likely that the *proportion* doing so is similar, minute-by-minute, at each dose level.

In the fetus, drug uptake by the brain is briefly slowed, but not prevented, by the buffering mechanisms enumerated above. While the actual concentrations of thiobarbiturate in the fetal brain are not known, it is safe to assume that they quickly equilibrate with, and thereafter decline parallel to, concentrations in the fetal bloodstream. Two questions then arise. Are the undetermined levels in brain above the threshold for depression? How long before they fall below depressant levels?

Answers are suggested by the Apgar scores (table 3). After 4 mg/kg, the high incidence of favorable scores suggests that peak barbiturate levels in fetal brain rarely, if ever, exceed the threshold for depression (subsequent decline is therefore irrelevant). After 8 mg/kg, the apparent trend of lower Apgar scores from three minutes onward suggests that by this time concentrations of thiobarbiturate in the brain may exceed threshold levels. Subsequently, of course, continued redistribution of thiobarbiturate within the fetus results in diminution in drug concentrations in the fetal brain below depressant levels. Meanwhile, drug levels in maternal blood continue to decline, tending to establish a reverse gradient from the fetus outward. Both of these effects would contribute to lessening of depression with time. These tentative conclusions are compatible with the finding that thiobarbiturate concentrations in maternal antecubital vein (and in the intervillous space) were consistently below 15 mg/l three and a half minutes after injection of 4 mg/kg, but not until more than eight minutes after 8 mg/kg (figs. 1 and 4; table 8).

To recapitulate, the initial thrust on the fetal brain of a single relatively small dose (4 mg/kg) of thiobarbiturate to the mother is to some extent buffered by: slight delay in transit from the placental intervillous space to the fetal bloodstream; extraction of drug by the fetal liver, strategically located at a vital vascular crossroads; progressive dilution by admixture with various components of the fetal circulation; and extensive right-to-left shunting of fetal blood. Continued drug transfer, now more feebly impelled by the rapidly falling concentrations in the maternal blood, proceeds at modest levels which do not endanger the fetus. Simultaneously, due to the shunting, equilibration of drug concentration between the umbilical vein and artery begins to occur, but should not be misinterpreted to indicate diffusion equilibrium within the fetus as a whole.

With larger dosage (*e.g.*, 8 mg/kg) the sequence is repeated, but the initial surge of drug does not wane so fully. With higher levels sustained in the intervillous space, drug transfer to the fetus can continue to the point of obvious depression and a poor Apgar score, although, curiously, in this group low scores did not seem related to individual drug concentrations in the umbilical vessels.

The early rapid decline in blood levels of the anesthetic barbiturates is in sharp contrast to the contour of blood concentrations of anesthetic gases or vapors administered for cesarean section. Maternal blood levels of the inhalation agents are sustained with relative constancy throughout the procedure, tending to "load" the fetus to a considerable degree, despite the several protective processes described. For this reason, inhalation agents were avoided in the present study except where dictated by investigational time requirements or, following ligation of the umbilical cord, for completion of the operation.

It is now possible, in semiarbitrary fashion, to propose safe limits for thiobarbiturate dosage during cesarean section. From the present studies, it is clearly evident that thiobarbiturates may be administered intravenously in dosage of 4 mg/kg to the mother without danger to the fetus. In these cases low Apgar scores must be ascribed to causes other than anesthetic depression. As noted previously (table 2), Apgar scores were slightly less favorable but still within acceptable limits (75 to 80 per cent good, 18 to 20 per cent fair) after a single maternal injection of 6 mg/kg or after two or three injections totalling 5¼ or 6⅓ mg/kg, respectively. It therefore seems reasonable to recommend restriction of total dosage of thiobarbiturates for elective cesarean section to about 6 or 7 mg/kg, presumably a borderline dose. (While the safety of 7 mg/kg has not been ascertained, 8 mg/kg does seem excessively depressant to the fetus.)

This recommendation is consistent with the findings of Finster *et al.*[25] that after administration of thiopental, 400 mg, to six mothers, five of the six infants delivered by cesarean section were depressed at birth without evidence of undue intrauterine asphyxia. Subsequently, Finster and Poppers[26] obtained favorable results (75 per cent of infants classed as good) with administration of a lesser dose of thiopental (250 mg) to mothers undergoing cesarean section. Similarly satisfactory results after single injections were obtained by Cohen *et al.*[27] with thiopental doses of 120 to 180 mg; by Crawford (1965),[5] using thiopental in doses of 200 to 300 (usually 250) mg; by Hodges *et al.* (1961),[9] with thiopental doses of 200 to 250 mg; and by Sliom *et al.* (1962),[28] with thiopental, 250 mg, or methohexital, 100 mg. The safety of an average dose of 243 mg (range 150 to 375 mg) of thiopental in a thiopental–succinylcholine–nitrous oxide sequence for cesarean section was inferred in the report of Stenger *et al.* (1967)[29]; although Apgar scores were not quoted, the authors did state that the technique avoided the 50 per cent incidence of depression in the newborn encountered in their unit with cyclopropane anesthesia.

