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BY

JOHN W. DUNDEE, HENRY L. PRICE, AND ROBERT D. DRIPPS

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Brit. J. Anaesth. (1956), **28**, 344

ACUTE TOLERANCE TO THIOPENTONE IN MAN

BY

JOHN W. DUNDEE, HENRY L. PRICE, AND ROBERT D. DRIPPS

From the Department of Anesthesiology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

ONE of us (J.W.D.) noted that although much smaller doses of thiopentone were given to patients at the Hospital of the University of Pennsylvania than at most centres in the British Isles, recovery of consciousness appeared to be equally prompt in all cases. To test the accuracy of this observation anaesthesia records from various hospitals in Liverpool were compared with those of the Philadelphia institution.

CLINICAL DATA

The anaesthesia technique compared was the intermittent administration of thiopentone, combined with nitrous oxide-oxygen, using the semi-open circuit at flow ratios of 4.5 : 1.5 or 6 : 2 litres per minute. No cases were included who received a volatile anaesthetic agent, a muscle relaxant or an intravenously administered analgesic. Records dealing only with surface operations were selected. The minimum duration of the procedures was 70 minutes, so that dosage figures for at least one hour of surgical anaesthesia were available for analysis.

Selection of cases was limited to patients of good physical condition under the age of 55 and suffering from no pathological condition other than that which necessitated the operation. The premedication consisted of 10 mg (1/6 grain) morphine for all patients combined with either 0.6 mg (1/100 grain) atropine or 0.4 mg (1/150 grain) scopolamine. Approximately one-third of the administrations in each country were by consultant anaesthetists, the remainder being given by residents or registrars with varying degrees of experience.

Table I gives details of the patients from each centre. The average total amount of thiopentone administered at 15-minute intervals is shown in figure 1. Irrespective of whether the actual dose in mg or the dose expressed in mg/kg is compared the British patients received approximately twice as much thiobarbiturate as the Americans for any given duration of anaesthesia. The average 30-minute requirements are significantly different by recognized statistical tests ($p<0.01$).

The possibility of factors peculiar to to the two different hospital groups being involved in this difference in requirements of thiopentone was excluded by a small series of 27 cases anaesthetized at the Hospital of the University of Pennsylvania with double its average induction dose (7.84 mg/kg thiopentone). The average total amount of thiopentone administered to these patients at the end of 30 minutes of anaesthesia was 14.9 mg/kg, which

TABLE I

Details of patients and nature of operations in a series of cases from America and Britain in whom thiopentone requirements were studied, together with the average induction and 30-minute dosage of the drug in each series.

Series	Hospital of the University of Pennsylvania	United Liverpool Hospitals
Number of cases	120	100
Average age (years)	40.0	44.8
Average weight (kg)	60.1	60.0
Nature of operations: for varicose veins	96	72
for plastic surgery	24	28
Average induction dose of thiopentone	212 mg 2.5 mg/kg	500 mg 8.3 mg/kg
Average dose administered at end of 30 minutes ...	411 ± 10.8 mg 7.0 ± 0.18 mg/kg	905 ± 22.0 mg 15.1 ± 0.13 mg/kg

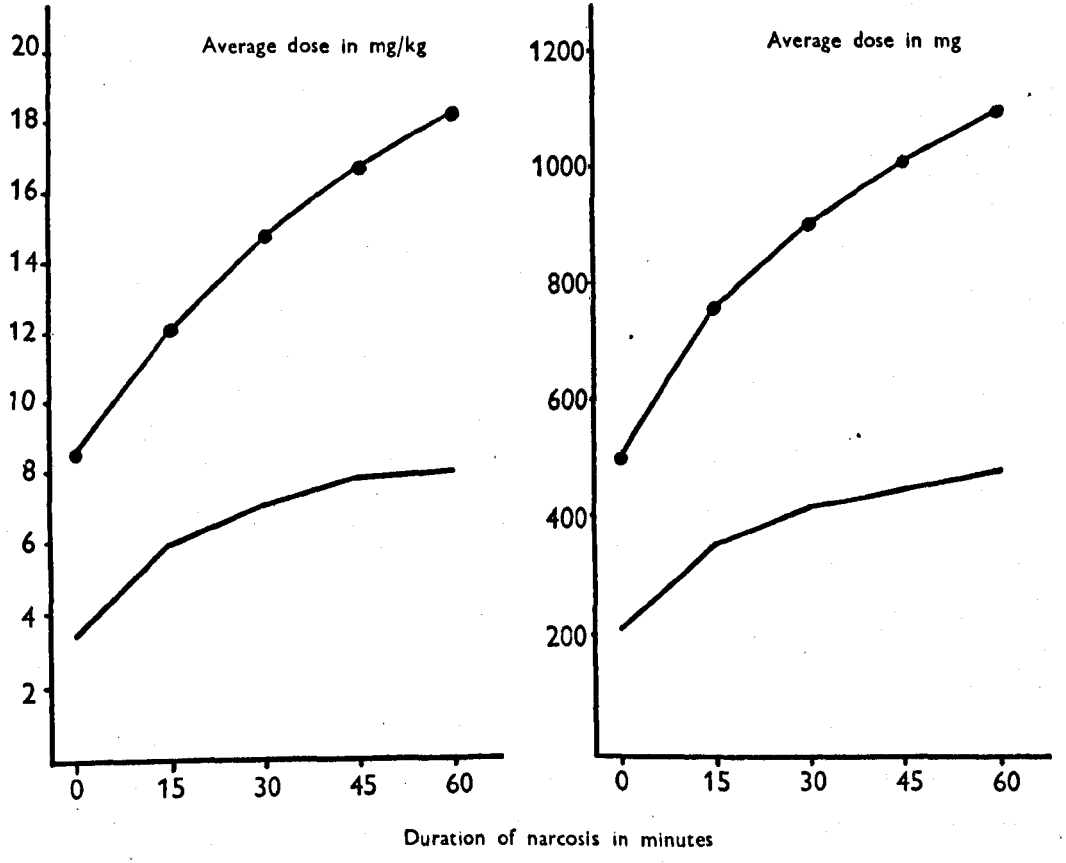

FIG. 1

Comparison of the average doses of thiopentone required during anaesthesia in two series of patients referred to in the text.

——— Hospital of the University of Pennsylvania.

●———● United Liverpool Hospitals.

compares closely with the figures (15.1 mg/kg) for the British patients. Conversely, Dundee (1955a) has described 21 patients, anaesthetized in Britain in whom the initial and 30-minute requirements of thiopentone were similar to those used in the Philadelphia hospital (2.4 and 4.6 mg/kg respectively). The awakening time for both groups was the same.

DISCUSSION

Since the return of consciousness was thought to be equally prompt in all patients studied, the possibility existed that either the thiopentone was removed more rapidly from the central nervous system in the British patients or that these subjects awakened with a higher brain content of the drug.

The pharmacologically active concentration of thiopentone in the blood depends on the degree of binding of the drug to the plasma proteins. This varies with the albumin content and the pH of the blood and also with the concentration of thiopentone (Goldbaum and Smith, 1954). The former two factors are unlikely to vary widely in the essentially normal patients studied. With increasing barbiturate concentration the percentage of the bound drug diminishes, although the total amount increases. Thus the patients who received the large amounts of thiopentone will have proportionately more free drug per mg/kg injected than those receiving the smaller doses, and the observed differences in dosage cannot be explained by differences in plasma binding.

In 1952 Brodie showed that the plasma concentrations at the time of orientation following small total doses of thiopentone were lower than the corresponding levels following larger total doses. The amounts of thiopentone given by Brodie (22–65 mg/kg) were well above those used in clinical anaesthesia, but if his findings apply with total doses varying from 5 to 18 mg/kg, they would throw light on why the return of consciousness in the British patients was as prompt as in those anaesthetized in the United States. However, they do not explain why the increment doses required in the British series of cases was approximately double those of the American series (fig. 1).

The higher induction doses of thiopentone administered to the British patients may be the important factor in determining why these patients required larger increments of the drug to maintain anaesthesia, since the greater initial brain concentration of thiobarbiturate may result in increased tolerance to supplementary doses of the drug. When the increment doses required every 15 minutes are compared with the initial dose (fig. 2), it can be seen that the ratio is the same for both series of cases. This suggests that, within the range of dosage of this study, the greater the initial dose of thiopentone the greater will be the increments of drug required to maintain surgical anaesthesia.

EXPERIMENTAL DATA

This hypothesis was investigated by a study of blood thiopentone levels at recovery in a series of 119 patients anaesthetized with single doses or intermittent injections of thiopentone, combined in the latter case with nitrous oxide-oxygen. Atropine 0.4–0.6 mg (1/150–1/100 grain) was the only drug given prior to anaesthesia.

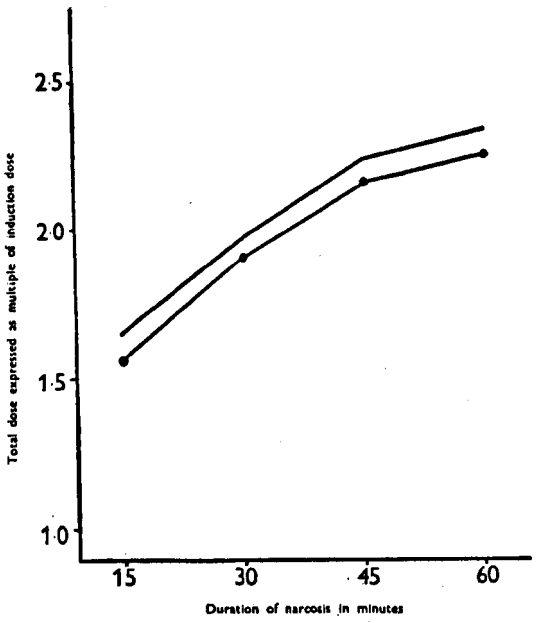

FIG. 2

Comparison of ratio of total dose of thiopentone required during anaesthesia to the induction dose in same series of patients.
——— Hospital of the University of Pennsylvania.
●———● United Liverpool Hospitals.

The subjects were fit female adults within the weight range of 110–160 pounds (50–73 kg), with ages varying from 16 to 44 years. All patients had a pre-operative haemoglobin of 11 g per cent or over. The operations were either minor gynaecological procedures or body surface operations such as plastic surgery. It was felt that the degree of pain following these was so little as not to act as a stimulus and hasten recovery from anaesthesia. The occurrence of hypotension, severe blood loss, or hypoxia excluded cases from this study.

The exact moment of return to consciousness is difficult to define and in the early cases several endpoints were used. From these the moment when the patient would open her eyes in response to a command was selected as being the most reliable. Blood was drawn slowly over a period of 30 to 60 seconds so that the average blood thiopentone level for the period immediately following the return of consciousness could be determined. In order to be certain that the patients were awakening from the effects of thiopentone and not because of elimination of nitrous oxide no patient was included in whom the desired endpoint was elicited within five minutes of withdrawal of the inhalation agent.

It has been shown by Price and Conner (1956) that two minutes after rapid intravenous injection of thiopentone the brachial arterial and jugular venous blood levels of the drug differ little and thereafter decline in a parallel manner. This does not necessarily apply to venous blood drawn from the forearm or anticubital fossa, as some thiopentone may diffuse into the muscles and fat of the limb. In an attempt to obtain samples which would give readings similar to those of jugular venous or arterial blood the veins on the dorsum of the hand or around the wrist were used whenever possible.

Thiopentone determinations were carried out on whole heparinized blood using the technique described by Brodie et al. (1950) for plasma. Where possible several samples were drawn before and after recovery from anaesthesia and these revealed that the decline in blood barbiturate concentration was rarely more than 1 mg/litre during the period from five minutes before to five minutes after the return of consciousness. Thus, if the assessment of the endpoint was not accurate, the degree of error was not gross.

Figure 3 shows the blood levels at awakening in 15 patients who received varying single doses of thiopentone. There is a significant ($p<0.01$) relationship between the dosage and the blood thiopentone level at recovery (correlation coefficient (r) $= +0.74$).

Thus Brodie's observations are applicable for single injections of thiopentone within the range of dosage used in clinical anaesthesia. However, these findings do not indicate whether the initial dose of the drug, the total dose, or the duration of anaesthesia is the important factor in determining the blood level of thiopentone at which consciousness will return following intermittent injections of this substance.

Figure 4 shows the blood thiopentone levels at awakening in 72 cases, to whom the drug was administered for periods not exceeding 20 minutes and in whom the total duration of anaesthesia did not exceed 40 minutes. This reveals a striking relationship ($r= +0.88$; $p<0.01$) between the blood thiopentone level at awakening and the induction dose of the drug, and no significant relationship between the blood level and total ($r= +0.20$; $0.05<p<0.10$) or increment doses ($r= -0.06$; $0.50<p<0.60$). Within the limits of the duration of administration and anaesthesia set out above, the following regression equation applies:

$$\text{Blood thiopentone level at awakening in mg/litre} = 1.88 \times (\text{induction dose of thiopentone in mg/kg}) + 0.45.$$

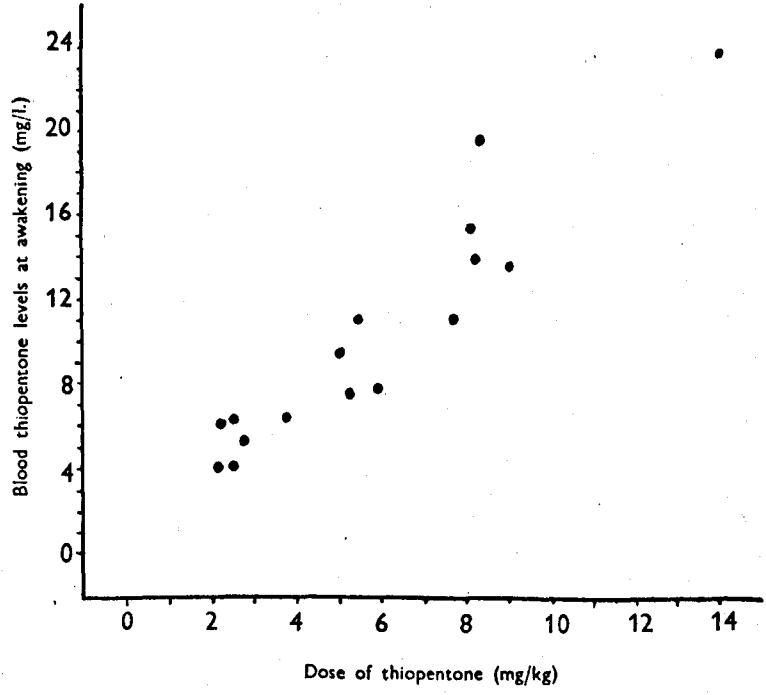

FIG. 3
Blood thiopentone levels at awakening in 15 patients who received single injections of the drug.

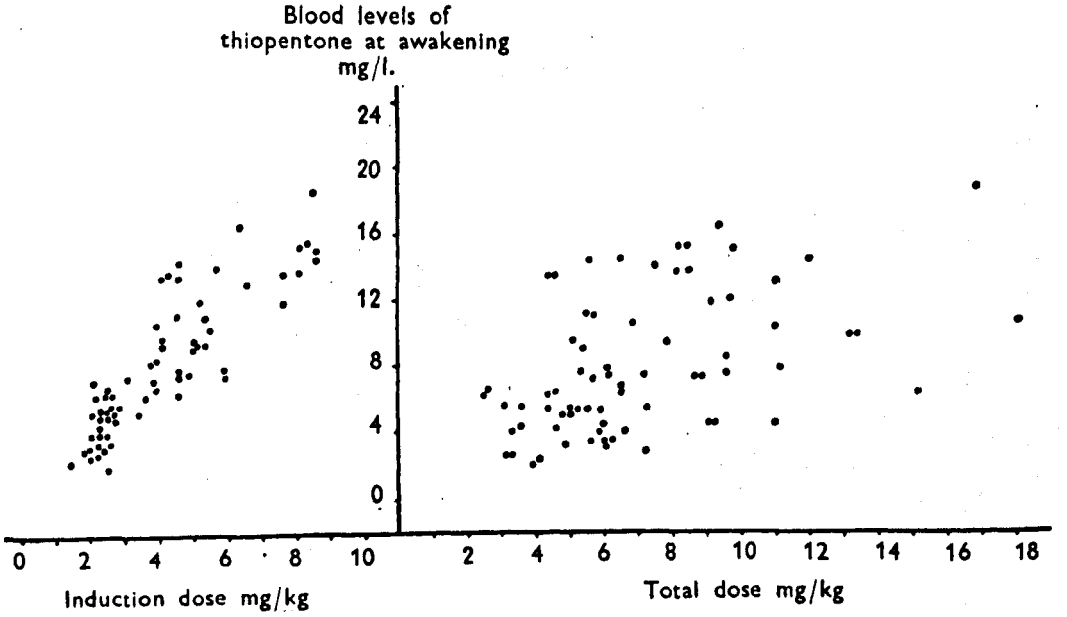

FIG. 4

Relationship between the blood thiopentone levels at awakening and the induction and total doses of the drug in 72 patients who were anaesthetized by intermittent injection of thiopentone. In these subjects the duration of administration did not exceed 20 minutes and the total period of unconsciousness was 40 minutes or less.

If the limitations of duration of anaesthesia and unconsciousness set out above were exceeded, it was found that the blood thiopentone level at awakening was dependent on both the initial ($r = +0.18$; $0.10 < p < 0.20$) and total ($r = +0.25$; $0.10 < p < 0.20$) doses of the drug, although the degree of correlation with either of of these factors was not great.

The part played by the total dose in determining the blood thiopentone levels at recovery was investigated in 58 patients. These received an initial dose varying only from 2.25 to 2.75 mg/kg, with a wide variation in the total amounts administered. No time limit was placed on the duration of the administration (1–58 minutes) or the total period of anaesthesia (2–105 minutes). The results, shown in figure 5, reveal that with total doses up to three times the induction dose the blood thiopentone level at recovery was fairly constant. Above this limit there was a gradual but inconsistent increase in the blood thiopentone levels at recovery from anaesthesia. Analysis of these data (table II) shows that, despite the wide scatter of readings, the increase in blood thiopentone levels at awakening is statistically significant.

In the patients receiving intermittent injections of thiopentone, no relationship could be found between the blood thiopentone levels at awakening and the duration of anaesthesia, although such a relationship did exist after a single injection of the drug.

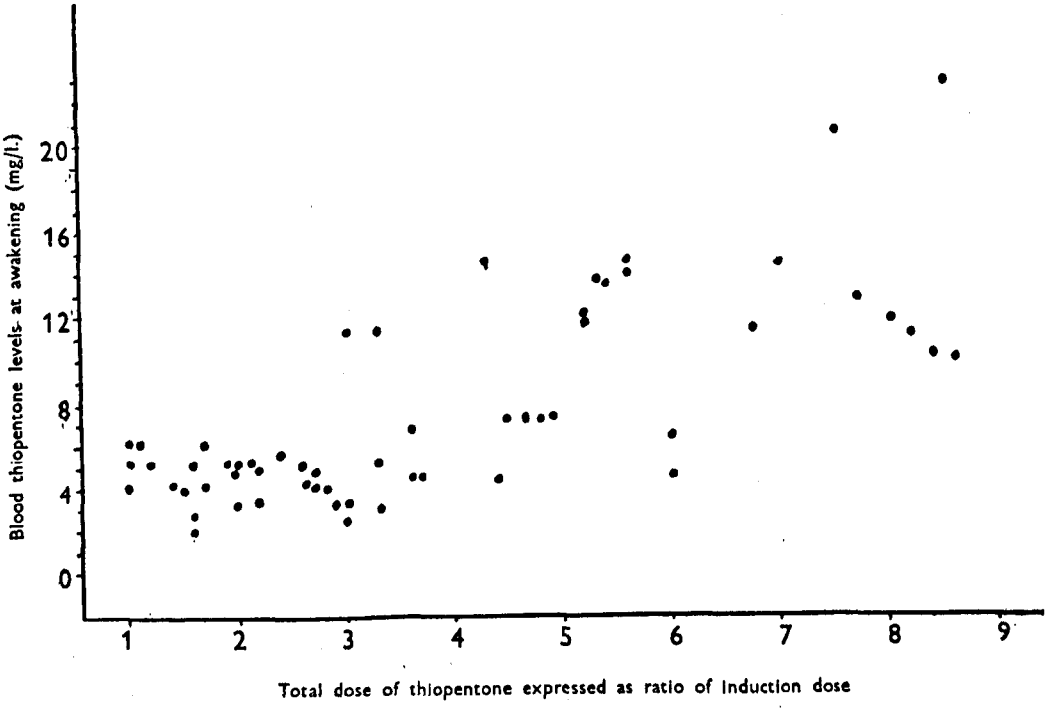

FIG. 5

Blood thiopentone levels at awakening in 58 subjects who received intermittent injections of thiopentone following an induction dose of 2.25–2.75 mg/kg related to the total dose administered (expressed as a ratio of the induction dose).

TABLE II

Analysis of blood levels of thiopentone on return of consciousness, related to total dose administered in patients receiving a constant induction dose of 2.25–2.75 mg/kg. Using "students" t test, each of the above average blood levels differs significantly from the others, the values for t being A-B 14.9, A-C 7.2, B-C 3.2.

	Ratio of total dose to induction dose	Number of observations	Average blood level on recovery (mg/litre)
A	Under 3	30	4.73 ± 0.152
B	3–6	19	8.20 ± 0.330
C	Over 6	9	12.56 ± 2.253

DISCUSSION

These observations show that there is a wide variation in the blood thiopentone levels at which normal patients awake from the doses of the drug used in clinical anaesthesia. The blood thiopentone level thus is not a reliable guide to the depth of anaesthesia. Contrary to the view expressed by Harris (1951) the degree of anaesthetic depression does not depend on the concentration of thiopentone in the circulating blood.

Brodie (1952) has suggested that the response of the central nervous system to thiopentone appears to depend on either the peak concentration or on the time of exposure of the tissues to the drug. From our results one can state that, with total doses of thiopentone not exceeding three times the induction dose, this latter determines the blood level at which patients

will awaken. With total doses exceeding three times the initial dose, the total amount of thiopentone administered also seems to be an important factor.

Our data suggests that the peak thiopentone concentration reached in the brain, whether this be attained during the induction or maintenance of anaesthesia, determines the blood level at which a patient will awaken from anaesthesia. With small total doses (relative to the initial dose) this peak is most likely to be reached during the induction period, while with the larger total doses, this peak concentration may be exceeded by one of the late supplementary injections. The greater the magnitude of the incremental doses, the more likely is this to occur, and the scatter in blood levels in figure 5 may be due to the variation in the size of the supplementary doses.

With the intermittent administration of thiopentone the time of exposure of the nervous system to thiopentone is not a factor *per se*, in determining blood levels at awakening.

The phenomenon of adaptation of the central nervous system to the narcotic effects of thiopentone has been called "acute tolerance", a term first used by Schmidt and Livingstone (1933) to describe the effects of morphine on the circulation. In contrast to chronically acquired tolerance, acute tolerance appears to develop rapidly after a single dose of drug. This is shown in figure 1, by the higher increment doses required to maintain anaesthesia in subjects induced with a large dose of the drug. Brodie (1952) has stated that adaptation of the central nervous system to the narcotic effects of thiopentone is not persistent and may last for less than one week. Apart from the fact that subjects have been shown to awaken at approximately the same blood level on three or four occasions within one hour, after repeated injections of thiopentone, our study throws no light on the duration of the effects of acute tolerance to thiopentone.

The agreement between the results of the dosage studies and the observations on blood thiopentone levels at awakening show that an unnecessarily large amount of thiopentone appears to have been used in the British cases. Unfortunately, it was not possible to compare the effects of such doses on the cardiovascular, respiratory or other systems with those produced by the smaller doses in the American series. However, as with all anaesthetic agents, it would seem desirable to administer the smallest amount of drug necessary to produce satisfactory operating conditions. Price and Helrich (1955) have found a linear relationship between the percentage reduction of the functional efficiency of the dog heart-lung preparation and the concentration of thiopentone to which it is exposed. Large doses also have a deleterious effect on liver function, the degree of impairment being roughly proportional to the total amount of thiopentone administered (Dundee, 1955b). There is as yet no evidence to suggest that acute tolerance develops to the effects of thiopentone on structures other than the central nervous system.

For these reasons it is suggested that the induction of anaesthesia should be accomplished with smaller doses of thiopentone than are currently in use in many centres in Britain. The initial injection, which can be given slowly, should not be

more than that required to produce sleep. Supplementary doses during the maintenance of anaesthesia should be kept to a minimum, except where momentarily deep anaesthesia is required. By these means the maximum concentration of the drug in the brain will be kept low and since this appears to govern the blood thiopentone concentration at which patients awake from anaesthesia, the total requirements of the drug should be appreciably reduced.

SUMMARY AND CONCLUSIONS

An analysis of average doses of thiopentone used in combination with nitrous oxide-oxygen to produce surgical anaesthesia was carried out in comparable series of patients anaesthetized at the Hospital of the University of Pennsylvania and at various hospitals in Liverpool. It was found that, for any given period of anaesthesia, the British anaesthetists administered approximately twice as much thiopentone as their American counterparts. Recovery appeared to be equally prompt in each centre.

Irrespective of the initial dose of thiopentone, a constant relationship was found between the total dose and the initial dose of the drug at any given duration of anaesthesia. Within the dosage range used in clinical anaesthesia, a linear relationship was found to exist between the blood thiopentone level at which patients awaken from a single injection of the drug and the amount injected.

Where the total dose of thiopentone did not exceed three times the induction dose, there was a striking relationship between the latter and the blood thiopentone levels at which patients awaken from anaesthesia, but no correlation could be found between the blood thiopentone levels at awakening and the total dose of the drug. When this range of dosage is exceeded, the total dose also played a part in determining the blood thiopentone level at which patients recover.

The above findings can be reconciled by the hypothesis that acute tolerance to the depressant effects of thiopentone on the central nervous system develops rapidly, the degree of adaptation being proportional to the peak concentration of thiopentone in the brain, whether this occurs during the induction of anaesthesia or following a supplementary dose of the drug.

The clinical application of these findings are discussed.

ACKNOWLEDGMENT

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ACQUIRED TOLERANCE TO INTRAVENOUS THIOBARBITURATES IN ANIMALS

BY

JOHN W. DUNDEE

Department of Anaesthesia, University of Liverpool

SEEVERS (1954) has defined tolerance to narcotics as "the partial or complete immunity to quantities of these substances which would otherwise diminish or completely abolish the functional activity of certain neurophysiological and other mechanisms." The repeated administration of medium-acting barbiturates leads to the development of tolerance to their narcotic effects. This applies to amylobarbitone and isopropyl-β-bromallyl-barbiturate in rabbits (Fitch, 1930) and delvinal and pentobarbitone in guineapigs and rats (Carmichael, 1941, 1948). The above workers and Gruber and Keyser (1946) have convincingly demonstrated that tolerance to one barbiturate produces a cross tolerance to other drugs of the same series.

Mice develop a tolerance to the daily administration of thiopentone. This effect is maximal in five to six days and amounts to a decrease in sleeping time by about fifty per cent (Hubbard and Goldbaum, 1949). Thrice weekly administrations of thiopentone to the dog lead to a forty per cent decrease in the duration of sleep by the end of the third week (Dundee, 1953). Green and Koppanyi (1944) found that dogs rendered tolerant to thiopentone showed cross tolerance to hexobarbitone and *vice versa*. The author has verified this with thiopentone, thialbarbitone, thiamylal and hexobarbitone.

In the course of clinical work the author has encountered several cases of tolerance to thiobarbiturates, in which the patients had been receiving large doses of sedative or analgesic drugs. In none of these patients could the resistance be attributed to acquired tolerance to medium-acting barbiturates. Similarly the drugs being administered to each of the resistant patients varied daily, but in each case they were limited to one type of drug such as D.D.A. analgesics or aspirin-like analgesics.

Experiments were carried out in dogs and rats to see if the daily administration of one type of sedative or analgesic did, in fact, increase the tolerance to thiobarbiturates. All thiobarbiturates were given by the intraperitoneal route, and during the experiment the interval between these injections was such as to avoid tolerance from the drugs themselves. Several control readings were done before the daily administration of sedatives or analgesics was started. All medication was stopped for 24 hours before injection of the thiobarbiturates, but drugs were frequently given when the animals wakened. At the

TABLE I

Effect of increasing doses of analgesics on the duration of narcosis with intraperitoneal injection of 30 mg/kg thiopentone and thiamylal in the dog. Each reading is the average of 4 observations. Unless stated above all analgesics were administered per os.

Days	Drugs administered	Narcosis			
		Thiopentone		Thiamylal	
		Onset (min)	Duration (min)	Onset (min)	Duration (min)
	Thiobarbiturate control (average of 4)	7.0	42	5.2	56
1	Morphia 15 mg (I.M.) Amidone 20 mg				
2	Pethidine 100 mg : Phenadoxone 60 mg				
3	Levorphan 12 mg				
4	Amidone 20 mg : Levorphan 4 mg (I.M.) Dilaudid 2 mg (I.M.) : Hyperduric morphia 32 mg (I.M.)				
5	Hyperduric morphia 65 mg (I.M.)				
6	Morphia 15 mg (I.M.) : Phenadoxone 60 mg				
7	Pethidine 600 mg + 100 mg (I.M.)				
8	*Thiobarbiturates* ... ... Levorphan 3 mg	10.2	14.0	6.0	52.1
9	Amidone 20 mg : Morphia 32 mg (I.M.) Pethidine 100 mg (I.M.) : Amidone 10 mg (I.M.)				
10	Hyperduric morphia 100 mg (I.M.)				
11	Amidone 15 mg : Dilaudid 4 mg (I.M.) Pethidine 100 mg (I.M.)				
12	*Thiobarbiturates* ... ... Phenadoxone 30 mg	7.0	21.2	8.0	29.0
13	Levorphan 9 mg				
14	Amidone 50 mg				
15	Levorphan 9 mg : Morphia 16 mg (I.M.) Dilaudid 2 mg (I.M.)				
16	Amidone 60 mg : Levorphan 2 mg (I.M.)				
17	*Thiobarbiturates* ... ... Levorphan 3 mg	10.2	5.0	12.0	24.5
18	Levorphan 15 mg : Pethidine 100 mg Pethidine 100 mg (I.M.)				
19	Hyperduric morphia 100 mg (I.M.) Pethidine 100 mg (I.M.)				
20	Amidone 70 mg				
21	Pethidine 600 mg : Amidone 30 mg ...				
22	*Thiobarbiturates* ... ... Levorphan 6 mg	11.0	16.0	8.2	23.2
23	Amidone 80 mg				
24	Hyperduric morphia 128 mg (I.M.)				
25	Levorphan 15 mg + 4 mg (I.M.)				
26	Pethidine 600 mg : Phenadoxone 60 mg				
27	Amidone 100 mg				
28	*Thiobarbiturates* ... ... Levorphan 3 mg	—	0	9.0	12.5
29	Morphia 64 mg (I.M.) : Pethidine 100 mg				
30	Amidone 40 mg				
31	Amidone 20 mg : Levorphan 3 mg				
32	Amidone 10 mg : Levorphan 1.5 mg				
33	Morphia 16 mg (I.M.)				
35	*Thiobarbiturates*	7.0	51	6.2	75
40	*Thiobarbiturates*			6.0	66
45	*Thiobarbiturates*	7.0	60	4.0	56

TABLE II

Effect of increasing doses of analgesics on the duration of narcosis with 60 mg/kg thialbarbitone in 32 rats. All analgesics were given by I.M. injection

Days	Drugs administered to each animal	Narcosis	
		Per cent asleep	Average duration (min)
0	Control (average of 3 readings)	81	18.4
1	Pethidine 5 mg/kg		
2	Levorphan 0.1 mg/kg		
4	Levorphan 0.2 mg/kg		
7	Levorphan 0.2 mg/kg		
8	Levorphan 0.2 mg/kg : Amidone 1 mg/kg		
9	Morphia 1.5 mg/kg : Amidone 1 mg/kg		
10	*Thialbarbitone*	75	6.2
11	Morphia 2.2 mg/kg : Pethidine 15 mg/kg		
12	Morphia 4.4 mg/kg		
14	Morphia 2.2 mg/kg : Pethidine 15 mg/kg		
15	—		
16	Levorphan 0.3 mg/kg : Pethidine 15 mg/kg		
17	*Thialbarbitone*	67	1.9
18	Morphia 2.2 mg/kg : Pethidine 15 mg/kg		
19	Pethidine 30 mg/kg		
21	Levorphan 0.45 mg/kg : Morphia 2.2 mg/kg		
22	Levorphan 0.67 mg/kg		
23	Levorphan 0.45 mg/kg : Morphia 3.3 mg/kg		
24	*Thialbarbitone*	0	—
25	Levorphan 0.45 mg/kg : Pethidine 30 mg/kg		
26	Levorphan 0.9 mg/kg		
28	Pethidine 20 mg/kg : Levorphan 0.45 mg/kg		
29	Pethidine 40 mg/kg : Levorphan 0.45 mg/kg		
30	Pethidine 40 mg/kg : Morphia 4.4 mg/kg		
31	*Thialbarbitone*	0	—
37	*Thialbarbitone*	73	13.1

end of the procedure inert placebo tablets were given and the anaesthetic repeated several times at intervals of five to six days.

RESULTS

The average effect of the daily administration of increasing doses of potent analgesics on the duration of action of three thiobarbiturates is shown in tables I and II. In each of these series there was a gradual reduction in the duration of narcosis with the thiobarbiturates, but within five days of stopping the analgesics the duration of action of the narcotic returned to normal. Table III shows that the less potent analgesics of the aspirin type produced a similar although less marked effect.

In table IV is shown the average effect of the daily administration of non-barbiturate sedatives on the duration of action of thiopentone in the dog. These drugs likewise induce tolerance to thiobarbiturates which is as marked as that from the D.D.A. analgesics. Anti-histamines of varying types were given to the animals of table V, and again there was a gradual shortening of the action of the thiobarbiturate, although not as marked as with the other drugs studied. Chlorpromazine similarly induces a mild degree of tolerance to thiobarbiturates.

TABLE III

The effect of repeated oral administration of mild analgesics on the duration of narcosis following intraperitoneal injection of 30 mg/kg thiopentone and thiamylal in the dog. Each reading is the average of 4 administrations.

Day	Drugs administered to each animal	Narcosis			
		Thiopentone		Thiamylal	
		Onset (min)	Duration (min)	Onset (min)	Duration (min)
	Thiobarbiturates control (average of 5)	8.0	46.2	4.0	86.2
1	Aspirin 325 mg : Phenacetin 400 mg				
2	Aspirin 650 mg : Aspirin & Dovers 2 tabs.				
3	Aspirin 650 mg : Aspirin & Dovers 2 tabs.				
4	Aspirin 1950 mg : Aspirin & Dovers 6 tabs.				
5	Tabs. Codeine Co. 12 tabs.				
6	Saridone 4 : Mephosol 3 tabs.				
7	Aspirin & Dovers 4 : Mephosol 2 tabs.				
8	Cefonin 6 tabs.				
9	Mephosol 3 tabs. : Aspirin 1950 mg				
10	*Thiobarbiturates* ... ... Tabs. Codeine Co. 3 tabs.	11.0	11.0	6.0	60
11	Neurodyne 4 tabs. : Aspirin 925 mg				
12	Neurodyne 4 tabs. : Tabs. Codeine Co. 4 tabs.				
13	Nephosol 6 tabs.				
14	Aspirin & Dovers 3 tabs. : Tabs. Codeine Co. 4 tabs.				
15	*Thiobarbiturates*	9.2	25.0	7.8	56
16	Nephosol 3 tabs.				
16	Arthipax 7 tabs.				
17	Aspirin 2600 mg				
18	Mephosol 8 tabs.				
19	Aspirin 2600 mg.				
20	*Thiobarbiturates* ... ... Mephosol 2 tabs.	12.0	10.3	10.0	45.5
21	Mephosol 6 tabs. : Aspirin & Dovers 2 tabs.				
22	Aspirin 1040 mg : Tabs. Codeine Co. 4 tabs.				
23	Mephosol 8 tabs.				
24	Aspirin 3300 mg				
25	*Thiobarbiturates* ... ... Mephosol 6 tabs.	10.0	4.5	9.0	33.5
26	Aspirin 3900 mg				
27	Mephosol 10 tabs.				
28	Neurodyne 8 tabs.				
29	Cefonin 4 tabs. : Saridone 6 tabs.				
30	*Thiobarbiturates*	—	0	9.0	38
31	Aspirin & Dovers 4 tabs.				
32	Tabs. Codeine Co. 2 tabs.				
33	Mephosol 3 tabs.				
34	Aspirin & Dovers 2 tabs.				
35	Mephosol 2 tabs.				
36	Mephosol 2 tabs.				
40	*Thiobarbiturates*	6.0	60.0	5.5	95.0
45	*Thiobarbiturates*	5.5	58.5	4.0	77

The analgesics referred to above contain the following per tablet:

Saridone (Roche)

phenyl-dimethyl-isopropyl-pyarazolon	150 mg
acetiphenetidin	250 mg
caffein	50 mg

Aspirin & Dovers (Tabs. Acetylsalicyli c Ipicac et Opio. N.F.)

Acetylsalicylic acid	162 mg
Pulv Ipecac et Opio	162 mg

Neurodyne (Wade)

Acetylsalicylic acid	260 mg
Calcium Carbonate	65 mg
Magnesium Carbonate	25 mg
Phenacetin	195 mg
Codeine phosphate (B.P.)	6.5 mg

Tabs. Codeine Co. (N.F.)

Codeine phosphate	8 mg
Acetylsalicylic acid	260 mg
Phenacetin	260 mg

Cefonin (Honmel)

Phenylsemicarbazide	260 mg
Caffein	42 mg
Lactose	325 mg

Arthipax (Clinical Products Ltd.)

Mephenesin	65 mg
Salicylamide	325 mg
Dihydroxyaluminium glycinate	100 mg

Mephosol (Crooks)

Mephenesin	125 mg
Salicylamide	250 mg
Homatropine methyl bromide	0.4 mg

TABLE IV

Average effect of daily oral doses of non-barbiturate sedatives on the duration of action of thiopentone (30 mg/kg) in the dog. Each reading is the average of 3 observations.

Days	Drugs administered	Narcosis	
		Onset	Duration
0	Thiopentone control (average of 3)	6.3	53
1–10	Sedatives		
11	Thiopentone	6.0	35
12–16	Sedatives		
17	Thiopentone	7.0	12
18–25	Sedatives		
26	Thiopentone	—	0
27–30	Sedatives		
31	Thiopentone	10.0	40
40	Thiopentone	7.0	51

Sedatives included:
K Br, Chloral hydrate, Rhysoval, Bromisovalerylurea, Carbromalum, Chloretone, Methylpentynol, Persodon

TABLE V

Effect of daily oral administration of increasing doses of various anti-histamines or thiamylal narcosis (30 mg/kg) in the dog. Each reading is the average of 4 observations.

Days	Drugs administered	Narcosis	
		Onset	Duration
0	Thiamylal control (average of 3)	4.7	74.2
1–8	Anti-histamines		
9	Thiamylal	5.5	55.0
10–15	Anti-histamines		
16	Thiamylal	6.0	48.0
17–23	Anti-histamines		
24	Thiamylal	6.2	45.0
25–30	Inert placebos		
31	Thiamylal	5.0	66.0
36	Thiamylal	4.0	67.0

Anti-histamines administered include:
Phenergan, Dibistin, Ancoran, Synopen, Antistin, Dramamine, Theophrin and Benadryl.

DISCUSSION

Many suggestions have been offered to explain acquired tolerance to narcotics. These include increase in rate of detoxication of the drugs, interference with chemical mediators or hormones by repeated doses of the drugs and enzyme adaptation. None of the aforementioned hypotheses has been confirmed. Hubbard and Goldbaum (1949) found that mice rendered tolerant to the daily administration of thiopentone awaken at higher tissue levels than controls. The above results show that the onset of anaesthesia was delayed after intraperitoneal injection of thiopentone and thiamylal in dogs who had received large doses of analgesics or narcotics. These findings suggest that tolerance is an adaptation of the nervous system to higher thiobarbiturate levels.

The narcotic effects of morphine (and similar drugs) have been explained by a combination of the drug with receptors near, or on the surface of the neurone. Tolerance consists of a maximal, but never complete saturation of these receptors comparable to that postulated for tachyphylaxis with other agents. Cross tolerance to drugs with a similar chemical

TABLE VI

Effect of daily administration of chlorpromazine on narcosis induced by intraperitoneal injection of 30 mg/kg thiamylal in the dog. Daily doses of chlorpromazine started at 4–5 mg/kg by oral administration and gradually increased to 12–15 mg/kg.

Days on chlorpromazine	No. of observations	Average total dose of chlorpromazine given		Average narcosis in minutes	
		mg/kg	mg	Onset	Duration
0	12	—	—	4.5	54 ± 7
17	4	120	1500	6.0	45 ± 9.5
24	4	190	2180	7.0	29 ± 0
29	4	240	2880	7.0	38 ± 7.0
39	4	290	3480	6.5	43 ± 12.5
52	4	445	5340	7.0	36 ± 4.7
4 days after stopping chlorpromazine	4	—	—	5.0	60

structure can be explained by similarity of the "anchoring groups". This does not explain cross tolerance between compounds of entirely dissimilar chemical characteristics such as thiobarbiturates and opiates. Seevers (1954) has suggested that this is related to the increase in latent hyperexcitability of the neurone rather than to any specific competitive effect.

ACKNOWLEDGMENTS

I am indebted to the following firms for general supplies of drugs: May & Baker Ltd. (Thiopentone), Parke Davies & Co. (Thiamylal), Imperial Chemicals (Pharmaceuticals) Ltd. (Thialbarbitone), and Roche Products Ltd. (Levorphan). Thanks are also due to Mr. G. Norton for technical assistance.

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THIOPENTONE AND OTHER THIOBARBITURATES

THESIS

Presented (in conjunction with the book of the same name)

for the degree of

Ph.D.

at the University of Liverpool

by

JOHN W. DUNDEE

M.D., (Belfast), F.F.A.R.C.S., D.A.

September 1956.

CONTENTS

CHAPTER 4

APPENDIX 1

PREFACE

This collection of published papers, and of work in the process of being prepared for publication, is submitted for the degree of Ph.D. in conjunction with the book, "Thiopentone and Other Thiobarbiturates". In some instances (e.g. pages 73, 75 and 105) original work has been included in the book which it is not proposed to publish elsewhere, and this is not included in this thesis.

Since personal work on the thiobarbiturates only deals with isolated aspects of their pharmacology and clinical use, it has proved difficult to prepare this thesis with the same continuity of context as is found in the book. For this reason, a completely different method of arrangement of reprints has been adopted, but references are frequently made to the appropriate pages and chapters of Thiopentone and Other Thiobarbiturates.

As is to be expected, with advances in our knowledge of the thiobarbiturates, the discussion in some of the early papers is now open to criticism. Where this applies, a commentary on the contents of the paper is included before the reprint, and attention is drawn to statements which are no longer believed to be true.

One paper included in this collection, contains work which has been presented elsewhere in a thesis for another degree, but

attention is drawn to this in the accompanying commentary, which also gives the reasons for including it in this thesis. Where a study has been carried out with other workers, the reprint gives the names of those concerned, or in the case of a non-published paper, the names of the other workers are given in the text.

One of the more recent investigations is described in detail, with inclusion of the data from which the results were obtained.

Because of variations in size of reprints from different journals (and differences between American and British standard sheets of paper) this thesis cannot be arranged as neatly as would be desired. In numbering pages, for the sake of simplicity, where a reprint is smaller than quarto size, only the first page is numbered.

It is a pleasure to express my thanks to Dr. T. Cecil Gray, under whose guidance the main part of this work has been carried out, for his continuing interest, encouragement and constructive criticism, and above all for allowing the full resources of his department to be put at my disposal during the past five years. Similar thanks are due to Professor Robert D. Dripps, for his assistance during my stay at the University of Pennsylvania. I am also grateful to the many colleagues, past and present, who helped with the investigations, especially Drs. J. E. Riding, W. E. B. Scott, David Annis, Henry L. Price and Eugene H. Connor. Finally, thanks are due to Miss M. Garrett for typing this thesis as well as helping with much of the statistical work in the papers.

29th September, 1956. John W. Dundee.

Chapter 1.

VARIATIONS IN RESPONSE TO THIOBARBITURATES

This subject is reviewed fully in Chapter 5 (pages 115 - 144), of "Thiopentone and Other Thiobarbiturates".

Personal studies on this subject can be divided as follows:-

A. Variations in Healthy Subjects.

(a) Body weight and sex and age.

(b) Tolerance - acute
- acquired

(c) Cumulative action of thiobarbiturates

(d) Respiratory alkalosis

B. Pathological Factors Influencing Dosage.

(a) Hepatic dysfunction

(b) Anaemia

(c) Uraemia

C. Potentiation by Other Drugs.

(a) Phenothiazine derivatives

Variations in Healthy Subjects.

(a) Body weight, sex and age.

"THE INFLUENCE OF BODY WEIGHT, SEX AND AGE ON THE DOSAGE OF THIOPENTONE"

Reprinted from British Journal of Anaesthesia (1954), Volume 26, pages 164 - 173.

Concurrent with this study, the effects of the same factors on the dosage of d-tubocurarine chloride and laudexium (Laudolissin) was examined. All of the 500 cases in whom the requirements of thiopentone were analysed are included in the study on muscle relaxants.

For the safe comparison of the effect of body weight, sex and age on dosage of thiopentone and muscle relaxants, the following reprint is included.

"THE RELATIONSHIP OF THE DOSAGE OF D-TUBOCURARINE CHLORIDE AND LAUDOLISSIN TO BODY WEIGHT, SEX AND AGE"

Reprinted from British Journal of Anaesthesia (1954), Volume 26, pages 173 - 180.

Reprinted from the

British Journal of Anaesthesia

Vol. XXVI, No. 3, May 1954

ALTRINCHAM
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Brit. J. Anaesth. (1954), **26**, 164.

THE INFLUENCE OF BODY WEIGHT, SEX AND AGE ON THE DOSAGE OF THIOPENTONE

BY

JOHN W. DUNDEE

Department of Anaesthesia, University of Liverpool

"... there is no definite dosage which will suit all patients. The amount required to produce anaesthesia varies greatly with the type of the patient." (Murphy, 1946).

THIS quotation accurately outlines the present-day approach to the use of thiopentone. Knowledge of the various pathological states which influence the dosage of this thiobarbiturate is accumulating. These include sensitivity in patients with liver damage (Shideman, Kelly and and Adams, 1949; Dundee, 1952a), severe anaemia (Dundee 1952b), shock (Adams and Gray, 1943; Halford, 1943), malaria (Ashworth, Pleasance, Goldman and Johnson, 1946) and uraemia (Dundee and Richards, 1953), resistance being observed in subjects who are receiving daily large doses of sedative or analgesic drugs (Dundee and Gray, 1951; Pratt, 1951). Racial factors as a cause of variation in dosage have been the subject of recent publications (Ashberry, 1953; Galley, 1953; Scott, 1953). The influence on the dosage of thiopentone of analgesics such as pethidine (Wolfers, 1953), methorphinan or morphine (Brotman, Cullen and Wilkins, 1950) or of the recently introduced mixtures used by the French workers with or without hypothermia has been reported (Huguenard, 1953; Dundee, Gray, Mesham and Scott, 1953).

This paper is concerned with the variation in dosage of thiopentone used during operations on adult patients in whom none of the above-mentioned factors was present. In comparing the requirements of the drug in any two series of patients variables must be reduced as far as possible. The drug or pathological condition under study should be the only factor of difference in the two groups. Nevertheless, even under these circumstances it is not known whether dosage should be recorded as the average amount of thiopentone administered during a fixed time, or whether dosage should be calculated on a weight basis, as so many mg. per kg. Likewise, there is no information available as to how similar two series should be as regards sex and age for them to be comparable. The present study was carried out to elucidate these points.

CLINICAL OBSERVATIONS

Anaesthetic records of 500 adult patients, in whom the operating time exceeded 2 hours, were studied. In all of these the sole drugs used were thiopentone, nitrous oxide-oxygen (1 litre of each per min.) and a muscle relaxant (d-tubocurarine chloride, Laudolissin or gallamine triethiodide). Morphine gr. 1/6 (10 mg.) and atropine gr. 1/100 (0.65 mg.) given

1–1½ hours before operation was the premedication. The cases were divided into three groups:

A. Abdominal operations, during which respiration was manually controlled throughout.

B. Abdominal operations with aided or spontaneous respiration.

C. Thoracic operations with manually controlled respiration.

Previously, it has been shown that controlled respiration reduces the amount of thiopentone required during abdominal operations (Dundee, 1952c), and therefore it was necessary to subdivide the abdominal cases (groups A and B). The anaesthetists and surgeons for the complete 500 cases varied, but within each of the series the personnel was the same. Details of the operations performed, the sex, age and weight of the patients and the relaxants used are shown in table I.

In all cases the amounts of thiopentone and relaxant administered were the minimum which would produce satisfactory operating conditions. Within limits, the larger the dose of relaxant used the smaller will be the requirements of thiopentone and *vice versa*. However, with one team of anaesthetists administering all the anaesthetics in one group of cases, it may be assumed that the barbiturate-relaxant ratio will be constant within each series, and since the requirements of patients in one group are never compared with those in another group, this factor is eliminated as far as possible.

The total dose of thiopentone administered was recorded every quarter of an hour for two hours in each case. For analysis of the requirements, both the actual amount of barbiturate given at any one time, and the dose in mg./kg. body weight were available.

TABLE I

Details of operations performed, sex of patients, average age and weight of patients and relaxants used during anaesthesia in 500 cases in whom the requirements of thiopentone were studied.

	Abdominal cases		
	Controlled respiration	Aided respiration	Thoracic cases
No. of cases	151	100	249
Sex			
Males	107	59	164
Females	44	41	85
Average age	46.7	48.4	42
„ wt. (kg.)	62	62	55
Operations			
Gastrectomy	92	65	
Operation on bile ducts	11	10	
Enteroanastomosis	14	5	
Hysterectomy	8	6	
Incisional hernia	7	6	
Bilateral inguinal hernia	6	3	
Colectomy	5	1	
Lumbar sympathectomy	4	4	
Nephrectomy	4		
Lobectomy			91
Pneumonectomy			66
Segmental resection			55
Oesophago-gastrectomy			22
Thoraco-lumbar sympathectomy			10
Diaphragmatic hernia			5
Relaxants used			
d-Tubocurarine chloride	100	100	232
Laudolissin	47		
Gallamine triethiodide	4		17

RELATIONSHIP TO BODY WEIGHT

In a series of 500 cases it would seem simple to plot the dose of thiopentone required at the end of two hours' anaesthesia against body weight and thus determine if there is a linear relationship. Figure 1 shows the result in the abdominal cases with controlled respiration. While there is a tendency to larger doses when the body weight exceeds 70 kg., the scatter of dosage is too great to draw any definite conclusions. Even in abdominal cases with aided or spontaneous respiration, when the scatter of both dosage and body weight

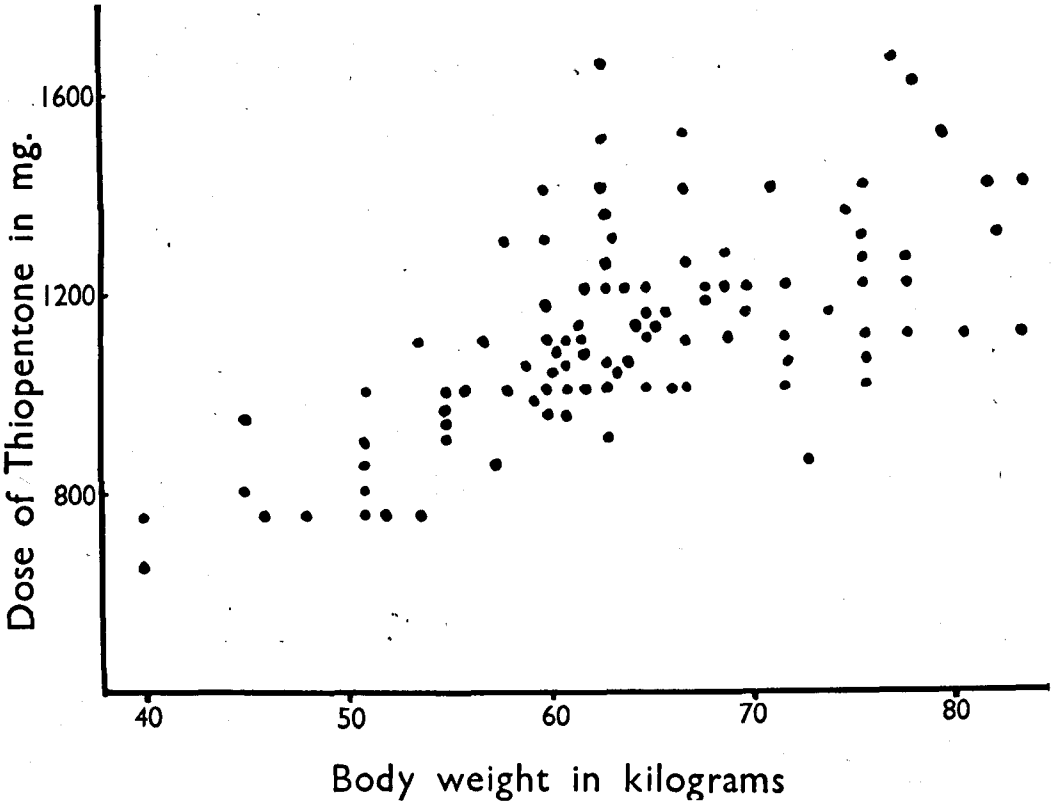

FIG. 1

Relationship of dosage of thiopentone, required to produce anaesthesia for two hours, to body weight in 151 patients undergoing abdominal operations during which respiration was controlled throughout.

is much less (fig. 2), it is still not possible to draw any definite conclusions although the relationship is more marked than in figure 1. Thoracic cases show a similar picture to figure 1.

An alternative method of approaching this problem is to calculate the scatter of actual dosage required for two hours' anaesthesia in each series. This may be compared with the scatter of the same dose expressed as mg./kg. body weight. If the latter is appreciably less than the former, not only is there a relationship between dosage and body weight, but one can assume that it is better to express the average dose of thiopentone in a series of cases as mg./kg. than as the average of the actual requirements. To simplify matters the term "weight-corrected dose" has been introduced. This is the equivalent dose for a 10 stone subject, that is to say the dose in mg./kg. multiplied by 63. This calculation does not affect the coefficient of variation for dose expressed as mg./kg., and it has the advantage of expressing mean requirements of thiopentone in figures with which everyone is conversant.