A major difference between the present study and all the others listed is the exclusion of nitrous oxide or other inhalation anesthetics for the reason stated above. With nitrous oxide induction Finster and Poppers did observe a modest but significant increase in incidence of neonatal depression (30.2 per cent with Apgar score 6 or less) as compared with thiopental (24.7 per cent), each being followed by succinylcholine and nitrous oxide for maintenance of anesthesia.[26] Similarly, Cosmi and Marx,[30] observing depression even 55 minutes after only 150 mg of thiopental, suggested the accompanying nitrous oxide anesthesia (2:1 mixture) as the cause.

The use of nitrous oxide, although perhaps disadvantageous to the fetus, does facilitate anesthetic management of the mother. Conversely, deletion of nitrous oxide from the anesthetic sequence imposes the added burden on the anesthesiologist of insuring that his patient does not begin to awaken during the operative procedure. Using the method proposed by the authors, the single injection of thiobarbiturate, 4 mg/kg, followed by succinylcholine and oxygen, will usually suffice for patients in whom delivery is effected within five minutes. This result can be expedited by completing all the preliminary procedures (preparing the skin, draping the field, etc.) prior to injection of barbiturate, with skin incision following promptly upon induction of anesthesia. Even in skilled hands, however, some deliveries will require more than five minutes. Supplementary injections of barbiturate at five minutes and again at 15 minutes can maintain anesthesia in the mother and provide satisfactory operating conditions for an I.D.I. of up to 25 minutes. Low Apgar

scores obtained under these circumstances may be attributed to other factors, such as the longer operating time, the supine position and additional handling of the fetus, all resulting in varying degrees of fetal asphyxia. (This last was not quantified in the present study which, unfortunately, did not include measurements of the acid–base status of the infant at birth.)

The preceding comments are not intended to prescribe a cookbook routine of thiobarbiturate administration for cesarean section, but only to suggest that total dosage should probably lie within the range of 4 to 7 mg/kg. The size and timing of fractional doses of barbiturate administered are subject to the discretion of the anesthesiologist. Nor is it meant to imply that 8 mg/kg is an absolute maximum dose, not to be exceeded under any circumstances. Indeed, the one patient who was inadvertently given 10 mg/kg of thiopental produced a baby scoring 10, mute evidence of individual variation in response to depressant drugs. Nevertheless, the guidelines suggested would seem to be useful.

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Anesthesia

BRONCHOSCOPY Utilizing the energy of compressed oxygen, ventilation is accomplished by blowing oxygen or a mixture of halothane–oxygen through a simple attachment which is affixed to the proximal end of the bronchoscope. The technique permits bronchoscopic examination without interruption and is applicable for patients of all ages. Blood gas studied showed Pa_{O_2} 200 mm Hg over prolonged periods of time; Pa_{CO_2} values remained near normal. (*Mette, P. J., and Sanders, R. D.: Ventilation Bronchoscope, a New Technique, Der Anaesthesist 17: 316 (Oct.) 1968.*)

METHEMOGLOBINEMIA The development of methemoglobinemia was studied in volunteers following injection of 2, 3, 4, 5 and 6 mg/kg body weight of prilocaine (Citanest). In all groups there were statistically significant increases in methemoglobin, which were dose-related. Since it is difficult to predict in any given patient the tendency to form methemoglobin, this side-effect of prilocaine is considered a disadvantage. (*Nolte, H., Dudek, J., and Hultzsch, B.: Studies on the Influence of Dosage in the Production of Methemoglobin during Use of Prilocaine, Der Anaesthesist 17: 343 (Nov.) 1968.*)

SIR HUMPHRY DAVY At the Pneumatic Institution in Bristol, Davy experimented with breathing of nitrous oxide, or "laughing gas." These experiments, undertaken when Davy was only 20, were to have far-reaching consequences, and were embodied in his book, *Researches, Chemical and Philosophical; Chiefly Concerning Nitrous Oxide, or Dephlogisticated Nitrous Air, and Its Respiration.* This work, published in 1800 when Davy was only 21, clearly indicates his genius. It included his explicit suggestion that the gas be used for surgical anesthesia, which unfortunately was not put to use by anyone until much later. (*Keys, T. A.: Sir Humphry Davy and His Safety Lamp for Coal Miners, Mayo Clin. Proc. 43: 865 (Dec.) 1968.*)