Table II shows that in each series of cases there is much less scatter with the

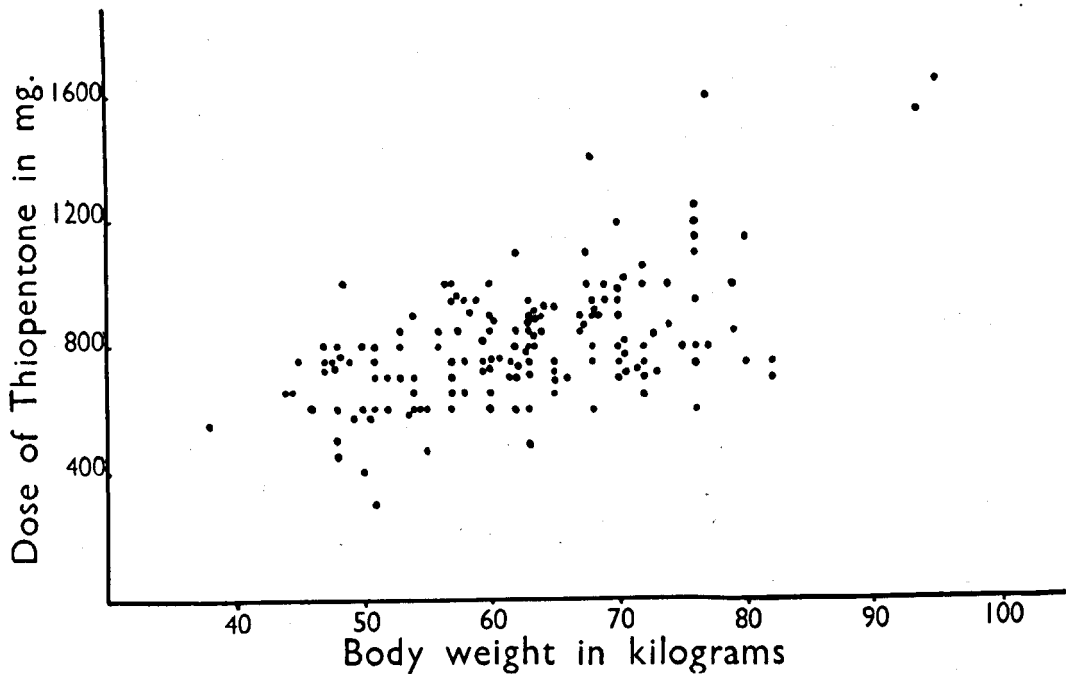

FIG. 2
Relationship of dosage of thiopentone, required to produce anaesthesia for two hours, to body weight in 100 patients undergoing abdominal operations during which respiration was spontaneous or aided throughout.

TABLE II
Mean values and scatter of average of actual doses and weight-corrected doses of thiopentone administered after 12 hours anaesthesia in the 3 series of cases listed in table I. Similar figures are also shown for dosage during the course of the anaesthesia in the abdominal surgery series in whom respiration was controlled throughout.

Series of cases	Actual dose		Weight-corrected dose	
	Average mg.	Coefficient of variation	Average mg.	Coefficient of variation
120 minutes anaesthesia				
Abdominals (B)	1100 ± 6.31	5.70	1107 ± 3.33	2.94
„ (A)	806 ± 17.16	25.20	819 ± 13.02	18.80
Thoracic	718 ± 11.96	25.50	830 ± 10.39	19.15
Abdominal cases, controlled respiration				
Induction	467 ± 6.51	16.0	478 ± 10.73	27.0
60 minutes anaesthesia	742 ± 9.56	23.0	765 ± 33.81	46.0
90 „ „	782 ± 16.66	25.20	800 ± 10.86	16.05
120 „ „	806 ± 17.16	25.20	819 ± 13.02	18.80

weight-corrected dosage than with the actual dosage. This is shown graphically in figure 3. These findings confirm those of figures 1 and 2 in showing that the average dose of thiopentone required to produce anaesthesia for 2 hours in normal subjects bears a relationship to body weight. This relationship is not very marked, and in clinical anaesthesia large differences in body weight are necessary

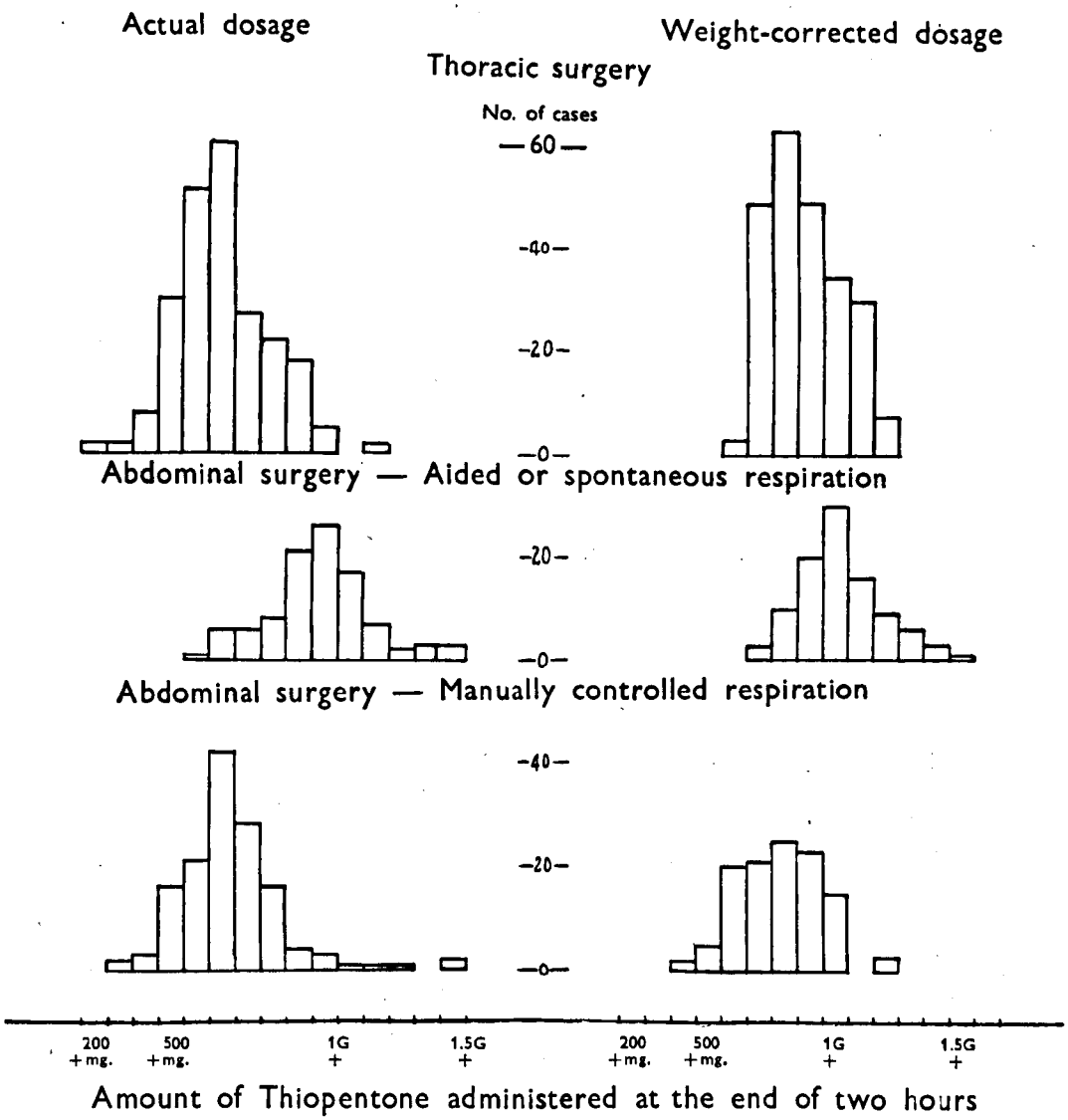

FIG. 3

Histograms showing scatter of actual dosage and weight-corrected dosage of thiopentone required to produce anaesthesia for two hours in 3 series of patients.

before any difference in reaction to thiopentone is observed.

Since requirements of the barbiturate were known throughout the course of all the operations, it was felt that it might be of interest to determine whether the relationship of dose to body weight was present throughout the anaesthetic. This was done in the series of abdominal operations with controlled respiration, results being shown in table II and figure 4. These are interesting as they show that, at the induction of anaesthesia, there is a very small scatter of the actual dosage of

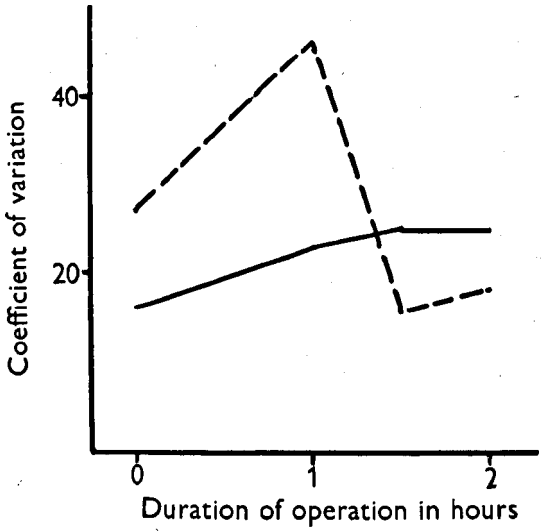

FIG. 4
Coefficient of variation of
——— actual dosage
- - - - weight-corrected dosage
of thiopentone requirements during the course of abdominal operation on 151 subjects in whom respiration was controlled throughout.

thiopentone indicating a tendency to administer a fixed dose rather than one related to body weight. This tendency is more marked after one hour, but, during the last half hour of the administration, the coefficient of variation of the weight-corrected dose is less than that of the actual dose indicating that dosage is then related to body weight. It may be that, had figures been available for requirements after 3 hours, the relationship of dose to weight would have been even more marked. It would seem that the longer an operation proceeds the more will the dose of thiopentone administered approximate to the true requirements of the patients.

RELATIONSHIP TO SEX

A search was made through all the cases in table I, and 52 males and an equal number of females were found in whom it was possible to compare the requirements of thiopentone directly. These are listed in table III. For each male undergoing a particular operation there was a corresponding female having a similar procedure performed, and the age of the two patients did not vary by more than 1 year, or their weight by more than 2 lb.

The average amount of thiopentone administered to each of these series is shown in table IV, both the actual dose and

TABLE III
Details of age, body weight and operations performed in 52 males and 52 females whose requirements of thiopentone were compared.

Average age—males	44.7 years
—females	44.4 years
Average weight—males	130.6 lbs.
—females	129.3 lbs.
Operations (equal numbers for both sexes)	
Gastrectomy (B)	15
Gastrectomy (A)	5
Lobectomy	16
Pneumonectomy	7
Oesophago-gastrectomy	2
Hiatus hernia	2
Colectomy (B)	1
Colectomy (A)	1
Cholecystectomy (A)	1
Gastroenterostomy (A)	1
Segmental resection	1
Total	52

TABLE IV
Comparison of the average requirements of thiopentone in 52 male and 52 female subjects, details of whom are given in table III.

Time	Actual dose mg. Males	Actual dose mg. Females	Weight-corrected dose mg. Males	Weight-corrected dose mg. Females
Induction	491	461	554	529
15 mins.	614	549	680	642
30 ,,	745	612	770	673
45 ,,	747	659	825	751
60 ,,	788	698	869	790
75 ,,	824	729	905	824
90 ,,	858	744	943	852
105 ,,	886	779	973	885
120 ,,	900	793	987	899
S.E. (diff.)	±40.02	±34.97	±32.5	±37.13
at 120 mins.	53.10		44.72	
Diff. of average S.E. (diff.) at 120 mins.	2.015		2.191	

TABLE V

Average dose of thiopentone required to produce anaesthesia for 2 hours in subjects undergoing the under-mentioned operations in the stated age groups. Figures in brackets refer to number of cases of which the average was taken. "Weight-corrected" dose = dose in mg./kg. multiplied by 63. A refers to subjects having manually controlled respiration. B refers to subjects having aided or spontaneous respiration.

Age group	−15	16+	26+	36+	46+	56+	66+
Weight-corrected dose							
Series							
Gastrectomy (A)			821 (11)	809 (14)	810 (24)	829 (12)	670 (5)
Gastrectomy (B)		1242 (4)	1237 (14)	1148 (13)	1153 (18)	1147 (10)	1017 (6)
Pneumonectomy		884 (4)	853 (7)	882 (17)	854 (22)	706 (25)	
Lobectomy	974 (13)	859 (27)	808 (17)	832 (7)	740 (17)	604 (9)	678 (5)
Segmental resection		718 (5)	662 (4)	511 (3)	511 (3)	473 (3)	
Actual dose							
Series							
Gastrectomy (A)			955	820	790	819	620
Gastrectomy (B)		1300	1283	1112	1093	1090	900
Pneumonectomy		700	650	863	864	708	
Lobectomy	496	756	700	814	733	655	650
Segmental resection		600	607	550	475	600	

weight-corrected dose being recorded. The overall picture shows that males require, on the average, more thiopentone than females. There is a statistically significant difference in the requirements of the two sexes after two hours of anaesthesia.

RELATIONSHIP TO AGE

The average 2 hour requirement of thiopentone was calculated for different age groups in 5 series of operations—gastrectomy with controlled respiration (92 cases), gastrectomy with aided respiration (65 cases), pneumonectomy (66 cases), lobectomy (91 cases), and segmental resection of lung (55 cases). The average of the weight-corrected and actual dosage is given in table V, the findings being shown graphically in figure 5.

Results show that there is no definite relationship to age of the average of the

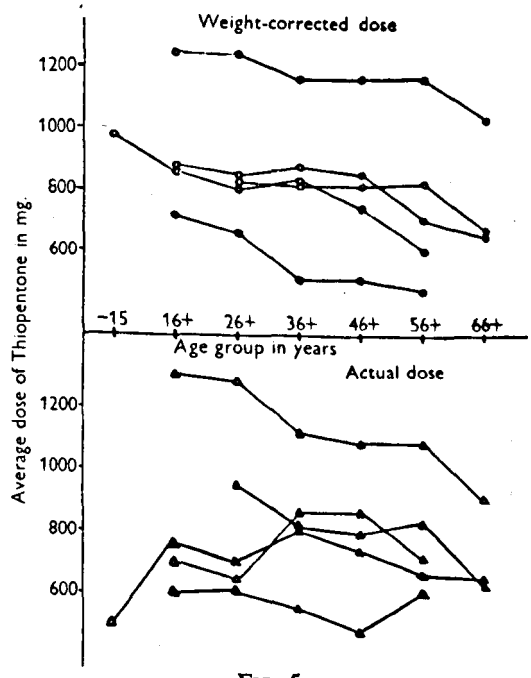

FIG. 5

The relationship of average dosage of thiopentone, required to produce anaesthesia for two hours, to age in 5 series of patients described in the text.

actual dose of thiopentone administered at the end of 2 hours of anaesthesia. The averages of the weight-corrected dose, however, show that requirements are fairly constant between 26 and 46 years of age. Patients aged 25 years and under require, on the average, more thiopentone than during middle life, and dosage declines in patients over the age of 46. In view of the fact that dosage bears some relationship to body weight it can be concluded that at the extremes of age there is a different tolerance to thiopentone as compared with requirements during the third and fourth decades of life.

DISCUSSION

For results in a study of this nature to be completely reliable one would have to study the response to thiopentone of a large number of volunteers of varying weight, sex and age, who were undergoing no surgical operation. The information derived from such a study is unlikely to be of such importance as to justify the risk involved—even though this is small—and the time required. In any anaesthetic only clinical judgment can estimate whether the dose of thiopentone administered is the minimal required for the particular operation. However, in a large series of administrations by experienced anaesthetists one is probably justified in concluding that the average of the actual dose administered approximates to the average of the actual requirements of the patients.

On this assumption these results show that body weight is a factor in determining the dosage of thiopentone required in healthy adult patients. The relationship is by no means striking, and only at extremes of weight is the difference in response clinically obvious.

The work of Brodie and his co-workers (Brodie, Mark, Papper, Lief, Bernstein and Rovenstine, 1950; Brodie, 1952; Brodie, Bernstein and Mark, 1952) has established that body fat is one of the factors in limiting the duration of action of thiopentone. Others which play a part are the volume of circulating blood and the efficiency of detoxicating mechanisms. In healthy subjects the blood volume and the size and weight of the liver and kidneys are proportional to the body weight. The same cannot be said of the amount of body fat, and it is likely that variations in this latter are the reason why a more marked relationship of thiopentone requirements to body weight was not found.

It is generally accepted that men have, on the whole, a more robust constitution than women, and are more resistant to poisons and to drugs in general (Gordh, 1950). This may explain the greater tolerance to barbiturates in males that was found in these cases.

It has been stated in the introduction that none of the patients whose thiopentone requirements were analyzed in this paper, had any of the pathological conditions known to affect the dose of thiopentone. Liver and kidney function tests, haemoglobin estimations, etc., were not carried out as a routine on every patient. Minor undetected disturbances in metabolism were almost certainly present in many of the elderly patients. While these were not of such severity as to be obvious clinically, their effect in decreasing the tolerance to thiopentone has become

apparent on analyzing requirements of the drug necessary to produce anaesthesia for 2 hours in a large number of patients. If the thiopentone requirements of a series of unselected cases were to be analyzed, one would expect the effect of age in reducing requirements of the barbiturate to be even more marked than has been found in these cases.

Guedel (1943) states that metabolic rate and reflex irritability are increased between birth and 20 years of age. Thereafter they both decrease gradually until the age of 80. This could account for the increased requirements of thiopentone found in the subjects under 25 years of age. Not only do they detoxicate the thiopentone at a rapid rate, but more of the drug will be necessary to obtund reflex activity, as compared with patients above this age.

CONCLUSION

In comparing the requirements of thiopentone in any two series of cases, the doses of the drug should be recorded in mg./kg. or in some figure which bears a relationship to body weight. Each series should be the same as regards males and females. Age of patients in each is not important between 25 and 46 years, but outside this range they should be balanced, with equal numbers at each extreme of age in each series.

SUMMARY

The factors known to influence the dosage of thiopentone have been listed. Thiopentone requirements have been observed in 500 normal adult patients undergoing abdominal and thoracic operations, in whom thiopentone was used as the sole narcotic.

The requirements of thiopentone in these patients have been analyzed for their relationship to body weight, sex and age. The significance of the findings is discussed.

The amount of thiopentone required to maintain anaesthesia for 2 hours in normal adult patients is related to the body weight. This relationship is not very marked and is only obvious clinically at extremes of weight.

Adult males, on the average, require more thiopentone than adult females.

Requirements of thiopentone are fairly constant in middle age, but are increased in patients under 25 years of age and decreased in those aged 46 and over.

In comparing the average requirements of thiopentone in any two series of patients allowance must be made for the above factors.

ACKNOWLEDGMENTS

I am indebted to Dr T. Cecil Gray and Dr. E. S. N. Fenton for placing records of anaesthetics at Liverpool Thoracic Surgery Unit (Broadgreen Hospital) at my disposal, and to Miss M. Garrett for her help with the statistics.

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THE RELATIONSHIP OF THE DOSAGE OF D-TUBOCURARINE CHLORIDE AND LAUDOLISSIN TO BODY WEIGHT, SEX AND AGE

BY

JOHN W. DUNDEE

Department of Anaesthesia, The University of Liverpool

THE factors which are known to influence the dose of competitive blocking relaxant agents are fewer than those for thiopentone, in combination with which they are commonly used. Sensitivity occurs in patients with myasthenia gravis, and occasionally when there is no obvious pathological condition (Gray and Halton, 1948; Condon, 1951; Dundee, 1951; Dundee and Gray, 1951; Howell-Jones, 1951). Resistance has been observed in patients with liver dysfunction or addiction to sedative or analgesic drugs. This has been attributed to the presence of a lowered pseudocholinesterase (Dundee and Gray, 1953), since it is considered that the liver is not a major factor in the detoxication of d-tubocurarine (Everett, 1948).

Work which has hitherto been reported on variations in response to relaxant drugs has been based on a comparison of the average requirements of large series of cases during surgical operations (Dundee, 1952), the average dose being given in mg./kg. body weight. It is not known whether the average requirements of relaxant drugs are related to body weight, or whether the averages of the actual dose administered should be compared. The importance of balancing series as regards sex and age is also not known.

This paper is an analysis of the doses of d-tubocurarine chloride or Laudolissin administered to adults during 553 operations of at least two hours' duration. These are divided into four series, details of which are given in table I. The anaesthetic combination in all cases consisted of a thiobarbiturate (thiopentone, thialbarbitone or thioquinalbarbitone), nitrous oxide-oxygen (1 litre of each per min.) and relaxant. Ether, pethidine or cyclopropane were not used in any of the cases. Except in one series of 100 abdominal operations controlled respiration was used throughout all the procedures. While the number of anaesthetists whose records were analyzed is fairly large, only 3–4 were concerned with any one series. The individual variations in technique are eliminated as far as possible, by avoiding comparison of the average requirements in any one series with those of another series.

RELATIONSHIP TO BODY WEIGHT

Since the actual dose of relaxants administered and the patients' weights were known, a direct relationship was sought between these two. Figure 1 shows the dose of d-tubocurarine chloride administered at the end of two hours to the two series of abdominal cases plotted against the patients' body weight. This

TABLE I

Details of operations performed; sex, average age and weight of 553 patients in whom the requirements of relaxants used during operation were studied.

Relaxant	d-tubocurarine chloride			Laudolissin
	Abdominals			
Series	Controlled respiration	Aided respiration	Thoracic	Abdominals controlled respiration
Number of cases	100	100	236	117
Sex:				
Male	70	59	157	79
Female	30	41	79	38
Average age	46.9	48.4	43	
Average weight (kg.)	63.0	62.0	59	60
Operations				
Gastrectomy	65	65		62
Operation on bile ducts ...	10	10		8
Enteroanastomosis	5	5		10
Hysterectomy	6	6		10
Incisional hernia	5	6		4
Bilateral inguinal hernia ...	4	3		2
Colectomy	1	1		8
Lumbar sympathectomy ...	4	4		8
Nephrectomy				5
Lobectomy			88	
Pneumonectomy			55	
Segmental resection ...			54	
Oesophago-gastrectomy ...			24	
Thoraco-lumbar sympathectomy ...			10	
Diaphragmatic hernia ...			5	

fails to reveal any close relationship except at the extremes of weight. A similar result was obtained in the abdominal cases where Laudolissin was the relaxant, or with d-tubocurarine in the thoracic cases.

The method adopted by the author in analyzing the requirements of thiopentone (Dundee, 1954) was used to see if the scatter of the actual doses of relaxant administered was different from that of the "weight-corrected" dose (dose in in mg./kg. multiplied by 63). The results, which are shown in table II, show that there is no appreciable difference in the coefficient of variation irrespective of how the dose of relaxant is expressed. Body weight would not seem to be a factor influencing the dose of muscle relaxants in adults.

Table II also shows an analysis of the amounts of d-tubocurarine chloride at varying intervals during the course of anaesthesia in the 100 patients undergoing abdominal operations, in whom respiration was controlled throughout. The initial dose of relaxant is related to body weight, but this relationship does not hold at the end of one hour, or at any subsequent time during the administration.

RELATIONSHIP TO SEX

This, and the subsequent study, was limited to d-tubocurarine chloride. Doses of the drug administered every 15 minutes

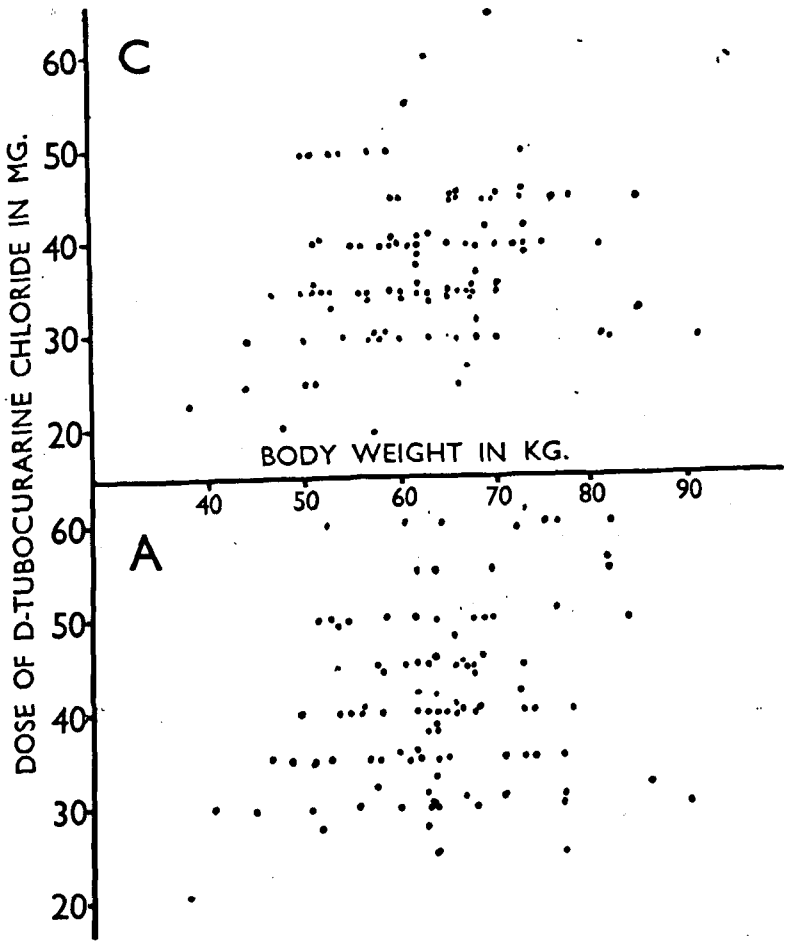

FIG. 1

Scatter diagram in which the two-hour requirements of d-tubocurarine chloride are plotted against the body weight.
C—100 abdominal cases with controlled respiration.
A—100 abdominal cases with aided or spontaneous respiration.

were compared in two comparable series of 52 males and an equal number of females. The comparison comprises both the average of the actual dose, and the weight-corrected dose in mg. Details of these have been given in a previous paper, in which the same cases were used for a study of the dosage of thiopentone (Dundee, 1954).

Despite the fact that the average dose of relaxant required by women was on the average slightly less than that administered to men (table III) the difference is not statistically significant.

RELATIONSHIP TO AGE

The average 2-hour requirement of d-tubocurarine chloride was calculated

TABLE II

Mean values and scatter of actual doses and weight-corrected doses of d-tubocurarine chloride and Laudolissin administered to the cases listed in table I.

Series of cases	Actual dose		Weight-corrected dose	
	Average mg.	Coefficient of variation	Average mg.	Coefficient of variation
120 *minutes anaesthesia*				
d-Tubocurarine chloride				
Abdominals (Aided)	40.53 ± 0.93	22.93	40.84 ± 0.96	23.60
Abdominals (Controlled)	38.83 ± 0.87	8.69	38.26 ± 0.26	8.69
Thoracic	43.85 ± 0.70	24.67	46.99 ± 0.47	15.07
Laudolissin	64.33 ± 1.40	23.90	61.79 ± 1.31	23.90
d-Tubocurarine chloride, Abdominal cases, controlled respiration				
Induction	20.90 ± 0.47	32.59	20.79 ± 0.17	8.25
60 mins. anaesthesia	35.10 ± 0.75	21.40	34.54 ± 0.74	21.50
90 mins. anaesthesia	37.61 ± 0.83	22.00	36.48 ± 0.52	14.37
120 mins. anaesthesia	38.83 ± 0.87	8.69	38.26 ± 0.26	8.69

TABLE III

Comparison of the average requirements of d-tubocurarine chloride in 52 male patients, and an equal series of comparable females, undergoing identical surgical procedures.

Time	Actual dose, mg.		Weight-corrected dose mg.	
	Males	Females	Males	Females
Induction	13.4	16.5	20.8	14.9
15 min.	22.7	20.1	25.8	22.0
30 min.	26.1	23.6	29.6	26.5
45 min.	29.2	27.1	33.0	30.6
60 min.	32.0	29.9	36.1	33.4
75 min.	35.0	32.2	39.2	36.0
90 min.	36.4	34.2	41.0	38.4
105 min.	33.4	35.4	43.0	39.5
120 min.	38.8 ± 2.55	36.6 ± 2.00	43.5 ± 3.20	40.6 ± 2.32
S.E. (diff.) at 120 mins.	3.32		3.94	

for different age groups in four series of patients—gastrectomy with controlled respiration (65 cases), gastrectomy with aided or spontaneous respiration (61 cases), pneumonectomy (55 cases) and lobectomy (85 cases). The average of the weight-corrected and actual dose for each group is given in table IV, and results are shown graphically in figure 2.

These fail to reveal any clear cut relation between the 2-hour dose of d-tubocurarine chloride and age. This applies irrespective of whether the average of the actual dose or the weight-corrected dose is analyzed.

DISCUSSION

This investigation has been unsuccessful in demonstrating any relationship between the doses of relaxants used in clinical anaesthesia in adults and body weight, sex or age. This is in distinct contrast to the findings obtained with thiopentone (Dundee, 1954). However, there are many differences between the effects of the two drugs, which may explain these findings.

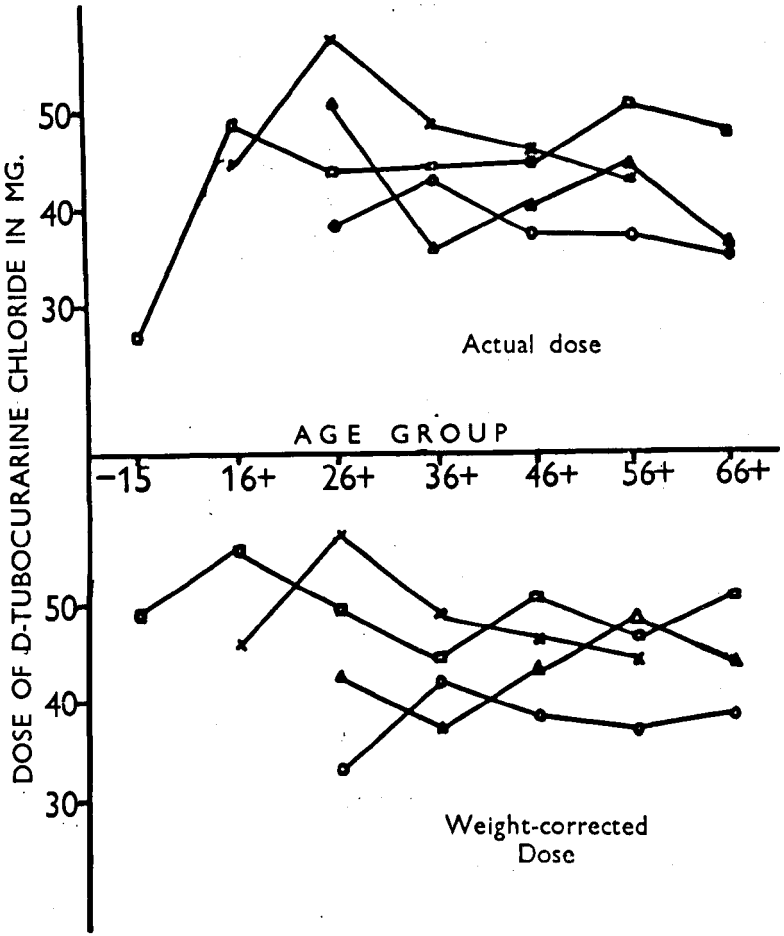

FIG. 2

Diagrammatic representation of table IV, showing relationship of average dose of d-tubocurarine chloride to body weight, in four series of patients.

Competition blocking relaxants are among the least toxic drugs known, as regards their effects on the cardiovascular system, the reverse applying to the thiobarbiturates (Prime and Gray, 1952). Should the effect of relaxants be prolonged beyond the duration of the operation an effective antidote is available for their reversal. In the case of thiopentone and similar drugs, analeptics are not a reliable means of terminating the narcosis.

For these reasons one is more prone to administer a dose of relaxant in excess of the patient's requirements than is the case with the barbiturates. This is illustrated by the incremental doses of the two types of drugs administered during the course of anaesthesia using the technique employed for the cases in this study. With d-tubo-

TABLE IV

Average dose of d-tubocurarine chloride in mg. required during 2 hours anaesthesia undergoing the various operations, in the stated age groups.

Age group	−15	16+	26+	36+	46+	56+	66+
A. Weight-corrected dose							
Series							
Gastrectomy (Controlled)			33.1 (10)	41.9 (12)	38.7 (28)	36.8 (10)	38.1 (5)
Gastrectomy (Aided)			42.8 (14)	36.5 (13)	42.8 (18)	47.9 (10)	43.5 (6)
Pneumonectomy ...		46.2 (5)	57.7 (5)	48.8 (10)	46.2 (18)	44.1 (17)	
Lobectomy	49.8 (12)	55.4 (29)	49.1 (8)	44.1 (9)	50.4 (15)	46.6 (8)	50.4 (4)
B. Actual dose							
Series							
Gastrectomy (Controlled)			38.5	43.0	37.5	37.2	35.6
Gastrectomy (Aided)			51.3	36.0	40.7	44.5	36.0
Pneumonectomy ...		45.2	57.7	48.8	46.2	44.1	
Lobectomy	27.0	48.0	44.0	44.0	45.0	51.0	48.0

Figures in parentheses refer to the number of cases of which the average was taken.
Weight-corrected dose=dose in mg./kg. × 63.

curarine chloride supplementary doses are in the order of 5 mg., and with Laudolissin 10 mg., these representing approximately 10–20 per cent of the total dose administered during a two-hour operation. The comparable 25–50 mg. thiopentone is only 3–5 per cent of the final total dose. Consequently any analysis of the clinical requirements of relaxants approximates less closely to the actual minimal requirements of the drugs than is the case with the thiobarbiturates.

These comments decrease the value of this paper as a guide to the relationship of clinical doses of relaxants to body weight, sex and age. However, while the above arguments apply, it is hoped that in numbers of the order analyzed in this study many of the errors will be eliminated.

In an early paper on the use of d-tubocurarine chlorine in anaesthesia Gray (1947) states, "Whilst a dose for weight scale is useless in adults, in children it is of great value, for in them the muscle mass upon which depends the requisite dose of curare bears a more certain relationship to body weight". No details were available of the build, etc., of the patients whose weights were known, and no light can be thrown on this subject. Since relaxants act at the myoneural junction one might expect to find a relationship

between their dosage and the number of motor end plates. However, the number of these does not increase after about the fifth month of foetal life (Le Gros Clark, 1953), and hence cannot be related to increase in body weight or muscle mass. It is impossible to find evidence to substantiate or disprove the findings of this paper that in healthy adults of average weight ($8\frac{1}{2}$–$11\frac{1}{2}$ st., i.e., 54.5–73.5 kg.) the clinical requirements of d-tubocurarine chloride or Laudolissin are not related to body weight. Outside the range of average weight there may be some relationship, but this is by no means definite.

Males, on the whole, are heavier than females, and in a large series there will be more of their weights outside the upper limits of normal, while more females will weigh less than normal. Apart from this there is no reason to suspect that dosage of relaxants should be related to sex. This is in keeping with the results of table III, in which weight and age were eliminated as variables, and where no relationship between dosage and sex could be demonstrated.

It has been suggested that the aged require greatly reduced dosage of d-tubocurarine chloride (Gray, 1947), but more recent reports suggest that the opposite might be true (Durrans, 1952) and that the aged show more resistance to relaxants. Considering patients as a whole, one would expect to find a greater incidence of reduced serum cholinesterase in elderly subjects with a consequent higher proportion of cases which show resistance to d-tubocurarine chloride or Laudolissin. However, in reasonably fit subjects, such as those whose requirements have been studied, there is no evidence that age plays any part in influencing the dosage of relaxants.

CONCLUSIONS

In comparing the dosage of relaxants used clinically by two series of patients, it is obvious that each series must be extremely large. There are no grounds for recommending that average dosage should be expressed in mg./kg. or mg./lb., or whether the actual dosage administered is sufficient in adults. Until more is known on this subject it is advisable that both the actual dose and dose in relation to weight be stated. Furthermore, for the difference in requirements in any two series of clinical cases to be significant, it must be greater than that demanded by recommended statistical tests, irrespective of the size of the sample.

There is no evidence to suggest that in adults of average build, the body weight, sex or age influences the requirements of d-tubocurarine chloride or Laudolissin.

SUMMARY

(1) Factors known to influence the requirements of relaxants which act by competition blocking are discussed.

(2) An analysis is made of requirements of d-tubocurarine chloride or Laudolissin in 553 adult subjects during abdominal or thoracic operations.

(3) The relationship of the dosage of these drugs to body weight, sex and age is discussed.

(4) Suggestions are made for comparing the requirements of competition blocking relaxants in any two series of cases.

ACKNOWLEDGMENTS

I am indebted to Drs. T. Cecil Gray and E. S. N. Fenton for placing records of anaesthetics at Liverpool Thoracic Surgery Unit (Broadgreen Hospital) at my disposal, and to Miss M. Garrett for her help with the statistics.

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Variations in Healthy Subjects.

(b) Tolerance - acute

- acquired

"ACUTE TOLERANCE TO THIOPENTONE IN MAN".

(published in conjunction with Drs. Henry L. Price and Robert D. Dripps)

Reprinted from British Journal of Anaesthesia (1956).
Volume 28, pages 344 - 352.

Full details of this investigation, statistical analysis and other data not included in the paper are included in Appendix 1 (page 177)

"ACQUIRED TOLERANCE TO INTRAVENOUS THIOBARBITURATES IN ANIMALS".

Reprinted from British Journal of Anaesthesia (1955).
Volume 27, pages 165 - 170.

Clinical observations on resistance to thiopentone and similar drugs in man are recorded in Appendix 4 of Thiopentone and Other Thiobarbiturates.

Variations in Healthy Subjects.

(c) Cumulative Action.

"OBSERVATIONS ON THE DOSAGE AND CUMULATIVE ACTION OF THIOPENTONE".

Reprinted from Anaesthesia (1955), Volume 10, pages 139 - 156.

"CUMULATIVE ACTION OF FOUR THIOBARBITURATES WITH SPECIAL REFERENCE TO THIOPENTONE AND THIAMYLAL"

Reprinted from Anaesthesia (1955), Volume 10, pages 391 - 400.

In addition to the cumulative action of thiopentone, the first paper discusses the distribution of the drug in the body and correlates clinical observations with experimental work.

VOL. 10, NO. ANÆSTHESIA April, 1955

OBSERVATIONS ON THE DOSAGE AND CUMULATIVE ACTION OF THIOPENTONE*

BY JOHN W. DUNDEE, M.D., F.F.A.R.C.S.,
LECTURER IN ANÆSTHESIA, UNIVERSITY OF LIVERPOOL

EARLY reports on the use of thiopentone in this country stated that the drug was rapidly broken down in the body leaving no ill effects[1]. Veal and Reynolds[2] were the first to dispute this and they pointed out that the injection of small fractional doses of thiopentone was not comparable to the administration of ether by the open drop method. In animals they found that the administration of repeated doses of the same amount resulted in a gradual lengthening of the duration of action with each successive injection. Immediately after an animal had wakened from the effects of thiopentone a further dose produced anæsthesia more similar in duration to that of the longer acting pentobarbitone. Recent studies by Wyngaarden, Woods, Ridley and Seevers[3 4] have confirmed these findings.

The explanation offered by Veal and Reynolds[2] of this phenomenon is interesting, although it is no longer believed. They postulated that normal organs are incapable of destroying more than a certain amount of thiopentone. Another factor was that the drug itself caused liver dysfunction[5]; the administration of an initial dose thereby reducing the ability of this organ to deal with supplementary doses.

Many workers have observed that the duration of narcosis with large doses of thiopentone is proportionally longer than after the injection of a small dose. When a large enough amount is administered the narcosis is similar to that produced by an equal dose of its oxygen analogue pentobarbitone. It has been suggested, in fact, that the breakdown of thiopentone may involve the formation of a longer acting barbiturate[6]. The exhaustion of the enzyme necessary for its breakdown is another explanation that has been offered for the long action of large doses of thiopentone[7].

Until about 1949 it was thought that the duration of effect of an intravenous injection of thiopentone was determined by the rate of its metabolic transformation. A new light has been thrown on the subject by the findings of Brodie and his associates[8 9 10 11 12 13 14 15]. A technique was devised for the quantitative determination of thiopentone in plasma and tissues[10], and using this they carried out plasma estimations in man and tissue estimations in dogs following various doses of the drug.

*Based on a paper read to the Yorkshire Society of Anæsthetists on 1st July, 1953.

After the injection of a small amount of thiopentone the plasma concentration fell rapidly and the subject quickly recovered from the anæsthesia. The early sharp decline in plasma concentration was not due to disappearance of the drug from the body, but to its redistribution, thiopentone being removed from the plasma and located extensively in a tissue depôt. Concentrations in plasma and liver were found to be maximal immediately following administration, whereas those of muscle continued to rise for a short time. Liver, muscle and plasma concentrations then declined rapidly and in a parallel manner for about one hour and then diminished more slowly for the next two to three hours. Amounts of drug in the fat, which were negligible at first, rose rapidly for the first hour, then more gradually, reaching a maximum in about three and a half hours; following this the fat content of thiopentone gradually diminished.

After a large dose of thiopentone, or after repeated small doses, the resulting equilibrium plasma level is above the anæsthetic level and is maintained there by the reservoir of drug in non-nervous tissues and in fat. Once equilibrium has been established the rate of decline of plasma thiopentone is only about 10–15% per hour (after two hours)—this representing the true rate of detoxication of the drug in vivo. Because of the slow rate of metabolism of thiopentone, anæsthesia continues for a considerable period of time after large doses of the drug.

The plasma and cerebrospinal fluid levels of thiopentone run parallel and changes in the former are almost instantaneously reflected in the latter[12 16]. Consequently the depth and duration of narcosis depends on the plasma content of thiobarbiturate[17].

There is fairly close agreement between the views expressed by Brodie and his co-workers and others who have since studied the removal of thiopentone from plasma and tissues. Brooks, Bollman, Flock and Lundy[18 19] studied the diffusion of thiopentone in rats. Following the administration of 40 mg./kg. a rapid diffusion occurred to non-nervous tissues. The greatest concentration was reached in each tissue within one minute of the injection and no specific accumulation of thiopentone occurred in the liver, kidney, plasma, brain or intestine. Their studies of distribution in fat were incomplete, but preliminary findings were in agreement with those of previous workers. The slow rate of decline that they found in tissue concentrations of thiopentone agrees with the slow rate of detoxication in the body. Studies of distribution of radioactive S^{35} of thiopentone in the rabbit and cat by Taylor, Richards and Tabern[20 21] produced similar results. Since their analyses were only carried out up to 10 minutes after injection, any delayed accumulation of the drug in body fat would have been missed.

It has recently been pointed out by Shideman, Gould, Winters, Peterson and Wilner[22] that there is a species difference in the time

of maximum location of thiopentone in fat. With the dog this occurs in about four hours, in the rat it only takes two hours, while figures available for man place the time between one and a half and two and a half hours. Their other conclusions as regards diffusion and detoxication are in complete agreement with those of Brodie et al[10].

In view of the above work it seems reasonable to assume that once anæsthesia is established with thiopentone, the amounts required to maintain a constant level of narcosis represent that removed from the blood stream (and hence cerebrospinal fluid) by diffusion and detoxication. It should be possible to divide the requirements of thiopentone into three stages as follows :

Induction and early saturation of non-fatty tissues

With the exception of muscle tissue, equilibrium is established within one minute of injection, the maximum concentration in muscles being reached within fifteen minutes. This explains the large dose of thipentone (7–9 mg./kg.) required for induction of anæsthesia, and the comparatively large supplementary doses used during the first quarter of an hour to maintain an even plane of narcosis. Not only do these doses saturate the non-fatty tissues, but they also make up for the loss by detoxication.

Diffusion of drug to fatty tissues

Supplementary doses will be required less frequently than before to make up for the amount of drug which diffuses from plasma to fat and for the amount detoxicated in the body. As duration of narcosis proceeds, smaller and less frequent increments will be required until equilibrium with fat is established. The duration of this stage will depend upon the amount of fat in the body and should be influenced by factors which affect the distribution of thiopentone between the aqueous and lipoid phases, e.g. *p*H of plasma[12 23]. With a raised *p*H the barbiturate is maintained longer in the plasma and vice versa.

Tissue saturation

During tissue saturation thiopentone can only be removed from the plasma by the slow process of detoxication.

This should occur after one and a half to two and a half hours anæsthesia[10] and subsequently very small doses at prolonged intervals will be required to maintain an even level of narcosis.

One would not expect that these stages would be in any way clear cut and they would be difficult to distinguish from each other, with the exception of the first and second. They are further confused by acute tolerance to the drug—as the duration of anæsthesia proceeds, the plasma (and hence C.S.F.) level of thiopentone at which a subject wakens or exhibits certain reflexes increases[12]. The response of the nervous system also appears to be related to the initial level of

barbiturate to which it is subjected[12 24]. The more quickly is an induction dose injected (and hence the larger will be the initial concentration to reach the brain) so the shorter will be the duration of narcosis.

These stages can be demonstrated experimentally in man by repeated injections of the same dose of thiopentone, each dose being given when the patient recovers sufficiently from the effect of the previous one to answer questions. The results of two such observations on fit male volunteers are shown in figure 1. The duration of narcosis with the first two doses was very brief (1–5 mins.). Over the next 60–90 minutes the duration of action of each successive dose became more prolonged, and finally after 90–120 minutes equilibrium appeared to have occurred and duration of narcosis with each dose was approximately the same. During this latter period tissue saturation was complete and consciousness was only regained by detoxication of thiopentone in the body. As stated previously, the division between stages 1 and 2 was more clearly defined than between 2 and 3.

A demonstration of stages 1 and 2 in cases undergoing surgical procedures under thiopentone anæsthesia was obtained, using a continuous infusion of the barbiturate to maintain a clinically constant level of surgical anæsthesia. A study of requirements in μg./kg./min. was undertaken in twenty-one subjects undergoing non-abdominal operations. Atropine 0.65 mg. (1/100 grain) was the sole premedication; anæsthesia was induced with the minimal dose of barbiturate necessary to produce sleep and maintained with a continuous drip of 0.3% thiopentone with oxygen. A constant pulse rate during operation proved a valuable guide that a constant level of anæsthesia was being maintained[25].

It was only possible to obtain average figures for anæsthesia of 65 minutes duration; in many instances it was difficult to make adjustments in the drip rate at times which would ensure that readings could be recorded exactly at minute intervals (the drip regulator described by Morton[26] was not available at the time). To compensate for this, the average of (odd + even) and (even + odd) minute readings were taken giving intermediate figures between the minutes. This should give a more even picture of thiopentone requirements.

Figure 2 shows a graphic representation of the results obtained. A rapid diminution in thiopentone requirements occurred during the first ten to twelve minutes, and thereafter a more steady decline in dosage administered. The rapid decline due to saturation of non-fatty tissues followed by a more gradual diminution of requirements is in agreement with the experimental evidence quoted above, and the views already expressed. By plotting the figures on a logarithmic scale (Fig. 3), a straight line was obtained for requirements between 15 and 65 minutes. This suggests an exponential rate of diminution of requirements, and hence an exponential rate of removal of

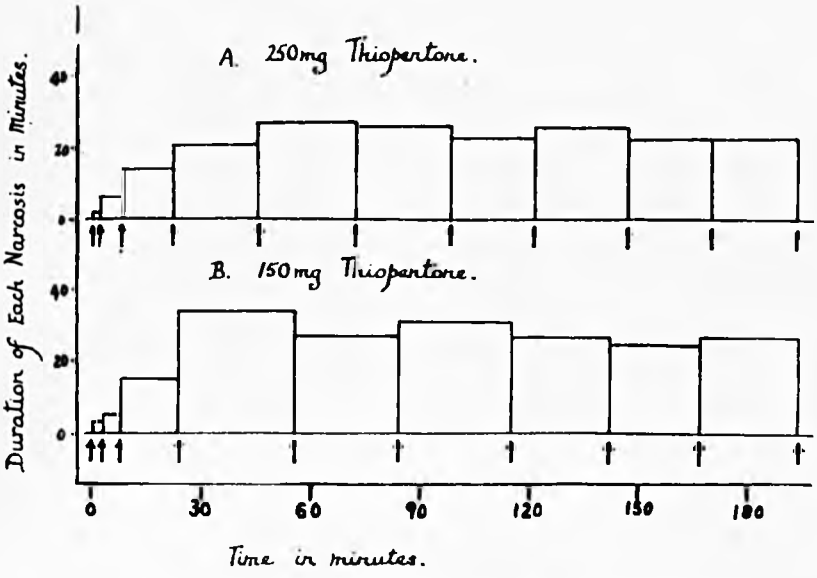

FIG. 1.—Diagrammatic representation of duration of narcosis following repeated injections of the same dose of thiopentone in two male volunteers.

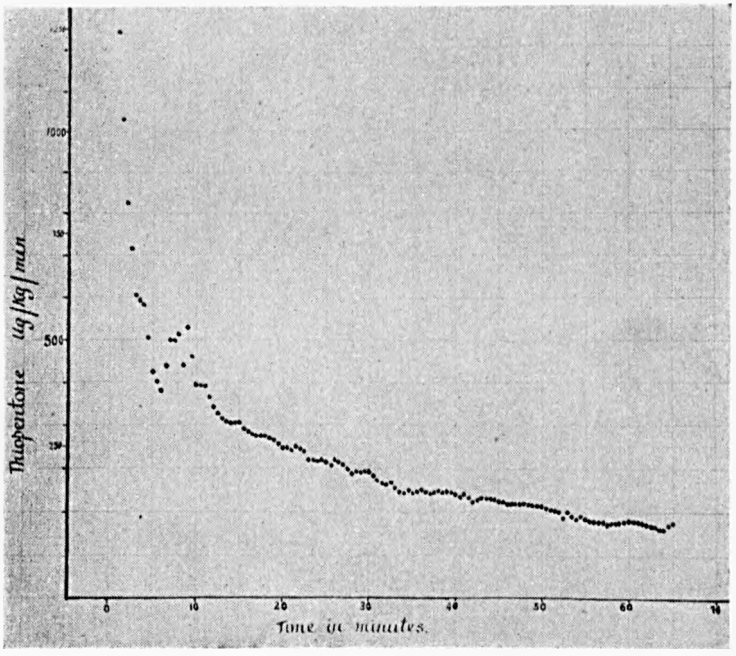

FIG. 2.—Graphic representation of average requirements of thiopentone in µg/kg/min. in 21 subjects to whom no other anæsthetic agent was administered.

thiopentone from the blood stream, both by diffusion and detoxication. An alternative presentation of the same results is shown in

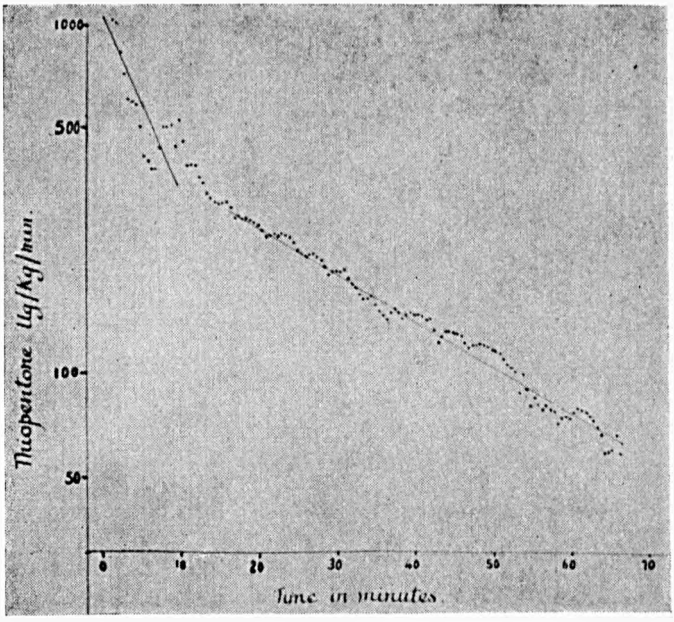

FIG. 3.—Average requirements of thiopentone in µg/kg/min. plotted on logarithmic scale.

figure 4. In this the average requirements in µg./kg./5 minutes are plotted against time, both on a linear and logarithmic scale. These graphs verify the findings of figures 2 and 3.

Thiopentone is seldom, if ever, used as the sole narcotic in major surgery, being usually combined with an analgesic mixture of nitrous oxide-oxygen and a muscle relaxant. From the practical point of view it is important to find whether the three stages of thiopentone administration apply when this technique is used. An analysis of average thiopentone requirements per 15 minutes was made in two series of patients undergoing major operations of at least two hours' duration. In one series the operations were performed by general surgeons and the other by thoracic surgeons. While the anæsthetists differed for each group, in each they were limited to three to four administrators who used identical techniques. All subjects received the same premedication, viz. morphine 10 mg. (1/6 grain) and atropine 0.65 mg. (1/100 grain) about one hour before induction of anæsthesia, and anæsthetic agents were limited to thiopentone, 50% nitrous oxide and oxygen, and a muscle relaxant. No patients were included in whom was present a factor which might interfere with [diffusion] or detoxication of thiopentone. These

included shock or severe blood loss before or during operation[27], liver dysfunction[28 29], anæmia[30], uræmia[20], and tolerance to analgesia and sedative drugs[31]. Details of each series is given in table 1.

TABLE 1

Series	General Surgery		Thoracic Surgery	
No. of cases	240		209	
Average age	46		42	
Average wt. (kg.)	63		57	
Operations	Gastrectomy	152	Lobectomy	91
	Ops. on bile ducts	21	Pneumonectomy	66
	Hysterectomy	13	Oesophago-gastrectomy	22
	Incisional hernia repair	12	Segmental resection	15
	Entero-anastomosis	13	Sympathectomy	10
	Inguinal hernia repair	10	for Hiatus hernia	4
	Colectomy	6	Heller's operation	1
	LumbarSympathectomy	9		
	Nephrectomy	2		
	Cystectomy	2		
Relaxants used	d-tubocurarine chloride	218	d-tubocurarine chloride	196
	Laudexium	22	gallamine triethiodide	13

Details of the two series of cases, anæsthetised with thiopentone, nitrous oxide-oxygen and a muscle relaxant, whose requirements of thiopentone have been studied during the first two hours of anæsthesia.

The average total dose of thiopentone, in mg./kg., administered in each of the series at 15 minute intervals is given in table 2. Figure 5 shows diagrammatically the average supplementary dose per 15 minutes in each series, the induction dose not being included. With the mixtures of nitrous oxide-oxygen used, the arterial concentration of the gas reaches equilibrium in about 20 minutes[32]. In view of this a correspondingly increased amount of barbiturate will be required for the first fifteen to twenty minutes, as compared with the remainder of the anæsthesia.

In the series of abdominal cases there is a gradual decline in thiopentone requirements for the first one and a half hours, after which equilibrium appears to have been established. The picture during the first half hour with the thoracic cases is quite different, the largest supplementary dose coming during the second quarter of an hour. In a random selection of fifty cases from each series the average time from induction of anæsthesia to the skin incision was 12.8 minutes in general surgical cases, and 18 minutes for thoracic cases. This may explain the differences in the early stages of the two graphs. Up to the time the incision is made, the patients, although asleep, may not be deeply enough anæsthetised to permit surgical intervention: the dose of thiopentone required to deepen the anæsthesia sufficiently would fall within the first fifteen minutes in one series, and in the second fifteen minutes in the other. In the

thoracic cases, there was a gradual decline in thiopentone requirements up to two hours, so that the end of the period of observation equilibrium, and hence tissue saturation was not established.

A possible explanation of the difference in times taken for the two series of cases to reach tissue equilibrium may be that in the

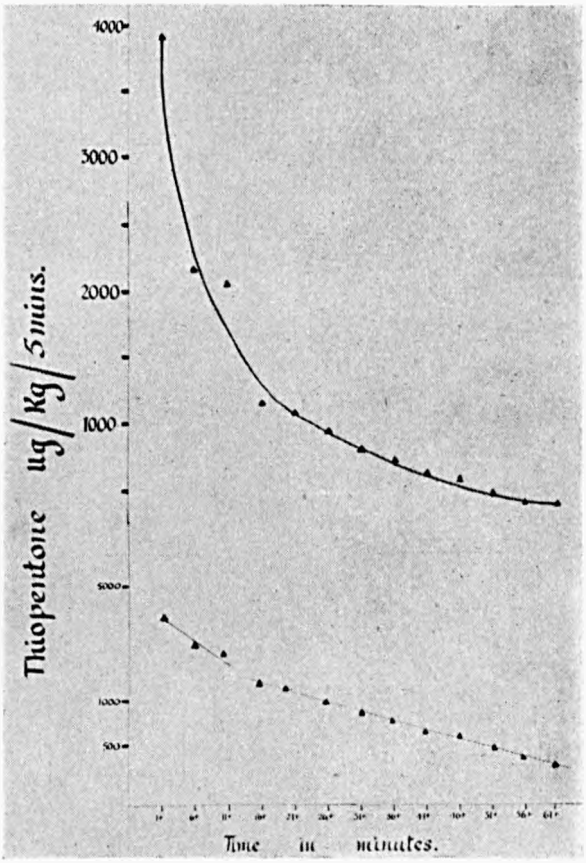

Fig. 4.—Average requirements of thiopentone in µg/kg/5 mins. in same cases as Figs. 2 and 3 plotted on both a linear and logarithmic scale.

patients undergoing thoracic operations respiration was controlled throughout, whereas in only one hundred of the general surgery cases was controlled respiration used, in the remainder the respiration being spontaneous or aided. The slight rise in blood *p*H which occurs with controlled respiration may have been sufficient to diminish diffusion of thiopentone from blood to fat[23] and thus prolong the time taken to reach stage three of the administration. When the average requirements of barbiturate in the general surgery group

of cases is divided into those with controlled and those with non-controlled respiration (Fig. 6) it will be seen that in fact this explanation holds true and that the production of apnœa and manual control of respiration prolongs the time taken for equilibrium to occur between plasma and fat.

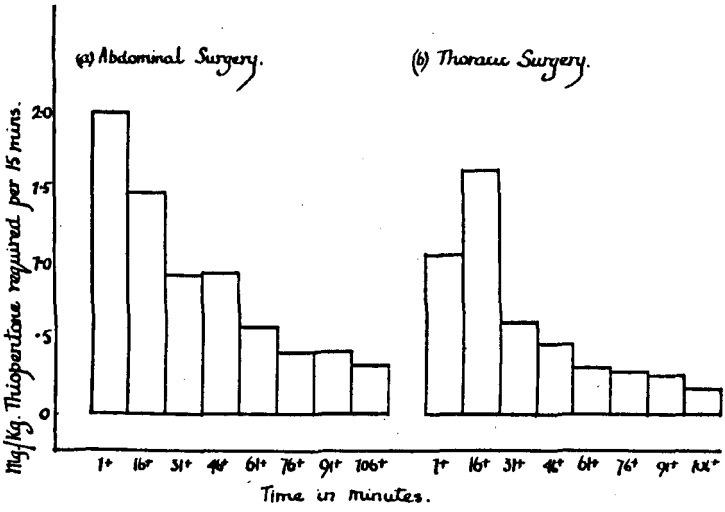

FIG. 5.—Diagrammatic representation of average supplementary doses of thiopentone, in μg/kg./15 mins., required to maintain anæsthesia in the two series of cases of Table 1.

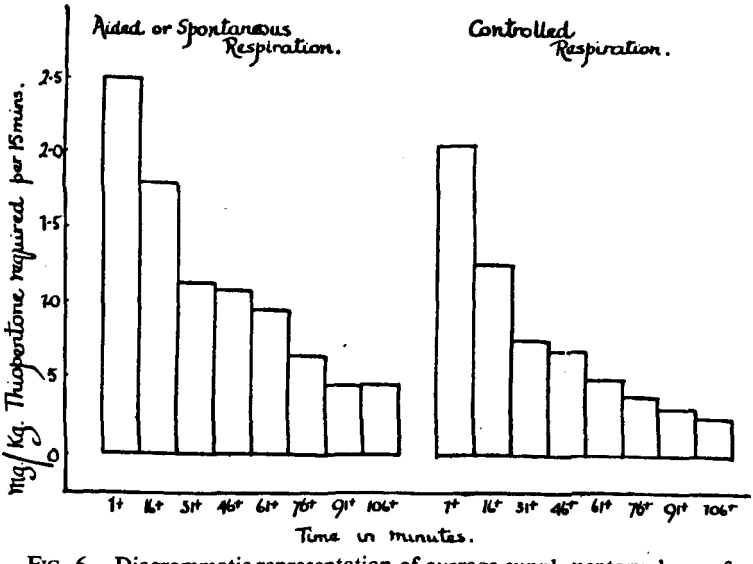

FIG. 6.—Diagrammatic representation of average supplementary doses of thiopentone in μg/kg./15 mins. of 240 general surgical cases, divided into:
(*a*) 140 with controlled respiration
(*b*) 100 with aided or spontaneous respiration.

In a smaller series of 36 cases, it was possible to record thiopentone requirements for a period of three hours, using the anæsthetic technique described above. In all of these cases respiration was controlled throughout. Details of operations, etc., and average

TABLE 2

Series	General Surgery	Thoracic Surgery
Thiopentone mg./kg.		
Induction	7.89	8.09
15 minutes	9.91	9.14
30 „	11.39	10.76
45 „	12.21	11.37
60 „	13.05	11.84
75 „	13.63	12.16
90 „	14.04	12.45
105 „	14.45	12.70
120 „	14.77	12.86

Average total dose of thiopentone in mg/kg. at 15 minute intervals in each of the two series of cases of Table 1.

total dose of thiopentone administered are given in table 3. Supplementary doses required per fifteen minutes are shown diagrammatically in figure 7. In this we have a steady decline in requirements from 30 to 135 minutes, and thereafter supplementary doses are relatively constant. Thus with controlled respiration, tissue equilibrium of thiopentone does not appear to be complete until after

TABLE 3

No. of cases	36
Average age (years)	43.7
Average weight (kg.)	59.3
Operations	
Pneumonectomy	18
Lobectomy	12
Gastrectomy	4
Segmental resection	1
Cystectomy	1
Average total dose of thiopentone in mg./kg.	
Induction	8.30
15 minutes	9.86
30 „	10.82
45 „	11.43
1 hr. 0 „	11.98
15 „	12.33
30 „	12.44
45 „	12.69
2 hrs. 0 „	13.10
15 „	13.26
30 „	13.33
45 „	13.45
3 hrs. 0 „	13.54

Details of 36 patients, in whom operations lasted at least 3 hours, with average total requirements of thiopentone in mg./kg. over that period.

135 minutes of anæsthesia, while with spontaneous or aided respiration this occurs in about 90 to 105 minutes.

A comparison of the average total requirements of the three series of cases (tables 2 and 3) is shown in figure 8. This confirms a previous statement of the author's[23] that controlled respiration markedly decreases the amount of thiopentone required to maintain surgical anæsthesia.

These clinical observations bear close agreement with the experimental studies referred to at the beginning of the paper. However, they are at variance with the views expressed by Harris[33]. He states that deviation of thiopentone to non-nervous tissues reaches its limit of usefulness in about thirty minutes, after which equilibrium is established. He gives twenty minutes as the maximum period during which rapid diffusion occurs. The evidence quoted in this paper shows that rapid diffusion occurs for 10–15 minutes, slow diffusion for a further 80–120 minutes and thereafter a slow removal of thiopentone from the blood stream by detoxication. It is difficult to reconcile any of these views with his statement that detoxication of thiopentone affords the greatest measure of protection against inadvertent overdosage. If the barbiturate be given in a single injection then diffusion to non-nervous tissues and acute tolerance provide a means of protection, but in the case of prolonged administration by drip of a dilute solution or by intermittent injection, there is no means of protection against overdosage, detoxication being much too slow.

O'Donel Browne[34] has reported very long periods of narcosis following the use of a 0.33% solution to control the convulsions of eclampsia. In his cases the average dose was 4.9 g. administered over 25 hours (range 1.75 g. in 10 hours—7.9 g. in 25 hours) and recovery of consciousness took 6–12 hours. He attributed the prolonged narcosis to the potentiation of thiopentone by glucose as demonstrated by Lamson, Greig and Robbins[35] and Lamson, Greig and Hobdy[36]. There is a great species variation in this potentiation and it has never been demonstrated in man. Liver dysfunction associated with eclampsia may have affected recovery by reducing the rate of detoxication, but this factor played no part in the series reported by Sur and Mitra[37]. They likewise encountered delayed recovery when large doses of a dilute solution of thiopentone had been given.

These show that when the administration of thiopentone is continued, either by intermittent injection or by a drip of dilute solution, for long periods, the body has no effective means of protection against inadvertent overdosage and delayed recovery may occur.

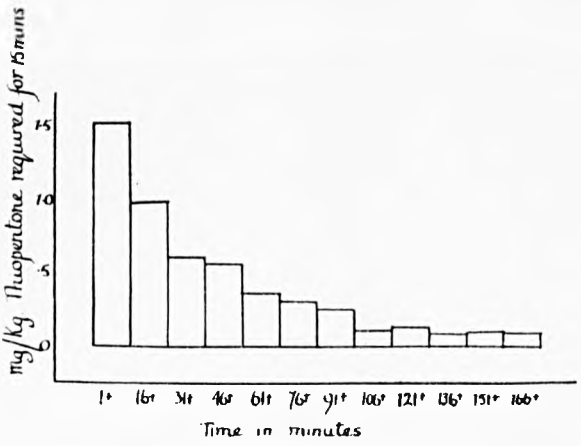

FIG. 7.—Average supplementary doses of thiopentone required per 15 minutes in 36 subjects in whom operating time exceeded 3 hours.

Cumulative Action of Thiopentone

As has been stated previously the rate of detoxication of thiopentone is 10–15% of the drug in the body per hour. This means that for a considerable time after injection there remains in the blood stream and fat depôts an amount of active barbiturate which may affect the duration of any subsequent administration. A theoretical calculation of the amount of undetoxicated thiopentone in the body is shown in table 4.

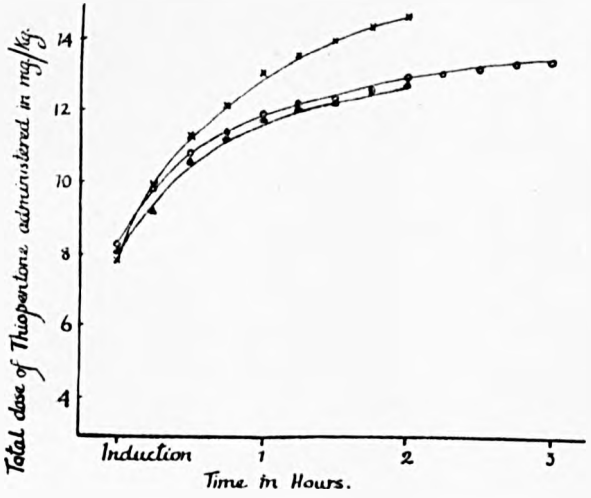

FIG. 8—Average total requirements of thiopentone in three series of patients:
(*a*) 240 abdominal operations; ×——×
(*b*) 209 thoracic operations. ▲——▲
(*c*) 36 operations lasting 3 hours and over. o——o

TABLE 4

Time after administration in hours	Percentage of drug remaining undetoxicated in the body
3	61–73
6	38–53
9	23–39
12	14–28
18	5–15
24	2–8
30	0.8–4
36	0.3–2
48	0.04–0.6

Percentage of undetoxicated thiopentone expected to be found in the body at varying times after intravenous injection. Based on exponential detoxication of 10–15% per hour.

Observations were made in humans and in dogs to find at what time after an induction dose, sufficient of the drug had been detoxicated so as to have no effect on the duration of action of a subsequent dose.

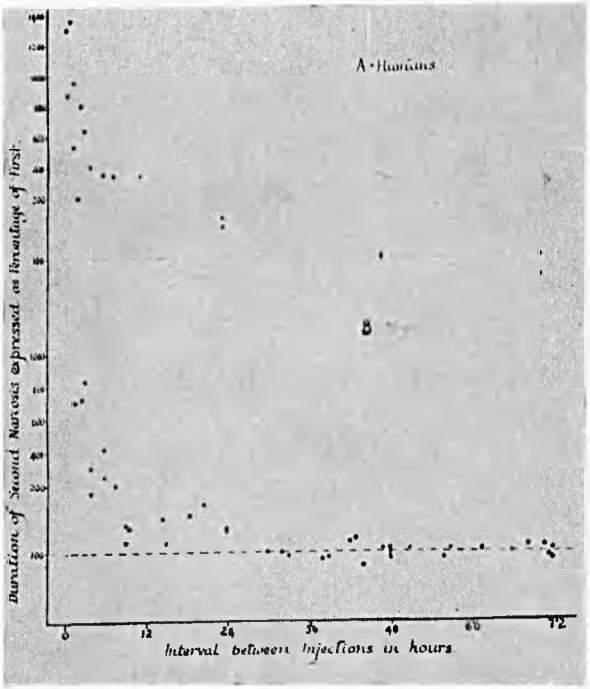

FIG. 9.—Comparison of duration of narcosis from two successive injections of the same dose of thiopentone given at varying intervals. Duration of second narcosis is expressed as a percentage of the first.

Humans.—The time taken for recovery of consciousness and ability to answer questions was noted in seventeen subjects who received two identical doses of thiopentone under the same conditions at intervals of less than 72 hours. Two of these subjects were volunteers and the remainder were undergoing minor operations, e.g. cystoscopy, bouginage, dilatation and curettage, or examination under anæsthesia. Only those who received a maximum of 500 mg. thiopentone were included. The duration of the second narcosis, expressed as a percentage of the first, is shown in figure 9A.

Dogs.—Using the method for measuring the duration of thiopentone narcosis described by the author[24] the period of anæsthesia resulting from two successive injections of thiopentone was estimated in ten dogs. The doses of the drug varied between 15 and 20 mg./kg., which is an average induction dose for the dog. In this experiment it was possible to arrange injections at varying intervals so as to cover completely the range of 2–72 hours. The animals had all apparently fully recovered from the first anæsthetic before the second administration. In all, 80 observations were made, giving 40 readings, results of which are shown in figure 9B.

Figures 9A and B bear close similarity and it would appear from these that up to about 30 hours following the injection of an induction dose of thiopentone, sufficient of the drug remains in the body to prolong anæsthesia with a subsequent dose of the drug. Table 5

TABLE 5

Times between administrations (hours)	Average duration of second narcosis expressed as percentage of first	
	Humans	Dogs
0–2	1160 (2)	—
2–4	585 (6)	553 (2)
5–7	340 (2)	357 (2)
6–8	—	215 (3)
11–13	—	140 (2)
17–19	—	163 (2)
23–25	158 (2)	132 (2)
29–31	—	100
35–37	—	94
47–49	105 (4)	102 (5)
59–61	—	97 (2)
71–73	87 (2)	102 (4)

Average duration of a second dose of thiopentone as compared with first, when doses are given at the time intervals shown. Figures in brackets show number of observations of which the average was taken.

shows average findings in both humans and dogs at time intervals corresponding roughly to those of table 4. It can be seen that the prolongation of action of a second dose of thiopentone is particularly marked if given within six hours of a previous dose. When the time

between the two injections is less than two hours, the duration of the second narcosis may be quite alarming.

With larger doses of thiopentone one might expect that the cumulative action of the drug would be more marked. In dogs, doses of thiopentone varying between 13 and 30 mg./kg. were administered at intervals of 48 hours. From previous results one would not expect any cumulative action with the smaller doses at this time interval. The results of 26 observations are shown in figure 10. Contrary to expectations there was not a

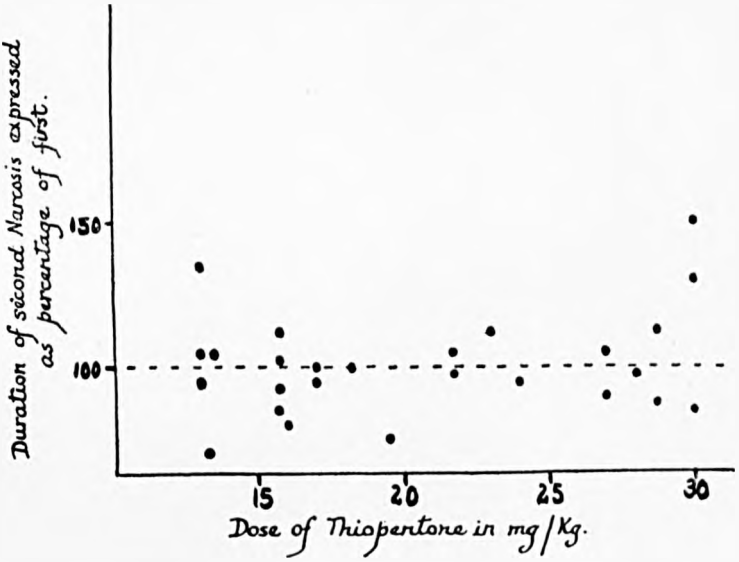

FIG. 10.—Comparison of the duration of action of two injections of the same dose of thiopentone in the dog at 48 hours intervals.

gradual increase in the duration of the second narcosis as the doses were increased. It was only when 27–30 mg./kg. were given that any cumulative action was observed. Such doses are well outside the range of those administered clinically, and even with these the percentage increase in the second narcosis was not as great as that obtained from smaller doses, repeated at 12 hourly intervals. This can be adequately explained by the exponential detoxication of thiopentone, since whatever the dose administered, at the end of 48 hours only 0.04–0.6% remains unaltered in the body.

In clinical practice, one rarely administers a second anæsthetic within 48 hours to patients who have not had a recent operation—the consequences of which (to be discussed later) one would expect to render the patient sensitive to thiopentone. Fortunately it was possible to observe five patients whose operations were of such a

minor nature as not to upset the subsequent anæsthesia. All of these subjects received morphine 10 mg. and atropine 0.65 mg. as premedication before the first anæsthetic, and only atropine, usually given intravenously, before the second. Details of these are as follows :—

CASE 1

Mrs. A. G., aged 27.—850 mg. thiopentone were administered for hysterosalpingography, the operation lasting ten minutes. The patient was conscious and talking five minutes after the end of the procedure. Twenty-five minutes later 250 mg. thiopentone sufficed for curettage and tubal insufflation lasting fifteen minutes, and the patient was deeply anæsthetised at the end of the procedure.

CASE 2

Mrs. S. H. B., aged 30.—Similar to case 1. 500 mg. thiopentone were administered for first procedure after which the patient was conscious and talking for half an hour before being re-anæsthetised. 250 mg. thiopentone produced anæsthesia for approximately the same time as did the first 500 mg. On the day following the patient had no memory of the period between the two anæsthetics.

CASE 3

Mr. K. J. L., aged 35.—1.5 g. thiopentone supplemented by nitrous oxide-oxygen was required for a difficult ureteric catheterisation. The patient was awake and answering questions on leaving the theatre. Two and a half hours later, when the catheter had to be reinserted, 400 mg. thiopentone was sufficient for the procedure of similar duration to the first one.

CASE 4

Miss B. S., aged 40.—Cystoscopy was carried out, the patient receiving 500 mg. thiopentone, and 700 mg. after five minutes. Two hours later the patient was quite awake when, with same stimulus, she reacted ten and a half minutes after 500 mg. thiopentone and twenty-five minutes after 700 mg.

CASE 5

Mr. S. G., aged 60.—500 mg. thiopentone was administered for insertion of suprapubic catheter, the patient reacting in three minutes and appearing fully conscious in ten minutes. Seven and a half hours later the procedure was carried out under 300 mg. thiopentone and consciousness was not regained for thirty minutes.

All these subjects were fully conscious before the second anæsthetic was administered. The subsequent events can be divided into two categories, (a) the administration of the same amount of thiopentone as was given originally resulted in anæsthesia of much longer duration at the second administration (Case 4), and (b) anæsthesia was on the second occasion produced for at least as long as on the first by only a fraction of the original dose (Cases 1, 2, 3 and 5). Either of these two findings substantiates the view that thiopentone is slowly broken down in the body and that (for at least 7½ hours) there remains in the non-nervous tissues an amount of thiopentone of sufficient magnitude to affect the course of any subsequent administration.

The following case report from a patient having treatment for eclampsia is different from those described above but illustrates the same points.

CASE 6

9 g. thiopentone were administered in 0.3% solution over 36 hours and the patient was completely conscious and rational within 24 hours of stopping the infusion. A supplementary dose of 250 mg. thiopentone at this stage re-established a satisfactory level of narcosis for over an hour. On recovery from this the same degree and duration of sedative was produced by 50 mg. Each time the patient wakened the desired effect could be reproduced by this same dose.

The 250 mg. thiopentone was presumably sufficient to " re-load " the fat depôts and replace that lost by detoxication since the infusion was stopped. After equilibrium had been re-established, supplementary doses of 50 mg. of barbiturate every hour or so maintained a blood level sufficient to ensure a satisfactory degree of narcosis, by replacing that lost by detoxication since the infusion was stopped.

When one has to administer a second anæsthetic to a patient within 24–36 hours of a previous administration, the circumstances which necessitate the second procedure may be sufficient in themselves to render the patient sensitive to thiopentone. Of these factors, hæmorrhage and shock are well known causes of reducing tolerance to thiopentone. For several days after operation there is a general upset of electrolyte balance[38], which may interfere with diffusion of the drug. Intestinal obstruction may have occurred, and this likewise engenders sensitivity to thiopentone[39]. If postoperative opiates have been administered, they may also affect the subsequent anæsthesia[40]. A major operation, especially upper abdominal, is followed by an appreciable degree of liver dysfunction[41 42], which is more marked if the operation is a long one[43] or if any blood pressure fall has occurred[44]. This will be accentuated by the use of ether[45] or trichlorethylene[46]. The liver dysfunction, while itself affecting the duration of a further dose of thiopentone, will also reduce the detoxication of the drug remaining in the body and thus prolong the time after which a further dose can be given with impunity. Thus, under many of the circumstances encountered in practice, the effect of a second administration will be much greater than that which occurred in the cases already described. This is illustrated by the following :—

CASE 7

Partial cystectomy and suprapubic diathermy of papillomata of the bladder were carried out under spinal cinchocaine (1.4 ml. of 1:200 solution in 6% glucose), blood pressure being maintained throughout with a 1:250,000 adrenaline drip[47]. During the procedure, which lasted 70 minutes, sleep was maintained with 900 mg. thiopentone.

Six hours later, when the patient was quite conscious, it was decided to re-explore the wound because of hæmorrhage from the bladder. The effects of the spinal analgesia had completely worn off. Atropine 0.65 mg. was given intravenously, followed by an induction dose of 250 mg. thiopentone. This was followed by nitrous oxide-oxygen and together with 15 mg. d-tubocurarine chloride was sufficient for the operation which lasted one hour. Consciousness was not regained for at least a further three hours.

Similar instances of two administrations of thiopentone within a short space of time occurred during the last war, although details of them are incomplete. A few cases were given a second dose of thiopentone at a Military General Hospital within a couple of days of having the drug at a forward unit. They needed surprisingly little at the second administration, and collapsed if given a " normal " dose[48]. Other factors, e.g. blood loss and opiates, presumably contributed to this sensitivity in addition to the amount of thiopentone remaining in the body. One obviously cannot predict the effect that a second dose of thiopentone will produce when given in circumstances such as those described above, and in such circumstances anæsthesia should be induced with extremely small doses, given very slowly in a dilute solution.

Conclusions

Thiopentone is slowly detoxicated in the body, its short duration of action after small doses, being mainly due to rapid diffusion to non-nervous tissues. It is possible to divide requirements during intermittent administration, into three stages; early diffusion, gradual saturation of fat depots and complete body equilibrium. Evidence produced shows that these stages can be recognised clinically, although the divisions between them are not clear cut. Raising the *p*H of the plasma prolongs the time taken to saturate the fatty tissues.

There remains in the body, for about 30 hours after administration of an induction dose of thiopentone, sufficient of the drug to affect the duration of a subsequent dose. This cumulative effect is enhanced by factors which are met with in clinical anæsthesia, due to operative procedures etc. Great caution should be exercised when it is necessary to administer a second dose of thiopentone within a short time of a previous injection.

Acknowledgements

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CUMULATIVE ACTION OF FOUR THIOBARBITURATES

With Special Reference to Thiopentone and Thiamylal

BY JOHN W. DUNDEE, M.D., F.F.A.R.C.S.
DEPARTMENT OF ANÆSTHESIA, UNIVERSITY OF LIVERPOOL

IT is now established that thiobarbiturates are slowly broken down in the body and that recovery after small doses depends on diffusion of the drug to non-venous and fatty tissues. Brodie[1] has shown that only between ten and fifteen per cent of the thiopentone in the body is detoxicated per hour. He was unable to find any difference between the rate of breakdown of thiopentone, thialbarbitone, thiamylal and hexobarbitone.

The author[2] has demonstrated a cumulative effect in man and in the dog when two doses of thiopentone were administered at intervals of less than thirty hours. Among the advantages claimed for the recently introduced thiamylal (sodium 5-allyl-5'-(methyl-butyl)-thiobarbiturate; surital sodium) is that it is less cumulative than thiopentone. Wyngaarden, Woods, Ridley and Seevers[5] have shown that the increase in duration of action of repeated doses given at hourly intervals to the dog is less than when equipotent doses of thiopentone or thioethamyl (sodium 5-isoamyl-5'-ethyl-thiobarbiturate; venesetic) are given. They attribute this difference to the greater potency of thiamylal as compared with the other two drugs. However, their observations were carried out in the dog, in which the time taken for maximum diffusion of thiobarbiturates to fat differs from that of man[4].

In this paper the cumulative action of thiopentone, thialbarbitone (sodium 5-cyclohexenyl-5-allyl-thiobarbiturate; kemithal) thioethamyl and thiamylal are compared in the rat. This animal was chosen because it has been shown[1] that the time taken for maximum location of thiopentone in its fat (2-2·5 hours) is very similar to that for humans. A detailed study is made of the differences between thiopentone and thiamylal, both in the rat and the dog.

Method

Female rats of the Wistar strain, weighing approximately 200 g. and mongrel dogs of varying sex and weight, were the animals used for the experiments.

In the dog the thiobarbiturates were given by intravenous or intraperitoneal injection. When the intravenous route was used the duration of narcosis was measured by the method described elsewhere by the author[9]. After intraperitoneal injection sleeping time was taken as the period when the animal was unable to stand unaided. The intraperitoneal route was used in the rat, the appropriate

amount of drug being dissolved in 0.5 ml. distilled water. The duration of sleep was measured from the time the righting reflex was lost until the animals were able to walk. The reliability of this as a means of measuring the duration of narcosis was tested as a preliminary investigation. The results obtained from the administration of the same dose of the drug at weekly intervals to the same batch of rats (Table 1) shows a fairly constant response.

It was also necessary, as another preliminary experiment, to find the dose of thiopentone, thialbarbitone, thioethamyl and thiamylal which would produce narcosis of the same duration. 40 mg./kg. thiopentone was taken as the standard, and the doses of the others which produced sleep of a similar duration in the same animals,

TABLE 1

Results obtained when the same batch of rats were anæsthetised 2-3 times with the same dose of thiobarbiturate at weekly intervals.

Drug	Thiopentone	Thialbarbitone	Thiamylal
Dose mg./kg.	32	80	30
No. of rats in each series ...	43	26	41
First injection			
No. asleep	23	25	28
Average duration of narcosis in mins.	16.0	31.3	20.2
Second injection			
No. asleep	27	24	28
Average duration of narcosis in mins.	17.2	31.8	20.3
Dose mg./kg.	40	—	40
No. of rats in each series ...	37	—	34
First injection			
No. asleep	27	—	28
Average duration of narcosis	27.3	—	34.0
in mins.	± 1.29	—	± 2.12
Second injection			
No. asleep	27	—	27
Average duration of narcosis	27.7	—	38.0
in mins.	± 1.43	—	± 1.93
Third injection			
No. asleep	23	—	25
Average duration of narcosis	27.5	—	36.2
in mins.	± 1.32	—	± 1.80

TABLE 2

Showing doses of the four thiobarbiturates studied which were taken as equipotent in the rat as regards duration of narcosis, together with the evidence for this assumption.

Drug	Thialbarbitone	Thiopentone	Thioethamyl	Thiamylal
Dose mg./kg. ...	80	40	70	34
No. of animals ...	52	101	47	58
% anæsthetised ...	94	88	94	84
Average duration of narcosis in mins. ...	31.5 ± 3.9	31.3 ± 4.54	29.4 ± 5.0	31.7 ± 2.0

TABLE 3

Average duration of narcosis when repeated equipotent doses (or fractions of equipotent doses) of four thiobarbiturates were administered to rats at the time intervals shown. Each figure is the average obtained from twelve animals.

A.					
% Equipotent dose	50	50	30	20	—
Time interval (hrs.)	—	1	1½	1½	—
	Average duration of narcosis in mins.				
Thiopentone ...	0	10	22	27	—
Thialbarbitone ...	0	14	20	34	—
Thiamylal	0	6	4	4	—
B.					
% Equipotent dose	100	100	10	15	—
Time interval (hrs.)	0	12	4	1	—
	Average duration of narcosis in mins.				
Thialbarbitone ...	31	53	14.5	39	—
Thioethamyl ...	23	62	14.0	24	—
Thiamylal	21	29	3.5	17.5	—
C.					
% Equipotent dose	100	100	25	60	50
Time interval (hrs.)	—	17	4	20	3
	Average duration of narcosis in mins.				
Thiopentone ...	31	40	11.8	19.0	24
Thialbarbitone ...	34	34.5	12.0	16.0	19.0
Thioethamyl ...	39	57.0	12.7	13.3	23.0
Thiamylal	33.3	29.0	1.7	10.0	6.8
D.					
% Equipotent dose	60	50	100	100	80
Time interval (hrs.)	—	24	27	12	16
	Average duration of narcosis in mins.				
Thiopentone ...	8.5	10.9	33	99	57.4
Thialbarbitone ...	9.0	11.1	30	53	53.2
Thioethamyl ...	8.0	8.0	23	62	—
Thiamylal ...	8.0	8.0	31	29	25.6

are shown in Table 2. On examining Tables 1 and 2, it can be seen that the duration of narcosis produced by the same dose of thiobarbiturate varies for different batches of rats. This variation is allowed for in the subsequent experiments; the duration of narcosis in one batch of animals is never compared with that of another batch.

The cumulative effect was measured by noting the duration of narcosis with two doses of the same or a different thiobarbiturate, given at varying intervals to the same batch of animals in the case of rats, or to the same animal in the case of dogs. With the exception of one experiment, only one series of readings (*i.e.* two administrations) was done on the same animals each week, to avoid the development of tolerance.

Results

The findings with the administration of equipotent doses of thiopentone (40 mg./kg.), thialbarbitone (80 mg./kg.), thioethamyl (70 mg./kg.) and thiamylal (34 mg./kg.) at intervals of between 2 and 72 hours, are shown in Fig.1. In these the duration of the second narcosis is expressed as a percentage of the first, and each reading is the average for twenty-four animals. This shows that there is an appreciable increase in the duration of the second narcosis with thiopentone, thialbarbitone and thioethamyl, if the interval between injections is less than 18 to 24 hours. There does not appear to be any difference in the degree of cumulative action of these drugs in the doses given. In the case of thiamylal this cumulative effect was not observed when the interval between injections was greater than twelve hours. Even at the shorter time intervals (under eight hours), the percentage increase in the second narcosis was never as great with thiamylal as with the other thiobarbiturates.

This finding is verified in Table 3, which shows the actual duration of narcosis when a series of injections of each drug was given at intervals of between one and thirty-six hours. In each of the four observations reported an equipotent dose (or fractions of an equipotent dose) of thiopentone, thialbarbitone, thioethamyl or thiamylal was given on each occasion. There is no difference between the times recorded with the first three drugs, but once again the sleeping

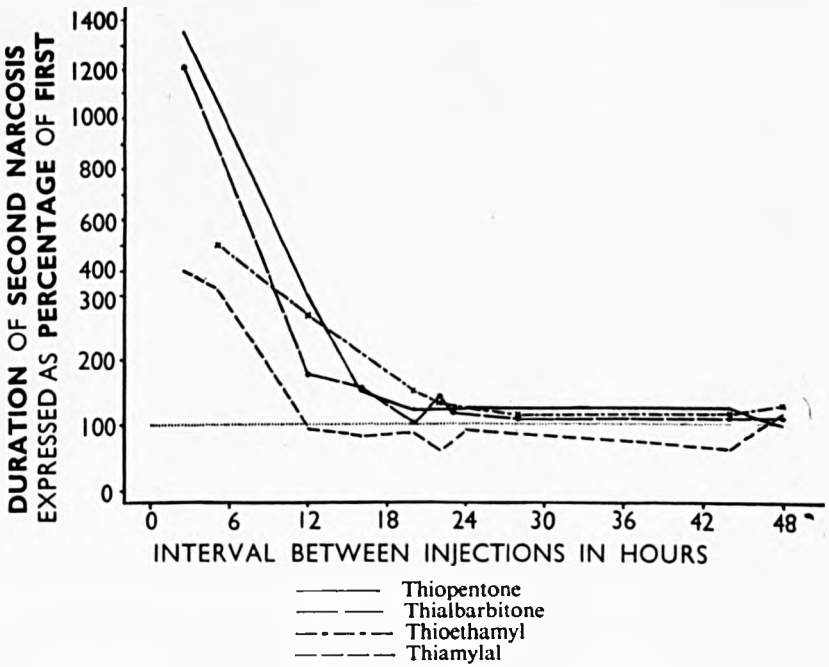

FIG. 1. Comparison of the cumulative action of equipotent doses of four thiobarbiturates in the rat.

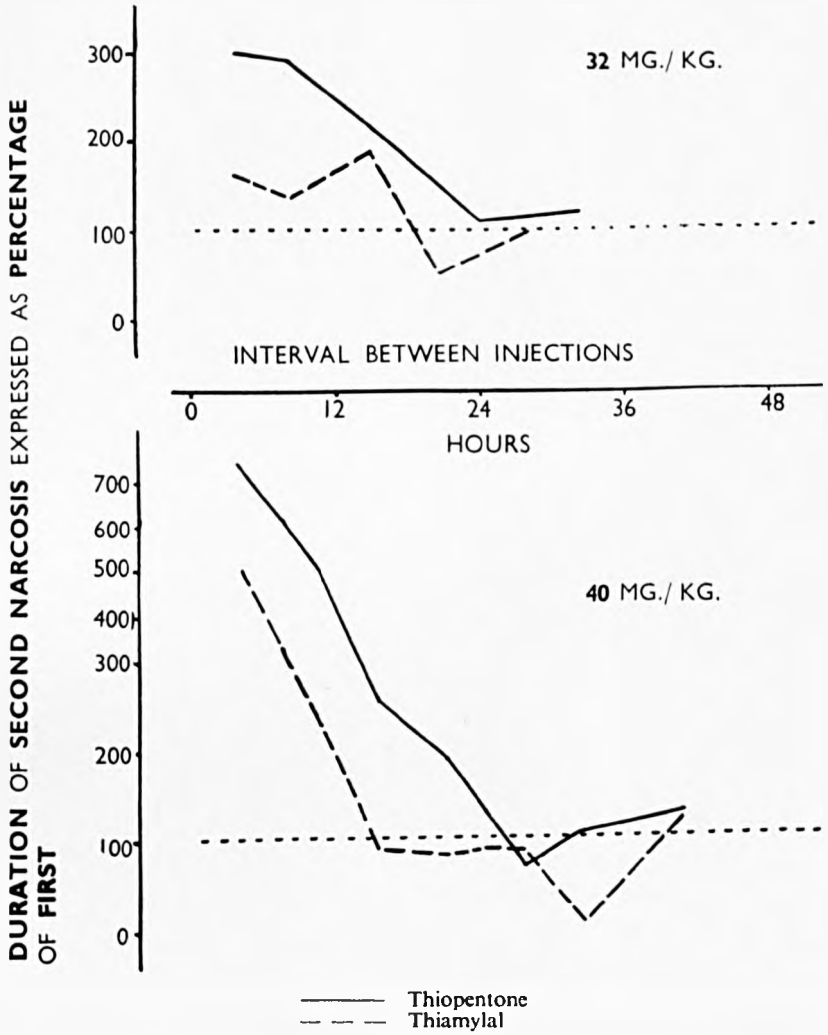

FIG. 2. Comparison of the cumulative action of equal doses of thiopentone and thiamylal in the rat.

Each reading is the average of 20 administrations.

time with thiamylal was much shorter than for any of the others when a second or subsequent dose was given.

The remaining observations are concerned solely with a comparison of the cumulative action of thiopentone and thiamylal. The findings when equal doses of both drugs are given at intervals of between four and forty hours to the rats are shown in Fig. 2. With both the doses employed thiamylal exhibits less cumulative action, both in degree and duration, than does thiopentone. These findings were also confirmed in the dog with intravenous doses 15 mg./kg. of

each drug. (Fig. 3.) As with the rat the duration of action of a second dose of thiopentone was prolonged when given within twenty-four hours of a previous injection, this effect not being observed with thiamylal at intervals of more than twelve hours.

For a further verification of this finding thiopentone was administered to rats at intervals of between fifteen and twenty-three hours after thiamylal and vice versa. In this case the duration of action of the second dose of thiobarbiturate was compared with the average " normal " sleeping for the same drug in the same batch of animals. A " normal " reading was done one week before and one week after the experiment in all cases. Fig. 4 shows the results obtained,

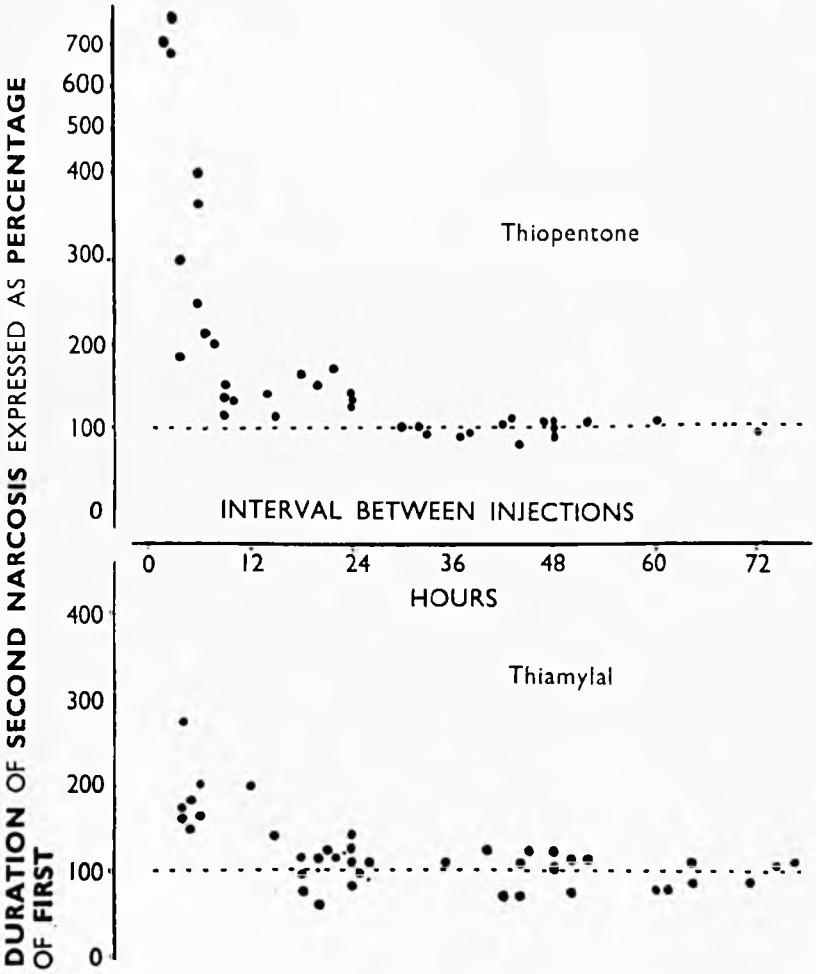

FIG. 3. Comparison of the cumulative action of equal doses of thiopentone and in the dog.

Each observation was carried out in four dogs.

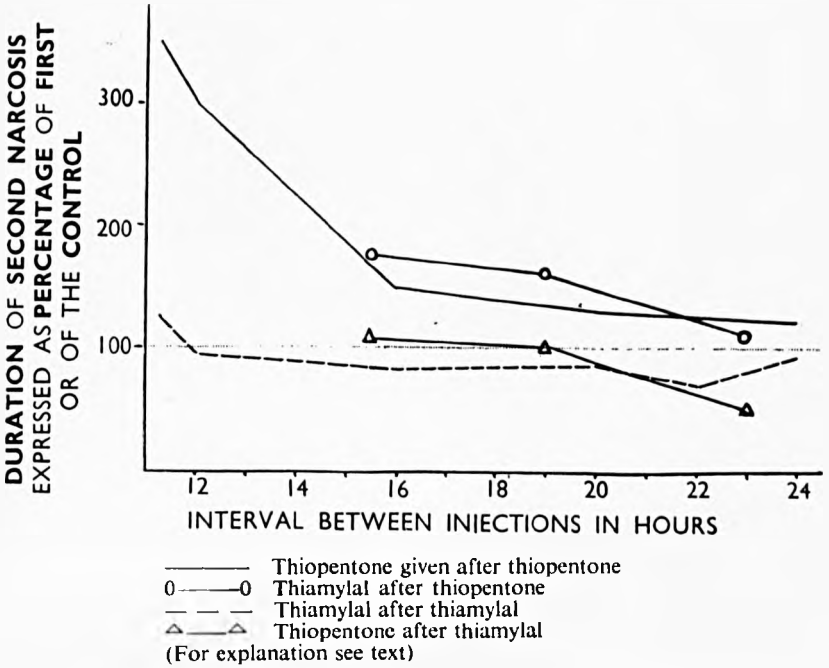

FIG. 4. Comparison of the cumulative action of combination o ithiopentone and thiamylal in the rat.

superimposed upon those of Fig. 1, which refer to the same time interval, each reading being the average for twenty rats. The increase of duration of anæsthesia when thiamylal was given following thiopentone, expressed as a percentage of the normal average for thiamylal alone, is similar to that obtained when two doses of thiopentone are given at the same time interval, and is much greater than for two doses of thiamylal. Similarly, thiopentone administered after thiamylal gives a picture similar to that produced by two doses of thiamylal.

In Table 4 are shown the effects of both equal and equipotent amounts of thiopentone on the duration of a dose of thialbarbitone which invariably produced narcosis in the batch of rats used. At the time interval employed (eighteen hours) there was a significant prolongation of the action of thialbarbitone ($t = 2{\cdot}4$) when given after thiopentone, but no similar effect after thiamylal. A comparable series of observations were made in dogs with thialbarbitone, thiamylal and thioethamyl given intraperitoneally twenty hours after large doses (45 mg./kg.) of thiopentone and thiamylal. Again a cumulative effect was observed following thiopentone, but not after thiamylal (Table 5). The difference in the effect of these two latter drugs onthe duration of narcosis with the subsequently administered thiobarbiturate was statistically significant.

Discussion

These results show that thiobarbiturates exhibit a cumulative action on repeated injection in the rat and the dog. They verify previous observations of the author[2] in man and the dog that the cumulative action of thiopentone can be detected for twenty-four hours after injection. There is no appreciable difference in the duration or degree of cumulative effect of the equipotent doses of thiopentone, thialbarbitone and thioethamyl. However, thiamylal is less cumulative than any of the above drugs.

Wyngaarden and his colleagues[3] have observed that with equipotent doses of thiopentone and thiamylal, less cumulative action was observed with the latter drug. They attributed this effect to the greater potency of thiamylal. This explanation is not in keeping with the results reported above, since when equal doses of the two drugs are given, thiamylal still causes less potentiation of a subsequent dose of any of the thiobarbiturates studied than occurs with thiopentone.

The cumulative effect of thiobarbiturates is due to their slow rate of breakdown in the body. When a second dose is given, if the fat depots, to which diffusion normally occurs, are already partly filled with the drug, the plasma level will remain high with subsequent prolongation of narcosis. Since removal of the drugs from the fat is dependent on detoxication, the results suggest that thiamylal is broken down more quickly than any of the other drugs studied. This is contrary to Brodie's statement[1], which appears to be based on the plasma levels of the drugs in one man. Clinical reports in which the action of thiopentone and thiamylal are compared suggest that with the latter there is a more rapid recovery from an equal depth of anæsthesia than occurs with thiopentone[5 6 7]. There is no statistical data to support this view.

Thiamylal is a more powerful drug than thiopentone; their relative potency based on blood levels being 1.39/1[3] or 1.36/1 based on clinical assessment[8]. If the above hypothesis that thiopentone is more slowly broken down than thiamylal is true, then one would expect the relative potency of the drugs to vary with the dosage.

TABLE 4

Effect of equal and equipotent doses of thiamylal and thiopentone on the duration of action of 80 mg./kg. thialbarbitone. The interval between thialbarbitone and previous thiobarbiturate was 18 hours, the control reading being done 1-2 weeks previously.

Thiobarbiturate	Dose mg/Kg.	No. of Rats	Duration of narcosis (mins.) with thialbarbitone 80 mg./kg. intraperitoneally		
			Control	18 hours after previous dose of thiobarbiturate	(S.E.) diff.
Thiamylal ...	34	73	18.0±1.33	15.0±0.78	1.82
Thiopentone...	40	76	19.2±1.57	25.4±1.54	2.22
Thiamylal ...	40	72	17.2±1.35	13.8±1.00	1.72

TABLE 5

The effect of 45 mg./kg. of thiopentone and thiamylal on the duration of a subsequent dose of thialbarbitone, thiamylal and thioethamyl in the dog. All drugs were given by intraperitoneal injection.

A. *CONTROLS*

Drug	mg./kg.	No. of observations	Onset of narcosis (mins.)	Duration of narcosis (mins.)
Thiopentone	45	38	4.4±0.54	198 ±14.3
Thiamylal	45	38	4.4±0.90	210 ±21.9
Thialbarbitone	60	30	5.7±0.27	59.6± 8.5
Thiamylal	30	24	4.8±0.39	50.2± 5.4
Thioethamyl	60	12	6.0±0	55.0± 6.2

B. *NARCOSIS 20 hours after 45 mg./kg. thiopentone and 45 mg./kg. thiamylal*

Drug	mg./kg.	No. of observations after each drug	Onset of narcosis (mins.)		Duration of narcosis (mins.)	
			After thiopentone	After thiamylal	After thiopentone	After thiamylal
Thialbarbitone	60	20	4.6±0.10	5.3±0.50	93± 6.1	52.5± 5.6
Thiamylal	30	12	3.3±0.18	4.3±0.20	154±12.4	84.3±12.9
Thioethamyl	60	6	5.3±0.12	5.0±1.50	72± 6.0	59.0± 8.5

C. *Increase in Narcosis in each individual animal after previous dose of thiobarbiturate*

Drug	mg./kg.	No. of animals	Average increase from control (mins.)		Percentage increase from control		Percentage difference in increase (A-B)
			After thiopentone	After Thiamylal	After thiopentone (A)	After thiamylal (B)	
Thialbarbitone	60	10	35.6	−3.6	59.9± 7.9	−10.2± 5.7	70.1±12.0
Thiamylal	30	12	103.8	34.1	201.0±30.3	68.0± 8.7	133.0±28.0
Thioethamyl	60	6	17.0	4.0	45.1±20.8	7.1± 6.5	38.0±12.1
Average	—	28	60.8	14.2	118.0±27.2	27.2±51.7	90.8±30.2

TABLE 6

A comparison of the duration of narcosis with equal doses of thiopentone and thiamylal in the rat. The same series of animals was used for each drug, but because of the smaller percentage of those falling asleep with thiopentone, the reading had to be repeated in some of these so that the number from which the average was obtained would be approximately the same for each drug.

Dose of Thiobarbiturate in mg./kg.	THIOPENTONE			THIAMYLAL			Duration with thiopentone − duration with thiamylal
	No. of Animals	% Asleep	Average duration of narcosis (mins.)	No. of Animals	% Asleep	Average duration of narcosis (mins.)	
24	96	44	3.8± 0.3	53	66	8.7± 1.06	0.44
32	127	54	16.0	121	85	29.4	0.54
40	111	69	27.5± 1.34	102	80	36.4± 1.85	0.74
48	24	100	64 ±12	24	100	64 ±15	1.00

With a large enough dose the more slowly detoxicated thiopentone may even produce narcosis of longer duration than does an equal dose of thiamylal. It was possible to prove this in part in the rat (Table 6). With doses of 24 mg./kg., thiamylal produced narcosis, greater in duration than twice that produced by an equal dose of thiopentone, while with twice this dose the duration of action of both drugs was approximately the same. When the dose was increased above 48 mg./kg., the mortality was over 50%, thus invalidating any comparison between the two drugs.

Conclusion

A cumulative action is obtained when two doses of thiopentone, thialbarbitone or thioethamyl are administered to the rat within an interval of twenty-four hours from each other. A same effect is observed with thiamylal, but it is not demonstable when the interval between the injections is greater than twelve hours. Thiopentone produces a more marked cumulative effect than thiamylal, both as regards duration and intensity. This difference is not due to the greater potency of the latter.

The relative potency of thiopentone and thiamylal as regards their duration of action, varies with the dose employed.

The evidence presented suggests indirectly that the rate of breakdown of thiamylal in the body is greater than that of thiopentone.

Acknowledgements

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Variations in Healthy Subjects

(d) Respiratory alkalosis.

"INFLUENCE OF CONTROLLED RESPIRATION ON DOSAGE OF THIOPENTONE AND D-TUBOCURARINE CHLORIDE REQUIRED FOR ABDOMINAL SURGERY"

Reprinted from British Medical Journal (1955) 2, Volume 2, page 893.

While the dosage data and pH studies in this paper are still valid, the discussion is open to criticism in the light of more recent publications.

No mention is made of the differences in rate of uptake of nitrous oxide with controlled and spontaneous respiration (Gray 1954); in fact the potency of approximately 50% mixtures of nitrous oxide and oxygen was not approximated at that time. Controlled respiration results in better alveolar mixing of nitrous oxygen with oxygen, nitrogen and carbon dioxide and provides a higher pressure gradient for diffusion across the alveolar membrane than does spontaneous respiration. The importance of this is shown by the observation that, using the anaesthetic technique of nitrous oxide - oxygen - relaxant (without previous barbiturate), cessation of controlled respiration results in lightening of the anaesthesia, even if the flow rate of gases is not altered. Total flow rates of gases are not mentioned in this paper, and while

they were roughly the same in each series (1 litre of nitrous oxide and oxygen per minute). If any leaks occurred in the circuit, higher gas flows would be needed in patients on manually controlled respiration, with the result that alveolar nitrogen would be removed more in these patients, with resulting increased efficiency of the nitrous oxide.

On closer study of the *in vivo* distribution of thiopentone (see page 34 Thiopentone and Other Thiobarbiturates) it is apparent that the reasoning on page 6 of the reprint is open to questioning. Blood thiopentone determinations have been carried out in 6 patients with spontaneous respiration and 6 with manually controlled respiration. Even though the former subjects had received more thiopentone to maintain surgical anaesthesia than the latter (as expexted) blood thiopentone levels did not differ significantly between the 30th and 90th minute of anaesthesia in the two series. This substantiates the sentence "..one would expect that, for equal doses of thiopentone, plasma levels of the drug would be much higher during manually controlled respiration than during aided or spontaneous respiration..." While the cerebrospinal fluid concentration runs parallel to the unbound plasma thiopentone level, it cannot be concluded that the brain concentration itself would be greater in controlled respiration. Raising the plasma pH will alter the partition of the drug between the aqueous and organic phases and result in more thiopentone being in the plasma, but less in the brain. This is substantiated by the work of Rayburn, Whitehead and Draper (1953).

Mention is not made of the importance of the induction dose in determining the response to further doses of thiopentone (this was not appreciated at the time). Fortunately, there was not a significant difference in the initial doses of thiopentone in the two series, and the recorded differences in requirements cannot be explained on the basis of acute tolerence as shown in the accompanying table.

	Aided or Spontaneous respiration	Manually Controlled respiration
Average initial dose of thiopentone mg/kg	8.51	7.54
Duration of Anaesthesia	Ratio of total to induction dose of thiopentone	
30 minutes	1.50	1.38
60 minutes	1.75	1.55
90 minutes	1.92	1.65
120 minutes	2.07	1.70

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INFLUENCE OF CONTROLLED RESPIRATION ON DOSAGE OF THIOPENTONE AND D-TUBOCURARINE CHLORIDE REQUIRED FOR ABDOMINAL SURGERY

BY

JOHN W. DUNDEE, M.D., D.A.
Lecturer in Anaesthesia, University of Liverpool

In using the anaesthetic sequence D-tubocurarine chloride/thiopentone/nitrous oxide/oxygen, an impression was formed that smaller doses of barbiturate were required when the patient was rendered apnoeic and respiration was manually controlled than when the respiratory excursion was only aided or spontaneous respiration was thought sufficient to ensure full oxygenation (Gray and Rees, 1952). Thiopentone and D-tubocurarine chloride being drugs whose dosage can be accurately measured, it was decided to find out whether manual control of respiration actually does reduce the amount of thiopentone required to produce narcosis.

Experimental Procedure

The average requirements of thiopentone and D-tubocurarine chloride for two comparable series, each of 100 cases (for abdominal surgery), were noted. No patient was included in either series in whom any factor was present which might influence the dose of barbiturate or relaxant required to produce narcosis. These factors included liver dysfunction (Dundee, 1952a), raised blood urea (Richards, Kueter, and Taylor, 1950), severe anaemia (Dundee, 1952b), or acquired tolerance to analgesic or sedative drugs (Dundee and Gray, 1951). Cases in which severe blood loss occurred during operation were also excluded.

All subjects were anaesthetized by the technique recommended by Gray (1948), save that the drugs used were limited to thiopentone, D-tubocurarine chloride, and 50% nitrous oxide and oxygen. In one series of cases apnoea was produced following induction of anaesthesia, and respiration was manually controlled throughout the operation. Spontaneous respiration was allowed to persist, or respiration was aided periodically in the second series of subjects. Premedication was the same for all patients—morphine 1/6 gr. (10 mg.), with atropine 1/100 gr. (0.65 mg.), given 45–60 minutes before induction of anaesthesia. Once anaesthesia was induced, supplementary doses of barbiturate and relaxant were given in amounts not exceeding 50 mg. and 3 mg. respectively, so that at no time did the dose

TABLE I.—*Showing Details of the Two Series of 100 Cases*

	Aided or Spontaneous Respiration	Manually Controlled Respiration
Average age	48·4 years	46·9 years
Number of Males	59	70
Number of Females	41	30
Operations:		
Gastrectomy	65	65
Operation on bile ducts	10	10
Hysterectomy	6	6
Incisional hernia	6	5
Entero-anastomosis	5	5
Lumbar sympathectomy	4	4
Bilateral inguinal hernia	3	4
Colectomy	1	1

administered to the patient exceed the requirements by more than these amounts. The series were limited to operations lasting two hours or over. Most patients were anaesthetized personally, and for the remainder, so far as was possible, the same anaesthetist was employed for an equal number of cases from each series. The cases were further balanced so that approximately equal numbers of operations in each series were performed by the same surgeons in the same hospitals.

The weight of all patients was noted before operation and the total amount of drugs administered was recorded in mg./kg. every 15 minutes for two hours. Details of the patients and the operations performed in each series are given in Table I. It will be seen that two series of cases were obtained whose requirements of thiopentone and D-tubocurarine chloride were directly comparable.

Results

Table II shows the result of this investigation, which is represented graphically in Fig. 1. These show that subjects

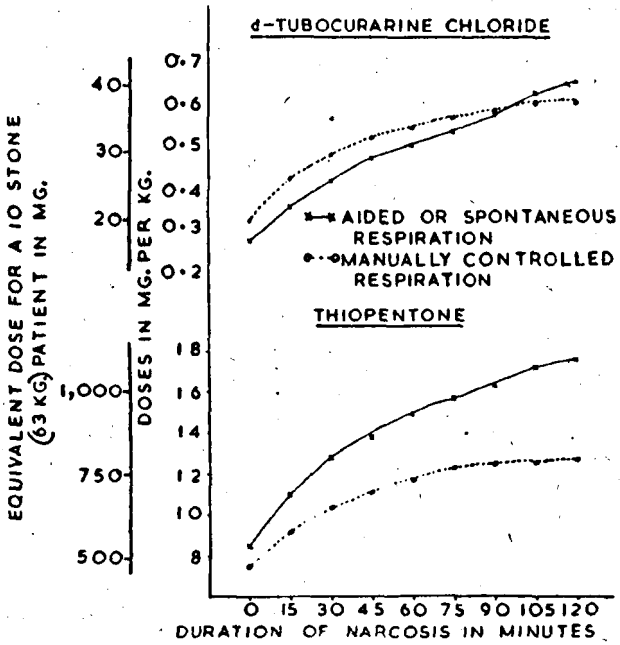

FIG. 1.—Diagrammatic representation of Table II.

in whom respiration is manually controlled during operation require on the average appreciably less thiopentone than subjects in whom aided or spontaneous respiration is employed. The difference in average amounts of thiopentone administered was found to be statistically significant at 60 minutes (S.E. of difference=0.224), 90 minutes (S.E. of difference=0.314), and at two hours (S.E. of difference=0.381). The potentiation of action of thiopentone that occurs during manually controlled respiration becomes more pronounced as duration of operation proceeds. One feels that if it had been possible to obtain a series of cases in which the operations lasted three to four hours the subjects whose respiration was manually controlled may have required only about half the amount of barbiturate administered to subjects with aided or spontaneous respiration.

The picture obtained with D-tubocurarine chloride is rather different. Despite the fact that this substance in no way potentiates the action of thiopentone (Paulson, Lundy,

TABLE II.—*Average Doses of Thiopentone and* D-*tubocurarine Chloride Required at 15-minute Intervals for two Series of Patients Anaesthetized with Thiopentone/*D-*tubocurarine Chloride/Nitrous Oxide/Oxygen*

Time	Thiopentone				D-Tubocurarine Chloride			
	(*a*) Aided or Spontaneous Respiration		(*b*) Manually Controlled Respiration		(*a*) Aided or Spontaneous Respiration		(*b*) Manually Controlled Respiration	
	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.
Induction	8·51	536·4	7·54	473·2	0·269	16·91	0·316	19·92
15 min. anaesthesia	11·01	693·8	9·16	577·0	0·352	22·19	0·417	26·29
30 ,, ,,	12·79	806·1	10·44	657·8	0·413	26·04	0·478	30·13
45 ,, ,,	13·79	868·7	11·10	694·1	0·468	29·48	0·521	32·80
60 ,, ,,	14·93±0·20	940·6	11·73±0·10	739·0	0·500±0·013	31·47	0·546±0·013	34·42
75 ,, ,,	15·66	986·7	12·28	773·5	0·533	33·60	0·573	36·11
90 ,, ,,	16·35±0·29	1,029·9	12·46±0·15	785·1	0·579±0·017	36·47	0·596±0·013	37·19
105 ,, ,,	17·20	1,083·9	12·52	788·8	0·631	39·74	0·602	37·91
120 ,, ,,	17·61±0·36	1,109·6	12·81±0·13	806·4	0·657±0·012	41·42	0·605±0·014	38·13

(*a*) 100 subjects with spontaneous or aided respiration. (*b*) 100 subjects in whom respiration was controlled throughout the operation.

and Essex, 1949; Gray *et al.*, 1951), it might be argued that the administration of large doses of relaxant will decrease the dose of thiopentone required to produce good operating conditions. For this reason an attempt was made to administer approximately the same doses of D-tubocurarine chloride to the cases in each series. In order to produce apnoea at the beginning of the operation the dose of D-tubocurarine chloride administered to the subjects with aided or spontaneous respiration during the first 45–60 minutes of anaesthesia was found to be significantly greater than that administered to subjects with aided or spontaneous respiration (S.E. of difference at 60 minutes= 0.0161). However, after two hours' anaesthesia the position was reversed, and subjects whose respiration was controlled now required significantly less D-tubocurarine chloride than their counterparts whose respiration was spontaneous or aided (S.E. of difference=0.0161). An impression was formed that, had an attempt not been made to administer approximately equal amounts of relaxant to both series of cases, this difference would have been more marked. As with thiopentone, it would appear from Fig. 1 that in operations lasting three to four hours the amount of relaxant required when respiration was manually controlled would be very much less than when respiration was periodically aided or spontaneous.

Since the only difference between these two series of cases is the respiratory excursions, it should be possible to relate the differences between manually controlled and aided or spontaneous respiration to the differences in average requirements of thiopentone recorded in Table II. When thiopentone and a relaxant drug are administered and little attempt is made to compensate for respiratory depression, an accumulation of carbon dioxide is inevitable, and if prolonged will result in a decrease in the *p*H of the blood. Studies on diffusion respiration in dogs (Whitehead *et al.*, 1949) show that, although adequate oxygenation can be maintained for long periods with little or no respiratory movement, this is not accompanied by a corresponding removal of alveolar carbon dioxide. These authors have recorded rises in CO_2 content of arterial blood from 36 vols.% to 75 vols.%, and a fall in arterial blood *p*H from 7.45 to 6.72 over 45 minutes, during which time arterial oxygen content was barely altered. Provided manually controlled respiration approximates to the patient's normal respiratory excursions, and CO_2 absorption is efficient, the *p*H of blood in subjects in whom this was performed should remain unchanged throughout the operation. During thiopentone narcosis the amount of drug distributed between plasma and body fat varies with the *p*H of the blood (Brodie *et al.*, 1950). Decreasing the *p*H to 6.8 (by inhalation of CO_2) results in a fall in the blood thiopentone level of about 40%. When CO_2 inhalation was

stopped the *p*H rose rapidly to its normal level and was accompanied by a rise in the plasma content of thiopentone.

Changes in Blood *p*H During Operation

The changes in blood *p*H which occurred during manually controlled and aided or spontaneous respiration were investigated, using a Muirhead glass electrode battery-operated *p*H meter. The findings in 25 cases from each series are shown in Fig. 2. For the sake of simplicity actual figures are not given, but changes from the pre-operative *p*H of the blood are shown. There is a wide scatter of the readings from each series, due to variations in the respiratory excursions and the efficiency of the soda-lime, but both series of cases show the same tendency. Fig. 2 confirms that a fall in blood *p*H occurs with aided or spontaneous respiration, but unexpectedly reveals an equally great rise in *p*H with manually controlled respiration, indicating hyperventilation in the latter series of cases.

During anaesthesia with thiopentone in man, when adequate ventilation is maintained, the variations in *p*H (between 7.34 and 7.56) are not enough to affect the plasma concentration of thiopentone (Brodie *et al.*, 1950). In the two series of cases under discussion the average differences resulting from the two types of respiration are much greater—approximately 0.4. From this one would expect that, for equal doses of thiopentone, plasma levels of the drug would be much higher during manually controlled respiration than during aided or spontaneous respiration (Brodie, 1952, personal communication). The concentration of thiopentone in the cerebrospinal fluid (and hence brain concentration) runs parallel to the plasma concentration (Hubbard and Goldbaum, 1950). From this it follows that the duration of narcosis with a fixed dose of thiopentone would be longer with manually controlled respiration than with aided or spontaneous respiration. This is in agreement with the findings of Table II and Fig. 1.

Further Evidence for Potentiation Effect of "Controlled Respiration"

Confirmatory evidence for this was obtained in investigating the effect of hyperventilation with oxygen on the time taken for various subjects to react to a constant stimulus. The investigation was carried out on fit male patients aged between 31 and 49 years, and the constant stimulus employed was the passage of a cystoscope. Selection of subjects and premedication were the same as for the previous two series of cases. Anaesthesia was induced with doses of thiopentone varying between 450 and 700 mg., injected at a fixed rate of 100 mg. in five seconds. In alternate patients a face-mask was applied immediately consciousness was

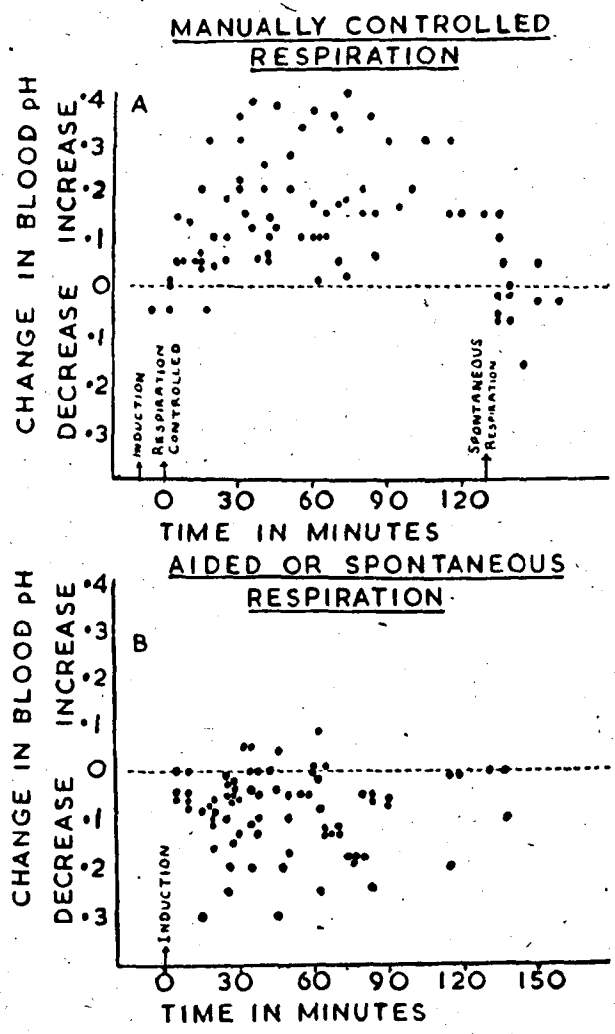

FIG. 2.—Changes in *p*H recorded during operation on 25 of each of the two series of subjects referred to in Table I. Changes in *p*H are recorded as deviations from the pre-operative level.

lost, and hyperventilation was carried out with large flows of oxygen (8–10 litres per minute). This proved impossible in some subjects because of difficulty in obtaining an air-tight fit of the face-mask or because of the gases blowing up the stomach. As a result, only 37 out of 102 patients

were hyperventilated; the other 65 were allowed to breathe normally.

Cystoscopy was performed immediately the patient was asleep, and the first reaction to this stimulus was taken as

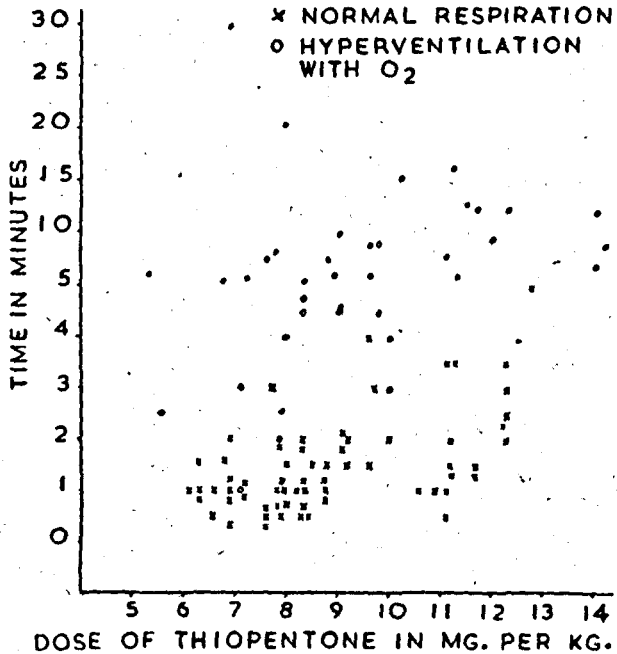

FIG. 3.—Scatter diagram showing times taken for 102 male subjects to react to the stimulus of a cystoscope following varying doses of thiopentone.

the end-point. Duration of narcosis was thus measured from the end of the injection of thiopentone to the first movement of the patient.

Fig. 3 shows the duration of narcosis in subjects who were allowed to breathe spontaneously and in those hyperventilated with oxygen, plotted against the dose of thiopentone administered in mg./kg. No direct relation between the dose of thiopentone and the duration of narcosis could be demonstrated in either series, presumably because of acute tolerance to the drug (Mark *et al.*, 1949). However, the results clearly demonstrate a much more prolonged narcosis in subjects who were hyperventilated with oxygen than in those allowed to breathe spontaneously. For the sake of completeness, changes in blood *p*H were measured in a few cases from each series (Fig. 4), and these show the same picture as Fig. 2.

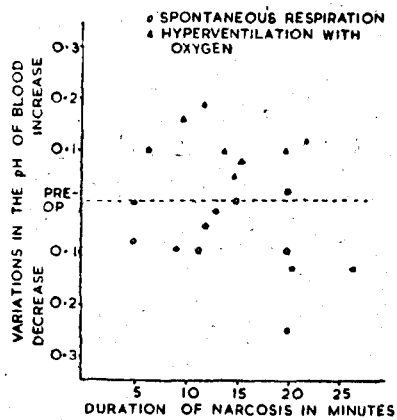

FIG. 4.—*p*H changes recorded during cystoscopy in 18 of the cases referred to in Fig. 3.

Discussion

From these investigations it can be concluded that a moderate degree of hyperventilation, such as occurs in manually controlled respiration, results in a prolongation of the action of thiopentone. While the most likely explanation of this phenomenon is the effect of the altered *p*H of the plasma on the distribution of thiopentone in the body, one cannot be dogmatic and assume that is the sole explanation.

Overventilation for any length of time is accompanied by oliguria and decreased urea clearance (Smith, 1951). In one recorded case of acapnia following hyperventilation the rate of urea clearance was reduced to one-fifteenth of normal (McCance, 1935). It is known that the presence of a high blood urea prolongs thiopentone narcosis (Richards *et al.*, 1950). The possibility exists that during prolonged manually controlled respiration a sufficient rise in blood urea may occur to potentiate the action of the thiopentone and thus reduce the amount of barbiturate required to produce anaesthesia. This possibility was investigated, and Fig. 5 shows actual changes in blood urea recorded during thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen anaesthesia with manually controlled respiration. It can be seen from the results of seven cases investigated that the degree of hyperventilation that occurs during manually controlled respiration has a negligible effect on the blood urea, and in only one case was there any possibility of urea being incriminated as a cause of potentiation of thiopentone. It is interesting to note that in the one case in which a rise in urea was noted an excessive degree of hyperventilation was produced for investigational purposes. It would seem

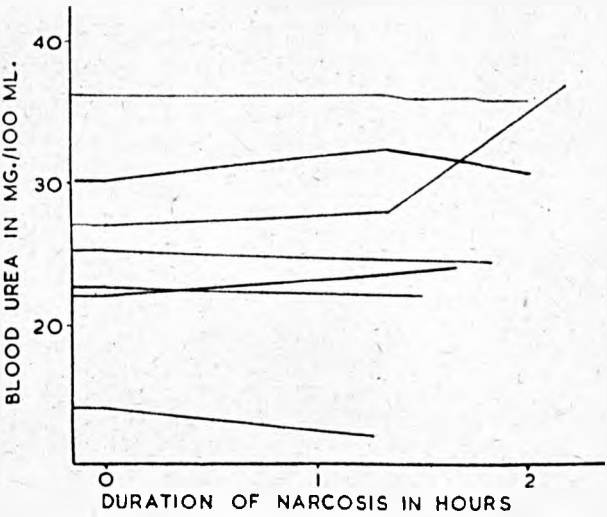

FIG. 5.—Changes in blood urea recorded during operation in seven cases with manually controlled respiration.

that with controlled respiration as carried out during anaesthesia there are no deleterious effects on kidney function and no marked rise in blood urea.

Loss of consciousness can follow hyperventilation if this is carried to extremes (McCance, 1935; Seevers *et al.*, 1939). A diminution in cerebral blood flow of the order of 30% (part of a general peripheral vasoconstriction) with an average increase of 15% in cerebral oxygen consumption has been reported (Kety and Schmidt, 1946). These would lead to a certain degree of cerebral anoxia, which may be aggravated by the effects of lowering the CO_2 tension on the oxygen dissociation curve of blood. While more oxygen can be taken up by the blood in the lungs, less will be given off to the tissues (Barach *et al.*, 1947). While it is known that potentiation of barbiturate anaesthesia can be accomplished by any means whereby central anoxia is produced (Peterson, Shideman, and Linares, 1950), this could not have played a part in the potentiation of thiopentone observed during manually controlled respiration. In these cases the degree of hyperventilation was so slight that none of the anaesthetists concerned realized that they were in fact hyperventilating the patients until they were told of the *p*H changes of the blood. Furthermore, using the thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen sequence with manually controlled respiration of the same degree as in the series of cases referred to earlier, Prime and Gray (1952) found peripheral vasodilatation rather than vasoconstriction.

The fact that a patient is not breathing spontaneously will reduce the tone of the intercostals and hence abdominal muscles. If thiopentone/nitrous oxide/oxygen were used without a muscle relaxant, controlled respiration would reduce the amount of barbiturate required to produce satisfactory relaxation. This does not apply directly to the cases described above, but is the probable explanation of the lowered requirements of D-tubocurarine chloride observed at the end of two hours' anaesthesia with manually controlled respiration, as compared with patients who were allowed to breathe spontaneously.

All of the arguments quoted above are applicable to the anaesthetic technique described by Brennan (1952). With doses of 500 mg. of thiopentone for a large healthy adult he was able to produce long periods of narcosis. Undoubtedly he used a higher percentage of nitrous oxide (75%) to obtain a better analgesia, but it is doubtful if this actually resulted (Seevers *et al.*, 1937). Hyperventilation was purposely carried out from the beginning of the operation, and the changes in *p*H of the blood must have been greater than those recorded in either Fig. 2 or Fig. 4.

Conclusions

1. Subjects anaesthetized with thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen require appreciably smaller amounts of barbiturate when respiration is manually controlled than subjects in whom respiration is aided or spontaneous.

2. More D-tubocurarine chloride is required for the first 45–60 minutes of the operation when respiration is controlled, but after two hours of anaesthesia requirements of relaxant are less than for subjects whose respiration is spontaneous or periodically aided.

3. With this sequence of drugs, aided or spontaneous respiration is accompanied by a fall in the *p*H of the blood. Manually controlled respiration results in a rise in blood *p*H, indicating some degree of hyperventilation.

4. The changes in the *p*H of the blood, by affecting the distribution of thiopentone in the body, could account for conclusion 1.

5. Hyperventilation with oxygen prolongs the duration of thiopentone narcosis.

6. Other effects of hyperventilation which have been discussed are unlikely to have any potentiating effect on thiopentone.

I am grateful to Professor C. A. Wells and other members of the staff of the Professorial Surgical Unit of Liverpool Royal

Infirmary for providing cases and co-operating in this investigation. My thanks are also due to Miss G. C. Jones for her help in the biochemical investigations.

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Pathological Factors Influencing Dosage.

(a) Hepatic Dysfunction.

THIOPENTONE NARCOSIS IN THE PRESENCE OF HEPATIC DYSFUNCTION

Reprinted from British Journal of Anaesthesia (1952).
Volume 24, pages 81 - 100.

This work has already been presented in a thesis (for M.D. degree of the Queens University of Belfast) and is included here because the most important clinical significance of the experimental findings was not appreciated at the time of publication.

In the discussion on Figure 1, it is concluded that, since the duration of anaesthesia following the initial dose of thiopentone is not increased after the administration of chloroform, diffusion of the drug was not interfered with by the liver. An alternative, and probably more correct explanation is that recovery from small doses of thiopentone is to a large extent due to redistribution of the drug, and not dependent wholly on detoxication. With increasing doses, as tissue depots become "loaded", breakdown of the drug plays a more important part in recovery from anaesthesia. This alternative explanation is put forward on page 127 of Thiopentone and Other Thiobarbiturates. This does not distract from the value of the work in implicating the liver as a site of

detoxication of thiopentone.

In section B of the reprint (pages 89 - 98) some of the conclusions drawn from Figure 3 and Tables 2 and 3 are unjustified. In a variable percentage of patients from each group respirations were manually controlled. On looking up the anaesthesia records, it was discovered that this happened in approximately half of the patients with liver function and moderate liver damage, and in almost all the subjects with severe liver damage. In light of the preceeding paper, there are no grounds for the conclusion that "subjects with severe hepatic dysfunction require much less thiopentone to produce anaesthesia for long operations than normal subjects". The truth of this statement cannot however be derived on the basis of subsequent clinical impressions, but it is not proven in this paper.

"VARIATIONS IN RESPONSE TO RELAXANT DRUGS"

(published with Dr. T. Cecil Gray)

Reprinted from The Lancet (1951). Volume 1, page 1015.

On pages 5 to 8 of this paper is a case report which describes marked resistance to thiopentone in a patient who was receiving large doses of sedative and analgesic drugs. As liver dysfunction and toxaemia supervened, this resistance was changed to exquisite sensitivity. The response to thiopentone is compared with the patient's reaction to muscle relaxants.

Reprinted from the *British Journal of Anæsthesia*, Vol. XXIV, No. 2, April 1952

THIOPENTONE NARCOSIS IN THE PRESENCE OF HEPATIC DYSFUNCTION*

By JOHN W. DUNDEE

IT can be assumed that, if the liver plays a major part in the detoxication of thiopentone, an increase in duration of narcosis will result when the drug is used in the presence of liver damage. Despite the fact that thiopentone has been in use since 1934 its detoxication is still imperfectly understood (Hewer, 1948). Some workers (Carraway and Carraway, 1943) use the drug indiscriminately in the presence of hepatic dysfunction, and report no prolongation of narcosis. Others (Pleasance, 1943) consider liver damage to be an absolute contraindication to the use of thiopentone. It is hoped that the experimental and clinical observations presented in this paper will be a guide to the use of thiopentone in the presence of liver damage, and help to elucidate the part played by the liver in its detoxication.

A. EXPERIMENTAL DATA

The duration of thiopentone narcosis in animals, before and after liver damage, has been investigated by several workers. Scheifley and Higgins (1940) and Mason and Beland (1945) found no alteration after partial hepatectomy in the rat. Similar results were found by Richards and Appel (1941) using carbon tetrachloride to produce liver damage. On the other hand, Shideman et al. (1947) and Kelly et al. (1947) found an increase in duration of nar-

* Part of a thesis presented for the M.D. degree of The Queen's University of Belfast.

cosis ranging from 751–1169 per cent after the production of liver dysfunction. This liver dysfunction was produced by three methods, (*a*) injection of carbon tetrachloride (mice); (*b*) 80–90 per cent hepatectomy (rats) and (*c*) production of Eck fistula (rats). A smaller, though significant, increase in duration of narcosis (350 per cent) after partial hepatectomy in rats was found by Walker and Wynn Parry (1949). An important feature of their results was that sleeping time tended to return to normal as liver regeneration occurred.

It can be seen that experimental evidence in animals has produced two diametrically opposed views, viz. liver damage has no effect on the duration of thiopentone narcosis and liver damage markedly prolongs the duration of narcosis. Certain seemingly legitimate criticisms as to the methods employed by the earlier workers (Scheifley and Higgins, 1940; Mason and Beland, 1945; Richards and Appel, 1941) have been made by Shideman (1949). These objections, together with the fact that no actual times are given to support their statements, would seem to invalidate the results of the workers who found no increase in duration of narcosis after the production of liver damage in animals.

A significant increase in the duration of the action of thiopentone was found by Shideman et al. (1948) and Shideman (1949) in 6 human subjects with abnormal liver function, as compared with 10 subjects with normal liver function. In the following experiment the duration of action of thiopentone was noted with the same subjects before and after the administration of a hepatotoxic agent, viz. chloroform. This eliminates the variation in response of different individuals which occurred in Shideman's investigation.

Technique of Experiment

It has been shown (Mark et al., 1949) that, on administering the same dose of thiopentone to humans at intervals of several days, the corneal reflex always returned at the same plasma level. The return of the corneal reflex was used as the end point, and when it reappeared the time was noted and an additional dose of thiopentone administered. Fourteen fit male volunteer subjects were used for the experiment and liver function was estimated by the bromsulphalein excretion test. Before administration of the chloroform less than 4 per cent of the dye was found in the blood stream 30 mins. after intravenous injection of 2 mg. per kg. body weight; this being taken as evidence of normal liver function (Rosenthal and White, 1925).

No premedication was given and the subjects were induced with 0.4–0.5 g. thiopentone. Following the return of the corneal reflex the time was noted and an additional dose of 0.2–0.25 g. administered. Each time the corneal reflex returned the time was noted and a supplementary dose of thiopentone administered to a total of 1.0–1.5 g.

A clear airway was maintained throughout the administration and it was possible to avoid cyanosis in all subjects without the administration of oxygen.* The rate of injection of thiopentone was kept constant throughout the experiment, viz. 1 ml. 5 per cent solution every 5 seconds.

In 7 of the subjects, once the respiratory excursion had returned to normal, following the last injection of thiopentone, chloroform was administered for 30 minutes, after which the patient was allowed to recover. The remaining subjects were used as controls and no chloroform was administered.

* It is appreciated that this does not exclude the occurrence of anoxia.

The thiopentone was repeated in exactly the same doses as before 48 hours later in 13 subjects, and 24 hours later in 1 subject. The rate of injection was the same as before and the return of the corneal reflex was again used as the end point. Prior to the administration of the thiopentone, liver function was estimated by the bromsulphalein excretion test in 5 of the 7 subjects who received chloroform.

Results

There was an increase in the time taken for return of

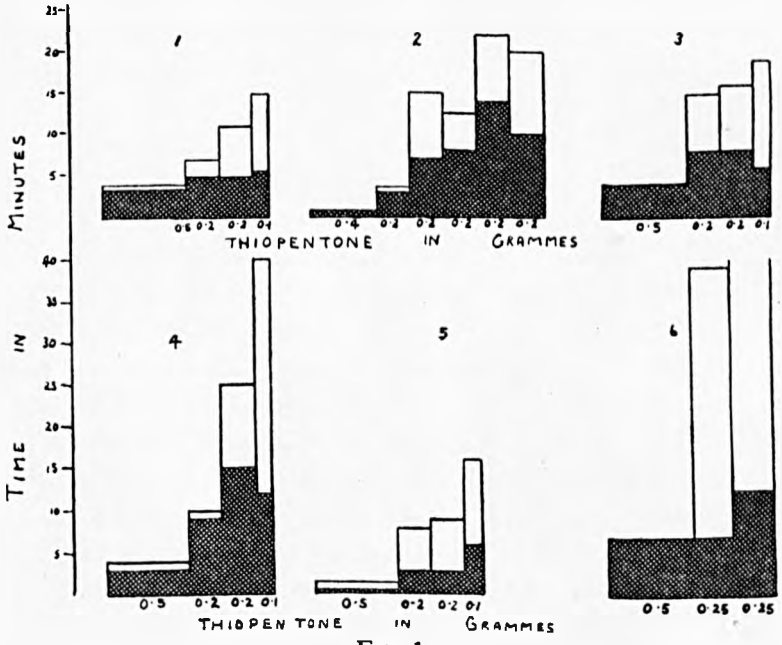

FIG. 1

Diagrammatic representation of the times taken for return of the corneal reflex following intermittent injection of thiopentone in six subjects, before and 48 hours after administration of chloroform. The shaded areas show the times before the administration of the chloroform, the non-shaded areas representing the increase in time at the second administration.

the corneal reflex in all subjects at the second administration of thiopentone. Details of the times in subjects 1–6, i.e. those in whom the second administration followed 48 hours after the chloroform, are shown in figure 1. The sum of the times for all subjects is shown in table I. This table shows a statistical analysis of the total times taken for return of the corneal reflex in subjects 1–6 and 8–13, following the intermittent administration of 1.0 g. thiopentone. In each of the groups the figures are directly comparable and it can be seen that a significant increase occurred in the subjects who received the chloroform, while that which occurred in the controls, although present in all cases, is not statistically significant. Table I verifies that chloroform produced a demonstrable degree of liver dysfunction. This is greater than that obtained by Waters (1951), but in these cases the open mask method of administration was used and the accompanying anoxia may have been a factor (Goldschmidt et al., 1937). Case 7, in whom the second administration followed 24 hours after the first, is not directly comparable to the others and is only included for the sake of completeness.

Discussion

From figure 1 it can be seen that the times taken for return of the corneal reflex after the induction dose of thiopentone were barely altered after the administration of chloroform. In 3 cases the increase was very slight for the second dose, but in all cases the increase in time became more marked with each successive dose of thiopentone. Recovery from a small dose of thiopentone is due to a rapid diffusion of the drug to non-nervous tissues (Brooks et al., 1948, 1950; Mark et al., 1949). As repeated doses are administered equilibrium is set up until eventually

TABLE I

Table showing sum of times taken for return of corneal reflex following intermittent doses of thiopentone in 14 male subjects.

CASES RECEIVING CHLOROFORM								CONTROLS					
Subject	Age in yrs.	Thiopentone in grammes	Time in Mins. A	Time in Mins. B	% increase in time 100(B−A)/A	% bromsulphalein retention 5 mins.	% bromsulphalein retention 30 mins.	Subject	Age in yrs.	Thiopentone in grammes	Time in Mins. A	Time in Mins. C	% increase in time 100(C−A)/A
1	29	1.0	19	37	95	35	10	8	54	1.0	43	45	2.3
2	32	1.4	43	73	75	30	10	9	38	1.0	66	99	50
3	37	1.0	26	54	104			10	23	1.1	77	101	30.1
4	25	1.0	40	88+	120+			11	25	1.5	72	80	11.1
5	44	1.0	12½	42½	240	37	17	12	28	1.0	25	30	20.0
6	40	1.0	26½	96½+	270+	40	17	13	44	1.0	53	67	26.4
7	36	1.5	10	92	820	85	35	14	44	0.8	45	67	48.8
Average times of cases 1-6 for 1.0 g. thiopentone			24	58.6	144.2			Average times of cases 8-13 for 1.0 g. thiopentone			48.2	61.6	27.7
S.D.			±3.4	±4.1				S.D.			±9.5	±16.7	
Coefficient of Variation			8.16	9.84				Coefficient of Variation			13.3	23.4	
			34	16.7							26.9	37.8	
Standard error of difference between the 2 averages			5.21					Standard error of difference between the 2 averages			11.0		

A. First administration.

B. Exactly 48 hours after administration of chloroform in subjects 1-6, and 24 hours after chloroform in subject 7.

C. Exactly 48 hours after first administration of thiopentone, no chloroform being given.

Percentage bromsulphalein retention shows amount of dye in blood 5 mins. and 30 mins. after injection of 2 mg./kg. intravenously 48 hours after administration of chloroform.

A statistical analysis is included of 6 comparable cases in each series. Average is taken from sum of times taken for return of corneal reflex, following doses of thiopentone totalling 1 g. in each series.

recovery from narcosis depends on detoxication of the drug. From figure 1 it can be concluded that, whatever was the mechanism of prolongation of the time taken for return of the corneal reflex after the administration of thiopentone, it was not interference with diffusion of the drug to the tissues.

This is confirmed by figure 2. For the first 5–10 minutes of the narcosis, during which time the shift of thiopentone from the plasma to the tissues was occurring, there was no significant difference in the amounts of thiopentone required by the subjects at the two administrations. However, at 30 minutes, the subjects who had received

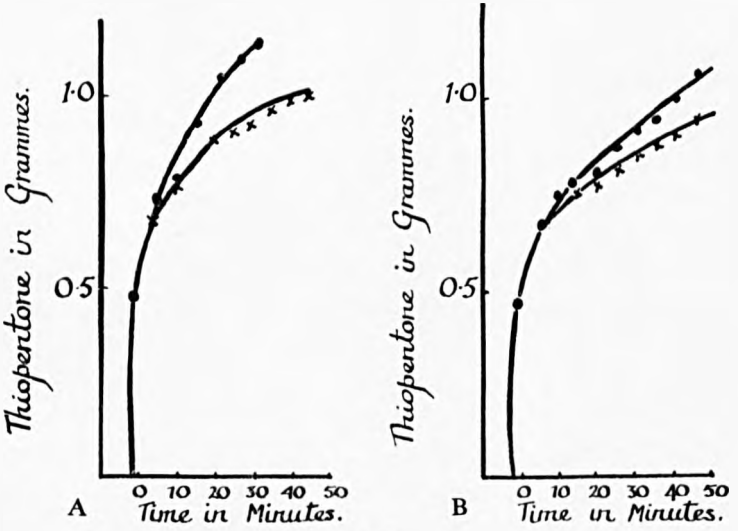

FIG. 2

Graphic representation of average amounts of thiopentone required by six subjects to produce anæsthesia of sufficient depth to obtund corneal reflex, on two occasions 48 hours apart.

A. Chloroform was administered for 30 mins. following the first thiopentone.

B. Controls, to whom no chloroform was administered.

•—•—• First administration of thiopentone.

×—×—× Second administration of thiopentone 48 hours later.

chloroform required much less drug on the second administration (0.3 g), than did those not having chloroform. By this time diffusion of the drug to the tissues would be fairly complete (Mark et al., 1949), save that to fat (Mark et al., 1950). Since return of the corneal reflex signified that the plasma thiopentone had reached a certain level—the same for each subject—it follows that by some means or other the detoxication of thiopentone is impaired by the previous administration of chloroform.

Hepatic dysfunction was certainly present in these subjects in whom detoxication of thiopentone was impaired (table I). However, chloroform is a general protoplasmic poison (Gould, 1949), with deleterious effects on kidneys and blood (Adriani, 1946). These latter could have played a part in the impairment of the detoxication mechanism of thiopentone. Its effects on the central nervous system must also be considered. Barbital is known to be excreted unchanged in the urine, its duration of narcosis being unaffected by partial hepatectomy (Pratt, 1933), yet narcosis with it became prolonged and more profound 24 hours after the administration of chloroform (Koppanyi et al., 1936). Although it was completely eliminated from the central nervous system, the chloroform may have sufficiently injured the nerve cells to render them more susceptible to the action of the barbiturate. This "extrahepatic factor" (Koppanyi et al., 1936) may have played a part in the prolongation of narcosis in cases 1–7. The longer the time that elapses between the administration of the chloroform and the barbiturate the less important would it be. The difference between the degree of prolongation of narcosis in case 7 (820 per cent) and cases 1–6 (average 144 per cent) could be due to this effect of the chloroform on the central nervous system, since the

second administration of thiopentone in the former case took place 24 hours before that in the others.

Conclusions

These experiments prove that chloroform impairs the detoxication of thiopentone. This impairment occurs in the presence of demonstrable hepatic dysfunction, but it cannot be assumed that this dysfunction is the sole cause of the decreased rate of detoxication of the thiopentone.

B. CLINICAL DATA

The same controversy exists in the clinical reports of the administration of thiopentone in subjects with hepatic dysfunction as in the experimental evidence to which reference has already been made. No prolongation of narcosis was reported by Ruth et al. (1939) following the administration of thiopentone for laparotomy in the presence of massive cancer of the liver. They do not mention the dose of the drug used. Lundy (1942), although not advising the use of the drug on purely theoretical grounds in patients with liver dysfunction, has found that such patients tolerate thiopentone satisfactorily. The Carraways (1939, 1943) similarly find that thiopentone is a satisfactory anæsthetic agent for subjects with liver disease.

On the other hand, prolonged narcosis has been reported by Miller and Tovell (1940) in cases in which thiopentone was given in the presence of considerable hepatic dysfunction. Macintosh and Bannister (1947) report a slight prolongation of narcosis in jaundiced patients. Sherlock (1950) stresses that short-acting barbiturates are detoxicated slowly in the presence of liver disease and are safe only in small doses for the induction of anæsthesia.

The purpose of the present investigation is to discover

if subjects with marked liver damage require less thiopentone than normal subjects to produce surgical anæsthesia. The amounts of thiopentone and d-tubocurarine chloride required to produce satisfactory operating conditions in a series of subjects having upper abdominal operations were noted at five-minute intervals. All subjects received $\frac{1}{6}$ gr. (10 mg.) morphia and 1/100 gr. (0.65 mg.) atropine as premedication. The anæsthetic technique was the same for all cases, viz. balanced light anæsthesia with thiopentone, d-tubocurarine chloride, nitrous oxide-oxygen (1 litre each per minute), respiration being controlled or assisted throughout as required. Supplementary doses of thiopentone were given in increments of 0.05 g., so that, after the effect of the induction dose had worn off, at no period had the subject received a dose of thiopentone which exceeded the minimal requirements to produce satisfactory anæsthesia by this amount.

Subjects were divided into three groups: (*a*) normal subjects, (*b*) subjects with a mild degree of hepatic dysfunction and (*c*) subjects with severe liver damage. Because of the diversity of its functions, any single laboratory test, devised as a means of assessing hepatic function, only tests one or a group of related functions and must not be taken as an indication of the liver with respect to other of its functions (Glynn, 1949). For this reason positive findings were required in a series of tests before a subject was proven to have liver dysfunction. With three or more of the following findings a subject was considered to have severe liver damage, while one or two only were taken as evidence of mild hepatic dysfunction.

(*a*) History of recent severe attack of jaundice.

(*b*) Urinary urobilinogen present to a dilution greater than 1 in 20.

(*c*) Thymol turbidity of more than 4.
(*d*) Cephalin cholesterol + + + or + + + +.
(*e*) Diminished serum albumin/globulin ratio.
(*f*) Liver damage shown by biopsy.

Subjects in whom any factor occurred which might influence the response to thiopentone were excluded from the series. These included a raised blood urea (Richards et al., 1950), severe anæmia—Hb under 70 per cent, or marked hypotension. Where shock or severe blood loss occurred during the operations observations were restricted to the period before this happened.

Results

The average findings for each group of subjects are shown in table II and figure 3. It can be seen that subjects with severe hepatic damage required much less thiopentone to produce anæsthesia for 60 minutes than did normal subjects. Before deciding whether the difference between the figures is significant, other factors will have to be

TABLE II

Comparison of Anæsthetic Requirements for Upper Abdominal Surgery in 3 groups of Patients all anæsthetized with the same technique.

Group	A		B		C	
No. of Cases	121		31		21	
Average Age	46 yrs		49 yrs.		52 yrs.	
	T	C	T	C	T	C
Induction	0.52	17.2	0.50	15.5	0.38	18
Up to 15 mins.	0.75	20.07	0.73	21.0	0.47	23.3
„ „ 30 „	0.88	24.45	0.81	25.0	0.50	26.5
„ „ 45 „	0.92	27.2	0.87	26.7	0.52	28.5
„ „ 60 „	1.04	29.2	0.91	28.0	0.54	30.0

A = Normal Subjects
B = Subjects with Moderate Liver Damage
C = Subjects with Severe Liver Damage

T = Total dose of thiopentone administered in g.
C = Total dose of d-tubocararine administered in mg.

considered. d-Tubocurarine chloride is known to have no effect on the duration of thiopentone narcosis (Paulson and Essex, 1949; Gray et al., 1951), yet it may be argued that administration of large doses of relaxant will decrease the dose of thiopentone required to produce good operating

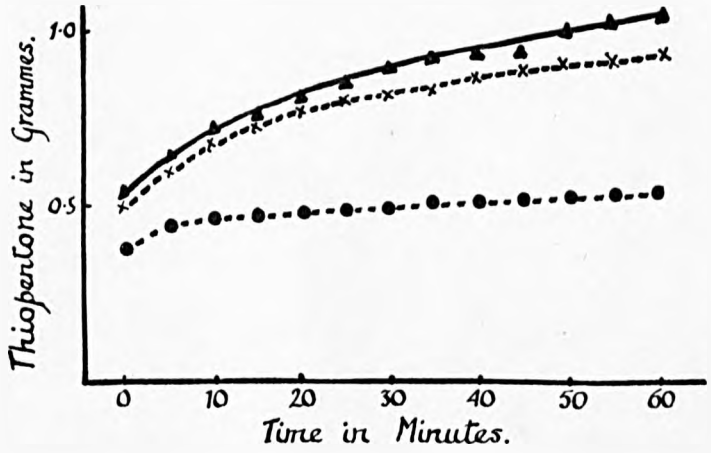

FIG. 3

Graphic representation of average thiopentone requirements of three groups of subjects during upper abdominal operations.
Δ—Δ—Δ Normal subjects.
× — × — × Subjects with mild hepatic dysfunction.
• — • — • Subjects with severe liver damage.

conditions. That this did not occur in this series can be seen from table II, where the average amounts of d-tubocurarine chloride are approximately the same for each group. The average age for each group of subjects does not vary significantly, but unfortunately the weights of all subjects were not recorded. Of the 121 normal subjects, the average weight of 80 was 132 lb.; only 7 of the subjects with mild liver dysfunction were weighed (average 128 lb.) while the average for 17 of the 21 subjects with severe liver damage was 140 lb.

A statistical analysis of average thiopentone requirements for all cases is shown in table III. No significant difference exists between the thiopentone required by the normal subjects and those with a mild degree of liver dysfunction—standard error of difference between two mean values for 60 minutes being .075. Comparing the requirements for normal subjects and those with severe liver damage, apart from the induction dose, subjects with severe liver damage require a significantly smaller amount of thiopentone; the difference being more marked as the duration of the operation proceeds. The difference between the two means for one hour is 7 times the standard error of difference. These figures leave no doubt that subjects with a severe degree of liver dysfunction require less thiopentone than normal subjects to produce satisfactory

TABLE III

Statistical analysis of Average Requirements of Thiopentone required to produce Surgical Anæsthesia in 3 groups of Subjects referred to in text.

	Normal Subjects	Subjects with Liver Damage	
		Mild	Severe
No. of Cases	121	31	21
Induction dose	0.52 ± 0.02	0.50 ± 0.02	0.38 ± 0.30
S.D.	0.18	0.11	0.14
Coeff. of Variation	36.7	22	37
Anæsthesia for 15 mins.	0.75 ± 0.02	0.73 ± 0.064	0.47 ± 0.012
S.D.	0.175	0.35	0.085
Coeff. of Variation	23	48	17.8
Anæsthesia for 30 mins.	0.88 ± 0.01	0.81 ± 0.05	0.50 ± 0.023
S.D.	0.09	0.28	0.11
Coeff. of Variation	9.8	35	22
Anæsthesia for 60 mins.	1.04 ± 0.02	0.91 ± 0.029	0.54 ± 0.023
S.D.	0.27	0.16	0.11
Coeff. of Variation	38.6	17	20.5

anæsthesia. This is well illustrated by details of the 21 cases with severe liver dysfunction shown in table IV.

Discussion

Failure to find a marked difference in the amount of thiopentone required by any of the three groups of subjects to produce anæsthesia for 10–15 minutes, shows that diffusion of the drug from plasma to tissues occurs normally in the presence of hepatic dysfunction. Tolerance, however, is comparatively unaffected in cases with mild liver dysfunction, but is markedly decreased in the presence of gross hepatic damage. No extraneous factors were present in these subjects, which could have interfered with detoxication of thiopentone, other than liver damage. The findings in subjects in whom demonstrable liver damage occurs, but who, for the purpose of this investigation, were classified as having mild hepatic dysfunction, could explain some of the anomalies reported in the literature. The body contains liver tissue far in excess of the minimal amount necessary for normal physiological function (Wright, 1942). The degree of liver dysfunction present must be very great before a subject shows diminished tolerance to thiopentone. This applies particularly to short operations.

Conclusions

Considering these findings in the light of previous evidence it can safely be concluded that the liver plays a major role in the detoxication of thiopentone. However, a severe degree of liver damage must be present before this decrease in detoxicating power is clinically manifested. This conclusion is in agreement with the *in vitro* experiments of Dorfman and Goldbaum (1947) and Shideman et al. (1947), in which incubation of thiopentone with liver resulted in a degradation of the thiobarbiturate. A similar

TABLE IV

Details of 21 patients with severe hepatic dysfunction referred to in text.

Evidence of Liver Dysfunction									Duration of Operation		Anæsthetic		
Sex	Age	History of Jaundice	Flocculation tests: Urinary Urobilinogen	Flocculation tests: Thymol Turbidity	Cephalin Cholesterol	Serum Alkaline Phosphatase	A/G Ratio	Confirmed by Biopsy	Hrs.	Mins.	Thiopentone in g.: Induction	Thiopentone in g.: Total	Total d.t.c. in mg.
F	33	yes	1 : 20	16	+++	52 units %	0.7/I	yes	1	0	0.5	0.6	28
F	60	yes		1	++	35 units %		yes	1	0	0.35	0.4	30
M	46	yes	normal	7	+++	15 units %	0.62/I	yes	1	30	0.4	0.7	25
F	52	no	normal	5	++++	5 units %		yes	2	10	0.5	0.8	40
M	49	no	1 : 40	3	++++	17 units %	1.21/I	yes	1	0	0.35	0.6	
F	69	yes	1 : 80					yes	1	0	0.4	0.6	13
M	69	yes	1 : 40					yes	1	10	0.4	0.6	25
F	25	no	1 : 100	3	+++				1	15	0.5	0.7	25
F	22	yes		9	++++	15 units %	1.3/I	yes	2	0	0.3	0.65	45
F	61	yes		4	++++	85 units %	1.1/I		1	40	0.3	0.65	30
F	57	yes	1 : 100				1.1/I		1	0	0.4	0.5	15
M	52	yes		1	++++	95 units %	1.3/I		1	10	0.3	0.5	40
M	69	yes	normal	1	—	70 units %	1.25/I		1	50	0.3	0.55	40
M	65	yes		1	—	52 units %	1.5/I	yes	2	0	0.2	0.65	47
M	60	yes	1 : 50	7	+++				1	20	0.5	0.65	30
F	46	yes		16	++++	14 units %	1.28/I	yes	2	30	0.3	0.6	
F	60	yes	1 : 100	7	+++	8 units %		yes	2	30	0.4	0.8	45
F	43	yes	1 : 50	1	++++	6 units %	0.79/I	yes	2	15	0.3	0.5	
F	49	no	normal	2	++++	7 units %		yes	3	45	0.45	0.9	40
M	60	no		7	++++			yes	1	0	0.4	0.4	28
M	29	no	1 : 50					yes	1	0	0.5	0.5	25

breakdown has been reported with the heart-lung-liver preparation (Kelly and Shideman, 1949) and with cell-free homogenate of liver (Gould and Shideman, 1951). Other tissues, e.g. blood (Richards, 1947) and kidney (Kelly et al., 1947; Dorfman and Goldbaum, 1947) may well play a part, but this will not be discussed here.

C. THE USE OF THIOPENTONE IN THE PRESENCE OF HEPATIC DYSFUNCTION

In anæsthetizing subjects with liver damage, the amount of thiopentone required during the first 10–15 minutes of the operation is approximately that which one would expect to use in a normal subject of similar weight. As anæsthesia progresses the supplementary doses of the drug are required much less frequently than normal. The decreased tolerance to thiopentone in subjects with severe liver dysfunction only becomes clinically obvious after prolonged administration of intermittent doses of the drug.

It is not advisable to administer large doses of thiopentone for induction of anæsthesia for short operations in subjects whose liver function is under suspicion. When plasma-tissue equilibrium has occurred, the amount of the drug remaining in the plasma may well be above that required to produce narcosis. This will have to be removed by the slow process of detoxication, which may be markedly impaired, and prolonged narcosis ensue. The following cases illustrate this point.

Case 1. Male aged 32, wt. 147 lb. (67 kg.). Admitted to hospital with compound fracture of tibia and fibula. Surgical toilet carried out under thiopentone-nitrous oxide-oxygen-ether anæsthesia. Exact amount of thiopentone given not known, but thought to be in the region of 1 g. Anæsthesia was uneventful with no delay in recovery.

Five days later the fracture required re-manipulation. The patient felt ill; temperature was 102°F., pulse 90/min. He was

shivering and complaining of pain in both loins. 0.4 g. thiopentone was given quickly to produce relaxation, followed by 0.3 g. three minutes later. At the end of the operation he was deeply unconscious and a pharyngeal airway was inserted. He showed no reaction to supraorbital pressure three hours after his operation and he did not cough out the airway for a further two hours. Consciousness was not regained until 18–19 hours after the thiopentone administration.

Jaundice appeared on the day following operation, and his subsequent progress proved this to be due to Weil's disease. The leptospira icterohæmorrhagica was later recovered from the urine.

In Weil's disease the liver is severely damaged. The jaundice is probably due to a toxic hepatitis (McNee, 1920). Changes in the liver vary from cloudy swelling to acute parenchymatous degeneration (Dawson et al., 1917; Himsworth, 1947). The onset of hepatic dysfunction is the most feasible explanation for the altered response to thiopentone which this subject exhibited at the second administration.

Case 2. A male aged 32 was admitted to hospital from the out-patient department because of delayed recovery following incision of a paronychia under thiopentone anæsthesia. The dose again was not known, but was said to be "just over half a gramme". It appeared that this patient requested thiopentone instead of gas as he had been given it on several previous occasions with no ill effects. When he gained consciousness 6 hours later he had symptoms of acute gastritis and was kept under observation with the tentative diagnosis of acute cholecystitis. The diagnosis of infective hepatitis was eventually made and 8 days later liver function tests produced the following results.

Van den Bergh	biphasic reaction
Serum bilirubin	11 mg. per cent
Thymol turbidity	6 units
Cephalin cholesterol	++++
Urinary urobilinogen	slight excess

The association of symptoms of acute gastritis and acute hepatitis is well known (Bank and Dixon, 1946) and it is

easy to understand how a tender liver led to the diagnosis of acute cholecystitis. The liver lesion in infective hepatitis is usually mild in nature (Lane, 1942), but it is difficult to postulate any other possible cause for the delayed recovery, other than its being due to hepatic dysfunction.

Another factor which must be considered is the possibility of a toxic action of the thiopentone on an already damaged liver. This has been observed in dogs by Walton et al. (1950), but they attributed their findings to the hypoxia which accompanied the respiratory depression following the thiopentone. The effect of thiopentone on liver function will be the subject of a later communication.

SUMMARY

1. Liver damage produced experimentally by chloroform significantly prolongs the duration of thiopentone narcosis in man.

2. Clinical observations show that subjects with severe hepatic dysfunction require much less thiopentone to produce anæsthesia for long operations than normal subjects.

3. A mild degree of hepatic dysfunction does not materially affect human tolerance to thiopentone.

4. Evidence is submitted to implicate the liver as the major site for detoxication of thiopentone in man.

I am deeply indebted to the 14 volunteers who took part in the experiment described and without whose co-operation this investigation would not have been possible. My thanks are also due to Doctors C. M. Valliant and E. T. Downham who provided facilities for this experiment, and to the many surgeons who permitted me to anæsthetize the cases with liver damage described.

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VARIATIONS IN RESPONSE TO RELAXANT DRUGS

JOHN W. DUNDEE
M.D. Belf., D.A.
LECTURER IN ANÆSTHESIA

T. CECIL GRAY
M.D. Lpool, F.F.A.R.C.S., D.A.
READER IN ANÆSTHESIA

UNIVERSITY OF LIVERPOOL

"DIFFERENCE in resistance to anæsthesia is largely a difference in the metabolic state of the patient." This observation of Guedel (1937), which refers to general anæsthetic agents, is not applicable to the relaxant drugs, which have different modes of action and detoxication mechanisms. Patients will vary in their response according to their body-weight or, more correctly, muscle mass; but there are other factors, as yet unknown, which play a part in determining the reaction to relaxant drugs.

HYPERSENSITIVITY

Myasthenia Gravis

Patients with myasthenia gravis show sensitivity to *d*-tubocurarine chloride (Eaton 1947) and gallamine triethiodide ('Flaxedil') (Dundee 1951a). Both these drugs produce neuromuscular block by the same mechanism—i.e., by competition block at the motor end-plate.

Decamethonium, on the other hand, although exerting its effect in the same region, acts by depolarisation. It might therefore be expected that patients with myasthenia gravis would show a normal response to decamethonium (Scurr 1951).

The difference between the responses to decamethonium and to *d*-tubocurarine chloride in a patient with myasthenia gravis are well illustrated by case 1.

Case 1.—A woman, aged 37, had symptoms of myasthenia gravis which had been getting progressively worse since the age of 25. On admission to hospital she was taking neostigmine 90 mg. orally every four hours and 5 mg. parenterally three times daily.

Before thymectomy her response to decamethonium was tested, the result being shown in fig. 1, which also shows her response to *d*-tubocurarine chloride, which was what one would expect in a myasthenic patient. It will be seen that

after thymectomy (9 days) a similar dose of *d*-tubocurarine chloride produced much less effect on respiration than before operation, although the patient had subjective symptoms of respiratory distress.

The response of this myasthenic patient to decamethonium is within the limits of normality. This agrees with the findings during operation of Sellick (1950).

Non-myasthenic Patients

Hypersensitivity to *d*-tubocurarine chloride is a well-recognised clinical entity (Gray and Halton 1948, Howell-Jones 1951) even in patients who show no signs of myasthenia gravis. Similar cases have been reported with gallamine triethiodide (Condon 1951). Two other cases which fall into this group have recently been brought to our notice.

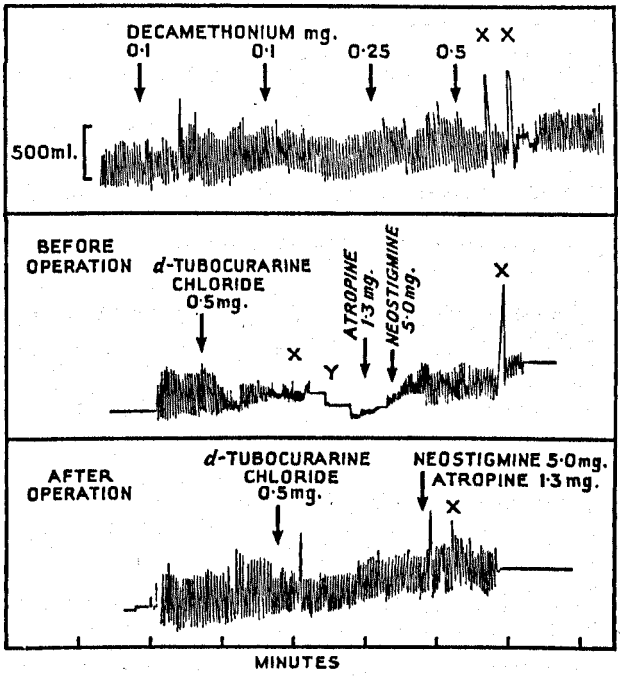

Fig. 1—Effect of decamethonium and d-tubocurarine chloride on respiration in myasthenia gravis (case 1): X, patient was asked to take a deep breath; Y, face-mask raised to expose patient's face.

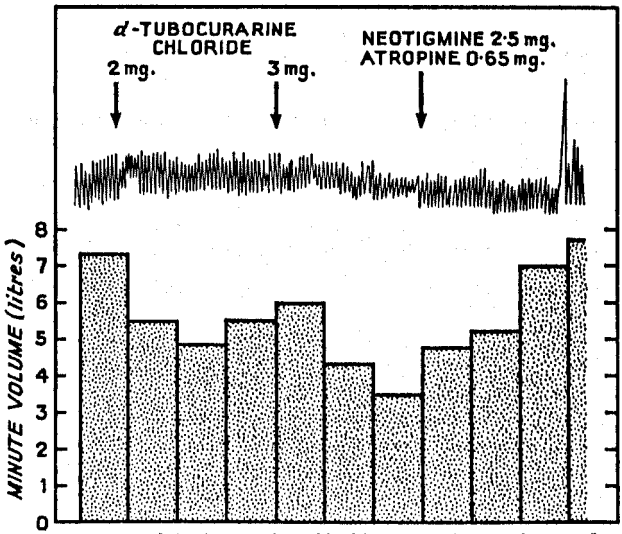

Fig. 2—Effect of *d*-tubocurarine chloride on respiration in case 3.

Case 2.—A man, aged 40, weighing 11 st. (70 kg.).

Operation.—Bilateral Caldwell-Luc. Premedication: pethidine 50 mg., atropine gr. $^1/_{100}$ (0·65 mg.). Anæsthesia was induced with a mixture of thiopentone 0·5 g. and gallamine triethiodide 80 mg., which allowed easy oral intubation and was followed by complete apnœa. Controlled respiration was carried out throughout the operation. To ascertain whether hyperventilation and resulting acapnia were prolonging the respiratory depression, artificial ventilation was stopped occasionally for periods of 2–3 minutes. Although cyanosis did not develop, the pulse volume became poor, only to improve when artificial ventilation was resumed. Despite the apnœa the patient showed a tendency to cough, and on two occasions it was deemed necessary to administer doses of thiopentone 0·25 g. and pethidine 25 mg. The operation was finished in 70 minutes, and pharyngeal toilet was completed under direct vision with excellent relaxation.

Diaphragmatic respiration began 80 minutes after the original injection, but the tidal volume was insufficient to maintain oxygenation. Neostigmine 2·5 mg. and atropine 0·65 mg. were administered, and as there was no increase in tidal volume nikethamide 5 mg. and later picrotoxin 2 mg. were injected intravenously. 25 minutes later the patient had recovered consciousness, but there was still intercostal paralysis. He could now maintain oxygenation when breathing air. The intercostal muscles had not completely recovered $3^1/_2$ hours after the injection of gallamine triethiodide.

Post-operatively liver-function tests were normal, there was no excess of urobilinogen in the urine, and the blood-urea level was 36 mg. per 100 ml. Frequent doses of pethidine and pentobarbitone were given at night without any untoward effect.

Three weeks later a sensitivity test was made with gallamine triethiodide. $1^1/_2$ minutes after administration of 8 mg. of the drug his minute volume of 8325 ml. (measured with a Glover spirometer) was reduced to 5700 ml., and in less than 2 minutes there were complete intercostal paralysis and obvious compensatory overactivity of the diaphragm. At 3 minutes a further dose of 8 mg. was given, which led, within 1 minute of the injection, to further respiratory difficulty and extreme apprehension.

Examination of this patient by a physician failed to reveal any evidence of myasthenia gravis, yet on two occasions a small dose of gallamine triethiodide produced profound respiratory depression. This case-record shows the folly of mixing thiopentone with a muscle relaxant, and emphasises the importance of first administering a test dose of gallamine triethiodide before inducing anæsthesia.

Case 3.—A woman, aged 49, weighing 7 st. 10 lb. (48 kg.).

Operation.—Nephrectomy. Premedication: morphine gr. $^1/_6$ (10 mg.) and atropine gr. $^1/_{100}$ (0·65 mg.). Anæsthesia was induced with a new relaxant 2,5-bis-(3-diethylamino-propylamino)-benzoquinone-bis-(benzyl chloride) ('Win. 2747'), thiopentone, nitrous oxide, and oxygen. A test dose of 3 mg. of relaxant produced decided ptosis and slight respiratory distress. These signs were ignored by the anæsthetist, who administered a further 9 mg., followed by thiopentone 0·35 mg. Over-anxiety to produce complete relaxation led the anæsthetist to administer a further 3 mg. of relaxant, although there was no indication for this. Throughout the operation, which lasted 60 minutes, the patient remained apnœic. At the end of the operation the administration of atropine gr. $^1/_{50}$ (1·3 mg.), followed in 2 minutes by neostigmine 5 mg., led to the return of some diaphragmatic, but not intercostal, activity. The corneal reflex was now active. Atropine and neostigmine in the same doses 7 minutes later brought no improvement. The lungs were inflated with oxygen for a further 60 minutes, when a third injection of atropine gr. $^1/_{100}$ and neostigmine 2·5 mg. was given. This led to vigorous coughing and an increase in the minute volume of respiration from 3200 to 4100 ml. The patient was now conscious, but the intercostals were still inactive and there was considerable tracheal tug. There were signs of lower intercostal activity 40 minutes later, and there was continuous improvement from then on. Ptosis and paresis of the facial muscles were still apparent $4^1/_2$ hours after the original injection of the relaxant.

A fortnight later a sensitivity test to *d*-tubocurarine chloride was made. The effect on respiration is shown in fig. 2. From this it seems that the patient was hypersensitive also to *d*-tubocurarine chloride. Further, it suggests that 2,5-bis-(3-diethylaminopropylamino)-benzoquinone-bis-(benzyl chloride) produces neuromuscular block by the same mechanism as does *d*-tubocurarine chloride.

HYPOSENSITIVITY

Drug Tolerance

Hyposensitivity is a much rarer clinical entity than hypersensitivity. Gray and Halton (1948) observed that patients who showed a natural or acquired tolerance to the opiates or to the barbiturates tend to require a larger dose of *d*-tubocurarine chloride than normal. The following case-record seems to indicate that tolerance may develop after protracted administration not only of opiates and barbiturates but also of sedatives and analgesics in general.

Case 4.—A man, aged 20, had a long series of operations.

Aug. 28, 1949.—Gangrenous appendix removed.

Jan. 9, 1950.—Ileo-ascending colostomy done for subacute intestinal obstruction.

June 6.—Abscess in loin incised under thiopentone (0·4 g.) and cyclopropane anæsthesia.

Sept. 10.—Readmitted to hospital with severe pain in lumbar region and hypogastrium. Large doses of sedative and analgesic drugs were being administered—pethidine 50 mg. and 2 tab. codeine co. four-hourly, 'Seconal' gr. 3 (200 mg.), chloral hydrate gr. 15 (1 g.), tinct. opii min. 15 (0·88 ml.) and potassium bromide gr. 15 (1 g.) at night. On Oct. 10 his hæmoglobin was 85%, and his weight 9 st. (57 kg.).

Oct. 11.—Laparotomy and drainage of numerous intra-abdominal abscesses. Premedication: morphine gr. $^1/_6$ and atropine gr. $^1/_{100}$. Anæsthetic: *d*-tubocurarine chloride, thiopentone-nitrous oxide-oxygen and ether (Coxeter-Mushin absorption). The patient was very resistant to all these agents, and *d*-tubocurarine 80 mg., thiopentone 2·5 g., and ether 56 ml. were required during the operation, which lasted 2 hours 15 minutes. In spite of these large doses respiration was never very depressed and no neostigmine was required at the end.

Slight jaundice appeared 12 hours after operation and lasted for 24 hours. Urinary urobilinogen was present to a dilution of 1 in 60, the serum-bilirubin level was 1·0 mg. per 100 ml., cephalin cholesterol +++, but other liver-function tests were normal. Pus from the abscesses contained actinomyces.

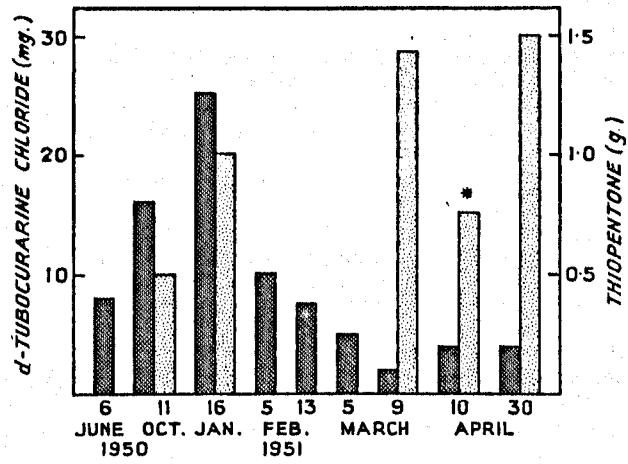

Fig. 3—Variation of response to thiopentone and *d*-tubocurarine chloride in case 4 : *hatched columns*, amount of thiopentone required during first 15 minutes of anæsthesia ; *stippled columns*, average dose of *d*-tubocurarine chloride per 15 minutes of anæsthesia ; *asterisk*, patient was not relaxed with this dose of *d*-tubocurarine chloride.

Jan. 9, 1951.—Hb 58%, general condition poor. Doses of drugs required to alleviate pain had greatly increased—pethidine 100 mg. and 2 tab. codeine co. four-hourly, and morphine gr. $^1/_6$ as required. Urobilinogen had disappeared from the urine, and the serum-bilirubin level was normal.

Jan. 16.—Evacuation of pus from loin. Premedication : morphine gr. $^1/_6$, atropine gr. $^1/_{100}$. Anæsthetic : *d*-tubocurarine chloride, thiopentone, cyclopropane, and ether. The patient's resistance to anæsthetic drugs was maintained, *d*-tubocurarine chloride 20 mg. and thiopentone 1 g. being required for endotracheal intubation, which was followed by violent coughing and very little respiratory depression. Large amounts of cyclopropane and ether were required.

Feb. 5.—The patient had deteriorated a lot and was emaciated, weighing 8 st. (51 kg.). A sinus was explored down to the lumbar spine under thiopentone (0·5 g.) and cyclopropane anæsthesia. Very little cyclopropane was required.

Feb. 13—The wound was packed under thiopentone (0·25 g.) and cyclopropane anæsthesia. Again very little cyclopropane was required.

Feb. 22.—Liver-function tests gave the following results : van den Bergh direct reaction negative ; serum-bilirubin level less than 0·8 mg. per 100 ml. ; serum-alkaline phosphatase level 17 units per 100 ml. ; serum-colloidal gold 3 units ; zinc turbidity 13 units ; thymol turbidity 8 units ;

thymol flocculation + + + ; cephalin cholesterol + ; albumin/globulin ratio 0·55/1 (Howe's technique), 0·26/1 (Cohn's technique) ; hippuric-acid excretion impaired.

March 5.—Wound again packed. Very little thiopentone (0·25 g.) required. Next day tests showed deterioration of liver function : A/G ratio 0·38/1 (Howe's technique) ; much excess urobilinogen in the urine, and only 0·7 g. of hippuric acid excreted in 1 hour after 1·77 g. sodium benzoate given intravenously. Hb 60%. Increasing addiction to sedatives and analgesics.

March 9.—Perforation of abscess with peritonitis. Morphine gr. $^1/_6$ and atropine gr. $^1/_{100}$ given as premedication before induction of anæsthesia for laparotomy. Anæsthesia was induced with thiopentone 0·1 g. followed by cyclopropane, with *d*-tubocurarine chloride given when the skin was incised. 30 mg. of *d*-tubocurarine chloride was required before the abdomen could be explored. In spite of this dose the tidal volume was never less than 250 ml. A total dose of 54 mg. of *d*-tubocurarine chloride was given during the first 45 minutes of the operation, with only fair relaxation. The operation lasted 55 minutes, and at the end the tidal volume was 400 ml. There was a slight tracheal tug, but it was doubtful whether intercostal paralysis was present or not. The patient tried to cough out the endotracheal tube after atropine 1·3 mg. and neostigmine 2 mg.

April 9.—Total drugs given during 24 hours were now pethidine 800 mg., 15 tab. codeine co., and butobarbitone gr. 9 (600 mg.).

April 10.—Incision of abscess. Anæsthesia : thiopentone and *d*-tubocurarine chloride. No relaxation of jaw was

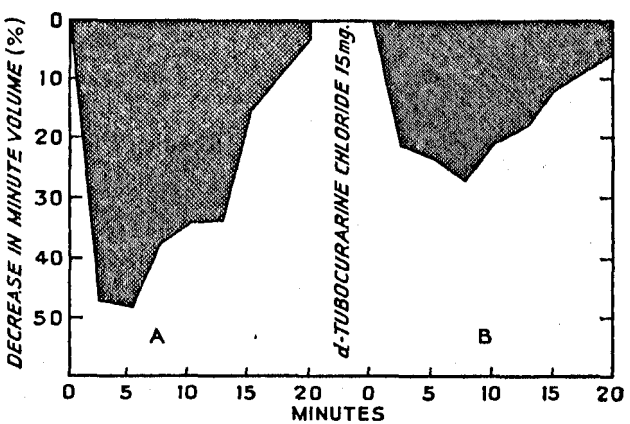

Fig. 4—Average degree of respiratory depression produced in ten persons with decamethonium 4 mg. : A, at beginning of anæsthesia ; B, after *d*-tubocurarine chloride 15 mg.

obtained after 15 mg. of *d*-tubocurarine chloride, and the effect on respiration was negligible.

April 12.—Sedatives increased to 'Omnopon' gr. $^2/_3$ (40 mg.) three-hourly, with an additional gr. 6 (400 mg.) of butobarbitone at night.

April 30.—A plaster jacket was applied. A test dose of gallamine triethiodide 20 mg. produced no effect, and there was no distress after a further 60 mg., even after an interval of 5 minutes. Intubation required a further 60 mg. of gallamine triethiodide with 0·2 g. of thiopentone, and was followed by negligible respiratory depression. Very little cyclopropane was required to complete the operation.

The picture presented by this patient was one of increasing resistance to drugs of the curare series. This can be contrasted with the difference observed in response to thiopentone, to which he was in the first place extremely resistant; but, as liver damage and toxæmia supervened, he became hypersensitive (fig. 3).

The increasing tolerance to *d*-tubocurarine chloride shown throughout must be attributed to the large doses of sedatives and analgesics that the patient was taking. This is the most feasible explanation for the resistance to thiopentone shown by the patient in the early anæsthetics.

Tolerance to one barbiturate leads to cross-tolerance to other drugs in the same series (Gruber and Freedman 1945, Carmichael 1948), and case 4 suggests that tolerance to pethidine, opiates, and other analgesics might establish a cross-tolerance to thiopentone. The development of sensitivity to thiopentone coincided with the onset of demonstrable liver damage, but this latter did not engender any sensitivity to *d*-tubocurarine chloride, to which the patient showed ever increasing resistance. The effect of hepatic dysfunction on the duration of action of these two drugs is clearly contrasted—i.e., it prolongs thiopentone narcosis (Shideman et al. 1949) but has no effect on the degree of paralysis or duration of action of *d*-tubocurarine chloride (Everett 1948).

The jaundice that followed the fourth anæsthetic could have been due to the thiopentone. In doses of the order administered (2·5 g.) thiopentone is a hepatotoxic agent (Dundee 1951b). An excess of bilirubin is formed after operations (Elton 1931) owing to absorption of extravasations of blood. The normal liver can deal with this excess pigment, and a "postoperative latent jaundice" occurs. Depression of liver function by thiopentone may have led to the jaundice becoming clinically evident.

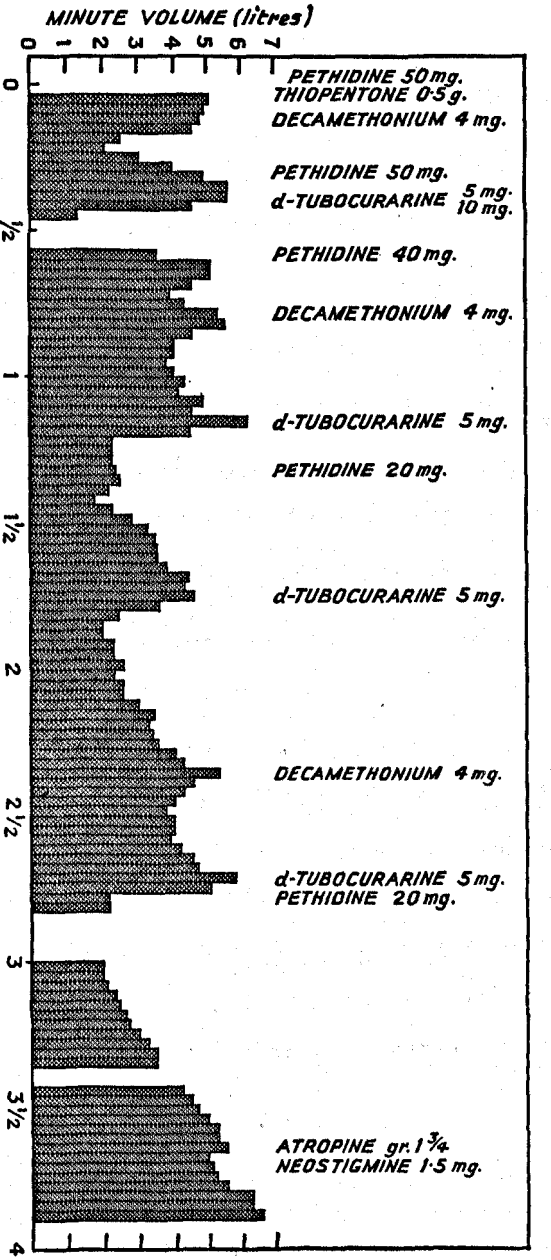

Fig. 5—Minute volumes in case 5.

Antagonism between Decamethonium and True Curare-like Drugs

Since the mechanisms of production of myoneural block by *d*-tubocurarine chloride and decamethonium are diametrically opposed (Paton and Zaimis 1950), it is known that *d*-tubocurarine chloride can antagonise the effects of decamethonium. The degree of this antagonism has been investigated in ten persons.

Second-plane anæsthesia was established with thiopentone-nitrous oxide-oxygen, pethidine, or cyclopropane. A dose of decamethonium 4 mg. was injected, and minute respiratory volume recorded for 20 minutes. 15 mg. of *d*-tubocurarine chloride was next injected in divided doses. The respiratory volume was allowed to return to normal, and then a further 4 mg. of decamethonium was injected. The degree and duration of respiratory depression were again measured.

Fig. 4 shows the average findings in the ten cases. The amount of respiratory depression which followed the second dose of decamethonium was 54% of that which followed the first dose. However, the time taken for return of normal respiration was similar before and after the *d*-tubocurarine chloride. This is the reverse of the effect seen when *d*-tubocurarine chloride is given after decamethonium; in this case the paralysant effects of *d*-tubocurarine chloride are increased. Both these phenomena are well illustrated by case 5.

Case 5.—A man, aged 51 and weighing 12 st. 4 lb. (78 kg.) was anæsthetised for vagectomy and partial gastrectomy. Premedication: morphine gr. $^1/_6$ and atropine gr. $^1/_{100}$. Pethidine 50 mg. was injected intravenously five minutes before induction with thiopentone 0·5 g. Anæsthesia was maintained with nitrous oxide-oxygen-pethidine, and doses of relaxant drugs were given as required. Save for brief periods, when respiratory depression necessitated assistance, the minute volume was measured continuously throughout the operation.

The resulting minute volumes are shown in fig. 5. The degree of respiratory depression became less after each successive dose of 4 mg. of decamethonium, whereas with *d*-tubocurarine chloride the degree and duration of respiratory depression increased with each dose.

SUMMARY AND CONCLUSIONS

The factors determining hypersensitivity and hyposensitivity to relaxant drugs are discussed, and the respiratory effects of sequences of agents acting by depolarisation and competition block are illustrated.

It is concluded that hypersensitivity to agents acting by competition block exists in patients with myasthenia gravis and in some non-myasthenic persons.

Hyposensitivity to this class of relaxants may occur in patients who have acquired a tolerance to sedatives and analgesics.

These facts demonstrate again the importance of administering a test dose.

Drugs acting by depolarisation block produce a normal effect in myasthenic patients and a reduced effect in patients who have received previous doses of a competition blocking agent. On the other hand, they increase the effect of the latter when given previously.

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7, Adam Street, Adelphi, London, W.C.2

Pathological Factors Influencing Dosage.

(b) Anaemia.

"THE USE OF THIOPENTONE IN ANAEMIC SUBJECTS"

Reprinted from the Journal of the Irish Medical Association, (1952). Volume 31, pages 351 - 356.

"ACQUIRED SENSITIVITY TO THIOPENTONE"

Reprinted from the British Medical Journal (1950). Volume 2, page 332.

The comment on this case report is largely out of date, in the light of the previous two reprints, but the history suggests that gross anaemia was the cause of the sensitivity.

Reprinted from the Journal of the Irish Medical Association, December, 1952. Vol. 31, No. 186, p. 351.

THE USE OF THIOPENTONE IN ANAEMIC SUBJECTS

By John W. Dundee, M.D., D.A.

Lecturer in Anaesthesia, Liverpool University.

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THE USE OF THIOPENTONE IN ANAEMIC SUBJECTS.

OPINIONS in medical literature are very evenly divided on this subject. In 16 publications during the past ten years anaemia is listed among the contra-indications to the use of thiopentone. In an equal number the opposite view is taken and thiopentone is not considered to be contra-indicated in the presence of anaemia. Three further authors make a compromise and advise that the administration of a very small dose of thiopentone is permissible to anaemic patients.

Fig. I shows the percentage haemoglobin (Haldane standard) of 1,200 unselected patients coming for surgery. If the first view expressed above is correct, then about 7.5 per cent. of patients must be denied the use of thiopentone for the induction of anaesthesia.

Most of the statements in the literature, as to

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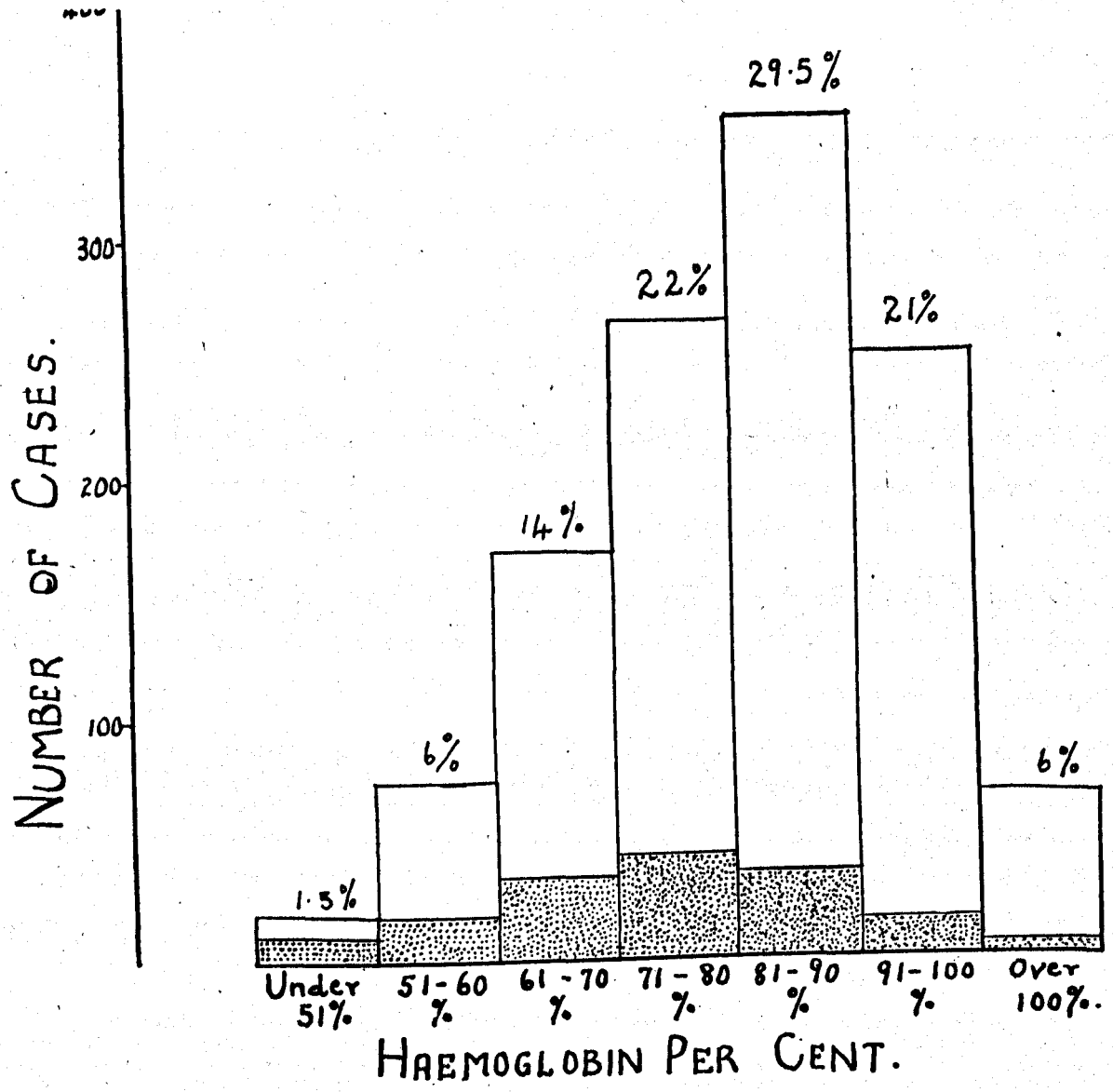


FIG. I.

Haemoglobin percentage (Haldane standard) of 1,200 unselected cases coming for surgery. (Stippled areas represent cases over 65 years of age).

whether or not the use of thiopentone is permissible in anaemic subjects, are made without any reason being given for them. The purpose of this paper is to ascertain

(*a*) the effect of thiopentone on the oxygen capacity of the blood;

(*b*) whether the blood picture in anaemia influences the action of thiopentone; and

(*c*) if there is any other action of thiopentone which prejudices its use in anaemic subjects.

Effect of Thiopentone on the Blood.

Adriani[1] states that barbiturates decrease the number of red cells in the blood, Amytal giving a 21 per cent. decrease in cell volume. Penrod and Hegraver[18] have found a 9 per cent. fall in packed cell volume following the use of thiopentone, i.e., about 20 per cent. haemodilution. Lundy [13] gives this haemodilution as his reason for considering thiopentone to be contra-indicated in anaemic subjects. A 20 per cent. decrease in haemoglobin would render a patient less able to stand any anoxia which may occur during anaesthesia. This applies particularly to anaemic subjects.

However, most of the experimental work in support of the view that thiopentone causes haemodilution has been done in animals (Hausner *et al.*[9], Pender and Lundy[17]; Tureman *et al.*[22]). Changes in the composition of the blood have been attributed in the main to dilatation of the spleen (Hausner *et al.*[9]). This organ in man is much less muscular than in animals (McDowall[16]) and it has never been demonstrated convincingly that it can dilate or contract to any appreciable extent. To ascertain if the results obtained from animal experiments are applicable to man, four investigations to detect haemodilution were carried out on a large number of subjects, all of whom were anaesthetized with thiopentone. While any one estimation would have been sufficient on its own, each one acts as a check on the others, and any degree of haemodilution which occurs would be shown by all four. Blood was examined before induction of anaesthesia and at five minute intervals thereafter for 20 minutes.

The results obtained are shown on Table I. This reveals that thiopentone causes a negligible degree of haemodilution in man. The series included some extremely anaemic patients and they were no more susceptible to haemodilution than normal subjects.

Actual changes in the oxygen content of arterial blood recorded during anaesthesia with thiopentone are shown in Fig. II. Unsupplemented thiopentone caused a fall in blood oxygen. This did not occur when 100 per cent. oxygen or 50 per cent. nitrous oxide in oxygen were administered concurrently. Similar findings have been reported by Barton, Wicks and Livingstone[3].

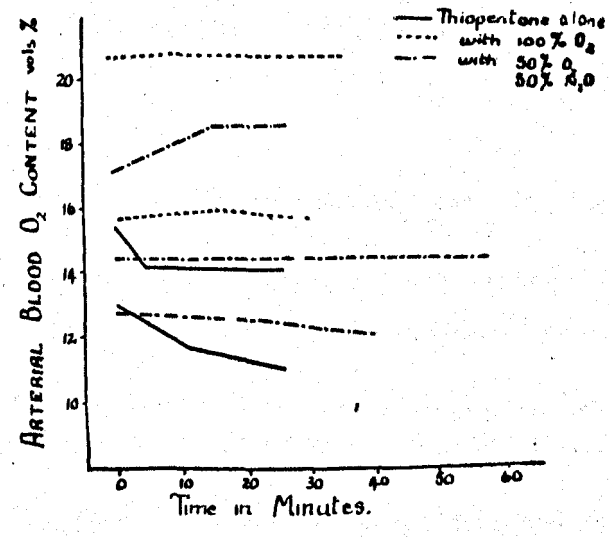


FIG. II.

Changes in oxygen content of arterial blood recorded during anaesthesia with thiopentone: (a) alone, (b) with 100 per cent. O_2 and (c) with 50 per cent. N_2O in O_2.

From this evidence it can be concluded that the administration of thiopentone to anaemic patients will not appreciably lower the O_2 capacity of their blood. If 100 per cent. O_2 or 50 per cent. N_2O in O_2 are administered concurrently, and respiratory depression avoided, the oxygen content of the arterial blood will not fall to a dangerously low level.

	Packed cell volume %	Hb. g.%	Red Blood Cells per cu. mm.	O_2 capacity vols. %
No. of cases	48	52	17	20
Time				
Pre-op.	46.69	12.67	4,563,000	17.37
5 mins. anaesthesia ..	46.56	12.62	4,498,000	16.97
10 „ „	46.13	12.67	4,563,000	16.81
15 „ „	45.88	12.59	4,578,000	16.98
20 „ „	46.02	12.52	4,649,000	16.97

TABLE I.

Showing average changes in blood recorded during anaesthesia with thiopentone.

Effects of the Blood Picture on the Action of Thiopentone.

Macintosh and Bannister[14] state that anaesthesia in anaemic subjects can be accomplished with very small amounts of thiopentone. Doses which would be correct for the average adult may be dangerously excessive for them, and in any case will lead to post-operative depression and delayed recovery. Investigations were carried out to ascertain the truth of this statement and the extent of the delayed recovery.

The time taken to react to a constant stimulus following 500 mg. thiopentone injected at the rate of 100 mg. per 5 seconds was noted in two series of patients. Apart from anaemia, the presence of any of the factors summarised by Dundee[7] as likely to influence the response to thiopentone, excluded a case from this investigation. In the first series of 253 male patients the constant stimulus was the passage of a cystoscope. In no instance was the thiopentone injected until the surgeon was ready to pass the instrument. Duration of anaesthesia was measured from the end of the injection to the first movement by the patient. Fig. III shows the duration of anaesthesia plotted against the haemoglobin (Haldane standard). The result of a similar investigation in 260 female subjects in whom the constant stimulus was a dilatation and curettage is shown in Fig. IV.

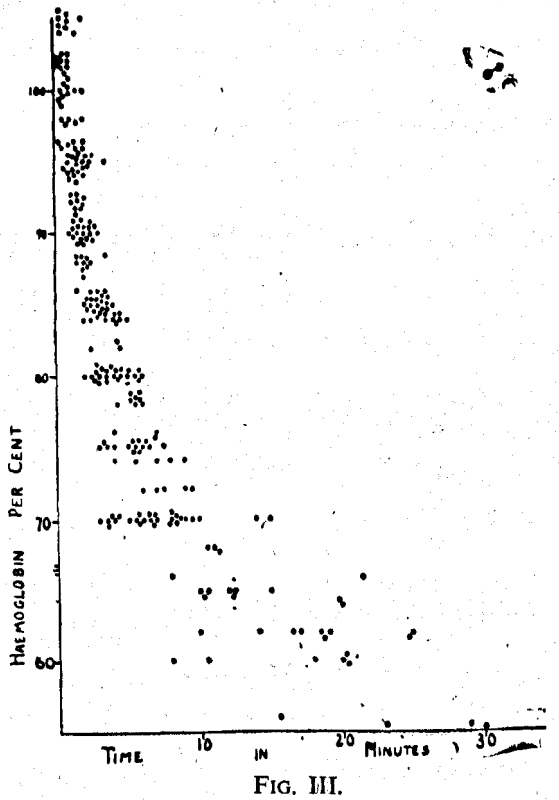


FIG. III.

Relationship of duration of narcosis following 500 mg. thiopentone in response to the constant stimulus of a cystoscope to haemoglobin content of blood in 253 male subjects.

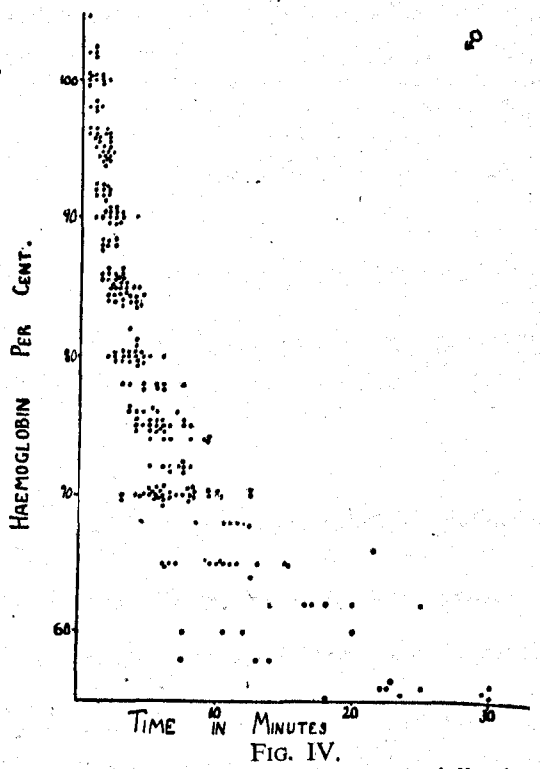


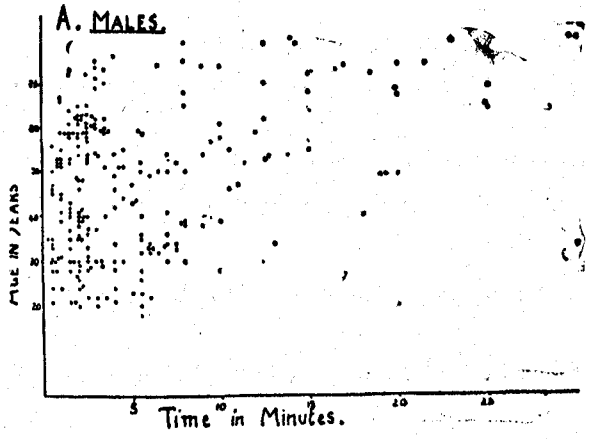
FIG. IV.

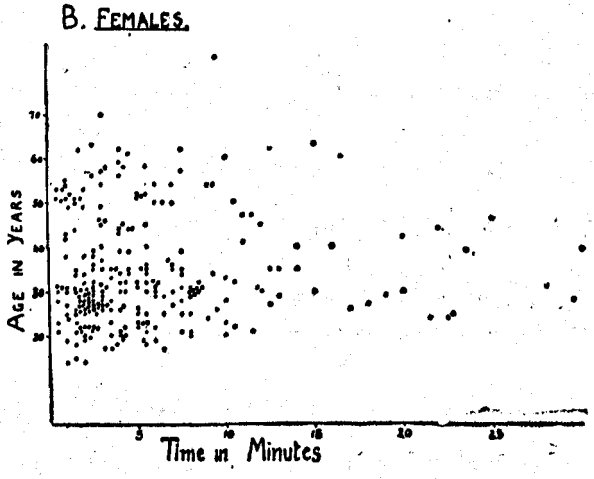
Relationship of duration of narcosis following 500 mg. thiopentone, in response to the constant stimulus of a dilatation and curettage to haemoglobin content of blood in 260 female patients.

The influence of age and body weight on the duration of anaesthesia in these two series is shown in Figs. V and VI. There is no direct relationship of either of these factors and they have been ignored in a further consideration of the findings.

Figs. III and IV give the impression that anaesthesia with 500 mg. thiopentone was more prolonged in subjects with a low haemoglobin content of blood. This prolongation became apparent in subjects with haemoglobin under 75 per cent. The dilution method of haemoglobin estimation employed is very unreliable and differences of 10 per cent. can occur with a single average observer (Macfarlane *et al.*[15]). This has to be borne in mind when carrying out a statistical analysis of the results of this investigation. Average duration of narcosis in two groups of patients, whose difference in Hb value should be outside the range of experimental error are compared in Table II. In both series there is a significant prolongation of narcosis in subjects with haemoglobin values between 70 and 74 per cent. Haldane as compared with the 90-94 per cent. haemoglobin group.

A further investigation was carried out on 91 subjects—all males of the 31-40 age group with weights ranging from 9 to 11 stones (57 to 70 kg.). The time taken to react to the stimulus of a cystoscope following 50 mg. thiopentone per stone body weight was noted. Fig. VII, which shows duration





of narcosis in these subjects plotted against Hb, gives the same impression as the previous investigations, viz. prolongation of thiopentone narcosis in anaemic patients.

These findings are confirmed by the following case report:

A male, aged 68, was admitted to hospital with Hb 40 per cent. due to haematuria from a papilloma of the bladder. Repeated cystoscopic examinations with diathermy of the tumour were carried out and over the next three months his Hb rose to 80 per cent. At each operation he was anaesthetized with 450 mg. thiopentone and given 100 per cent. O_2. Fig. VIII shows the duration of anaesthesia on six occasions plotted against the Hb. The duration of the same dose of thiopentone was much greater at the lower haemoglobin values.

In a discussion on anaesthesia in tropical climates Ashworth[3] reported that malaria engendered in the patients extreme sensitivity to thiopentone. Pleasance[20] considered that the average Indian soldier required 30-40 per cent. less thiopentone, as a rule, than the European. Both these facts could be explained partly by the presence of a severe chronic anaemia.

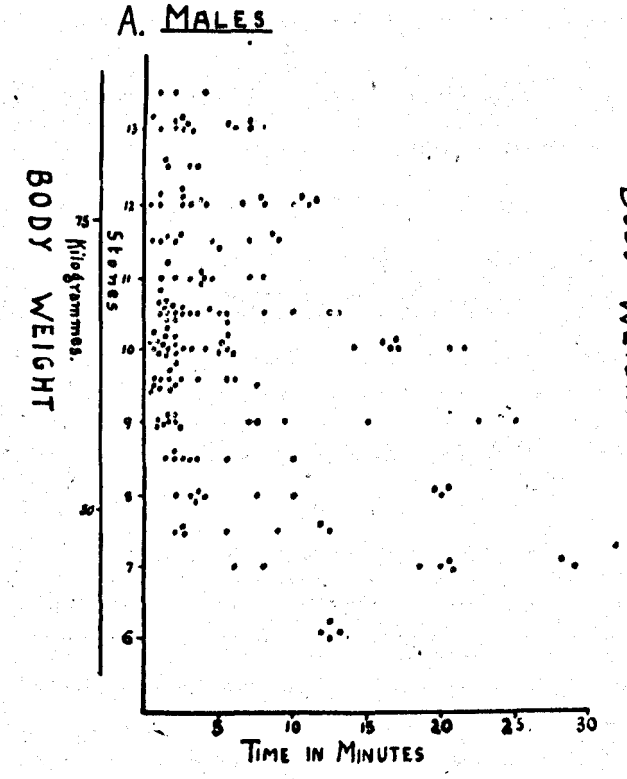
It is rather difficult to offer a satisfactory explanation for the prolongation of the action of thiopen-

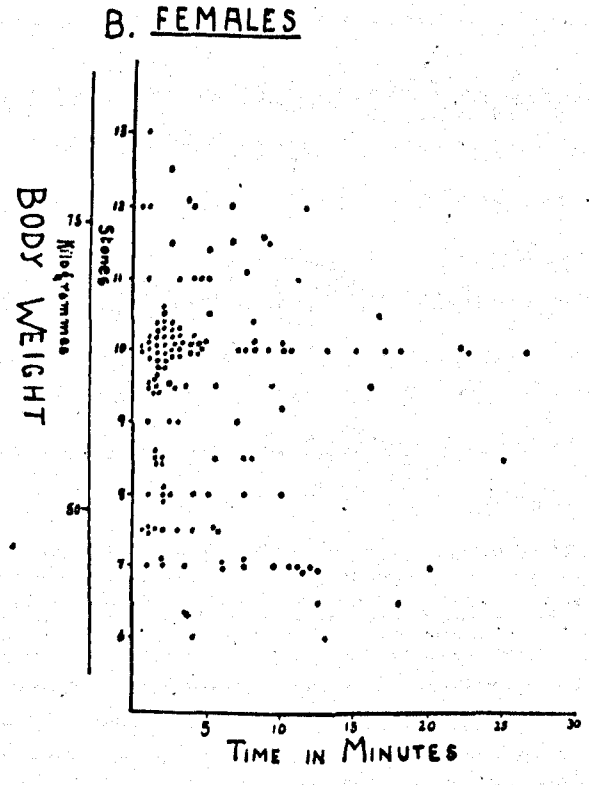
FIG. V (*left*).

Influence of age on the duration of narcosis in response to a constant stimulus in the two series of patients referred to in the text.

FIG. VI (*below*).

Influence of body weight on the duration of narcosis in response to a constant stimulus in the two series of patients referred to in the text.





tone which occurs in anaemia. Several possible contributory factors will be briefly mentioned. Richards[21] found that incubation of thiopentone with whole blood at 37° C significantly reduced the potency of the barbiturate. Plasma has no such effect (Kelly, Shideman and Adams[10]). This would suggest that erythrocytes are capable of detoxicating thiopentone. However, Richards[21a] thinks that the thiopentone is not destroyed, but that a linkage occurs between the erythrocytes and the thiopentone. In support of this view is the observation

Subjects Constant stimulus	Males Cystoscopy		Females Dilatation and Curettage	
Haemoglobin range ...	90—94	70—74	90—94	70—74
Number of cases	33	31	30	44
Mean values				
Age ...	43.6 ±1.33	47.3 ±1.01	32.8 ±2.16	34.8 ±1.85
Weight in lbs....	150 ±5.8	140 ±8.8	132 ±4.5	133 ±8.8
Duration of Narcosis in mins.	1.9 ±0.09	7.5 ±0.56	1.96 ±0.12	6.9 ±0.39
S.E. difference	0.54		0.45	

TABLE II.

Comparison of average, age, body weight and duration of narcosis following 500 mg. thiopentone in two groups of cases (a) with Hb 90—94 per cent. and (b) with Hb 70—74 per cent. from each of the two series of patients referred to in the text.

that thiopentone is bound to a greater extent than its oxygen analogue (pentobarbitone), which has a more prolonged action (Goldbaum and Smith[8]). Be this as it may, an inactivation of thiopentone is produced by red cells, and the fewer these are—as in anaemia—the less will be the amount of inactivation and hence the longer the action of the thiopentone.

Anaemia may well affect tissues which are known to play a part in the detoxication of thiopentone, particularly the liver. In a study of severe refractory anaemia Bomford and Rhoads[4] found liver damage at all of the 24 autopsies they reported. Whitby and Britton[24] likewise associate severe anaemia with liver dysfunction.

The picture of prolonged narcosis after a small dose of thiopentone is not like that caused by a failure of the body to detoxicate the drug. After small doses patients waken up, not because the thiopentone has been broken down, but because it has diffused to non-nervous tissues (Brodie[5]). Cerebral cells may have become more sensitive to thiopentone because of the anaemic anoxia. As will be seen later, the compensatory increase in circulation rate (which occurs in the presence of anaemia as a compensation for the lowered oxygen capacity of the blood) could easily be broken down by the effects of thiopentone on the cardiovascular system. It is known that thiopentone narcosis is prolonged by any factor which produces

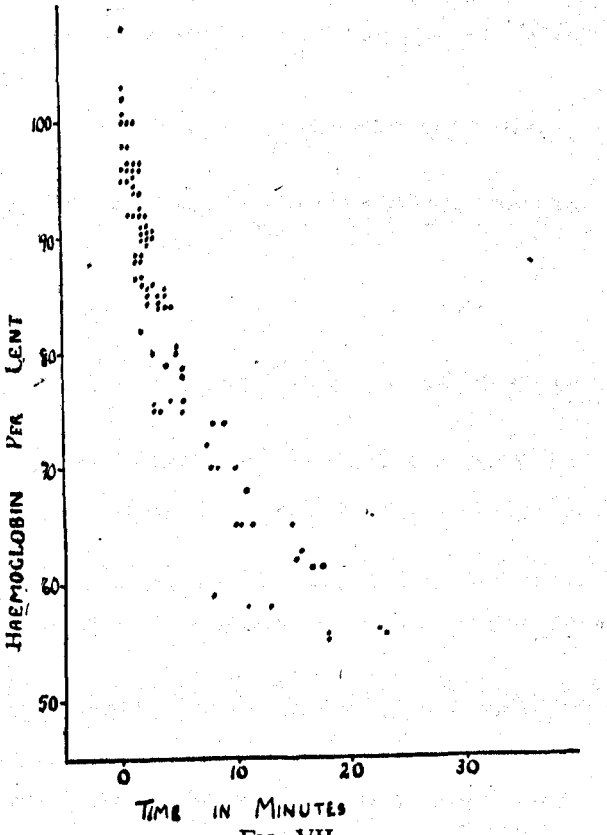


FIG. VII.

Relationship of duration of narcosis following 5(mg. thiopentone/stone in response to the constant stimulus of a cystoscope to haemoglobin in 91 mate subjects referred to in the text.

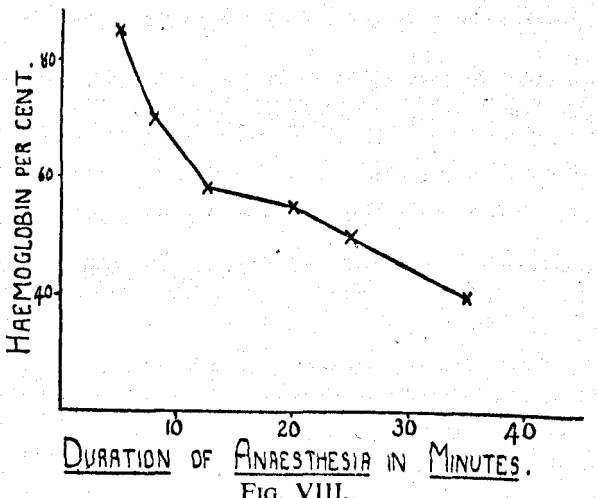


FIG. VIII.

Duration of narcosis following 450 mg. thiopentone at various haemoglobin levels in subjects referred to in text.

cerebral anoxia (Peterson *et al.*[19]). It may well be that anoxia plays a part in the prolongation of thiopentone narcosis in anaemic subjects.

Other Effects of Thiopentone.

Subjects with severe anaemia are generally considered to be poor risks and for this reason Cohen[6] advises against the use of thiopentone. This may be due to the effect of thiopentone on the circulation. Fatty degeneration of the heart is not an uncommon accompaniment of anaemia (Lewis[11]). As already mentioned the cardiac output and circulation rate are increased in an effort to overcome the decreased oxygen capacity of the blood. These, together with the lowered viscosity of the blood, should render anaemic subjects more prone to serious and prolonged falls in blood pressure following thiopentone than normal subjects. This is in full agreement with clinical observations.

The mean aortic blood pressure is one of the main factors which control the cerebral and coronary circulations. A fall in blood pressure, while having no deleterious effects on a normal subject because of the excess oxygen carried in the blood, may, in an anaemic patient, lead to a dangerous diminution of cerebral and coronary blood flow. Apart from the fact that this may prolong narcosis, the effects on the circulation to the brain will not be so serious because of the lowered oxygen consumption (Wechsler, Dripps and Kety[23]). The impaired blood supply through the coronary vessels will result in a defective nutrition of the heart, which would further depress the circulation.

The fall in blood pressure with thiopentone is roughly proportional to the dose and rapidity of injection. A slow injection of a dilute solution is the safest method we have of preventing a fall in blood pressure. The concentration of the drug which reaches the right side of the heart is kept low and consequently there is less depression of the myocardium. Mixing thiopentone with Methedrine, as suggested by Lockett[12], can never be recommended in the place of slow injection, since the vasopressor effects are produced by increasing the output of a heart which may already be working at its maximum capacity.

Summary and Conclusions.

1. Opinion is divided in the literature as to the advisability of using thiopentone in anaemic patients.

2. Thiopentone has no appreciable effect on the oxygen capacity of the blood. It will not reduce the oxygen content to a dangerously low level in anaemic subjects provided oxygen or 50 per cent. N_2O-O_2 is administered concurrently and respiratory depression avoided.

3. The duration of narcosis is increased in the presence of anaemia, compared with the effect of the same dose of thiopentone in a normal subject. Possible explanations of this phenomenon are discussed.

4. Anaemic patients are more prone to falls in B.P. following thiopentone than are normal subjects. The importance of avoiding hypotension—with possible deleterious effects on the cardiovascular system—are stressed.

5. Provided the above factors are kept in mind, I can find no reason for considering anaemia to be a contra-indication to the use of thiopentone.

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Acquired Sensitivity to Thiopentone

The following case illustrates how individual requirements for thiopentone can vary from time to time.

CASE REPORT

A woman aged 64 was to be operated on for acute intestinal obstruction. Her general condition was poor, she was ill-nourished, and had been vomiting for 24 hours, though cyanosis and jaundice were not present and she did not look anaemic. Her blood pressure was 180/100 mm. Hg, and pulse 100. Atropine sulphate, 1/100 gr. (0.65 mg.), and morphine sulphate, 1/6 gr. (11 mg.), were given one hour before operation and she was induced with 12 mg. of curare and 0.3 g. of thiopentone. Slight respiratory depression for about 10 minutes followed this, but no apnoea. Anaesthesia was maintained with cyclopropane and oxygen, and 3 mg. of curare was given after half an hour. A volvulus of the pelvic colon was found and resected, leaving a left inguinal colostomy. The operation lasted 65 minutes, and at the end the patient had completely recovered her cough reflex.

Failure of the colostomy to close necessitated another operation six weeks later. Her general condition had by now greatly improved. Premedication was given as before. After an initial dose of 0.2 g. of thiopentone she became apnoeic, and artificial respiration with oxygen, using a Coxeter–Mushin absorber, was undertaken. The surgeon at this stage commented on the satisfactory relaxation. The absorber was cut out of the circuit periodically lest the washing out of alveolar CO_2 had been serving to maintain the apnoea. After 20 minutes she was intubated orally and the pharynx packed without any sign of resistance from the patient. Later 3 ml. of nikethamide and 1.5 ml. of picrotoxin were given intravenously with no response.

After 50 minutes' apnoea spontaneous respiration began, and at the end of the operation, which lasted one hour, she was breathing normally. Consciousness was regained an hour later, and apart from mild bronchitis she made an uneventful recovery.

COMMENT

The altered response of this patient to thiopentone points to some change having occurred in her detoxicating powers.

Thiopentone detoxication is imperfectly understood (Hewer, 1948), but the drug is believed to be broken down

quickly in the tissues generally (Adams, 1944). The role of the liver in this process is very debatable, and, while some hold that it plays a major part (Shideman and Kelly, 1947a, 1947b ; Shideman, 1948, 1949 ; Walker and Wynn-Parry, 1949), Richards and Appel (1941), Lundy (1942), and Scheifley (1946) do not believe that liver damage prolongs thiopentone anaesthesia. Liver and kidney function tests done on the day after the second operation revealed gross dysfunction, and there were persistently high quantities of urobilin in the urine.

The patient was also grossly deficient in vitamin C. While this deficiency prolongs pentobarbitone ("nembutal") narcosis, of which thiopentone is the sulphur analogue, Adriani (1946) denies that it plays any part in the detoxication of thiopentone.

Fears that thiopentone administration might have a deleterious effect on patients undergoing sulphonamide therapy were abandoned after the experience gained in the last war (Adams, 1944). Nevertheless, it may be mentioned that in my case 21 g. of sulphadiazine had been administered two weeks previous to the second operation, and that a course of succinylsulphathiazole was started 24 hours before it. The precise bearing of this on the course of events is a matter for speculation.

Shortly before her discharge from hospital the patient informed us of her intention to resume the "injections for the blood," which she had been having thrice weekly prior to admission. Blood examination at that time showed : red cells, 1,430,000 ; white cells, 2,000 ; Hb, 40% ; the stained film being typical of pernicious anaemia. Her first operation being a night emergency, no pre-operative blood examination was feasible, and her satisfactory post-operative course gave no indication for haematological investigation.

On incubating thiopentone with blood at body temperature, Richards (1947a, 1947b) found a decrease in potency which did not occur when plasma was substituted for whole blood. This suggests that some enzyme in the red cells is capable of detoxicating thiopentone. In my case the deficiency in the red cells due to anaemia at the time of the second anaesthetic would mean loss of this enzyme and could account, at least in part, for the altered response to the drug.

Liver deficiency could have been secondary to the gross degree of anaemia that developed during the six weeks' abstinence from liver extract, and could have been a manifestation of anoxia. Thus the "acquired sensitivity" to

thiopentone can be attributed to a combination of gross anaemia and liver damage.

I am indebted to Mr. A. M. Abrahams and Dr. J. B. Hargreaves for permission to publish this case, and I would be interested to hear of any similar cases.

JOHN W. DUNDEE, M.B., D.A.,
Anaesthetic Registrar, Walton Hospital, Liverpool, 9.

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Pathological Factors Influencing Dosage.

(c) Uraemia

"EFFECT OF AZOTEMIA UPON THE ACTION OF INTRAVENOUS BARBITURATE ANAESTHESIA"

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EFFECT OF AZOTEMIA UPON THE ACTION OF INTRAVENOUS BARBITURATE ANESTHESIA *

JOHN W. DUNDEE, M.D.,† AND RICHARD K. RICHARDS, M.D.‡

Chicago, Illinois

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THE use of new and sensitive analytical techniques has contributed considerably to our increased knowledge of the distribution and fate of drugs in the body. Such procedures have also greatly increased our understanding of the mode of action of barbiturates. The fate of these drugs has recently been reviewed (1). A study of the available data indicates that considerably more effort has been devoted to the role of the liver as a site of detoxification for the short acting barbiturates than to any other organ. Today the predominant role of the liver in the metabolic degradation of the clinically important barbiturate derivatives as, for instance, thiopental or hexobarbital is sufficiently assured. On the other hand, it has often been assumed that the kidneys are of no special importance in the detoxification of these drugs. Only a limited amount of pharmacologic investigation has been directed to this subject. Masson and Beland (2), working on rats, did not consider the kidney of great importance in the detoxification of either thiopental or hexobarbital. However, more recent work in our laboratory (3–5) as well as by Dorfman and Goldbaum (6) and by Kelly and Shideman (7), casts some doubt upon this as far as thiopental is concerned. A review of prior work on this subject indicates that one of the standard procedures used to elucidate the role of the kidney as a limiting factor for the duration of action of ultra-short acting barbiturates was to determine sleeping time with a standard dose before and after bilateral nephrectomy. The in-

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† Department of Anesthesia, University of Liverpool, England.
‡ Department of Pharmacology, Abbott Laboratories, North Chicago, Illinois.

jection of the barbiturate in such studies was usually made as soon as the animal had recovered from the effects of the operative procedure. Thus the effect which the removal of kidney tissue exerted directly upon the destruction of the barbiturate could be estimated but what influence the metabolic disturbance which followed the removal of the excretory function of the kidneys may have upon the action of the drugs in question could not be determined.

In a series of experimental studies we have investigated the effect of hexobarbital and thiopental in experimental animals immediately after the removal of the kidneys and at various intervals following this operation during the development of increasing azotemia. Corresponding clinical studies were undertaken in suitable patients who had either an endogenous azotemia or in whom the blood urea level was artificially raised.

PHARMACOLOGICAL INVESTIGATIONS

Results of the pharmacological investigations which in part have been reported at other occasions (3–5) can be summarized in the following manner.

Groups of rabbits and rats were given thiopental (pentothal® sodium) or hexobarbital (evipal sodium®) intravenously in doses that produced about the same duration of sleep. Several days later bilateral nephrectomy was performed in the same or comparable groups of animals, under light ether or spinal anesthesia; in other animals a sham operation was done. Injections of the barbiturates were given at various intervals up to twenty-four hours after the operative procedure. The effect of hexobarbital remained unchanged when the drug was injected three hours after the operation, and only a moderate prolongation was noted in rats but none in rabbits after twenty hours had elapsed. With thiopental, however, a marked and increasing prolongation of the effect was noted in rabbits and even more so in rats. This effect was slight and inconstant when the barbiturate was given within one hour after the operation, but amounted to several times the original sleeping time beginning six hours after nephrectomy, especially in rats. Ligation of the ureters instead of nephrectomy led to similar results, but the effects came on more gradually. No change was noted on sham-operated animals.

Experiments on a large number of rats proved that the prolongation of anesthesia increased in a straight line relationship with the time after nephrectomy and also with the resulting increase in urea. In fact, rats or rabbits that were given injections immediately after nephrectomy of an artificially prepared solution of urea, designed to raise the plasma level far above normal, reacted to it with a marked prolongation of the thiopental sleep, similar to the reaction of animals whose plasma urea was permitted to reach the same level by passage

of time. We were not able to produce this phenomenon by injection of such urea solutions in normal rabbits.

The course of the thiopental plasma level was followed in normal rabbits and a few days later in the same animals about twenty-four hours after bilateral nephrectomy. Statistically proven results indicate that there is no significant difference in the plasma levels before and after operation for the duration of the thiopental effect for

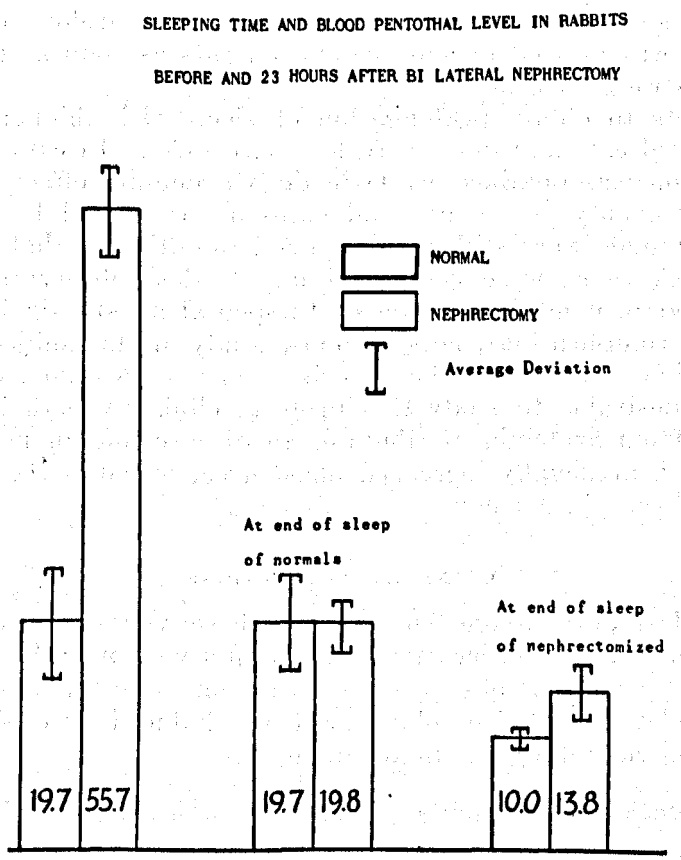

FIG. 1. All animals were given intravenous injections of thiopental, 25 mg. per kilogram. The figures inside of the first twin columns refer to sleeping time in minutes; inside the second and third twin columns to micrograms of thiopental per cubic centimeter of blood plasma.

normal animals. In other words, at the time when the normal rabbits awoke, the plasma level in the nephrectomized animals had fallen to the identical level, but the operated animals remained asleep and awoke much later. During this period of prolonged sleep, the plasma level of operated animals dropped at a significantly slower rate than in the normal rabbits which were already awake. The results of such an experiment conducted on the same 6 rabbits before and twenty-three

hours after bilateral nephrectomy are illustrated in figure 1. This indicates that at least two factors probably are responsible for the increased thiopental effect, namely, a greater sensitivity to a given barbiturate level and a slower metabolism of this drug. Careful checks of hemoglobin, hematocrit, hydrogen ion concentration of the blood, circulation, and so forth, showed that no marked changes had taken place within twenty-four hours after nephrectomy, during which period these experiments were carried out.

It was shown in separate studies (5) that a prolonged effect of thiopental was noticed in nephrectomized rats as soon as the threshhold doses were exceeded.

Attempts to obtain prolongation of sleep with thiopental in nephrectomized cats and dogs were less successful. In cats no certain prolongation was obtained while in dogs a definite effect was noted only after twenty-four hours had elapsed. It should be mentioned that the animals were still in fairly good condition at that time.

Although there were occasional unpublished observations of an unexplained prolonged duration of thiopental anesthesia in patients with renal complications, no systematic study of this subject came to our attention. In view of the experimental results reported above, it appeared desirable to study this problem clinically both in patients suffering from azotemia attributable to disease and in normal individuals with artificially increased blood urea, which is the main constituent of the plasma nonprotein nitrogen.

CLINICAL OBSERVATIONS

Clinical data available to support these views can be divided into two parts: (1) observations on patients with a pathological rise in blood urea and (2) observations on a small number of subjects in whom an elevated level of blood urea was induced by oral ingestion of urea and curtailment of fluid intake.

(1) *Observations on Patients with a Pathological Rise in Blood Urea*

In the anesthetic technique for prostatectomy described by Marcus and Gray (8) spinal anesthesia is induced with dibucaine (nupercaine®), blood pressure is supported with an intravenous epinephrine or norepinephrine drip, a light level of anesthesia is maintained by intermittent injection of 2.5 per cent thiopental and nasal oxygen is administered. It is not unusual to find a raised blood urea among subjects with long standing prostatic obstruction. Consequently, a sufficiently large number of persons whose thiopental requirements are observed with the above technique will form an ideal group of subjects in whom to observe the effects of a raised blood urea. Such observations were made on 46 subjects, 35 of whom had a preoperative blood urea of between 28 and 42 mg. per 100 cc. and in the remaining 11 it was over

50 mg. per 100 cc. Subjects with complications, other than a raised blood urea, that might alter the response to thiopental were excluded in the series. Such complications included severe anemia (Dundee, 9), hepatic dysfunction (Shideman *et al.*, 10; Dundee, 11), any excessive acute blood loss or prolonged period of hypotension. All subjects were premedicated with 10 mg. of morphine sulfate and 0.65 mg. of atropine sulfate subcutaneously one hour before operation and the

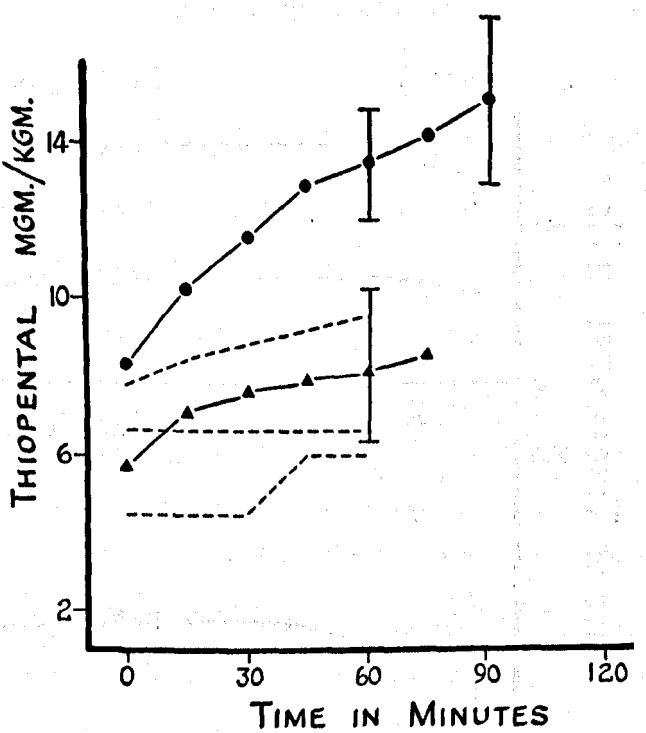

FIG. 2. Requirements of thiopental in patients undergoing prostatectomy.

●——● Average requirements of 35 patients with blood urea between 28 and 45 mg. per 100 cc.; average age 63 years.

▲——▲ Average requirements of 8 patients with blood urea of 51 to 80 mg. per 100 cc.; average age 66 years.

- - - - - - - - Individual requirements of 3 patients in the latter category in whom the operation was of too short duration to include in the average.

Vertical lines show three times standard error of mean.

amount of thiopental administered was noted at induction and at fifteen minute intervals thereafter.

Figure 2 illustrates the results obtained on the 35 subjects with "normal" blood urea and on 8 of the subjects with raised blood urea. Since the majority of the patients for prostatectomy fall within the former category it was possible to exclude all from this group for whom the operation lasted under ninety minutes and yet obtain a series large enough for statistical analysis. This was not possible for

patients whose blood urea was over 50 mg. per 100 cc., but an average was obtained from 8 persons for operations lasting seventy-five minutes and over. Figure 2 also shows individual requirements in 3 subjects whose operation was of too short duration to be included in the average.

Figure 2 reveals a marked diminution in thiopental requirements in subjects whose blood urea was over 50 mg. per 100 cc. compared with those whose range was within 28 to 42 mg. per 100 cc. The difference is too great to have arisen by chance.

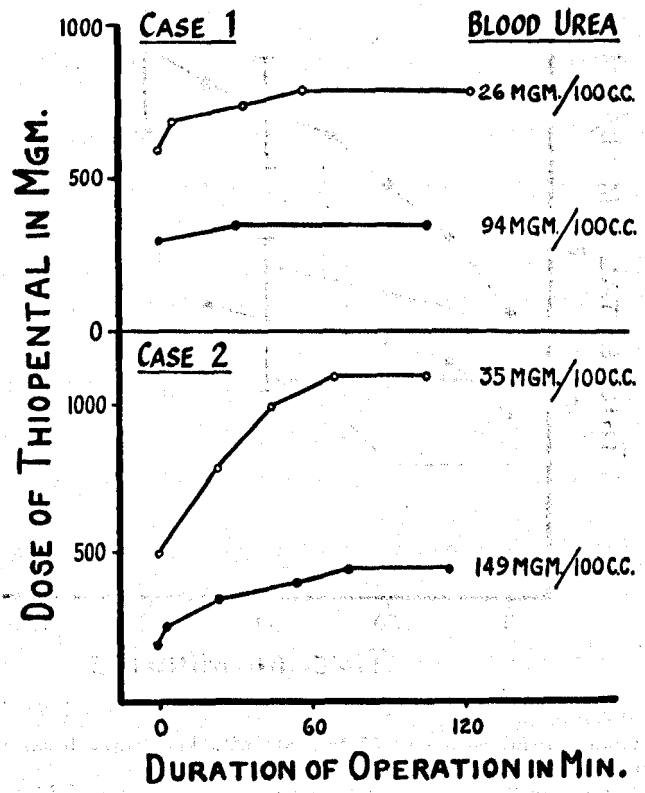

FIG. 3. Relation between thiopental requirements and blood urea level in 2 patients operated on at two different occasions. See text.

The following patients were subjected to thiopental anesthesia at varying intervals on two different occasions for similar operations—in each patient the blood urea was within normal limits at one time and on the other occasion there was a marked pathological rise. Requirements of thiopental were noted on each occasion.

Case 1. Two operations for transplantation of the ureters were performed on this subject. The interval between operations was three weeks. Anesthesia consisted of d-tubocurarine chloride-thiopental-nitrous oxide and oxygen at both operations. On the first occasion the blood urea was 26 mg. per 100 cc. and at

the second it was 94 mg. per 100 cc. Requirements of thiopental on each occasion are shown in figure 3, revealing a markedly increased sensitivity to the drug associated with the raised blood urea.

Case 2. Details are similar to those of case 1, except that at the first operation the blood urea was 149 mg. per 100 cc. and at the second it had fallen to 35 mg. per 100 cc. Requirements of thiopental are shown in figure 3, revealing a diminution in thiopental requirements associated with the raised blood urea.

Case 3. A man, aged 45 years, was admitted to the hospital with a history of passing blood clots through the urethra for nine months. Cystoscopy was performed on two occasions within one week. Each time the patient was extremely resistant to thiopental and required between 1 and 2 Gm. for the procedures lasting not longer than twenty minutes. On discharge from the hospital the blood urea was 34 mg. per 100 cc.

Three months later the patient was re-admitted to the hospital with clot retention. Only 90 ml. of urine had been passed during the preceding forty-nine hours. Blood urea was 175 mg. per 100 cc. Thiopental, 500 mg., produced satisfactory anesthesia for bouginage and cystoscopy lasting for more than one hour and the corneal reflex had not returned at the end of the operation.

Case 4. A man, aged 51 years, had a nephrolithotomy performed for removal of a large staghorn calculus. The preoperative blood urea was 37 mg. per 100 cc. Before a skin incision could be made a total of 1.0 Gm. of thiopental and 30 mg. of d-tubocurarine chloride was administered, and the operation was completed using nitrous oxide, cyclopropane and ether.

Following the operation the blood urea rose steadily and by the fifteenth day was 230 mg. per 100 cc., when a ureterolithotomy was carried out to re-establish flow of urine. For the whole procedure, which lasted thirty-five minutes, a total dose of 500 mg. of thiopental and 20 mg. of d-tubocurarine chloride, combined with nitrous oxide-oxygen, was sufficient.

Case 5. A urethral stricture was dilated in a 26 year old man; 1 Gm. of thiopental provided anesthesia to which the patient's response was described as "lively." This patient was subsequently admitted to hospital with a diagnosis of retention of urine owing to infection. Ten days after the initial procedure the blood urea was 128 mg. per 100 cc. Laparotomy was performed and a small perforation was found at the base of the bladder. Thiopental (400 mg.) d-tubocurarine chloride (25 mg.) and nitrous oxide were given during the operation which lasted eighty-five minutes, and the patient did not regain consciousness for a considerable time after its completion.

Two weeks later the blood urea had returned to normal and 500 mg. of thiopental was administered for further dilatation of the urethra. This procedure lasted fifteen minutes, at the end of which time the patient was moving vigorously.

These case reports further substantiate the view that tolerance to thiopental is greatly decreased in the presence of a pathological rise in blood urea. In all of these patients the elevated blood urea was only one manifestation of renal insufficiency, and many of them had biochemical disturbances of more serious import. It might be thought that these, and not the raised blood urea, could have been responsible for the sensitivity to thiopental which they exhibited. That an eleva-

tion in blood urea is at least in part responsible is shown by the following experiments.

(2) *Observations on Subjects in Whom a Raised Blood Urea Was Induced by Ingestion of Urea and Deprivation of Fluids*

Eight healthy volunteer subjects who were to undergo ligation of bilateral varicose veins were deprived of fluid for twenty-four hours

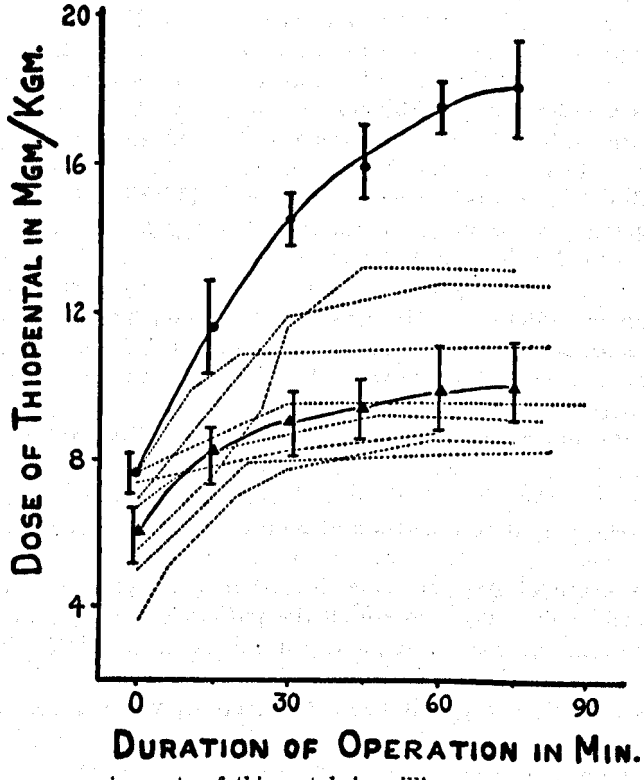

FIG. 4. Average requirements of thiopental, in milligrams per kilogram of body weight, in two series of patients undergoing ligation of bilateral varicose veins under thiopental-nitrous oxide-oxygen anesthesia.
●——● Average of 48 normal subjects (blood urea 21–30 mg. per 100 cc.).
▲——▲ Average of 8 subjects who received 15 Gm. of urea before operation (blood urea 42–62 mg. per 100 cc.).
..... Individual requirements of subjects to whom urea was administered.
Vertical lines show two times standard error of mean.

before operation. Urea, 15 Gm. dissolved in 75 to 100 cc. of water, was given orally between 110 and forty minutes before operation. The fluid restriction was necessary in order to prevent too rapid clearance of urea from the blood stream. Blood urea was estimated before the solution of urea was given and immediately before induction of anesthesia; it ranged from 21 to 30 mg. per 100 cc. before the urea administration of urea and rose to 42 to 66 mg. per 100 cc. after the medication,

just before anesthesia. All subjects received a hypodermic injection of 10 mg. of morphine sulfate and 0.65 mg. of atropine sulfate about one hour before induction of anesthesia. Intermittent injection of thiopental supplemented by 6 liters of nitrous oxide and 2 liters of oxygen was the technique used for all cases. As a control, observations were made on 48 normal subjects undergoing the same operation, subjected to the same preoperative preparation and the same anesthetic technique employed by the same anesthetist. Only patients having operations of seventy-five minutes' duration and over were included in the control series.

The results of this experiment are summarized in figure 4, giving the average requirements of thiopental in fifteen minute intervals for the control experiment as well as after the administration of urea. The illustration also shows the individual requirements for this barbiturate of the 8 patients under the influence of urea.

TABLE 1

PARTICULARS OF SEVEN ADMINISTRATIONS OF THIOPENTAL TO CASE 6, THREE WITH AND FOUR WITHOUT PREVIOUS ADMINISTRATION OF UREA. BLOOD UREA WAS ESTIMATED IMMEDIATELY BEFORE INDUCTION OF ANESTHESIA. SEE TEXT

No.	Thiopental (mg.)	Duration of Anesthesia (min.)	Dose of Urea Administered (gm.)	Blood Urea
1	400	1.5	—	25
2	900	7.0	—	
3	400	9.0	20	59
4	450	15.0	20	90
5	550	2.0	—	23
6	650	5.0	—	
7	350	4.0	22.5	60

The difference between the two series is very similar to the results shown on figure 2 and strongly suggests that an elevation in blood urea, even without the coincidental biochemical upset of uremia, is capable of markedly reducing the tolerance to thiopental in man.

The following case further substantiates this view.

Case 6. A man, age 49, was admitted to hospital at weekly intervals for dilatation of urethral stricture. On two occasions it proved difficult to obtain satisfactory anesthesia for the procedure with thiopental-nitrous oxide-oxygen owing to the patient's resistance to the barbiturate. He was then requested to take no fluid for twenty-four hours before coming to hospital and on admission 20 Gm. of urea was given orally. This procedure, carried out on two occasions, markedly increased the duration of the thiopental effect. Lest this be the result of the increasing ease of dilatation and hence reduction in the stimulus, the urea was omitted on two subsequent occasions and the original resistance to the barbiturate again became manifest. Details of anesthesia, and duration of thiopental effect on seven occasions in this patient, three with and four without previous administration of urea, are shown in table 1; events are recorded in

chronological order. Duration of anesthesia was reckoned from the end of the injection of thiopental to the first movement by the patient. At the fourth and seventh administrations several estimations of blood urea were carried out and figure 5 shows the degree and duration of elevation of blood urea that occurred.

In this last case in particular, and to a lesser extent in most of the previous ones, an undue degree of postoperative somnolence was observed. This was more apparent in those who received urea by mouth than in patients with a pathological rise in blood urea. In all cases (unless recorded to the contrary) consciousness was regained within thirty minutes of completion of the operation, and questions could

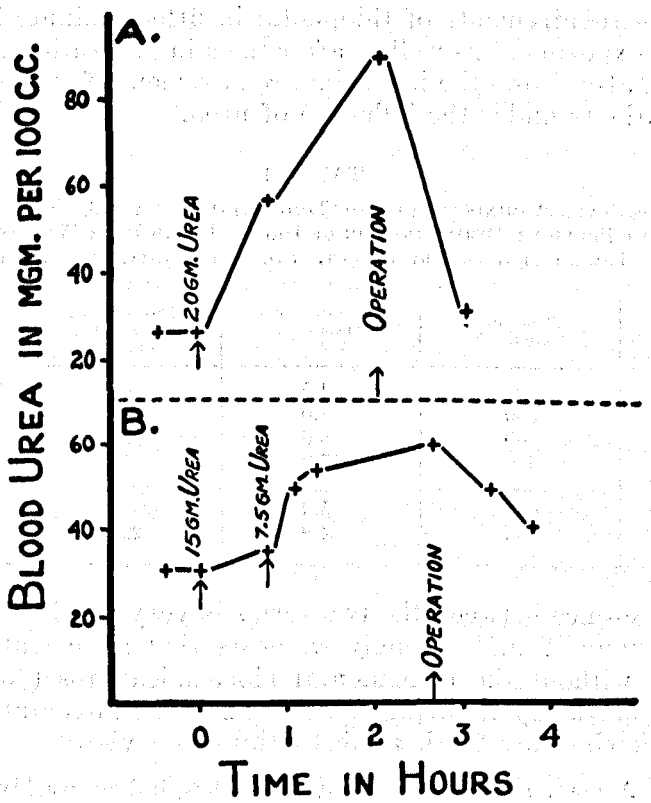

FIG. 5. Changes in blood urea following oral ingestion of 20 and 22.5 Gm. of urea and deprivation of fluids for twenty-four hours in Case 6.

be answered with a reasonable degree of accuracy. Although a tendency to fall asleep again when not being stimulated is common after the use of thiopental, an impression was formed by the nursing staff that in these patients this was more prone to happen than usual. Postoperative amnesia was also greatly increased. Only 2 of the 8 subjects who had urea by mouth remembered anything until the morning after operation, or an incidence of amnesia of 75 per cent. In

comparing this with the control series of 20 patients, amnesia was present in only 8 (40 per cent).

DISCUSSION

The above cited experimental and clinical evidence focuses the attention upon the role of kidney function as related to the duration of action of thiopental anesthesia. Although the results of animal experimentation and clinical observations differ in some aspects they are in essential agreement in the most important points. Significant increase in sensitivity to a standard dose of thiopental, evidenced by marked increase in sleeping time or, vice versa, the need for smaller doses for a comparable duration of anesthesia, could be demonstrated in animals in experimental azotemia and correspondingly in human beings having an increased blood urea level owing to obstruction of the urinary passages. Since, in animals, such an effect is only moderate and inconstant when this barbiturate is injected immediately after bilateral nephrectomy, the role of the kidney as a directly detoxifying organ appears to be of only moderate importance. Consequently, the impairment or loss of normal kidney function must be held largely responsible for the rapidly increasing sensitivity to the action of thiopental.

Of the experimental animals studied the rat seems to be most likely to show prolongation of thiopental action after nephrectomy. This applies both to the speed with which increased sensitivity developed following nephrectomy and to the degree of prolongation which may reach more than ten times the normal sleeping time. The mouse and the rabbit also demonstrate this phenomenon while the dog and cat react less in this respect. As we have reported earlier, we could produce a marked prolongation of sleeping time with thiopental in rabbits immediately after nephrectomy when the blood urea of the animals was acutely raised by intravenous injection of an artificial solution of urea. This could not be done in normal rabbits. The clinical experiments reported here, however, show that in the healthy human being the temporary increase of the blood urea level following oral administration of urea produces an effect upon thiopental anesthesia similar to that of endogenous azotemia. Since animal experimentation proved that similar, though quantitatively less pronounced, effects could be obtained by the injection of equally hyperosmotic amounts of sodium chloride or sucrose solution instead of the urea solution in freshly nephrectomized animals, it appears that physical-chemical changes which accompany artificial as well as endogenous azotemia play an important part in this phenomenon. Here one has to think of the changes of osmotic pressure in the body fluids and especially with regard to urea of its effect upon cell permeability. Other factors which may contribute to the prolonged action of thiopental in azotemia

are still being investigated. The work on animals cited above gives evidence of a greater sensitivity of the azotemic animal toward thiopental; this is in agreement with the clinical findings. The decreased speed in the fall of the thiopental level in nephrectomized animals after equilibrium between blood and tissue has once been reached indicates a somewhat impaired rate of detoxification, probably partially attributable to metabolic disturbances resulting from the azotemia and partially to the loss of kidney tissue, which has some ability to destroy thiopental.

Newer experimental data reveal (12, 13) that the albumin fraction of the plasma proteins decreases after nephrectomy. Since thiopental is to a considerable extent bound on albumin the decrease of this protein fraction leaves a larger part of the injected drug unbound in the plasma. Only this free barbiturate is able to penetrate the blood-brain barrier; consequently, an azotemic animal has more active thiopental in his blood stream than a normal one given the same dose per kilogram. The fact that hexobarbital is much less bound to plasma proteins and also much less affected by experimental azotemia is in agreement with this viewpoint. It is not yet possible to quantitate the role that these and other factors may play in the over-all effect.

The clinical data show consistently a significant reduction of the dose of thiopental necessary to maintain anesthesia in patients with urinary obstruction as well as in normal individuals after administration of urea. For the first group, the average dose necessary to induce sleep was 73 per cent of that used in patients undergoing the same type of surgical procedure but having a normal blood urea level. Determinations of the additional amount needed to maintain anesthesia in the pathological group calculated in fifteen minute intervals showed these to be 60 to 73 per cent of the normal requirements. This is in agreement with the experiments in which thiopental requirements were determined in systemically healthy persons with and without oral administration of urea. Here, the urea treated group required 90 per cent as much of the drug for induction as did normal persons, probably not a significant difference, but only 55 to 64 per cent, very significantly less than the untreated ones, for the maintenance of an equally long sleep. The case reports further illustrate the remarkable correlation between blood urea level and thiopental requirements. This is particularly evident in case 6. The occurrence of long postoperative drowsiness in the above group of patients has been commented on occasionally by other observers.

Although it is obvious that much remains to be done in the elucidation of the pathophysiological and pharmacological mechanisms of these observations, certain clinical conclusions may be drawn. Additional observations of this type appear highly desirable and such studies should be extended to the action of the other anesthetic agents under

similar conditions. The present findings suggest that the anesthetist should expect a greater sensitivity of patients in azotemia to thiopental. The drug appears to be a safe and desirable anesthetic when its use is indicated and if properly administered, and no increased incidence of untoward reactions was noted during the course of the anesthesia.

SUMMARY

Although for some time the kidneys generally were not considered involved in the degradation of short acting barbiturates, recent work reveals that they possess some ability to destroy thiopental. New observations, however, appear to be of greater importance; these observations indicate that experimental animals, especially rats and rabbits, react with increasingly prolonged sleep to injections of thiopental as the time interval after nephrectomy or ligation of the ureters and the concomitant azotemia increases. Hexobarbital shows this change to a markedly lesser degree. Under appropriate conditions an acutely increased sensitivity to thiopental as measured by prolongation of sleeping time can be obtained by the injection of an artificial urea solution, leading to sudden azotemia.

Clinical studies are in essential agreement with these experimental findings. Patients undergoing prostatectomy and suffering from azotemia attributable to urinary obstruction required significantly less thiopental for induction and maintenance of anesthesia than a comparable group with normal blood urea level. Several patients subjected to thiopental anesthesia at different times with and without increased level of blood urea needed less of the drug during the azotemic stage. In normal human beings in whom the blood urea level was artificially raised by fluid restriction and oral administration of urea, anesthesia could be maintained with considerably smaller doses of thiopental than in a control group. The factors involved in these phenomena and their clinical significance are discussed.

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BARBITURATE NARCOSIS IN URAEMIA

by

JOHN W. DUNDEE and DAVID ANNIS

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BARBITURATE NARCOSIS IN URAEMIA

BY

JOHN W. DUNDEE
Department of Anaesthesia

AND

DAVID ANNIS
Department of Surgery
University of Liverpool

EARLY reports of the use of thiopentone sodium stressed the inadvisability of using the drug in the presence of liver and kidney dysfunction (Goodman and Gilman, 1940; Greene, 1942). This was based on the belief that thiopentone was detoxicated by the liver, and excreted by the kidneys. The role of the liver in the breakdown has been firmly established (Shideman, Kelly and Adams, 1947; Shideman, 1949; Walker and Wyn Parry, 1949; Dundee, 1952) but the breakdown products have little if any narcotic activity (Brodie, Mark, Papper, Lief, Bernstein and Rovenstine, 1950) and only after massive doses of thiopentone does any of the unchanged drug appear in the urine (Mark, Papper, Brodie and Rovenstine, 1949).

Renal tissue is capable of some inactivation of thiopentone (Dorfman and Goldbaum, 1947; Kelly and Shideman, 1949). This must be of little clinical importance since unilateral nephrectomy does not prolong thiopentone narcosis (Schiefly, 1946) and its duration of action is little or unaffected immediately following the removal of both kidneys (Richards, Kueter and Taylor, 1950). However, it has been observed that in uraemic patients anaesthesia could be induced and maintained with very small doses of the barbiturate (Dundee and Richards, 1954).

This paper is a study of the duration of action of medium-acting and short-acting barbiturates in the uraemic dog. A method of establishing a gradually increasing state of uraemia was required for these experiments. It was known from previous work that in dogs the implantation of both ureters into the terminal ileum resulted in such a state. Mann and Bollman (1927) showed that absorption of urea occurred when both ureters were implanted into the duodenum, and that the degree of reabsorption diminished the lower in the intestine the transplantation was performed. Boyce (1951) has shown that the implantation of both ureters into the caecum results in a gradual increase in the blood non-protein-nitrogen (n.p.n.) until the animal dies on the fifteenth to twenty-fourth day. At the time of death the average level of n.p.n. was 106 mg per cent.

PREPARATION

Under general anaesthesia the bladder was divided from the urethra and the divided ends were closed. The blood supply to the bladder and the ureters was preserved intact. An incision about three-

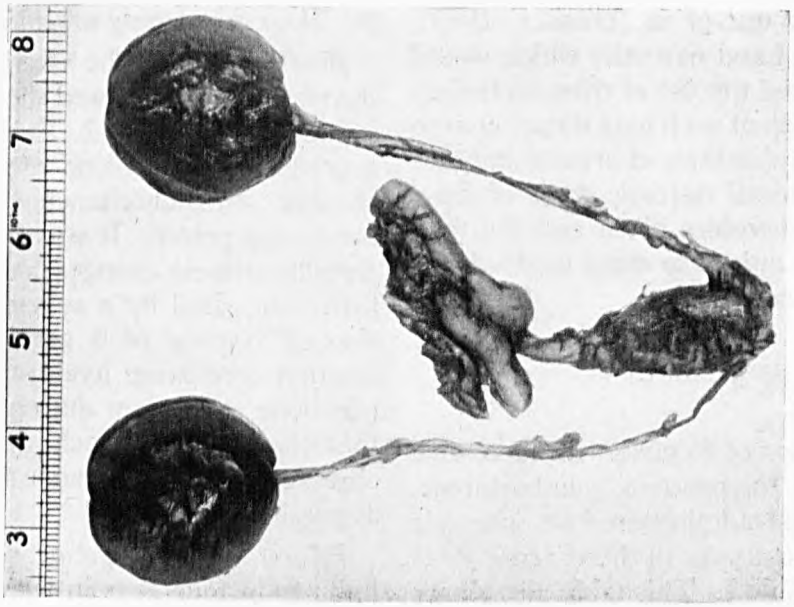

FIG. 1
Post-mortem specimen showing anatomical arrangement of operation described in text.

quarters of an inch in length was made in the fundus of the bladder. The appendix, which is capacious in the dog, was brought out and its tip excised. The open end of the appendix was anastomosed to the hole in the fundus of the bladder; thus all urine went from the bladder, through the anastomosis into the appendix, and thence into the caecum to pass around the large intestine before being discharged at the anus. A post-mortem specimen demonstrating the anatomical arrangement is shown in figure 1.

To establish control data, two mock operations were performed under similar circumstances, in which no anastomosis was made.

METHOD OF OBSERVATION

The duration of action of thiopentone on successive days after operation was studied in detail, and in four animals this was the sole drug used. Other barbiturates used in anaesthetic practice—thialbarbitone (Kemithal), hexobarbitone (Evipan) and thiamylal (Surital)—were studied in less detail. A few observations were made with the basal narcotics, pentobarbitone, quinalbarbitone, and amylobarbitone. The effects of successive injections of thiopentone, thialbarbitone, and thiamylal on non-operated animals were studied as controls.

All drugs were given intravenously by the closed vein technique. Doses of thiopentone ranged from 16 to 19.2 mg/kg. Equipotent amounts of the other members of the same series were used. The average of the times from the end of the injection to (*a*) appearance of corneal reflex, (*b*), spontaneous blinking, (*c*) head raising, (*d*) sitting up, and (*e*) standing unaided, was taken as the duration of narcosis. The reliability of this as a means of measuring the duration of narcosis has been described

elsewhere by one of us (Dundee, 1953). Doses of the basal narcotics which would have permitted the use of these endpoints produced sleep of such long duration as to make these indications of arousal impracticable. Minimal narcotic doses of these drugs were therefore given and the time taken for the animal to stand unaided was used as the endpoint.

RESULTS

(a) *Controls.*

The duration of narcosis with successive injections of thiopentone, thialbarbitone, and thiamylal administered at intervals similar to those used in the uraemic dogs is given in table I. This table also shows the results obtained in the sham operated dogs. It will be seen that there is no cumulative action or tolerance to the barbiturates at the time intervals adopted for observations and that laparotomy alone has no significant effect either on the duration of narcosis or on blood urea.

(b) *Dogs developing uraemia.*

Biochemistry. The changes in blood chemistry which followed the operation are summarized in figure 2. Each dog showed a gradual rise in blood urea and serum chloride with simultaneous fall in CO_2 combining power. It was found that the severity of these changes could be temporarily mitigated by a subcutaneous infusion of 200 ml of 5 per cent dextrose solution containing hyaluronidase. This was done at random during the series so that the effect of each drug could be observed at as wide a range of blood ureas as possible.

Effects on duration of narcosis. The findings in four dogs in which the course of thiopentone anaesthesia had been followed before and after operation until the death of the animals are shown in table II and summarized in figure 3. This figure shows a gradual increase in the duration of narcosis accompanying the increase in blood urea. Figure 4 shows the direct

TABLE I

Blood urea and duration of narcosis in non-operated and sham operated control animals. Numbers in brackets (operated animals) indicate the number of preoperation observations of which the control reading is the average.

	No operation						Laparotomy only			
Dog	209		239		262		163		175	
Barbiturate ...	Thiopentone		Thialbarbitone		Thiamylal		Thiopentone		Thiopentone	
mg/kg	17.3		30		16		13.8		15.8	
Days	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)
0	23	4.9	28	5.4	18	4.0	26 (7)	4.4	21 (4)	6.8
2nd	20	4.1	31	6.4	18	4.3	42	8.3	26	5.7
4th	20	3.5	24	4.8	21	4.7	30	4.3	22	5.8
7th	35	4.4	32	5.8	17	3.2	40	5.0	20	5.2
9th	26	3.9			26	5.2	37	3.1		
11th	20	4.9	28	4.8	18	4.8	40	4.2	24	4.1
14th	20	4.9	33	5.5	22	4.6	25	4.1	24	4.4
18th	20	4.8				4.3	20	3.4		
21st					21	4.0		4.9		

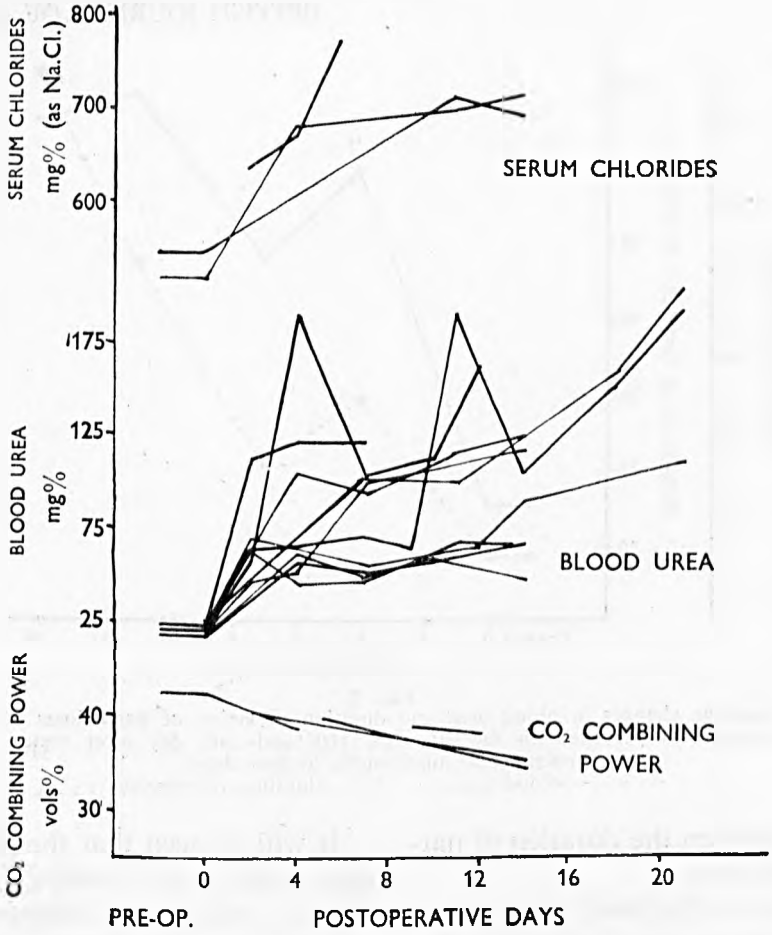

FIG. 2

Composite diagram illustrating changes in blood urea, serum chlorides and CO_2 combining power recorded in twelve dogs after vesico-appendicular anastomosis.

TABLE II

Summary of changes in blood urea and duration of thiopentone narcosis recorded in four dogs, before and at varying intervals following vesico-appendicular anastomosis.

Dog	162		176		208		222		Average	
Dose of Thiopentone in mg	250		150		150		180		182.5	
mg/kg	16.0		15.0		19.2		16.5		16.7	
	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)	Blood urea (mg%)	Duration of narcosis (min)
Control	23 2*	10.9	22 3*	7.3	22 10*	10.9	18 3*	7.2	21	9.0
Postop. days										
2nd	66	21.5	74	10.5						
4th	180	39.4	77	15.9	108	45.2	66	15.6	108	29.0
	107	18.1	90	20.5	88	35.7	56	12.0	85	21.6
9th			84	30.1						
11th	126	61.0	184	28.8	132	70.2	58	31.7	127	47.9
14th	177	133.5	107	38.0	150	84.5	43	29.6	119	71.6
18th			152	47.5						
21st			186	48.1						

* The number of control operations.

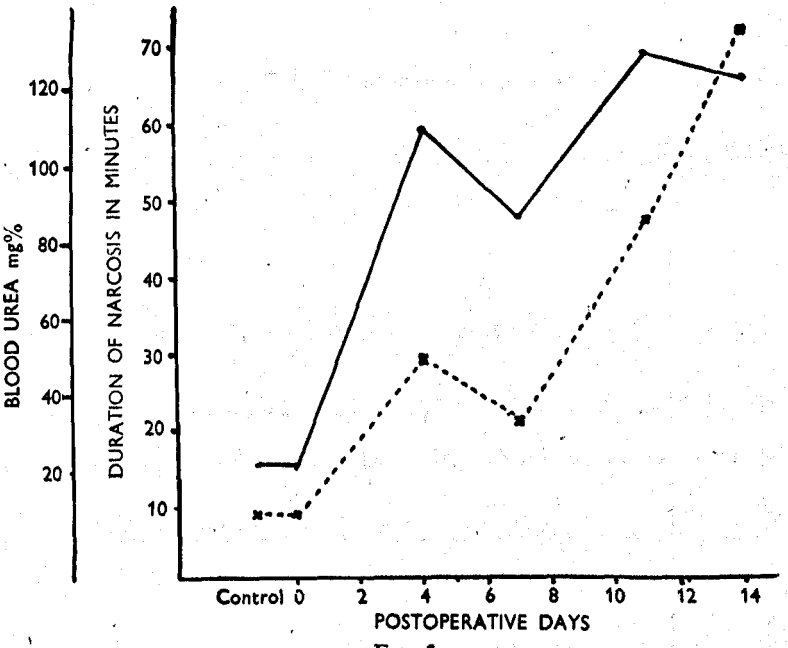

FIG. 3
Average changes in blood urea and duration of action of fixed doses of thiopentone recorded on the 4th, 7th, 11th and 14th day after vesico-appendicular anastomosis in four dogs
——— blood urea. – – – – duration of narcosis.

relationship between the duration of narcosis and blood urea.

Returning to the method of measuring narcosis, the average time taken for each of the signs to appear after injection of the thiopentone is shown in figure 5. The return of the corneal reflex was taken to indicate the end of surgical anaesthesia, while the others were indicative of lessening depths of narcosis. It will be seen that while the duration of surgical anaesthesia is only slightly prolonged the duration of sleep is very markedly prolonged.

Table III summarizes the effect of the operation on the blood urea level, and on the duration of action of the other barbiturates studied. In figure 6 the duration of narcosis is plotted against the postoperative days. Figure 7 shows its relationship to blood urea.

It will be seen that the other barbiturates which were studied behaved in a manner similar to thiopentone. Less reliance can be placed on the results obtained with hexobarbitone as the duration of narcosis produced by the same dose of this drug given under identical conditions varied widely. This unreliability of hexobarbitone is well known and is one of the factors which has led to its almost complete abandonment in modern anaesthesia.

DISCUSSION

Our experimental technique produced a progressively increasing state of urea retention in the animal, but it also produced other biochemical effects. There was a retention of chloride, and a state of acidosis developed in those dogs in which such evidence was sought. Boyce (1951)

TABLE III

Changes recorded in blood urea and duration of narcosis with varying doses of the barbiturates mentioned following vesico-appendicular anastomosis in the dog.

			Control			Postoperative readings		
Barbiturate	mg/kg	Dog	No. of observations	Average blood urea (mg%)	Average duration of narcosis (min)	Post-op. day	Blood urea (mg%)	Average duration of narcosis (min)
Thialbarbitone	31	221	3	28	5.9	14th	123	10.7
	33	223	3	18	7.0	2nd	34	14.8
						11th	102	54.0
	33	228	2	18	8.6	4th	69	21.5
Thiamylal	15	215	3	25	4.1	21st	190	25.4
	16	221	3	25	11.5	4th	44	26.7
	23	223	4	19	8.7	12th	96	26.1
						14th	144	29.1
	23	228	4	19	4.7	2nd	40	13.1
Hexobarbitone	41	221	3	25	18.2	18th	146	31.6
	34	223	4	19	4.5	4th	64	11.0
						7th	85	13.5
						21st	132	15.0
Pentobarbitone	16.4	206	3	20	0.3	2nd	60	15.3
	15	210	2	20	1.2	2nd	45	19.7
	16.4	215	3	19	1.8	4th	80	24.7
Quinalbarbitone	19	228	2	20	13.3	7th	86	24.8
	16.4	210	2	20	1.2	7th	48	14.8
						11th	82	21.0
Amylobarbitone	17	206	2	20	6.8	7th	82	15.3
						14th	88	17.2

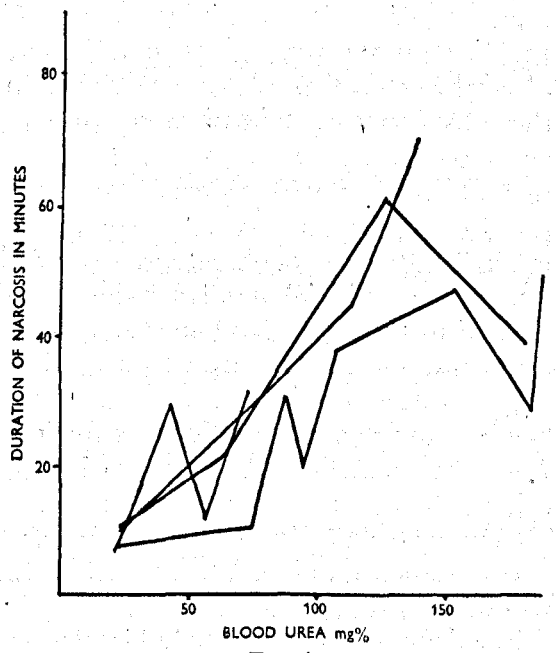

FIG. 4

Relationship between blood urea and duration of thiopentone narcosis in the animals described in the text

noticed a similar development of hyperchloraemic acidosis in his animals.

It seems likely that the biochemical derangements other than the urea retention were responsible for the clinical deterioration and death, because a high level of urea in the blood is not in itself fatal. This is also true in most of the clinical conditions in man which are labelled "uraemia", where nitrogen retention is only one of a number of biochemical derangements.

The results obtained in this investigation show that, in a condition bearing close similarity to uraemia in humans, there is an increased duration of narcosis with short-acting and medium-acting barbiturates in the dog. Furthermore, it would appear that the more severe the uraemia (as judged by the blood urea level), the greater is the increase in the duration of

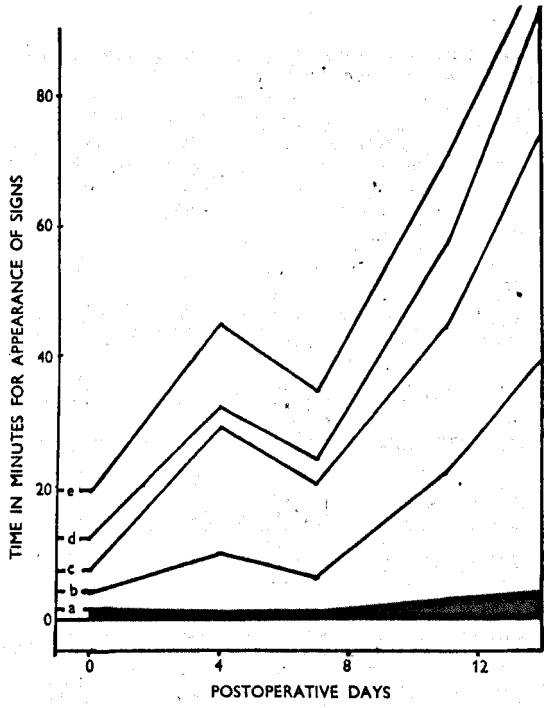

FIG. 5

Average time taken for return of various signs used to determine the duration of thiopentone narcosis in the dog after vesico-appendicular anastomosis.
a. return of corneal reflex. c. head raising.
b. spontaneous blinking. d. sitting up.
e. standing unaided.
The shaded area represents the duration of surgical anaesthesia.

narcosis. This agrees with the clinical observations of Dundee and Richards (1954), who demonstrated extreme sensitivity to thiopentone in uraemic patients. It also substantiates their statement that in humans the total duration of narcosis in the presence of a raised blood urea is increased out of proportion to the actual prolongation of the state of surgical anaesthesia. This correlation of findings is to be expected since, apart from the time taken to reach maximum concentration in body fat, the fate of thiopentone, is similar in man and the dog (Shideman, Gould, Winters, Peterson and Wilner, 1953).

The close relationship between the duration of the narcosis and blood urea was further demonstrated by the following observation.

Dog 267. After operation the blood urea rose as in the other animals, and this was accompanied by an increase in the duration of narcosis with thialbarbitone and thiamylal. On the 14th postoperative day it was noticed that the animal was passing urine per urethra. The blood urea gradually fell, and this was accompanied by a reduction in the duration of narcosis with the two drugs studied. By the 21st day the situation had almost returned to normal (fig. 8).

A urethrogram and systogram taken immediately after the animal was killed demonstrated that the passage for the flow of urine had become re-established (fig. 9). The opaque oil can be seen filling the bladder and overflowing into the caecum and colon.

It is interesting to compare these findings with those of Richards and his coworkers (Richards, Kueter and Taylor, 1950; Richards, Taylor, Davin and Isoshima, 1952; Taylor, Richards and Davin, 1953; Richards, Taylor and Kueter, 1953). They found in animals that *immediately* after bilateral nephrectomy performed under local or light ether anaesthesia, there was no change in the duration of action of thiopentone. If the barbiturate were given 6–24 hours after the operation, there was a rise in the blood non-protein-nitrogen (n.p.n.) accompanied by an increase in the duration of narcosis with thiopentone. This reaction to thiopentone could be produced immediately after nephrectomy by infusion of an artificial n.p.n solution, calculated to raise the blood level to several times the normal. There was a marked species difference in this response, rats being most, and dogs least sensitive. They did not find that hexobarbitone behaved in the same way as thiopentone. This may be explained by the great variation in response to hexobarbitone that we found in the dog.

Blood analysis showed the fall in plasma barbiturate to be the same during the "normal" sleep period in the control and nephrectomized animals. Thereafter,

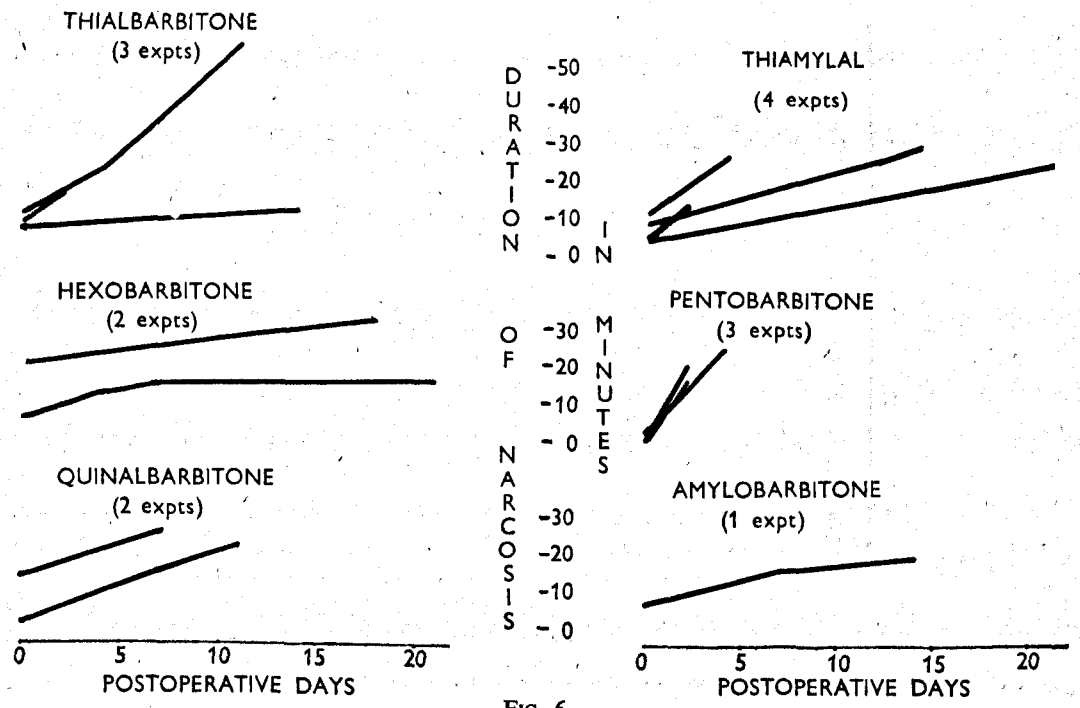

FIG. 6

Effect of vesico-appendicular anastomosis on the duration of narcosis following injection of various barbiturates, doses, etc., of which are given in Table III.

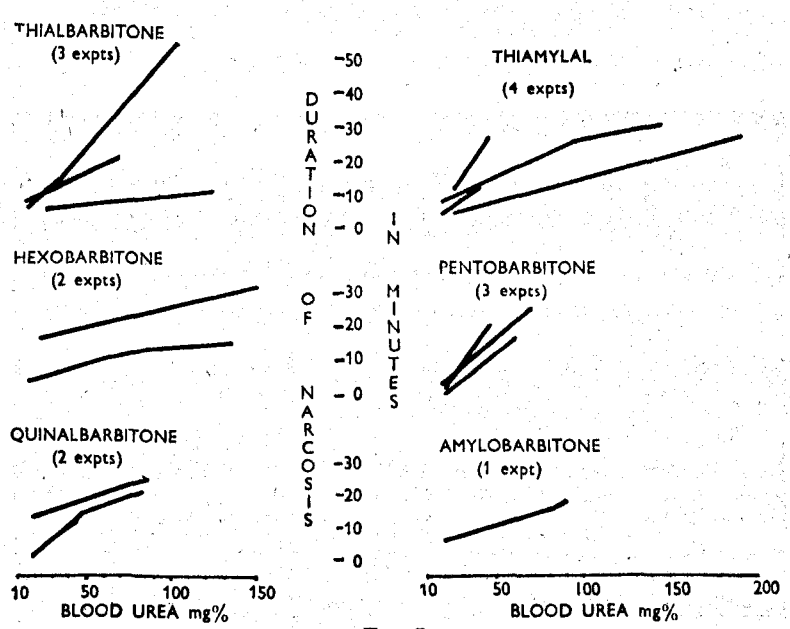

FIG. 7

Relationship of blood urea to duration of action of various barbiturates.

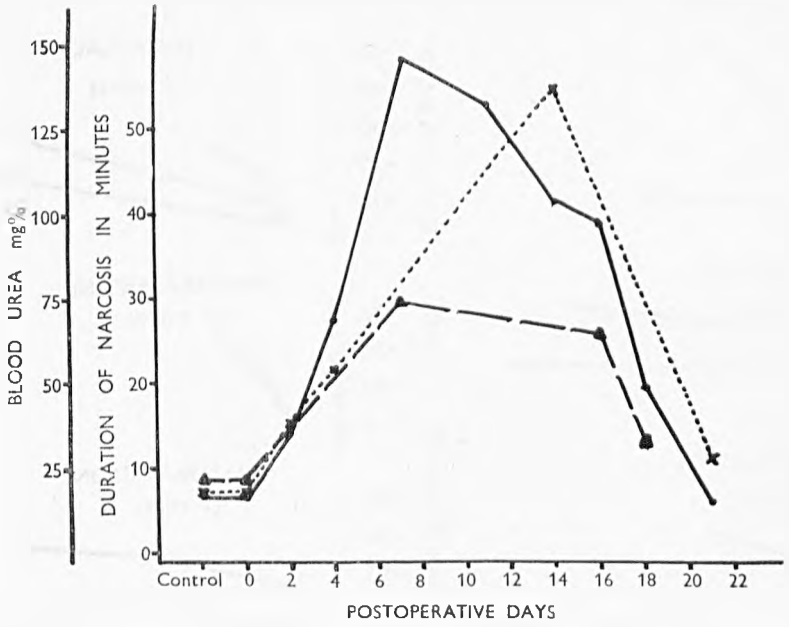

FIG. 8
Findings in dog 267 after vesico-appendicular anastomosis.

——— blood urea.
– – – – duration of action of thialbarbitone 40 mg/kg.
— — — duration of action of thiamylal 17 mg/kg.

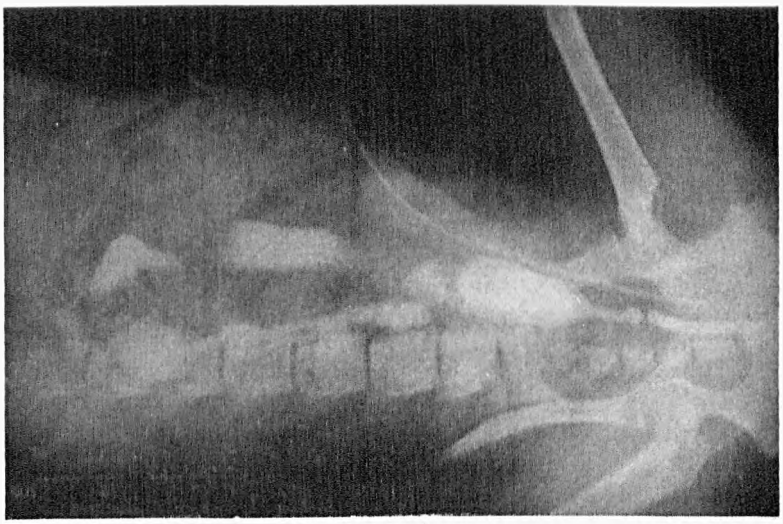

FIG. 9
Urethrogram of dog 267, taken on 21st day after operation

there was a slower decline in the operated animals and when these finally regained consciousness the blood thiopentone level had fallen significantly below the one at which these animals wakened during the control sleep. It appeared that not only was the postnephrectomy state associated with a slower degradation of thiopentone but also with a greater sensitivity to the drug.

Richards, Bertcher and Taylor (1952) have shown a similarity between the effect of urea on barbiturate anaesthesia and the potentiating action of glucose and its metabolic products which has been demonstrated by Lamson and his colleagues (Lamson, Greig and Robbins, 1949; Lamson, Greig and Hobdy, 1951a, b). No satisfactory explanation has been offered for this phenomenon but Richards, Bertcher and Taylor have suggested that a change in the permeability of the blood-brain barrier may be the cause of the increased sensitivity to barbiturates.

CONCLUSIONS

In the dog there is a prolongation of duration of narcosis with thiopentone, thialbarbitone, thiamylal barbitone, hexobarbitone, pentobarbitone, amylbarbitone, and quinalbarbitone in a condition closely resembling uraemia in man.

SUMMARY

(1) A method for simulating the clinical picture of uraemia in the dog is described.

(2) The biochemical changes found are discussed.

(3) Narcosis with short-acting and three medium-acting barbiturates is prolonged by uraemia in the dog.

(4) There is a relationship between the degree of uraemia and the prolongation of narcosis.

(5) The application of this finding to man is discussed and suggestions are made as to possible causes of the potentiation of the barbiturates.

ACKNOWLEDGMENTS

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Potentiation by Other Drugs.

(a) Phenothiazine Derivatives.

"THE EFFECT OF PHENOTHIAZINE DERIVATIVES ON THIOBARBITURATE NARCOSIS"

This paper, written jointly with Dr. W. E. B. Scott, has been submitted for publication to the Journal of Pharmacology and Experimental Therapeutics.

THE EFFECT OF PHENOTHIAZINE DERIVATES ON THIOBARBITURATE NARCOSIS

by

John W. Dundee

and

W. E. B. Scott

Department of Anaesthesia,

University of Liverpool.

In the first publication on the pharmacology of chlorpromazine, Courvoisier, Fournel, Ducrot, Kolsky and Koetschet (1953) reported that the drug prolonged and intensified the hypnotic action of hexobarbital (Evipal) and butobarbital in mice, guinea-pigs and dogs. The analgesic action of morphia and peperidine was also potentiated. Promethazine (Phenergen) was shown to possess similar properties, but to a lesser degree.

Although chlorpromazine and promethazine have been used extensively in the technique of "artificial hibernation", introduced by the French workers, Laborit and Huguenard (1951), they are usually combined with a variety of other drugs in the so-called "lytic cocktail" and there is little data of their effects on the action and duration of the commonly used barbiturates and thiobarbiturates. Burn (1954) found that chlorpromazine prolonged the sleep produced by pentobarbital in the cat, and was three times more effective in this respect than promethazine. Using the electroencephalograph as a means of defining the depth of anaesthesia in rabbits, Sadove et al. (1956) found that chlorpromazine potentiated the action of thiopental and thiamylal, but had less effect on that produced by thialbarbitone or Rapidal. Dundee (1956) has shown that the action of chlorpromazine in prolonging thiopental anaesthesia in the dog and rat can be detected for 24 hours after its intramuscular injection.

The clinical reports of its action in reducing the induction dose or prolonging the action of the intravenous barbiturates and thiobarbiturates are somewhat contradictory. Oljelund (1955) found that 50 mg chlorpromazine intramuscularly, together with half the routine dose of morphine, had little effect on the average induction dose of hexobarbital when this is compared with subjects who received the full routine dose of morphine alone. However, the increments of hexobarbital required to maintain anaesthesia for periods up to three hours were markedly reduced in the persons who received chlorpromazine. Dripps et al. (1955) reported that the addition of chlorpromazine to pentobarbital or morphine as pre-operative medication reduced the dose of thiopental required for two types of operations from an average of 580 mg (150-1500 mg) to 240 mg (0 - 1175 mg). They suggested that this was due to the effectiveness of chlorpromazine in adding to the potency of the pre-operative medication and the nitrous oxide used. Five and a half hours unconsciousness followed 600 mg thiopental in a patient who had been receiving 75 mg chlorpromazine daily for fourteen months, (Scanlon, 1955), but this subject also received gallamine triethiodide (Flaxedil), nitrous oxide, oxygen and an unstated quantity of ether. In contrast to these findings, Dobkin et al (1955) reported a 20% decrease in thiopental requirements for thoracic surgery in patients who received chlorpromazine as compared with similar cases who received a barbiturate and narcotic before induction. Because of the nature of the observations non of the above clinical data can be subject to rigorous

statistical examination, but they suggest that the pre-operative use of chlorpromazine probably does reduce the dose of thiobarbiturates required to induce and maintain narcosis.

PRESENT STUDY

This paper concerns the degree and duration of potentiation by chlorpromazine of three commonly used thiobarbiturates; thiopental (Intraval, Pentothal, Trapanal), thiamylal (Surital, Thioseconal) and thialbarbitone (Kemithal) in the rat and dog. Its effect in combination with other drugs in the 'lytic cocktail' has also been studied, as has its action in combination with an oral barbiturate and with morphia.

METHODS

The effect of various drugs on the duration of narcosis with different thiobarbiturates was measured by comparing the duration of sleep produced by the anaesthetic alone and that produced by the same dose of the same drug in the same animal after administration of the adjuvant. To reduce the liklihood of acquired tolerance to the anaesthetic agents a period of at least two weeks was allowed to lapse between successive administrations. Where possible, a control observation was done both before and after the administration of the adjuvant. Where the effects of various drugs were being studied simultaneously their nature was not known until completion of the experiment.

Female rats of the Wistar strain and mongrel dogs of varying size and age were used.

Rats were anaesthetized by the intraperitoneal route, the duration of narcosis being measured as the time taken from the loss to the turn of the righting reflex. The accuracy of this measurement has been discussed elsewhere (Dundee, 1955). Both the intravenous and intraperitoneal routes were used in the dog. With the former the duration of narcosis was measured by the method described by one author (Dundee, 1953). When the intraperitoneal route was used the time was measured from the end of the injection until the animal was unable to remain upright (time for onset of narcosis) and until the animal could again stand unaided, the difference in the latter two being taken as the duration of anaesthesia.

The drugs whose effect on thiobarbiturate narcosis was studied were chlorpromazine, other phenothiazine derivatives (promethazine and diethazine) meperidine, morphine and butabarbital. The dosage varied in different experiments, but where two or more drugs were compared the ratio of their dosage was the same as that used in man, except where there was a known species difference as in the case of morphine. Adjuvants were given by intramuscular injection or by the oral route, the time between their administration and the induction of anaesthesia varying in different studies.

RESULTS

Table 1 shows that the previous injection of chlorpromazine prolongs narcosis with equal doses of thialbarbitone, thiopental and thiamylal in the rat. The percentage of animals anaesthetised, and the mortality following anaesthesia increased with the dose of chlorpromazine.

The maximum degree of potentiation occurred between 2 - 2½ hours after the intramuscular injection of the chlorpromazine in the rat (Table 2). Whereas the action of chlorpromazine in prolonging thiopental narcosis could be detected up to 24 hours after its administration, table 2 shows that its action in prolonging the effect of an equipotent dose of thiamylal was less marked and could not be detected for longer than 12 - 15 hours after the chlorpromazine. The duration of narcosis with the two thiobarbiturates is statistically significant ($p < 0.01$) at periods between 1 and 2½ hours after the chlorpromazine.

The difference in the action of chlorpromazine in prolonging narcosis with thiopental and thiamylal was further studied in the dog (Table 3). Irrespective of whether the intravenous or intraperitoneal route was adopted for administration of the thiobarbiturate, the sleeping time following thiamylal was less prolonged by chlorpromazine than was that produced by thiopental. This table also shows that the time from the intraperitoneal injection of the thiobarbiturates to the

onset of narcosis was appreciably shortened by the use of chlorpromazine.

The time of onset of maximum potentiating action of chlorpromazine after oral and intramuscular use in the dog is compared in Figure 1, using thialbarbitone as the anaesthetic agent. Even with large doses given by mouth, the maximum increase in sleeping time did not occur until 3½ hours after the chlorpromazine, as compared with 1½ - 2 hours when the drug was given by intramuscular injection. Irrespective of the route of administration the action of the drug in prolonging thialbarbitone narcosis lasted about 24 hours, as was the case with thiopental. From Figure 1, it would appear that an oral dose of 4 mg/kg chlorpromazine was slightly less potent in prolonging thialbarbitone narcosis than half this dose given by intramuscular injection. Similar findings were observed with the other thiobarbiturates.

The effect of chlorpromazine and the other constituents of the 'lytic cocktail' on thiamylal narcosis is compared in table 4. Neither diethazine or meperidine produced any marked effect, while the prolongation of narcosis by promethazine was very variable. Chlorpromazine and meperidine together produced a degree of potentiation similar to that produced by chlorpromazine alone. When promethazine was added to the above combination the increase in duration of narcosis was doubled, but was not significantly greater than the sum of that produced by chlorpromazine and promethazine.

A comparison of the effect of the oral administration of

chlorpromazine and a barbiturate and opiate on the duration of thiopental narcosis is shown in table 5. This makes allowance for the known increase tolerance of the dogs (as compared with man) for morphine, but, despite this, comparable dose of either butabarbital or chlorpromazine, produced much more prolongation of narcosis than did morphine. The most important observation in this experiments was that a combination of chlorpromazine (especially with higher dosage) and either butabarbital or morphine produced a greater increase in the duration of action of thiopental than would be expected from a simple summation of the effects of the two drugs.

DISCUSSION

The evidence presented herein shows that chlorpromazine alone intensifies the action and duration of narcosis produced by three commonly used thiobarbiturates. The differences in response of animals who received thiopental and thiamylal is contrary to the findings of Sadove et al (1956), but is in keeping with the observation that other depressant drugs have less additive effect on thiamylal narcosis (Dundee, 1956). Although Brodie (1952) found the rate of disappearance of thiopentone and thiamylal from tissues to be similar, Wyngaarden et al (1949) and Dundee (1955) observed that thiamylal was less cumulative than thiopental. If this can be interpreted as indicating a more rapid breakdown or greater take-up by fat of thiamylal,

it might offer an explanation for the results found in these experiments. Since the onset of sleep following the intraperitoneal injection of the thiobarbiturates is hastened by the administration of chlorpromazine, one would expect that treated animals loose consciousness at a lower brain concentration of thiobarbiturates than in the control observations. The plasma thiopental level has been shown in a few animals to be lower at loss of consciousness when chlorpromazine had been given, than in the same animals after the same dose of thiobarbiturate when the drug was omitted. (It is unlikely, that chlorpromazine would aid absorption from the peritoneal cavity or affect the blood-brain barrier). If the plasma decay-curve of thiamylal were steeper than for thiopental, a slight lowering of the level at which consciousness is lost would therefore, have less effect on the duration of action of thiamylal than on thiopental.

Dubost and Pascal (1953) found that the maximum blood concentration of chlorpromazine occurred 1½ hours after subcutaneous injection, while the peak level was not reached until 3 hours after oral administration. This agrees with the times after administration when the maximum potentiating effect on barbiturate narcosis was observed. Its prolonged action is at variance with their findings as regards parenteral administration, for while they demonstrated an appreciable amount in the blood of rabbits, 24 hours after large oral doses, only negligible amounts were found at the same interval after subcutaneous injection. Dubost and Pascal's suggestion that chlorpromazine is well absorbed from

the alimentary tract does not agree with results of Figure 1, which suggest that only under half the oral dose is absorbed.

Sadove et al (1956) have suggested that the synergism between chlorpromazine and thiobarbiturates may be due to the fact that they both act on the same portion of the central nervous system. Magoun (1954) believes that the action of pentobarbital is essentially a depression of the ascending reticular arousal system, while Arduini and Arduini (1954) have shown the great susceptibility of the reticular formation of the brain stem to anaesthetics and depressants. A recent review of French work on chlorpromazine (Hopkin, 1955) concludes that its action is predominantly on the reticular formations 'because the poly-synaptic structure of this part of the brain facilitates a cumulative depressant effect on the passage of impulses through a large number of depressed cells'.

Another possible explanation for the synergism between chlorpromazine and the thiobarbiturates is the action of the former on the motor end plate of striated muscle. Chlorpromazine produces a hypotonicity although Dobkin, Gilbert and Lamoureux (1954) showed that it did not produce a myo-neural block of either the depolarising or anti-depolarising type. Burn (1954), however, showed that doses of 3 mg/kg caused a gradual failure of muscle contraction evoked by both nerve and direct stimulation. This shows a direct paralytic action on skeletal muscle, which is delayed in onset, and is preceeded by augmentation of contraction. This could produce an apparent prolongation of sleep, as

a higher level of consciousness would be required before the animal would move spontaneously in the presence of generalised hypotonia. The divergance of clinical results could also be due to the variation in different patients, some of whom would be quiet and relaxed, while others (with acute pain) would apparently waken more quickly.

It is suggested that both the central and peripheral action of chlorpromazine may be involved in its effect in prolonging the soporific action of the barbiturates.

CONCLUSIONS

1. Chlorpromazine prolongs the period of sleep produced by three commonly used thiobarbiturates.
2. The degree of potentiation is proportional to the dose of chlorpromazine used.
3. Thiamylal narcosis is less affected than that produced by thiopental.
4. The maximum effect of chlorpromazine appears 1½ - 2 hours after its intramuscular injection and three hours after oral administration.
5. Irrespective of the route of administration, the action of chlorpromazine lasts about 24 hours.
6. In the ratio of dosage used by the French workers, chlorpromazine is the most potent constituent of the 'lytic cocktail'.

7. It is suggested that both a central and peripheral action may be involved in the potentiating action of chlorpromazine on thiobarbiturate narcosis.

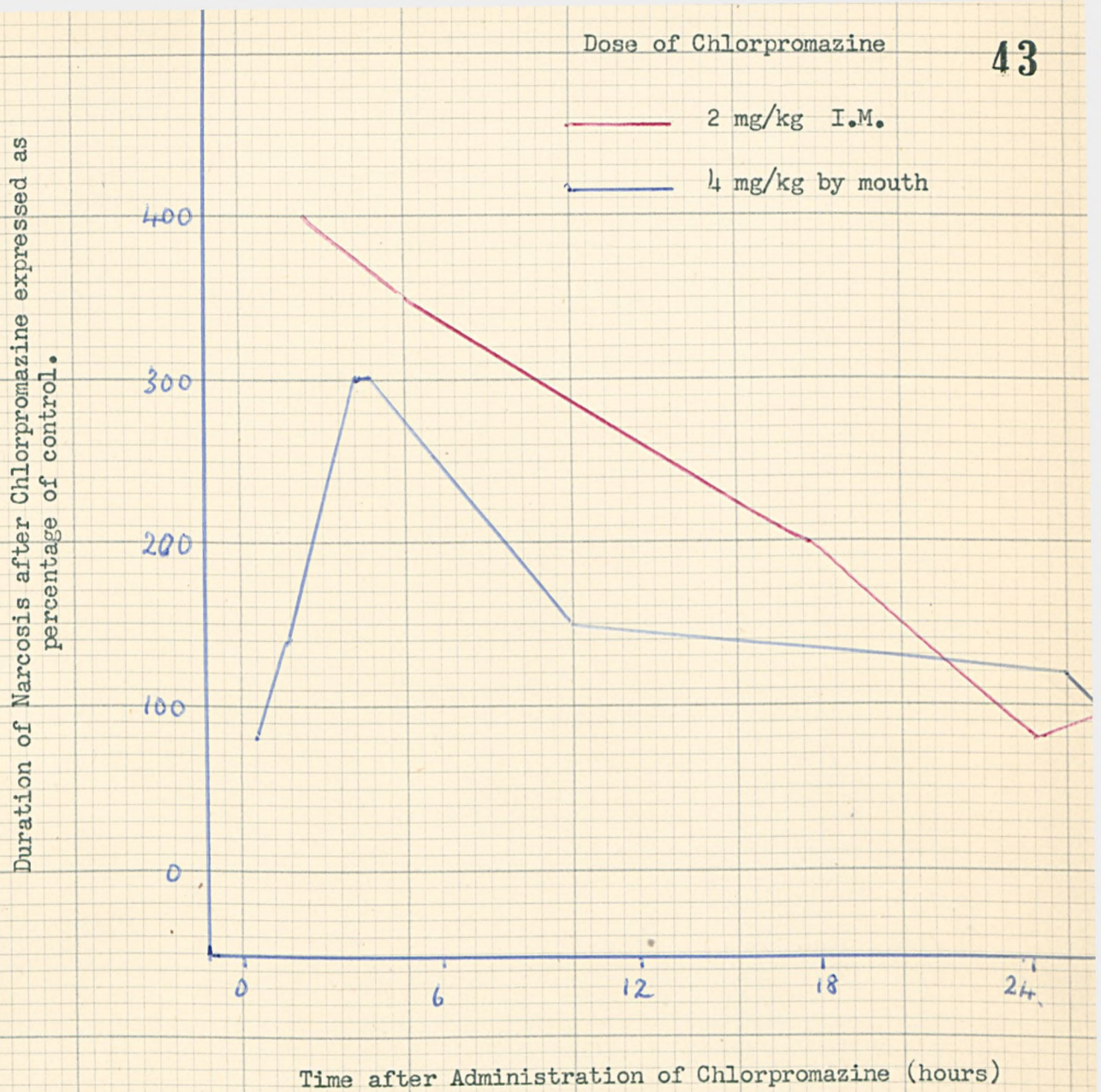

Figure 1.

Effect of pre-medication with chlorpromazine on duration of thialbarbitone narcosis (60 mg/kg I.V.)

Each reading is the average of eight observations

Thiobarbiturate		Dose of chlorpromazine given intramuscularly one hour before induction of anaesthesia (mg/kg)					
		0	1	2	3	4	5
Thialbarbitone (40 mg/kg)	Number of rats	20	20	20	20	18	16
	% anaesthetised	0	0	20	20	30	80
	Average duration of narcosis (minutes)	-	-	1	1	3.3	4.5
	% mortality	0	0	0	0	0	0
Thiopental (40 mg/kg)	Number of rats	27	-	20	20	-	10
	% anaesthetised	69		80	100		100
	Average duration of narcosis (minutes)	27.3		32.4	64.0		80.0
	% mortality	0		40	40		60
Thiamylal (40 mg/kg)	Number of rats	28	20	24	-	8	-
	% anaesthetised	80	80	100		100	
	Average duration of narcosis (minutes)	34.0	40.0	41.1		54.0	
	% mortality	0	20	17		25	

TABLE 1 Effect of intramuscular injection of various doses of chlorpromazine given one hour before induction of anaesthesia on duration of narcosis with intraperitoneal thialbarbitone, thiopentone and thiamylal.

TABLE 2. Effects of 4 mg/kg chlorpromazine, given by intramuscular injection, in potentiating narcosis by intraperitoneal injection of equipotent doses of thiopental and thiamylal in the rat.

Drug		Thiopental		Thiamylal	
Dose (mg/kg)		24		21	
Time between injection of chlorpromazine and Anaesthetic	No. of animals in each series	% asleep	Average duration of narcosis	% asleep	Average duration of narcosis
hrs			mins		mins
0	96	44	3.8 ± 0.3	40	3.6 ± 0.9
1	32	94	17.0 ± 0.6	57	5.5 ± 0.7
2	26	100	25.9 ± 2.2	92	18.0 ± 2.7
2½	26	92	22.6 ± 2.9	100	22.1 ± 1.6
3	14	86	16.4 ± 3.2	100	14.3 ± 5.3
4	24	83	26.2 ± 2.8	83	12.5 ± 0.8
6	10	100	7.1	75	7.3
8	20	-	-	40	4.3
16	12	75	12.3	25	1.5
18	14	86	7.9 ± 3.3	29	0.5
24	24	60	4.9 ± 1.4	60	4.9 ± 1.0
Overall Average *	-	74	15.5	69	8.1

*Excluding the 8 - hour reading (for which there was no observation made with thiopental) and control observation when no chlorpromazine was given.

(Dundee, J. W., 1956).

Drug	No. of observations	Average duration of narcosis (mins)		Average percentage increase in duration of narcosis per animal.	"t" value of difference
		Control	After chlorpromazine		
A. Intravenous Injection					
Thiopental	20	26.9	54.3	101.9 ± 28.2	3.2
Thiamylal	20	28.7	45.5	56.7 ± 4.5	

		Average time to onset of narcosis (mins)	Average duration of narcosis (mins)		
B. Intraperitoneal Injection					
Thiopental					
Control	33	6.4 ± 0.37	44.5 ± 5.1	137 ± 40.1	2.8
After chlorpromazine	22	3.3 ± 0.12	89.6 ± 12.0		
Thiamylal					
Control	33	4.8 ± 0.39	56.2 ± 5.4	69 ± 29.0	
After chlorpromazine	22	3.3 ± 0.27	84.2 ± 5.1		

Table 3. Effect of 2 mg/kg of chlorpromazine on the duration of action of equipotent doses of thiopental (30 mg/kg) and thiamylal (24 mg/kg) given by intravenous injection and equal doses (30 mg/kg) of the thiobarbiturates given by intraperitoneal injection in the dog. Chlorpromazine was given by I.M. injection 1½ hours prior to injection of the anaesthetic.

Adjuvant	mg/kg	No. of observations	Average time to onset of narcosis (mins)		Control duration of narcosis (mins)		Average percentage increase
			Control	After Adjuvant	Control	After Adjuvant	
Chlorpromazine	2	32	4.72	3.58	59.1	85.8	45.2 ± 7.3
Promethazine	2	15	5.10	4.67	50.3	69.9	39.8 ± 22.6
Diethazine	10	17	5.38	5.06	66.0	73.0	10.6 ± 19.0
Meperidine	4	16	5.25	5.44	60.5	72.0	18.9 ± 65.0
(Chlorpromazine (Meperidine	2 4	17	5.25	4.70	59.7	90.4	51.4 ± 12.9
(Chlorpromazine (Meperidine (Promethazine	2 4 2	20	4.99	3.45	52.3	108.3	106.0 ± 33.8

Table 4. Effect of various phenothiazine derivatives and meperidine, and combinations of these drugs, on the time of onset and duration of thiamylal (30 mg/kg by intraperitoneal injection) narcosis in the dog. Adjuvants were given by intramuscular injection 1½ hours before the thiamylal.

Adjuvant	mg/kg	Average time to onset of narcosis (mins)		Average duration of narcosis (mins)		Average percentage increase in ~~increase~~ narcosis.
		Control	After Adjuvant	Control	After Adjuvant	
Chlorpromazine	2	6.0	5.1	43.6	62.0	41.9
....	4	6.0	4.7	45.8	63.3	38.2
Butabarbital	9	5.6	4.8	49.2	82.0	66.4
(Butabarbital (Chlorpromazine	9 2	6.1	5.3	43.6	113.3	160.2
(Butabarbital (Chlorpromazine	9 4	6.1	3.6	43.6	190.3	337.0
Morphine	1.5	5.8	5.6	46.8	51.3	9.6
(Morphine (Chlorpromazine	1.5 2	6.0	4.0	44.0	62.2	57.3
(Morphine (Chlorpromazine	1.5 4	6.0	4.6	40.0	89.1	122.7

Table 5. The effect of the oral administration of chlorpromazine, butobarbital and morphine on the time of onset and duration of narcosis produced by 30 mg/kg thiopental given by intraperitoneal injection in the dog. Adjuvants were given two hours before thiopental. Each reading is the average of 10 observations.

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Chapter 11

USE OF THIOBARBITURATES IN CERTAIN PATHOLOGICAL STATES

A Porphyria

B Dystrophia Myotonia

C Adrenocortical Insufficiency

D Acute Intestinal Obstruction

Use of Thiobarbiturates in Certain Pathological States.

A Porphyria

"BARBITURATE NARCOSIS IN PORPHYRIA"

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BARBITURATE NARCOSIS IN PORPHYRIA

By JOHN W. DUNDEE, M.D., F.F.A.R.C.S.
LECTURER IN ANÆSTHESIA, UNIVERSITY OF LIVERPOOL
AND
J. E. RIDING, M.B., F.F.A.R.C.S.
SENIOR ANÆSTHETIC REGISTRAR, LIVERPOOL ROYAL INFIRMARY

THE harmful effects of barbiturates, especially thiopentone, on porphyria, have been noted by several writers. A recent article by Dean[1] has once more focussed attention upon the dangers of barbiturate anæsthesia in this disorder. Nevertheless, there is no mention of the anæsthetic management of patients suffering from porphyria either in the current anæsthetic textbooks or in specialist anæsthetic journals.

In this paper, the cases reported in the *British Medical Journal* (*see* refs. 1 to 15) and the *Lancet* (*see* refs. 16 to 20) during the years 1948-1953 are reviewed. Our object is primarily to draw the attention of anæsthetists to what appears to be an absolute contraindication to the use of thiopentone, or barbiturates in any form. We also aim to show how the anæsthetist may encounter porphyria in practice and describe the clinical features that may aid its recognition.

The exact ætiology of porphyria is unkown, but it is a disease of metabolism involving pyrolle pigments which take part in respiratory metabolism[1]. Many classifications have been suggested, but the following seems to meet with most approval[14 21].

Congenital.
Porphyria cutanea tarda.
Acute intermittent porphyria.

This division is by no means clear cut and overlapping appears to occur[22]. The congenital type is characterised by photosensitivity, pigmentation of bones and teeth, and is familial. The cutaneous variety shows photosensitivity and recurrent skin lesions, often of a blistering type, due to heat or minor trauma. Here again there is evidence of a familial background.

The acute attacks may occur without any known precipitating factors or in known porphyrics. In the latter several drugs have apparently been responsible. These include sulphonamides[11 18 23], sulphonal[2 11 23], the barbiturates[1 2 11 23] and possibly alcohol[23]. The clinical picture of acute attacks has been described as resembling lead poisoning in several respects[24]. It may be ushered in by abdominal pain, distension, nausea and vomiting followed by the passage of reddish coloured urine. It is at this stage that an exploratory laparotomy may be carried out. Weakness follows within a few days of the onset of the attack, followed by a lower motor neurone

paralysis[1]. This may similate paralysis of the Landry type[7], or that seen in familial periodic paralysis[18] or neuromyelitis[10]. The paralysis is often progressive and accompanied by mental confusion. Death may occur from respiratory paralysis or recovery takes place in 6—32 weeks.

Reported Cases

During the years under review, 37 attacks of acute porphyria are reported in 32 patients. It was noted that two-thirds of the patients were in the third or fourth decade of life, and that a similar proportion were women. Paralysis occurred in thirty instances and proved fatal in ten cases.

There were details of fifteen operations reported as follows:

Exploratory laparotomy ...	5
Gynecological	5
Nature unstated	2
Dental extraction	1
Varicose veins ligation ...	1
Appendicectomy	1

Thiopentone was administered in thirteen of these operations, the nature of the anæsthetic being unstated in the remaining two. Paralysis occurred in all of the thirteen thiopentone cases and five patients died.

The importance of recognising porphyria is best illustrated by the following cases reported by Dean[1].

CASE I

A women aged 29 with no relevant history became paralysed after three days following uterine curettage under thiopentone anæsthesia. Recovery took seven months. Two years later, after dental extraction under thiopentone anæsthesia, paralysis again occurred, recovery taking five months.

CASE II

After hysterectomy, for which a barbiturate was administered, the patient was unable to walk for six months. Nineteen years later she received thiopentone and the resulting paralysis proved fatal in six weeks.

Dean found a family history of sensitive skin in this patient who had previously been regarded as neurotic.

CASE III

A girl of 19 having had several attacks of paralysis following oral barbiturates, had thiopentone for an exploratory laparotomy in the acute stage of the disease. Within three days complete paralysis had occurred and this proved fatal five days later.

She had a family history of sensitive skin and porphyrinuria.

CASE IV

This women had a family history of five relatives who died from general paralysis after drugs and anæsthetics. She herself suffered from skin blisters. After two operations at which thiopentone was administered, she suffered from paralysis and delerium, but eventually recovered.

From these cases it can be seen that an anæsthetist may encounter porphyria at any stage of the disease. When in the latent phase there are some guides that may help in its detection. A history of paralysis following a previous operation (cases I and II) or after taking sedatives (case III) may be elicited. The skin changes of the

cutaneous variety may be obvious, *e.g.* scars from previous blisters of the hands or the patient may volunteer the history of a sensitive skin. As in case IV, there may be a history of relatives having died after anæsthetics, and while this may have no relationship to porphyria, at least it should arouse suspicion and lead to a more detailed questioning of the patient. Of more positive value would be a history of passing red urine, but except in the case of an elective operation such information is unlikely to be volunteered by patients, as they would see no relationship between this and their present complaint.

The most difficult case to detect is the " acute abdomen of unknown ætiology ". That there is no previous history of porphyria is apparent from the fact that a laparotomy is contemplated, and the stage of porphyrinuria may not have been reached.

So dire are the effects of barbiturates in any form in cases of porphyria, that in elective cases in whom there is any suspicion of the disease whatsoever, thiopentone should not be given. In the emergency laparotomies, one might think that the advice *par excellence* would be to avoid thiopentone in all patients in whom an exact diagnosis has not been made. However, whereas in the case of an elective operation it seems clear that thiopentone can precipitate an attack of acute porphyria with resulting paralysis, in the emergency operations the acute attack has already started and the chances of a patient having paralysis are already great, whether or not thiopentone be given.

Porphyria is a rare disease in this country, being more prevalent in the Scandinavian countries[23] and South Africa[1]. Thiopentone can precipitate an acute attack in elective cases, irrespective of the condition of the patient at the time. When a known case is encountered by an anæsthetist, or where there is any suspicion of the malady, no barbiturates whatsoever should be administered. Ether can be given with safety for the operation[1], and for pre- and post-operative sedation the best results have been obtained from the use of opiates, chloral hydrate and paraldehyde[15]. It is interesting to note that intravenous procaine (0.2%) has been used successfully to produce symptomatic relief of symptoms in two cases, although it has no effect on the ultimate course of the disease[25].

Conditions in which true sensitivity to anæsthetic agents or relaxants occur are extremely rare. In some of these, such as myasthenia gravis, the diagnosis is obvious and it is not necessary to advise the patient of their idiosyncrasy. Several cases have been reported of sensitivity to relaxants without any apparent signs of the disease[26 27]. It would seem reasonable, once such a patient is encountered, to give a letter explaining the position, and request that the patient hand it to the anæsthetist should another operation be necessary. This advice has already been given concerning patients receiving disulphiram (Antabuse)[27]. Cases of known or suspected

porphyria fall into the same category, and all such patients should be given a letter drawing attention to their disease, to be handed to the surgeon or anæsthetist before any operation is contemplated. By this arrangement the fatalities similar to those mentioned above might be avoided.

Summary

The ill effects of administration of thiopentone or barbiturates in any form, to cases of porphyria are pointed out. The circumstances under which such patients may be encountered by the anæsthetist are discussed.

Where there is any suspicion of the disease, thiopentone should be avoided in anæsthesia in elective cases, but it is not advised that the drug should be omitted in every acute abdominal emergency in which an exact diagnosis has not been made.

A suggestion is made that all patients with known or suspected porphyria should be given a letter stating same, to be shown when any operation is contemplated.

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Use of Thiobarbiturates in Certain Pathological States.

B Dystrophia Myotonia

"THIOPENTONE IN DYSTROPHIA MYOTONIA"

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Current Researches in Anesthesia & Analgesia

55

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Thiopentone in Dystrophia Myotonia.*

John W. Dundee, M.D., D.A., Liverpool, England
Lecturer in Anaesthesia, University of Liverpool

EVIDENCE IS ACCUMULATING to show that the response of patients to thiopentone varies according to their clinical condition. Examples of this are seen in shock,[1 2 3 4] liver dysfunction,[5 6] severe anaemia,[7] malaria[8] and Addison's disease,[9] in all of which patients are extremely sensitive to the drug. Resistance to thiopentone has been observed in patients who are receiving large doses of sedative or analgesic drugs.[10 11]

Sensitivity to thiopentone has recently been observed in 3 patients suffering from dystrophia myotonia. Such is the rarity of this disease and the unlikelihood of its sufferers coming to operation that no recorded cases of any form of general anaesthesia being administered to such patients can be found in the literature.

Dystrophia Myotonia

DYSTROPHIA MYOTONIA is a heredo-familial disease, characterised by wasting of the digital muscles of the limbs, of sternomastoids and of certain facial muscles; by a peculiar, delayed relaxation of certain muscles (myotonia); by testicular atrophy, baldness, cataract and mental deterioration.[12] The disease is essentially a muscular disorder,[13] the abnormality being one of excitability of muscle fibres, of such a nature that one excitation leads to repeated discharge of the action current mechanism of the muscle fibre. Changes in the muscles themselves have been found.[14 15] Some fibres are enlarged and rounded with an excess of nuclei in the sarcolemmal sheath and in the muscle substance itself. These enlarged fibres are found associated with numerous small ones in which there is also some increase in nuclei. The increase in sarcolemmal nuclei, due to degenerated muscle fibres and overgrowth of connective tissue is proportional to the degree of atrophy of the muscles. No pathologic change has been detected in the central nervous system.

Myotonia is in pharmacologic contrast to myasthenia gravis.[16] Theoretically the symptoms could be explained on the basis of an excess of acetylcholine. This in turn could be due to an excess production of acetylcholine at motor nerve endings, or decreased cholinesterase activity. It is more likely that the muscle fibres are abnormally sensitive to acetylcholine. Drugs effective in myasthenia gravis aggravate the symptoms of myotonia. Neostigmine which increases muscle tone in normal persons,[17] causes a pronounced exacerbation of the symptoms of myotonia.[18]

*Presented before the Twenty-Sixth Annual Congress of Anaesthetists, London, England, September 3-8, 1951.

Case Reports

CASE 1 was a woman, aged 56, height 60 inches, weight 63 kg. (140 lbs.). The features of her disease were a family history of muscle disorders, frontal baldness and hirsutism of the face for twenty years, progressive weakness of the legs, partial bilateral ptosis, weakness of the sternomastoids, myotonic tongue and slow relaxation of the grip. Following premedication with morphine 10 mg. and atropine 0.65 mg., 0.5 Gm. thiopentone was administered for endometrial biopsy. This was followed by complete apnoea for ten minutes, artificial respiration being carried out with oxygen and periodic addition of carbon dioxide. The ease of inflation resembled that of a curarised patient. Oral intubation was carried out without difficulty six minutes after the use of thiopentone and was not followed by any coughing. The respiration returned gradually and after thirty minutes the patient was able to maintain her colour when breathing oxygen but became cyanosed on air. The addition of carbon dioxide to the oxygen did not increase the respiratory volume. She appeared to be waking up and yet not having a full respiratory volume. The condition resembled that of a partially curarised patient recovering from general anaesthesia.

Nitrous oxide was added to the oxygen; the patient put in the lithotomy position, her limbs being toneless, and the operation carried out without any further anaesthetic being required. Forty minutes after injection of thiopentone she made a weak attempt to cough and five minutes later she could maintain her colour when breathing air.

The prolonged apnoea was not due to acapnia, as carbon dioxide was periodically added to the oxygen. The blood pressure did not fall during the procedure and liver and renal function tests performed postoperatively did not reveal any abnormality.

Case 2 was a man, aged 31, height 68 inches, weight 51 kg. (112 lbs.). The main features of his disease were a family history of muscular disorders, electrocardiographic changes, delayed puberty, ptosis and slow relaxation of the grip. He was operated upon for ptosis. Premedication was with omnopon 21 mg. and hyoscine 0.43 mg. The induction dose of 0.25 Gm. thiopentone produced apnoea, which persisted for three minutes. A no. 10 Magill oral endotracheal tube was passed with the utmost ease. Respiration was depressed throughout the forty minute operation, during which nitrous oxide-oxygen and minimal ether were administered.

Liver and renal function tests in this patient again revealed no abnormality.

Case 3 was a male volunteer, aged 35; the severity of his disease was similar to that of case 1, although of shorter duration. The diagnosis was confirmed by electromyography, which showed that the usual action potentials after voluntary contraction of the pronator

teres muscle persisted for ten to fifteen seconds after the muscle was relaxed and were followed by fibrillation potentials. The effect of a small dose (50 mg.) of thiopentone on respiration is shown on the spirometer tracing (fig. 1). This is contrasted with the effect of the same dose on a normal person of the same age and weight. Table 1 shows clearly that in this patient 50 mg. of thiopentone resulted in a depression of respiration (without loss of consciousness), whereas in normal persons the same dose results in a transient stimulation.

Considering that a constant finding in patients with this disease is an abnormality in the muscles themselves, it is reasonable to conclude that these muscles are hypersensitive to the action of thiopentone, small doses of which produce a profound degree of respiratory depression.

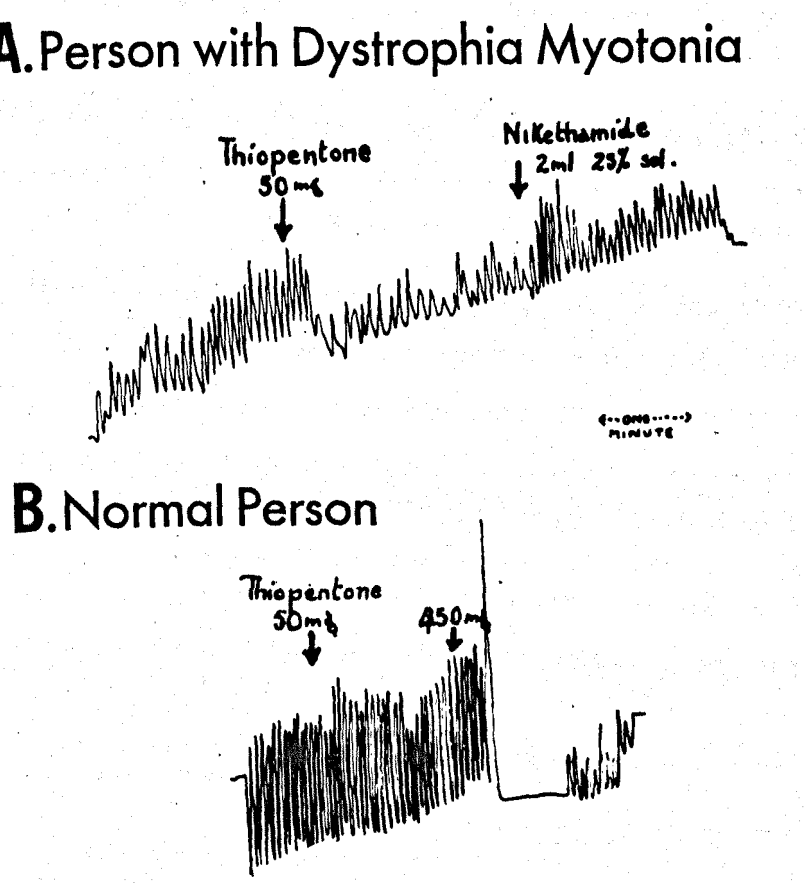

Fig. 1. Effect of 50 mg. thiopentone on respiration in (a) patient with dystrophia myotonia (case 3) (b) normal person of same age and weight.

The effect on respiration of small doses of d-tubocurarine chloride and mephenesin were also studied in this patient (fig. 2), without revealing any evidence of sensitivity to either drug.

Discussion

ALL THREE PATIENTS with dystrophia myotonia showed the same type of response to small doses of thiopentone, viz. profound respiratory depression and an abnormal degree of muscular relaxation. Failure of carbon dioxide to stimulate respiration and apparent return of consciousness before full respiratory volume was restored in Case 1 suggest that the overaction of the thiopentone was peripheral, rather than central in origin. In Case 3 this view is substantiated by the maintenance of consciousness, when respiration was decidedly depressed, and by the transient effect of nikethamide as a respiratory stimulant. The normal response to mephenesin excludes an abnormal action on the spinal cord. The action of d-tubocurarine in these patients is normal, and this would indicate that thiopentone sensitivity is not due to block of the substrate-competition type.

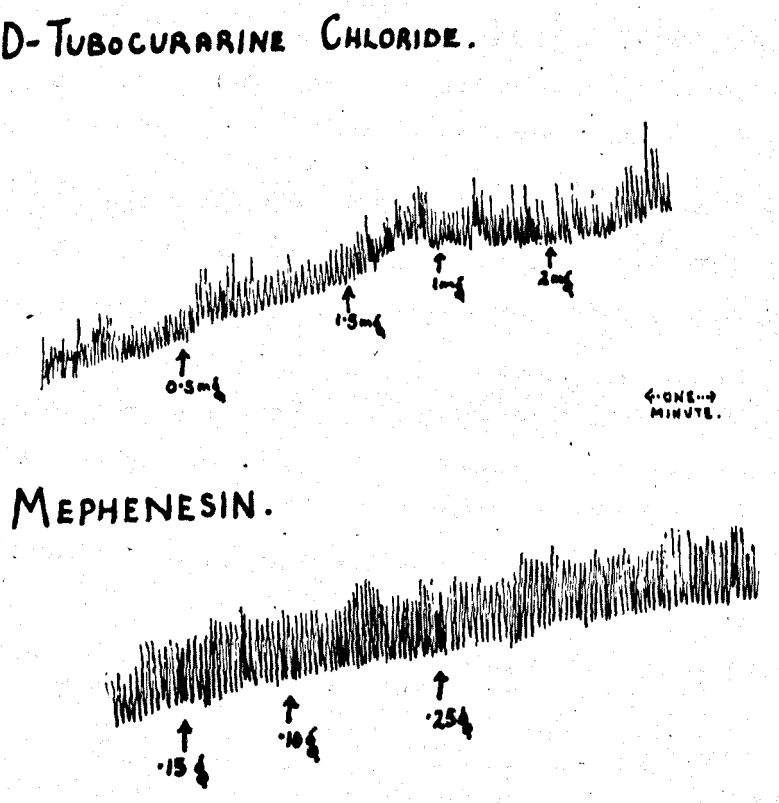

Fig. 2. Effect of d-tubocurarine chloride and mephenesin on respiration in patient with dystrophia myotonia (case 3).

TABLE 1

Effect of 50 mg. thiopentone on minute volume and respiratory rate of 6 normal persons and in the patient with dystrophia myotonia (average of 2 readings).

Allowance of 20 seconds is made for arm-brain circulation time following injection.

Subject	Before Thiopentone		After Thiopentone			
			1st Minute		2nd Minute	
	Min. Vol. in ml.	Resp. Rate per min.	Min. Vol. in ml.	Resp. Rate per min.	Min. Vol. in ml.	Resp. Rate per min.
Normal controls	5,700	20	11,700	24	11,000	22
	8,400	24	10,000	23	10,500	23
	8,700	16	11,000	18	11,000	18
	8,400	16	10,800	18	10,500	18
	6,100	18	7,200	13	8,800	16
	14,700	18	17,200	18	14,500	18
Average	8,660	18	11,316	19	11,050	19
Myotonia (case 3)	5,000	12	2,700	9	2,600	10

Myasthenia Gravis

IN MYASTHENIA GRAVIS, which is pharmacologically the opposition of myotonia,[16] thiopentone produces effects similar, though less pronounced than those described above. It is usually possible to perform oral intubation in myasthenic patients with doses of thiopentone in the order of one quarter to one third of that required in normal persons. The duration of action of the drug is not prolonged. These patients are, however, abnormally sensitive to the relaxant drugs which produce a competition block, viz. d-tubocurarine chloride[10] and gallamine triethiodide.[19] In contrast to the effect of thiopentone in myotonia, overaction in patients with myasthenia gravis may be due to its action on an abnormally sensitive myoneural junction.

Summary and Conclusions

1. The response of different subjects to thiopentone is shown to depend on the clinical condition of the subject.

2. The effect of thiopentone on 3 subjects with dystrophia myotonia is described.

3. The profound degree of respiratory depression which occurs following small doses is compared with the response of normal subjects.

4. Patients with dystrophia myotonia react normally to d-tubocurarine chloride and to mephenesin.

5. The action of thiopentone on abnormally sensitive muscles is postulated to explain the phenomena observed.

6. The response to thiopentone of subjects with myasthenia gravis is discussed.

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Use of Thiobarbiturates in Certain Pathological States.

C Adrenocortical Insufficiency

"THIOPENTONE IN ADDISON'S DISEASE"

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The discussion in this paper must be considered in the light of the following more extensive review.

"ANAESTHESIA AND SURGERY IN ADRENOCORTICAL INSUFFICIENCY"

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THIOPENTONE IN ADDISON'S DISEASE

By JOHN W. DUNDEE

OPERATIONS are very rarely carried out in subjects with Addison's disease. The reason for this is well expressed by Rowntree and Snell (1931) viz. " If treatment necessitates any surgical procedure, the risk is prohibitive and should be assumed only after most serious consideration." It is easy to understand why anæsthesia for these subjects receives no mention in the literature. Lundy's (1942) choice of agent would be di-vinyl ether, but he does not mention having anæsthetized any cases. Simpson (1950a) recommends local analgesia for D.O.C.A. implants but does not give any reasons for his dislike of general anæsthesia in this condition.

Examination of particulars of 14 reported operations in subjects with Addison's disease (Rowntree and Snell, 1931; Katz and Mainzer, 1941; Leavitt, 1945; Simpson, 1950b) reveals that a severe crisis followed operation in 11 instances. With two exceptions the crisis proved fatal. Sufficient details are not available to incriminate the anæsthetic agent as a cause of the Addisonian crisis in any of these cases. The relationship between the anæsthetic agent and the Addisonian crisis is clear in the following case.

CASE REPORT

July 4, 1950. A woman, aged 45 years, weighing 9 stones (57 kg.) was admitted to hospital in Addisonian crisis. She was vomiting persistently, B.P. was 96/60, blood sugar 45 mg. per cent and blood urea 75 mg. per cent. Treatment with Eschatin, D.O.C.A. and intravenous drip of 5 per cent dextrose in normal

saline did not produce a satisfactory response and 48 hours after admission B.P. was 80/50. Failure of response to treatment was attributed to urinary infection and when this was eliminated her condition improved immensely.

August 9, 1950. Clinical improvement was sustained; B.P. 110/70; Hb 75 per cent; R.B.C.s 3.5 million per cu. mm.

August 14, 1950. B.P. 100/65. Morphia gr. $\frac{1}{6}$ (10 mg.) was given as premedication prior to D.O.C.A. implants, which it was intended to insert under local analgesia. Owing to a misunderstanding 0.4 g. thiopentone was administered. This was not followed by any undue respiratory depression, but the following sequence of events ensued:

5 minutes	B.P. 50/30, oxygen administered.
25 minutes	B.P. 50/30, implant carried out without any response from the patient.
1 hour	B.P. 60/30.
1¼ hours	B.P. 60/30, reacted to supraorbital pressure.
2¼ hours	B.P. 65/30, regained consciousness.
3 hours	B.P. 70/40, very drowsy, 5 ml. Eschatin intramuscularly.
6 hours	B.P. 70/50, still drowsy, 5 ml. Eschatin intramuscularly.
12 hours	B.P. 70/50, still drowsy, intravenous drip of 5 per cent dextrose in normal saline commenced.
18 hours	B.P. 85/50, one litre of infusion given, blood sugar 75 mg. per cent.

Mild crisis continued for further 24 hours, followed by complete recovery.

February 8, 1951. Further implants of D.O.C.A. carried out under 1 per cent procaine analgesia. There was an uneventful convalescence with no Addisonian crisis.

COMMENT

There seems little doubt that the rapid deterioration in the patient's condition was due to the thiopentone, as the collapse occurred before the operation commenced. This view is substantiated by the uneventful convalescence on the second occasion, when no thiopentone was given. The narcosis was prolonged, as the subject did not react when the skin was incised 25 minutes after 0.4 g. thiopentone, did not regain consciousness for 2¼ hours, and remained drowsy for a further 10 hours.

DISCUSSION

A fall in blood-pressure of the severity and duration recorded above is abnormal as, in the absence of operative shock or blood loss, blood-pressure returns to normal 10–15 minutes after the injection of thiopentone (Lockett, 1951). Blood-pressure in subjects with Addison's disease is very labile and possibly unduly sensitive to the action of depressant drugs. It has been noted that more extreme falls in blood-pressure are seen following the use of thiopentone in subjects already suffering from hypotension (Adams, 1944).

The rapid recovery that follows small doses of thiopentone is due to rapid diffusion of the drug to body tissues (Mark et al., 1949; Brooks et al., 1948) and fat (Mark et al., 1950). This diffusion would be interfered with by hypotension. In the crises of Addison's disease there is retention of potassium and excessive excretion of sodium chloride, causing dehydration of intracellular tissues. Extracellular dehydration would further interfere with diffusion of thiopentone. Both these factors would result in prolongation of thiopentone narcosis.

The adrenalectomized animal, or the patient with Addison's disease, manifests a tendency to hypoglycaemia, more marked under conditions of fasting or stress (Simpson, 1950b). A drop of blood-pressure to 50/30 must be considered sufficient stress to bring on hypoglycæmia. The blood sugar of this subject 18 hours after the thiopentone was 75 mg. per cent. Since one litre of 5 per cent dextrose (50 g. glucose) had been given immediately before this estimation, it is very likely that hypoglycæmia played a part in prolongation of the thiopentone narcosis. Coma in Addison's disease is most commonly due to hypoglycæmia.

The possibility exists that hypoglycæmic coma followed the thiopentone, giving the impression that the action of thiopentone was prolonged.

Prolonged hypotension, persistent vomiting and inadequate food intake could cause hepatic dysfunction (Davison et al., 1946) and increase the duration of thiopentone (Shideman et al., 1949). Flocculation tests, hippuric acid excretion and urinary urobilinogen in this subject were all within the limits of normality and preclude any severe liver dysfunction. Oliguria and raised blood urea are features of Addisonian crises, such as occurred following the thiopentone. Although blood urea was not estimated in this subject, it is unlikely that the urea could have risen to an extent capable of potentiating thiopentone (Richards, 1950) in the short time before the subject gained consciousness.

SUMMARY

The administration of thiopentone to a subject with Addison's disease was followed by severe hypotension and a crisis lasting for 48 hours. The various factors that could have played a part in this sequence of events are discussed. Hypotension, electrolyte imbalance and hypoglycæmia are most likely to have engendered in this subject sensitivity to thiopentone.

I am indebted to Dr. W. Sutton for permission to publish this case.

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ANAESTHESIA AND SURGERY IN ADRENOCORTICAL INSUFFICIENCY.

Although pathological conditions of the "suprarenal capsules" have been described over a century ago by Thomas Addison (1855), it is only within the past two decades that any real knowledge of the functions of the adrenal cortex has materialised. It is now appreciated that the integrity of the adrenal cortex is essential for survival in a major stress, such as a surgical operation (Roche, Thorn and Hills, 1950).

The isolation of steroids from extracts of the adrenal cortex, and the synthesis of similarly active compounds have opened up new fields in the treatment of adrenal insufficiency. However, the prolonged use of such drugs themselves are not without danger, as far as anaesthesia and surgery are concerned.

This paper discusses some problems of anaesthesia related to adrenal insufficiency. These problems have become more acute as our knowledge of the function of the cortex increases, for by the use of substitution therapy, operations which were until recently considered to be a major hazard are now becoming more common.

It is not proposed to discuss the physiology of the adrenal cortex, or its regulator the anterior pituitary gland. A list of reviews dealing with this subject is given in Appendix 1.

CLASSIFICATION

Elrick (1950) divides adrenal insufficiency into three groups as follows.

1. Primary hypoadrenocorticism, or Addison's disease (due to tuberculosis, non specific destruction or Waterhouse - Friderischsen syndrome).

2. Secondary hypoadrenocorticism, due to anterior pituitary hypo - function.

3. Surgical removal of adrenal tissue.

This classification will be adhered to as closely as possible. Under secondary hyperadrenocorticism it is necessary to add drug - induced (cortisone or A.C.T.H.) insufficiency which has only been manifest recently since the clinical use of these hormones has become widespread.

Primary Adrenal Hypofunction.

Addisons's Disease.

Discussing this disease in 1931 Rowntree and Snell remarked, "If treatment necessitates any surgical procedure, the risk is prohibitive and should be assumed only after most serious consideration". Of 41 reported anaesthetics (in 37 cases), Addisonian crisis occurred in 26 instances and proved fatal in 12. (Rowntree and Snell, 1931; Katz and Mainzer, 1941; Leavitt, 1945; Simpson, 1950; Dundee, 1951; Papper and Cahill, 1952; Schwartz, Derrick and Papper, 1952; and Riches, 1956). These include local, spinal and general anaesthesia.

The introduction of deoxycortone acetate (desoxycorticosterone acetate, D.C.A., D.O.C.A) in 1938 and more recently cortisone and similar drugs, has changed the outlook for patients with Addison's disease. Adequate substitution therapy makes them amenable to anaesthesia

and major surgery. Papper and Cahill, (1952) and Schwartz, Derrick and Papper (1952) have examined records of 23 anaesthetics in 19 cases at Presbyterian Hospital, New York and Peter Bent Brigham Hospital, Boston and found that, proportionately, complications occurred as frequently in all anaesthetic groups and no particular technique was without a harmful effect. The occurrence of hypotension during or after anaesthesia (in 14 instances) was unrelated to the anaesthetic agents, but appeared to be the result of inadequate specific hormone therapy. Blood pressure fell suddenly, sometimes immediately after operation following an uneventful anaesthesia, and needed prompt treatment. The maintenance of blood pressure seemed to be the best guide to the necessity for administration of D.O.C.A. parenteral fluids and vasopressor drugs.

Best and Taylor (1945) and Thorn (1949) advise against the use of morphine in patients with Addison's disease. Five patients were given it in the above series; three of these died but they were not known to have the disease and all were unprepared for the stress of anaesthesia and surgery.

The author (1956) recently listed Addison's disease among the absolute contraindications to thiopentone. This view was based on the occurrence of severe persistant hypotension following the administration of 400 mg of the drug to a patient for D.O.C.A. implant (Dundee 1951). The action of the thiopentone also appeared to be prolonged as consciousness was not regained for 2¼ hours and drowsiness persisted for a further 10 hours. This patient received no substitution therapy before

operation and 10 mg morphine was given as pre-operative medication. With the advent of cortisone and other forms of substitution therapy this contraindication becomes only a relative one, indicating the necessity for caution in the use of thiopentone.

Case 1.

> Thiamylal, 150 mg, was given slowly over one minute, followed by cyclopropane and oxygen, for implantation of D.O.C.A. The patient, who had just recovered from severe Addisonian crisis was premedicated with 75 mg cortisone and 5 mg D.O.C.A. by intramuscular injection. Blood pressure remained steady throughout and after the operation and recovery of consciousness was prompt.

It cannot be conceived that the use of thiamylal instead of thiopentone, was of any significance. Three of the patients reported by Schwartz et al. (1952) received thiopentone. One subject, who was not then known to have Addison's disease, was unprepared for surgery, but there were no untoward effects from the thiobarbiturate. Another patient, also unprepared, was given thiopentone and ether and died on the third postoperative day in spite of treatment with blood, dextrose, Eschatin and phenylephrine. The third patient was anaesthetised on two occasions; without substitution therapy the blood pressure fell to 70/50 after thiopentone and ether, necessitating postponement of the operation; after treatment with adrenal extract, A.C.T.H. and dextrose the same anaesthetic caused a hypotension of 90/50, but the operation was completed and the patient recovered.

With regards to the use of thiopentone or deep ether anaesthesia, attention is drawn to the reductions in heart volume which were

reported by McGavack (1941) in patients with Addison's disease. These changes were not restored by restoration of blood volume without adequate hormone therapy.

Hypoglycaemia must always be considered as a possible cause of delay in return of consciousness after anaesthesia in subjects with Addison's disease.

Schwartz et al. (1952) concluded from their survey that, in Addison's disease, " anaesthetic management .... is largely a matter of doing the least harm, rather than the most good. Patient's respond to the stress of operation over a narrow range of compensation". They stress the importance of absolute precision in technique, to avoid hypoxia, asphyxia or hypotension, and emphasise that the specific chain of biochemical events leading to Addisonian crisis may be precipitated with relative ease by any of these factors. The loss of Na Cl in the urine, with an increase in K, results in the loss of large quantities of water and depletion of the circulating blood volume. They recommend that specific treatment with cortisone (or a related compound) be given immediately once hypotension has occurred.

Since Schwartz's report was published (1952), experience has been gained in the use of glucocorticoids and the following case report (Dr. J. E. Riding, personal communication) shows that their proper pre-operative use increases the scope of safe surgery and greatly decreases the hazards of anaesthesia in patients with Addison's disease.

Case 2.

A woman, aged 56, was first diagnosed as Addison's disease in 1953, from a history of weakness, wasting, loss of appetite, constipation, pigmentation in mouth and B.P. of 90/60. The result of Keplers test was abnormal and the injection of ACTH failed to cause a 50% fall in circulating eosinophils.

Over the next two years she was kept in reasonably good health with periodic DOCA implants.

In January 1956 she had a severe hypoglycaemic attack, which was not improved by DOCA. Cortisone therapy was started and the patient stabilised on a daily dose of 100 mg. Systolic blood pressure fluctuated from 125 to 140 mm Hg over the next few months.

Six months later for removal of a parotid tumour 80 mg cortisone was given I.M. with atropine 0.6 mg as pre-operative medication. Anaesthesia was induced by the slow injection of 100 - 150 mg thiopentone followed by 50 mg suxamethonium. Oral intubation was carried out after spraying the pharynx, larynx and trachea with 4% lignocaine and anaesthesia maintained at a light level with N_2O - O_2 trichloroethylene.

For a ten minute period the systolic blood pressure was lowered to 80 mm Hg with arfonad, but returned to normal when the infusion was stopped.

Recovery from anaesthesia was prompt. The B.P. on return to the ward was 125/80. Cortisone therapy was continued after operation and on the morning after operation B.P. was 120/80.

An uneventful recovery from two major thoracic operations performed under local analgesia, after adequate pre-treatment with cortisone is described by Riches (1956).

It is perhaps unwise to draw conclusions from the combined findings of several authors, where the data is not reported in the same detail by each. However, this is done in table 1, since it illustrates the importance of adequate pre-operative preparation of the patient with cortisone and/or DOCA, in decreasing the complications and mortality from anaesthesia and surgery in patients with Addison's disease. The glucocorticoids (cortisone and hydrocortisone) seem to be the drugs of choice for pre-operative administration, but the

Preparation	No. of cases	Anaesthesia	Hypotension during or after Anaesthesia.	Mortality
nil	18	14 G.A. 4 L.A.	89%	56%
Specific hormone therapy	20	15 G.A. 5 L.A.	55%	0

Table 1

The effects of anaesthesia and surgery in 38 published and unpublished cases of Addison's disease, related to the pre-operative preparation of the patients with D.O.C.A. and/or cortisone.

synthetic mineralocoricoid, deoxycortone acetate (DOCA) may be required in addition when the condition is severe. The additional stress of the anaesthesia and operation should be counteracted by increasing the dose of cortisone by 25 to 50 mg per day. If severe hypotension occurs it is best treated by infusion of 100 mg hydrocortisone, at a rate of about 25 mg per hour.

Waterhouse - Friderichsenn Syndrome. This is due to haemorrhage into the adrenal gland during meningococcal septicemia. Falcon, Reynolds and Beebe (1950) found that patients showed the same failure of the eosinophil count to fall after adrenaline or ACTH, as occurs in other forms of adrenocortical insufficiency. No details can be traced of anaesthesia or operation in patients who survived the acute episode, but management would be expected to be as for Addison's disease.

Tumours. Cecil (1933) found, in patients who died from removal of an adrenal tumour, that the contralateral adrenal gland could not be found at autopsy. In Cushing's syndrome, Marquardt (1955) considers that there is likely to be atrophy of the contralateral gland or remaining tissue. This is probably due to inhibition of ACTH output by the overactive gland. This cause of adrenocortical insufficiency will be discussed with surgical removal of the adrenal for other causes.

Secondary Hypoadrenocorticism.

This occurs in any conditions where there is hypofunction of the anterior pituitary gland, depriving the cortex of its normal stimulus of adrenocorticotrophin.

Simmond's Disease. Simmonds (1914) was the first to describe a clear relationship between a destructive lesion of the anterior pituitary gland and the clinical syndrome resulting from the lesions. Destruction can be brought about by a variety of pathological lesions e.g. ischemic necrosis during abnormal delivery of the puerperium , tumours, granulomas, injury, surgical hypophysectomy, spontaneous atrophy and fibrosis.

Sheehan (1937, 1949), Sheehan and Murdock (1938) and Sheehan and Summers (1949) have described hypopituitarism after difficult and complicated labours. This cause of pituitary hypofunction, now known as Sheehan's syndrome, is explained by Sheehan and his colleagues as follows. Normally after delivery there is a rapid involution of the pituitary from its physiologically hypertrophied state during pregnancy. The blood supply of the gland is thus suddenly reduced, and if this is complicated by circulatory collapse due to haemorrhage, the blood flow may be reduced to an extremely low level. Thrombosis may thus be precipitated in the sinuses of the gland with consequent infarction and necrosis. It has been suggested by Nassar, Greenwood and Shanklin (1950) that there may be a possible aetiological relationship between the administration of ergot alkaloids to exsanguinated patients and the incidence of post-partum destruction of the anterior portion of the pituitary.

Sheehan and Summers (1949) found the average weight of both adrenals in 26 cases of pituitary hypofunction was 4.7 g (2.2 to 7.8 g), the corresponding range for the normal adult being 10 to 15 g. The medulla remains almost unaffected but the cortex is reduced to about

0.2 to 0.4 mm in thickness, instead of the normal 1 - 2 mm. Investigations of cortical function discloses extremely low values or absence of urinary 17 - ketosteroids and 11 - oxysteroids. However the glands will respond to a limited extent to stimulation by ACTH and adrenaline (Knowlton and Jailer, 1950) in contrast with the complete depression of adrenal function in Addison's disease.

The thyroid is usually small and atrophic in Sheehan's syndrome, but the alteration of architectural structure are not as great as in myxoedema. The basal metabolic rate is usually low (-25 to -35).

Adrenal crisis have been described in cases of hypopituitarism and Heyde (1953) reports on their treatment with ACTH and DOCA. Prolonged coma is liable to occur, ushered in by marked hypotension and salt depletion (Wolff, 1950; Bloom and Wolff, 1955) and hypoglycaemic attacks are common. Hypothermia is another complication which may occur (Sheehan and Summers, 1952) and this may prolong the coma.

Israel and Conston (1952)., described sudden death during Caesarian section (spinal analgesia with amethocaine-dextrose) in an unrecognised case of pituitary necrosis. This shows that these cases of pituitary hypofunction which have not been prepared by specific hormone therapy are liable to collapse with the stress of surgery and anaesthesia, as cases of primary adrenocortical hypofunction.

The following case report (Dr. R. L. Cumming, personal communication) describes an abnormal response to anaesthesia in a fairly typical case of Sheehan's syndrome.

Case 3.

A married woman, aged 37, weight 116 lb (53 kg) complained of always feeling cold, lack of energy, absence of hair under the arms and in the pubic region, amenorrhoea and loss of libido. Ten years previously an uneventful gestation was followed by a severe haemorrhage. The above syptoms led to a diagnosis of Simmond's disease.

The patient was admitted to hospital for cystoscopy, because of dysuria and passage of dark red clots in the urine. On admission the B.P. was 130/100, pulse 70/min, oral temperature 96.8°F (36°C).

The serum electrolytes pre-operatively were:-

Chlorides -	94 m Equiv/l
Calcium -	8.8 "
Potassium -	4.6 "
Sodium -	135 "
Cholesterol	140 mg per 100 ml
Blood sugar	68 mg per 100 ml
Blood urea	30 mg per 100 ml

X-ray of the skull revealed a small pituitary fossa, with thickened bone.

The events on the day of operation were as follows:-

1000 hrs. Pre-operative medication of papaveretum 11 mg, scopolamine 0.2 mg.

1200 hrs. Immediately prior to anaesthesia the patient was drowsy, but responded to questioning and was co-operative.
Anaesthesia was induced with 10 mg d-tubocurarine chloride, followed by thiopentone. The latter was given slowly and the patient lost consciousness after 300 mg. A further 100 mg was given, making a total dosage of 400 mg of thiopentone.
The patient became completely apnoeic and controlled respiration was carried out with nitrous oxide (6l/min) and oxygen (2l/min), using a semiopen circuit, with expiratory valve near the face piece.

1215 hrs. Cystoscopy and retrograde ureteric catheterisation completed.
Patient still apnoeic.
Pulse of good volume 65/min.
Neostigmine 2.5 mg and atropine 0.65 mg given I.V. without response.

1230 hrs. Still apnoeic.
Nikethamide 1 ml I.V. without response.
Patient intubated.
Controlled respiration with oxygen and intermittent carbon dioxide.

1315 hrs. Nikethamide 1 ml I.V.
Respiration started and the patient coughed.
Extubated - respirations continued at the rate of 4 per minute.
Patient deeply unconscious - pupils small and not reacting to light.

1400 hrs. Respirations 4/minute. Pulse 58/min. B.P. 110/70
Still unconscious.

1445 hrs. Patient responded to stimuli.

1500 hrs. Respirations 5/minute. Pulse 60/min.
Blood sugar 70 mg/100 ml.
Blood urea 35 mg/100 ml.
Serum alkaline phosphatase 12 AK units
Serum cholesterol 321 mg/100 ml.

1630 hrs. Respiration 7/minute. Pulse 60/min.
Patient responded to questioning.

1800 hrs. Respirations 8/minute. Pulse 70/min.

2000 hrs. Respirations 14/minute. Pulse 70/min.

Patient appeared in every way normal, although she said she was very sleepy. The following morning, the patient was fully conscious, and had no adverse after effects. The B.P. was 110/70 with respiratory rate of 16 - 18 per min.

There is no doubt that this was an abnormal response to anaesthesia, regarding the aetiology of which one can only postulate several possibilities.

1.. The gradual return of the respiratory rate to normal is suggestive of an overaction of the opiate, rather than the thiopentone. As far as is known, the patient had not had opiates for several years prior to this event. A mistake in dosage, would have been detected earlier,

since two hours elapsed between the administration of the papaveretum and the induction of anaesthesia. Nevertheless, one must consider the already-mentioned recommendation by Best and Taylor (1945) and Thorn, (1949) that patients with adrenocortical insufficiency should not receive opiates.

2.. A low basal metabolic rate would interfere with the metabolism of both thiopentone and papaveretum.

3.. Synergism between two drugs to each of which the patient, by reason of her complaint, proved sensitive. The enhancement by morphine of respiratory depression by thiopentone has recently been convincingly demonstrated by Helrich, Eckenhoff, Jones and Rolph (1956).

4.. It is unlikely that there was a markedly abnormal responses to d-tubocurarine chloride, as slow respiration is not a clinical feature of partial curarisation, in the absence of hypokalaemia.

5.. Hypoglycaemia, as a cause for prolonged coma, can be excluded in the blood sugar reading before return of consciousness.

6.. Hypothermia is also unlikely as a cause of coma, since there was no previous history of similar attacks and two isolated readings of oral temperature during the procedure were 96.8°F (36°C) and 98°F (36.9°C). The enviromental temperature in the theatre was approximately 70°F (21.1°C).

7.. Hypotensive crisis cannot be excluded as the cause of apnoea early on in the procedure, but even in the absence of serial blood pressure readings, this was unlikely to have persisted for long without detection. The pulse rate of 65/minute is not in keeping with a severe

fall in blood pressure, although the anaesthetist commented that the pulse volume was weak after the end of the end of the operation.

8.. Because of the clinically accurate picture of pituitary hypofunction due to Sheehan's syndrome, it can be assumed that, since replacement therapy was not given, some degree of adrenocortical insufficiency was present. This was the first major stress that the patient had encountered since her pregnancy and delivery ten years previously (which was before the onset of hypopituitarism) and her response to anaesthesia must be considered to be an abnormal reaction to stress in the absence of a fully active adrenal cortex. The urinary infection may have acted as an additional stress.

Pituitary Tumours. Roche, Thorn and Hills (1950) have drawn to attention adrenocortical insufficiency occurring in patients with pituitary tumours. They describe a patient in whom the eosinophil count only fell 15% after ACTH. One dose of ACTH was given prior to craniotomy, but the patient developed such severe hypotension under ether anaesthesia that the operation had to be postphoned. Recovery took place after large doses of cortical extract, and six days later after continuous substitution therapy the patient withstood the same anaesthesia and surgical removal of a chromophobe adenoma satisfactorily.

Ingraham, Matson and McLaurin (1952) said that some degree of endocrine dysfunction is probably present in nearly all patients with craniopharyngiomas (supracellar cysts, Rathke's pouch tumours, adenomata, , cholesteatoma, hypophyseal duct tumour), although in

children it is less likely to be apparent than in adults. They review 187 operative cases with an overall mortality of 37%. In case/with[5] replacement of adrenocortical hormones there was no mortality. The mortality of unprepared adults was 41% and 25% in two series of adults as compared with 6% in children.

The operative procedure may in itself compromise pituitary function, where this is not already too depressed, and Ingraham and Matson (1954) suggest the use of pre-operative cortisone or ACTH as a routine procedure. Ingraham et al (1952) think that hormonal therapy might well be extended to any surgery in the parasellar region, as a prophylactic against the complication of operative trauma to the hypothalmus or pituitary gland.

Hayes (1954) describes two patients with pituitary adenoma, in whom adrenocortical insufficiency was diagnosed before operation (by the eosinophil test). Both were prepared for surgery by the administration of 100 mg cortisone daily for four days. In one patient the operation was carried out unevenfully, with a smooth postoperative course, despite the fact that the eosinophil count rose considerably during the operation. In the other patient in whom the operation was more difficult, two rises in the eosinophil count occurred and each was associated with marked hypotension from which recovery occurred after adrenal cortical extract. Hayes considered the preparation of these patients to be inadequate and since intramuscular deposits of cortisone which liberate it at a fixed rate, may not rise to the increased demand during severe stress unless sufficiently large doses are used.

The following report substantiates the importance of adequate abnormal sustitution therapy in such cases.

Case 4.

A fit male had an uneventful removal of a pituitary adenoma. Papaveretum 21 mg and scopolamine 0.4 mg was given as pre-operative medication. Anaesthesia was induced with 400 mg thiopentone and oral intubation carried out after 60 mg gallamine triethiodide. Maintenance was with nitrous oxide-oxygen-trichloroethylene with further increments of thiopentone, to a total of 800 mg. The B.P. and pulse remained steady throughout and all blood loss was fully replaced. Consciousness returned within 20 mins of the end of the operation.
Four hours postoperatively, the B.P. was found to be unrecordable and the pulse uncountable. The patient was unconsciousness with a hyperpyrexia of 104°F (40°C). Oxygen was administered and the patient was sponged with iced water. Infusion of adrenaline, followed by l-noradrenaline was without effect on the B.P. and the patient died two hours later.
Autopsy revealed no cerebral cause for the death : the adrenals were not examined.

The fatal outcome in this case is most likely to have been due to adrenal insufficiency, although this possibility was not considered at the time. Details for the pre-operative preparation, with cortisone or ACTH of patients for surgery of the pituitary gland are given by Ingraham et al. (1952).

Drug Induced Adrenocortical Insufficiency.

The simulation of hypofunction of the adrenal cortex produced directly by cortisone and similar drugs, or indirectly by ACTH, is accompanied by a wide variety of physiological and metabolic changes, some desirable and others unfavourable. Among the latter are alterations in the function of the anterior pituitary gland and adrenal

cortex, which maintain the ability of the body to withstand many different types of stress. The increased blood glucocorticoid level (which exogenous cortisone produces directly, and which exogenous ACTH produces by adrenal stimulation) leads to inhibition of endogenous ACTH. This in turn leads to marked hypoplasia of the adrenal glands.

Cortisone and similar compounds. Adrenocortical function has been studied in 19 patients who were receiving long-term cortisone therapy. In the first report, by Engleman, Krupp, Johnson, Welsh, Wrenn and King (1953), the drug had been administered for periods of 13 to 38 months and the more recent publication (Fredell, Johnson, Krupp, Engleman and McGrath, 1955) reports on the same subjects after 30 to 50 months cortisone treatment. Both studies revealed supression of adrenocortical function. It was uncertain whether the degree of suppression was proportional to the duration of treatment. The cortex was still responsive to stimulation by ACTH, but the response was delayed. Thyroid activity appeared to be unaffected by the prolonged cortisone therapy in these patients, although other workers (Wolfson, Beierwaltes, Robinson, Duff, Jones, Knopp and Eva, 1950; Fredrickson, Forsham and Thorn, 1952) have produced good evidence of hypothyroidism resulting from prolonged cortisone therapy.

Solassa, Bennett, Keating and Sprague (1953) found a decrease in the weight of the adrenal gland at autopsy when more than 5 days cortisone therapy had been given not less than 20 days prior to the death of the patients. If the drug had been stopped for more than 21

days before death, no significant changes were found in the adrenals. They stressed the fact that adrenocortical insufficiency may develop after as little as five days treatment with cortisone. Clinical reports (to be discussed later) suggest that adrenal insufficiency may persist, after withdrawal of the drug, for much longer than the 21 days when the glands regain their normal weight.

There is histological evidence that cortisone induced adrenal dysfunction is a reversible change (O'Donnell, Fajans and Weinbaum, 1951). One patient whose therapy had been stopped 51 days prior to death, had a zona glomerulosa of normal width and hypertrophic cells in the fascicular and reticular layers, similar to those seen after the administration of A.C.T.H.

O'Donnell et al (1951) and Solassa et al (1951) found that the adrenal changes after cortisone treatment resemble those seen in patients who had clinical and post-mortem evidence of hypopituitarism. This supports the theory that exogenous cortisone induces adrenal atrophy by suppressing the secretion of pituitary adrenocorticotrophic hormone.

Adrenocorticotrophic hormone (ACTH). Lewis, Robinson, Gee, Hacker and Eisen (1953) suggest that ACTH therapy is less likely to result in adrenocortical sufficiency, after its withdrawal, than is cortisone. Long-term ACTH administration leads to no decrease, or even an increase in adrenal size, because the exogenous ACTH more than compensates for the diminished ACTH output by the anterior pituitary. However Solassa et al. (1953) point out that it is unlikely that the use of ACTH will

entirely eliminate the risk, since, like cortisone, ACTH leads to histological changes in the pituitary and endogenous adrenocorticotrophic hormone output is therefore suppressed by the exogenous drug. After cessation of treatment with ACTH, the adrenal cortex is fully responsive to pituitary stimulation, if the function of this latter has not been too markedly suppressed, whereas after cortisone the adrenal is partially or wholly incapable of response to pituitary stimulation.

Thorn, Forsham, Frawley, Hill, Roche, Staehelin and Wilson (1950) have summarised drug-induced adrenocortical insufficiency as follows, - "Either preparation (cortisone or ACTH) induces anterior pituitary hypofunction owing to increased endogenous production of adrenal steroids after ACTH administration and to the administered steroid itself after cortisone. At the end of the administration of ACTH, the delayed return of the hypoactive pituitary function to normal deprives the hypertrophied adrenal cortex of stimulation and leads to transient adrenal hypofunction as measured by steroid excretion. After cortisone the marked cortical atrophy accentuated temporary adrenal hypofunction".

Sudden withdrawal. Headache, nausea, vomiting, restlessness and muscle and joint pains occurring 24 hours after sudden withdrawal of cortisone from patients previously receiving the drug over a long period, have been described by Henneman, Wang, Irwin and Burrage (1955); Lewis et al (1953) describes a syndrome similar to Addison's disease after sudden withdrawal of cortisone. They state that withdrawal of ACTH

seldom leads to the prompt relapses in disease and the quasi-Addisonian state which may follow sudden cessation of oral cortisone therapy. This may be due to the increased responsiveness of the patient's adrenal cortex fully compensating for the lessened pituitary adrenocorticotrophic output.

Anaesthesia and Surgery. Lundy (1952, 1953) drew the attention of anaesthetists to the possibility that a hypofunctioning adrenal cortex (induced by cortisone therapy, and persisting after discontinuation) maybe inadequate to maintain the patient through the usual stress of anaesthesia and surgery. An editorial in the Journal of the American Medical Association (1952) drew attention to this hazard, as have Wood-Smith and Payne (1955) in this country. Some of the published case reports which evoked these warnings are summarised below.

A patient who underwent major surgery after receiving cortisone for a period of eight months, died of immediate postoperative shock, in spite of normally adequate therapy (Fraser, Preuss and Bigford, 1952). Spinal analgesia and thiopentone were employed and the pre-operative B.P. of 140/80 did not fall below 118/80 during operation, with pulse rate varying between 72 and 80 per minute. Autopsy - marked bilateral adrenal atrophy.

Solassa et al (1953) describe two postoperative deaths (following a gastrectomy and bunionectomy) in patients who had been previously treated with cortisone.

Lewis et al (1953) reported a fatality in the immediate postoperative period in a patient who received cortisone (62.5 to 100 mg) daily for a period of 5 months (total dose 8.5 g) for rheumatoid arthritis. Operation was a corrective tendon lengthening, lasting 2½ hours. Anaesthesia was with thiopentone - nitrous oxide - oxygen, during which B.P. was 120-110/80-70, and pulse rate was 80-90/min throughout.

On return from surgery the B.P. dropped to 80/60. One and a half hours postoperatively the patient was restless,

pulse thready, rapid and uncountable with unrecordable B.P. Oxygen and blood transfusion produced some improvement.

Two hours postoperatively : some improvement, pulse rate 164/min, respiratory rate 48/min, hyperpyrexia had occurred and patient was still restless.

Cheyne-Stokes respiration developed 5½ hours after operation and the patient died 15 minutes later.

Autopsy : Both adrenals were smaller than normal.
Atrophy of both cortex and medulla.
Pituitary normal, save for slight hyperaemia.

The authors at first thought that this was a case of Waterhouse-Friderichsen syndrome, but it proved to be more than a simple haemorrhagic lesion. The disappearence of medullary tissue may have been an artefact.

The following case reported by Harnagel and Kremer (1955) is instructive, since prior to the incident described the patient had undergone seven identical procedures, before the onset of cortisone therapy, without incident.

Cortisone 1.9 g, had been given over one month for rheumatic spondilitis with peripheral joint involvement. Thiopentone (dose not recorded) was given for a manipulation which lasted about one minute. The recovery was somewhat slow as the result of which the patient missed the evening dose of cortisone.

Twelve hours after operation : patient was deeply comatose, cyanosed, sweating, B.P. unrecordable, pulse rate 140/min, eosinophils 240/cu mm.

Treatment was with l-noradrenaline infusion in 5% dextrose, containing 80 units ACTH per litre. Approximately 80 units were given per 24 hours. Adrenal cortical extract (Eschatin) was also given intravenously and cortisone administered rectally, then by I.M. injection.

The patient remained moribund and hyperpyrexic for 24 hours pulse 140-160/min. Twitching of muscles occurred resembling decebrate rigidity, and this was not affected by calcium gluconate.

Improvement began on the second postoperative day, the B.P. being 90/70.

The patient gradually regained consciousness and there were no untoward sequelae.

This patient had received no cortisone for 18 hours before operation, and for 30 hours before the onset of shock. The normal eosinophil count after surgery and after ACTH (Roche, Thorn and Hills, 1950) is indicative of adrenal hypofunction. The muscle twitchings were attributed by the authors to be due to cerebral anoxia. They point out the hazards of pre-operative preparation with oral cortisone, after which the peak blood concentration is attained in 4 hours, the drug being completely dissipated in 12 hours. The use of the intramuscular route provides a depot, from which the cortisone is gradually released into the circulation.

The following cases further illustrate the hazards that are attendant on the administration of cortisone, and for some time after cessation of treatment.

Case 5.

A 27 year old female medical student, who appeared to be in excellent health, had dislocated her shoulder, about four hours prior to anaesthesia. Atropine 0.6 (1/100 gr) was given intravenously, followed five minutes later by the very rapid administration of 500 mg 5% buthalitone sodium. This produced the desired relaxation, and the dislocation was reduced without difficulty and a sling applied. The whole procedure was completed in less than one minute.

The rapid return of consciousness expected after this anaesthetic technique did not occur. Ten minutes after the buthalitone the patient was still sound asleep, respirations were fast and shallow and there was slight cyanosis of the extremities. Silent aspiration of gastric secretions was suspected, but auscultation revealed good air entry on both sides of the chest. Inhalation of oxygen was commenced, but the cyanosis persisted. Controlled respiration was instituted five minutes later, with lessening of the cyanosis. The contents of all ampoules were checked to exclude the possibility of a relaxant being confused with atropine.

Twenty minutes after the anaesthetic, the B.P. was recorded for the first time and found to be 60/40, with pulse rate of 140. The patient was placed in 20° head down position and 2.5 mg methoxamine given intravenously and 5 mg by intramuscular injection. Within 5 minutes the pulse rate had dropped to 70, the patient opened her eyes, although the B.P. had only risen to 90/60. Oxygen inhalation was continued, but the respiratory volume was now adequate. Infusion of 5% glucose in normal saline was started so as to be available should the administration of l-noradrenaline be required.

The B.P. rose slowly over the next half hour, and was 110/75, with pulse rate of 60, over one hour after the induction. The patient was still slightly drowsy. Half a litre of the fluid (25 g glucose and 4.5 g Na Cl) had been run in quickly and the infusion was discontinued.

Consciousness had returned to normal and the patient was walking around, anxious to leave hospital, six hours later. She was retained overnight and in the morning E.C.G. serum K, Na and Cl and blood urea levels were all within the range of normality.

There was no previous history of collapse following anaesthesia, although appendicectomy had been performed two years previously (under spinal anaesthesia) and a cervical dilatation for dymenorrhoea was carried out (under thiopentone - cyclopropane anaesthesia) about 8 years previously. Her last illness was seven weeks before the dislocation, when arthralgia of unknown aetiology responded to cortisone therapy. Until 28 days before the above incident she had been taking 12.5 mg cortisone daily for one week, preceeded by 25 mg daily for a further week. The total dose given was not known, but she said that large doses were given to her at the beginning of the treatment.

The diagnosis of cortisone - induced adrenocortical insufficiency in this patient is based entirely on the history, and on the similarity of the postoperative course to that of the cases already described. In the next case, the presence of drug - induced cortical insufficiency is more certain.

Case 6.

A woman, aged 30 had been on oral cortisone therapy for almost two years, the daily maintenance dose being 25 mg in two divided doses. General health was good.

Operation was for uterine curettage.

The morning dose of 12.5 mg cortisone was taken at 7 a.m., pre-operative medication of quinalbarbitone 100 mg and hyoscine 0.4 mg was given I.M. at 1 p.m. and anaesthesia induced with thiopentone at 2.15 p.m. Maintenance of anaesthesia which was with intermittent thiopentone - nitrous oxide - oxygen was uneventful. B. P. on leaving the theatre (2.50 p.m.) was at the pre-operative level of 115/70, but pulse rate had increased from 84 to 116 per minute. As far as could be ascertained the return of consciousness was not delayed, and the condition of the patient on return to the ward did not cause any concern.

About 4 p.m. the patient was found to be moribund, with an uncountable pulse rate and unrecordable blood pressure. She was barely conscious. Respirations were fast and shallow.

Two possible diagnoses were considered (a) rupture of the uterus and (b) acute adrenocortical insufficiency.
Treatment : Immediate I.M. injection of 5 ml cortical extract (Eschatin). Blood transfusion and infusion of phenylephrine were started. One pint of blood given quickly had no effect on the blood pressure and as phenylephrine was also without value, l-noradrenaline was substituted after one hour. The blood transfusion was replaced by 5% dextrose containing 75 mg cortisone per 500 ml. The patient gradually lapsed into coma, and at 6 p.m. since the nor-adrenaline was ineffective in raising blood pressure, it was replaced by Dextran. Two further doses of Eschatin had been given. Oxygen therapy was also started.

At 9 p.m. about 125 mg cortisone had been given and preparations were being made for laparotomy when l-noradrenaline was re-started. This raised the systolic blood pressure to 60 mm Hg. In view of this improvement, surgical intervention was postponed. Twelve hours after operation the B.P. could be maintained at 70/40 by a slow infusion of l-noradrenaline. The patient was still unconscious, and the improvement, rather than the expected deterioration in her condition led to cancellation of the laparotomy. By now one litre of dextrose (150 mg cortisone) had been given and this infusion was stopped and 25 mg cortisone acetate given I.M.

On the morning after operation the patient was conscious but drowsy and slightly restless. B.P. was 90/50 without l-noradrenaline. Respirations were still fast and shallow and breath sounds were absent at the base of one lung. Oral temperature was 38.5°C (101.3°F). The improvement was not maintained, respiratory distress increased and the patient again lapsed into coma. A slow 5% dextrose in normal saline infusion containing 100 mg hydrocortisone was started and a further 25 mg cortisone given I.M. Massive doses of antiobiotics were given parenterally.

Tracheo-bronchial toilet was performed 20 hours after operation and much frothy mucous removed. This produced an almost immediate improvement and by the evening the patient was again conscious. B.P. was 100/70 (without l-noradrenaline) and all intravenous therapy was stopped.

In spite of the prompt treatment, enormous doses of cortisone and similar drugs were required during the first 24 hours after operation (Cortisone 150 mg I.V., 50 mg I.M; Hydrocortisone 25 mg I.V; Eschatin 15 ml I.M.) Roche, Thorn and Hills (1950) point out that the hypokalaemia and hypochloraemia which accompanies the administration of excess cortisone can cause muscular weakness and paralysis. It is a matter of speculation whether this played any part in the pulmonary collapse in this patient. The failure of blood pressure response to phenylephrine and the early poor response to l-noradrenaline are very different from the effects of methoxamine in Case 5. It is unlikely that this points to a preference for the latter pressor amine, as the duration and intensity of cortisone therapy and the degree of vasomotor collapse were much greater in the second patient.

Case 7.

Male aged 74, weight 150 lb (68 kg). Admitted to hospital with acute intestinal obstruction. Four months previously laparotomy was performed for perforated peptic ulcer, which was found to be due to an inoperable carcinoma of the stomach. For some unknown reason, the patient had been given 25 mg cortisone daily since his discharge from hospital. His general condition was fairly good until two days before admission to hospital when he began to vomit. He had not taken the cortisone during these two days.

The possibility of adrenocortical insufficiency, with its attendant dangers was fully appreciated before induction of anaesthesia. Pre-operative medication was with cortisone 150 mg I.M. and desoxycorticosterone acetate 5 mg I.M. and atropine 0.4 mg. The subsequent course of anaesthesia and the immediate postoperative period are shown in Figure 1.

A Oral intubation under topical (10% cocaine anaesthesia. Induction with 150 mg 2.5% thiopentone, followed by cyclopropane and oxygen. 0.2% suxamethonium infusion started.

B Slow blood drip started.

C Exploring abdomen : Blood pumped in fast 20 mg hydrocortisone acetate I.V.

D Operation stopped for 10 minutes.

E 1000 ml blood given : Saline infusion started containing 100 mg hydrocortisone acetate.

F Exploring abdomen.

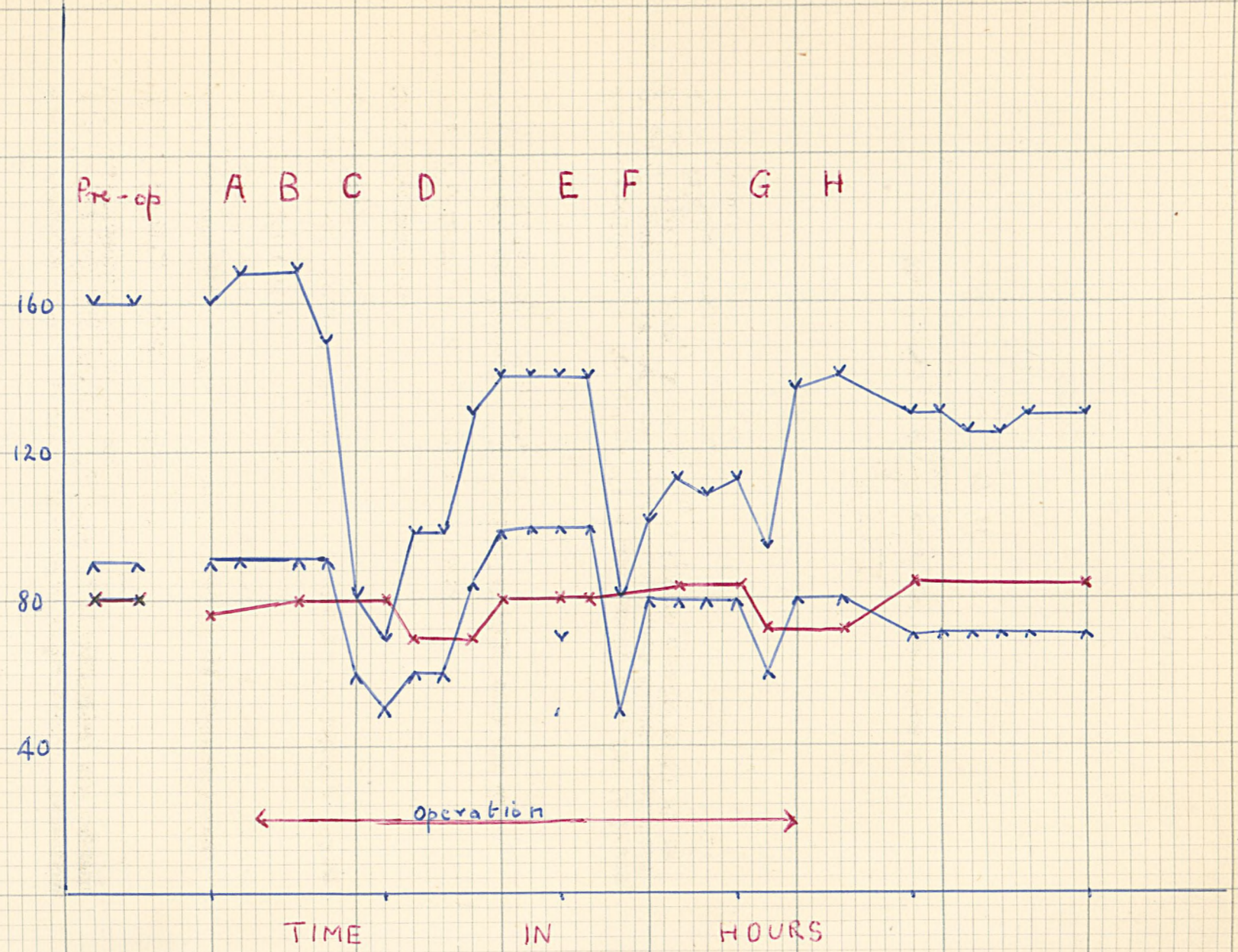
G Closing abdomen : suxamethonium stopped.

H Respirations spontaneous : Extubated : Skin warm and dry, colour satisfactory. Responds to name.

Post-operatively : Cortisone 50 mg six hourly I.M. for 24 hours; 25 mg six hourly for next two days. Parenteral fluids continued for 48 hours. Gradual decrease in cortisone dosage until 25 mg given B.D.

Figure 1

The Course of Anaesthesia and Operation in Case 7.


Pre-op
A
B
C
D
E
F
G
H
160
120
80
40
operation
TIME IN HOURS

Two severe blood pressure falls occurred during the operation, and the only evidence that they may have been partly due to adrenocortical insufficiency is the prompt response to intravenous hydrocortisone. This patient died on the 13th postoperative day from generalised peritonitis arising from his surgical condition, and atrophy of the cortex of both adrenal glands was found at autopsy.

Case 7 shows the value of pre-operative appreciation of the possibility of adrenocortical insufficiency in patient who have been or are still receiving cortisone or ACTH therapy. What the course of events in this patient would have been in the absence of the pre-operative administration of cortisone is a matter for speculation, but on the basis of previous reports the smooth postoperative course would not have been expected.

While the immediate recognition of postoperative collapse due to Addisonian crisis is obviously important and sometimes life saving (as in two of the above cases), it is vital that the possibility of adrenocortical insufficiency be appreciated pre-operatively and that substitution therapy be included in the pre-operative medication. Experience shows that it seems to be easier to prevent a collapse than treat already established hypotension.

The severity of the operation does not seem to be important as any operative procedure appears to be a sufficient stress to induce hypotension. Whether this would be caused by anaesthesia alone is not known. Roche, Thorn and Hills (1950) found that patients failed to show a fall in eosinophils after thiopentone anaesthesia

alone. They thought that anaesthesia may block a normal pituitary - cortex response, and a maximum stress may be needed to break through this inhibition. This probably depends on the method of administration of the thiopentone, as the severe hypotension which follows its rapid injection can obviously act as a stress in itself. In support of this view is the immediate collapse after its rapid injection in a case of Addison's disease (Dundee 1951) and a similar occurrence following the rapid administration of another thiobarbiturate (buthalitone) in case 1. In the two other cases of Addison's disease described previously and in cases 2 and 3 the drug was administered slowly. It is not possible to confirm or refute this hypothesis on the data given by other authors in the cases of drug - induced cortical insufficiency described above.

Pender (1954) discusses the anaesthetic management of cases of induced adrenocortical insufficiency in which the condition was recognised before induction. He advises substitution of pethidine for morphia and caution in the use of respiratory depressant drugs, unless reliable facilities are available for the maintenance of an adequate tidal volume. It would also seem advisable to avoid the drugs which cause severe falls in blood pressure such as deep ether or rapidly injected thiopentone.

Since patients with other types of adrenocortical insufficiency can, if properly prepared for operation, withstand controlled hypotension without ill effects, there is no reason to believe that, with the similar preparation, the patients in this group will behave differently. Again, it must be stressed that the first step in

treatment is awareness of possible adrenocortical insufficiency in patients receiving cortisone or ACTH, or who have received either drug within the past 12 - 18 months.

Solassa et al (1953) comments that many thousands of patients must have been operated on after cortisone without ill effects, and considers that the risk involved is not very great. It may be of significance that the first warnings of this danger came from the Mayo Clinic (Lundy 1952, 1953) and (Patrick et al, 1952; Pender, 1954), where the treatment of rheumatoid arthritis with ACTH and cortisone by Hench et al was described as early as 1949, and where the deaths reported by Solassa et al occurred. In this country, cortisone only became generally available on 5th December 1955, and as yet the percentage of patients who are receiving, or have received the drug is unlikely to be as great as in the United States. It use may increase in Britain and since there is no simple method of predetermining which patients are liable to collapse, all cases should be questioned before operation, as to previous cortisone therapy.

Many recommendations have been made on the pre- and post-operative dosage of cortisone in patients with adrenocortical insufficiency (Elrick, 1950; Huggins and Bergenstal, 19511 Ingraham, Matson and McLaurin, 1952; Lewis et al, 1953; Romagnoli, 1955). The more recent of these should be consulted for details. As a rough guide, 100 - 150 mg cortisone is given daily on the two days before operation and the same dose repeated by intramuscular injection one hour before the induction of anaesthesia. After operation 25 mg is

given parenterally every four to six hours, and the frequency of administration is gradually decreased over a period of 7 to 10 days, until a satisfactory maintenance dose is obtained, if such is necessary.

The increasing literature on the therapeutic uses of the glycocorticosteroids makes it difficult to keep abreast with the numerous conditions in which one should be on the outlook for drug-induced adrenocortical insufficiency. Appendix 2 summarises the uses of hydrocortisone and should be useful in this respect.

Surgical Removal of Adrenal Tissue.

Bilateral adrenalectomy for non-malignant tumours of the adrenals has become more widely practised for advanced carcinoma of the breast or prostate and in some cases of severe hypertension. Despite the fact that these patients may have extensive metastases or cardiovascular disease, since it it fully appreciated that adrenocortical insufficiency may occur and replacement therapy is administered as a routine. (Hollander et al, 1952; Galante and McCorkle, 1955; Govearts et al, 1955; Cade, 1956; Latham, 1956). The risk of severe hypotension occurring during or after operation is less than in less seriously ill patients (as in previous group) in whom adrenocortical dysfunction is not diagnosed before operation. Latham (1956) advises the administration of cortisone before removal of the first adrenal in patients with malignant disease, in case the second gland may be replaced by carcinomatous tissue. Occlusion of the veins of the second gland,

with resultant diminution of output of catechol amines, frequently results in an abrupt fall in blood pressure, which can be corrected by infusion of l-noradrenaline.

Collier (1955) has described the use of controlled hypotension (with hexamethonium) in an adrenalectomised subject. (Cortisone 150 mg was given by intramuscular injection two hours before induction of anaesthesia, the course of which appeared to be what one would expect in a normal subject). The blood pressure rose from 70/50 to 80/50 when the table was levelled but the return to normal was slightly delayed, and infusions of blood and dextran were given. Cortisone therapy was started two hours after operation, and almost certainly prevented postoperative hypotension. In light of the previous discussion it is worth recording that this patient received 10 mg morphine as pre-operative medication, and the same dose was repeated one hour and six hours after operation, without any detectable effect on the blood pressure.

Attention has already been drawn to the atrophy of one adrenal cortex that frequently accompanies hyperactivity of the other gland. The management of patients with hypercorticism may be difficult as the patient is plunged from hypercortical activity to adrenocortical insufficiency without time to allow opportunity for adjustment (Elrick 1950). Walters and Kepler (1938) reported 50% mortality from removal of 40 adrenal cortical tumours, before the introduction of cortisone. Perkoff, Jager and Tyler (1955) found that postoperative hypotension was more common after operations for Cushing's syndrome than after

adrenalectomy for causes not affecting the gland itself. In place of the 100 mg of cortisone which is given 48, 24 and one hour before adrenalectomy, Latham (1956) recommends double this dose in patients with Cushing's syndrome. Removal of a hyperfunctioning adrenal cortex may also be carried out in patients with female pseudohermaphroditism (adrenal virilism) and in the patients the use of large doses of cortisone is recommended before and after operation (Jones and Jones, 1954).

Unrecognised Adrenocortical Insufficiency

There is a growing accumulation of clinical data which suggests that in many cases, not fitting into any of the above categories, the appearance of intractable hypotension (not accounted for by blood loss, posture etc.) during anaesthesia and surgery may be a manifestation of failure of the adrenal cortex (Galante et al. 1954; Hayes, 1954). Howland, Schweizer, Boylan and Dotto (1956) describe 7 cases in support of this view and in addition, suggest that other signs such as respiratory depression or failure to react after anaesthesia may be part of the same syndrome. Their patients were mostly chronically ill and in poor general health and condition before operation. In all cases the response to intravenous hydrocortisone was rapid and sustained.

This new concept of intractable hypotension, based on the beneficial therapeutic effects of intravenous hydrocortisone (100 mg in 500 ml 5% dextrose) is worthy of serious consideration, in view of

the present unsatisfactory methods of treatment of so called "Irreversible shock". Although the following case report is complicated by the use of hypothermia, it is very suggestive of undiagnosed adrenocortical insufficiency.

Case 8.

A woman, aged 62, had complained of unsteadiness of gait for three years. Her general condition was fair and although she had mitral stenosis for many years, her excercise tolerance was good.

Premedication was with pethidine 50 mg and chlorpromazine 50 mg given by deep I.M. injection one and a quarter hours before induction of naesthesia. On arriving in the anaesthetic room, she was sleepy but could be roused quite easily.

Anaesthesia was induced with thiopentone and continued with nitrous oxide and oxygen. Hypothermia was induced according to the technique described by Burrows et al (1955). The subsequent course of anaesthesia is shown in Figure 3. Operation was cerebellar craniotomy with removal of a tumour from the cerebellar-pontine angle.

The comparatively sudden fall in blood pressure towards the end of operation, which was not due to operative intervention or blood loss, and its failure to improve with blood transfusion, methoxamine or l-noradrenaline, presented a problem which which was solved by the administration of hydrocortisone.

SUMMARY

The conditions in which adrenocortical insufficiency may be found are discussed.

The hazards of anaesthesia and operation in the cases of absence of suitable hormonal replacement is described.

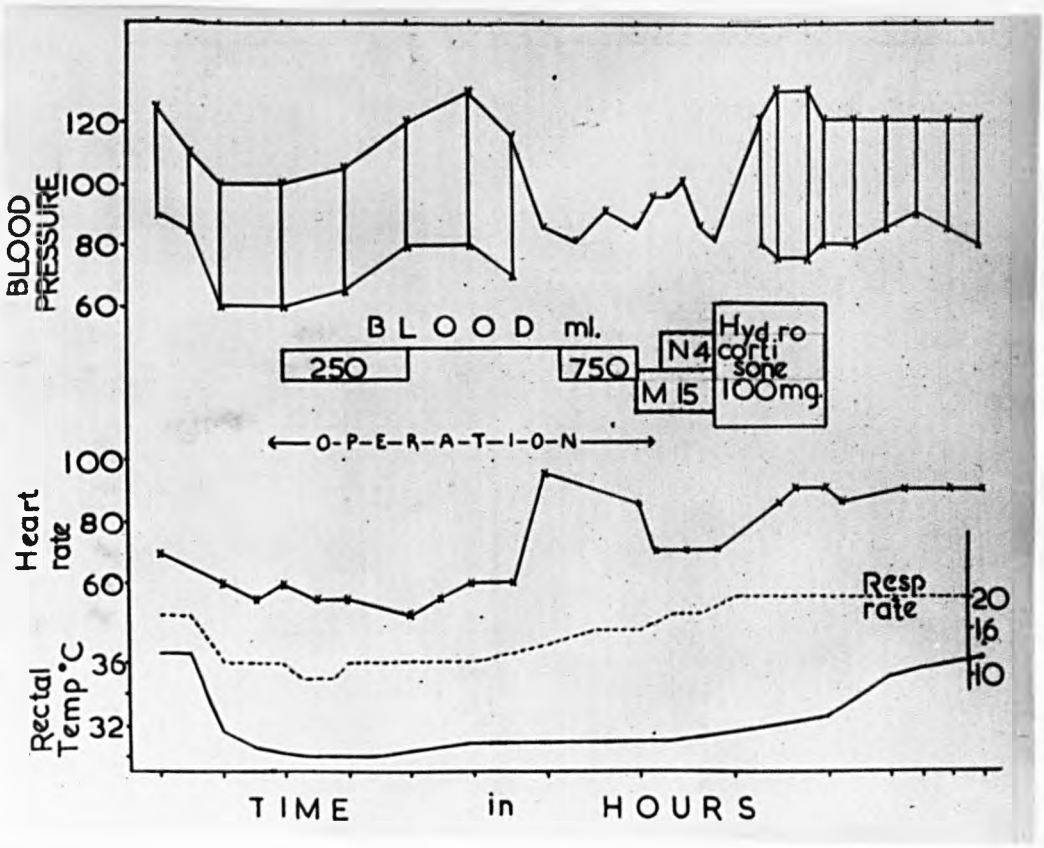


Figure 2.

The Course of Anaesthesia and Surgery in case 8.

M 15 = Methoxamine 15 mg.

N 4 = 1-nor-adrenaline 4 mg.

Appendix 1.

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Appendix 2.

Conditions Responding to Therapy with Hydrocortisone.

(by permission Merck - Sharp & Dohme Ltd.)

Arthritic Conditions

Rheumatoid arthritis including
  Rheumatoid spondylitis
  (Marie-Strumpell disease)
  Still's disease
Psoriatic arthritis
Acute gouty arthritis
Traumatic arthritis
Osteoarthritis

Acute Rheumatic Fever

Collagen Diseases

Dermatomyostis
Early periarteritis nodosa
Sclerodema
Disseminated lupus
  erythematosus

Allergic States

Bronchial asthma
Drug sensitivity
Angioneurotic oedema
Hay fever
Serum sickness
Transfusion reaction

Skin Diseases

Pemphigus
Atopic and other allergic
  dermatitis
Exfoliative dermatitis,
  including skin lesions
  secondary to drug reactions.

Eye Diseases

Iritis
Iridocyclitis
Chorioretinitis
Uveitis
Retinitis centralis
Herpes zoster ophthalmicus
Retrobulbar neuritis
Optic neuritis
Sympathetic ophthalmia
Choroiditis
Non-specific superficial
  keratitis
Deep keratitis
Acne rosacea keratitis
Phlyctenular keratoconjunctivitis
Allergic conjunctivitis
Retrolental fibroplasia
Corneal injuries - opacties,
  burns (thernal and chemical)
Recurrent marginal ulceration.

Blood Diseases

Acquired haemolytic anaemia
Allergic purpura
Idiopathic thrombocytopoenic
  purpura
Rh incompatibilities

Leukaemias and Lymphomas

Acute leukaemia (lymphocytic
  or granulocytic)
Chronic lymphatic leukaemia
Lymphosarcoma
Hodgkin's disease (transient
  involution of neoplasm)

Adrenal Insufficiency

Addison's disease
Waterhouse-Friderichsen syndrome
Adrenalectomy for hypertension,
Cushing's syndrome, or
neoplastic diseases.

Dental Conditions

Acute or chronic gingivitis
Hyperplastic gingivitis
Denture sore mouth
Gingivitis of pregnancy
Discrete aphthous ulcers
(canker sores)
Burns (limited to small areas
of oral mucous membrane)
Aphthous stomatitis
Allergic stomatitis

Other Conditions

Adrenogenital syndrome
Sarcoidosis
Berylliosis
Bursitis
Hunner's ulcer
Sprue
Nephrotic syndrome (in the
absence of uraemia, for
diuresis)
Trichinosis (only as applied
to allergic manifestations)
Thyroid crisis
Bell's palsy in acute inflammatory
reactions
Laryngeal oedema
Incurable malignant diseases (for
sense of well-being)
Non-suppurative thyroiditis (giant
cell thyroiditis and struma
lymphomatosa or Hashimoto's disease)
Ulcerative colitis (other treatment
failing - with observations for
perforation or haemorrhage)

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Use of Thiobarbiturates in Certain Pathological States.

D Acute Intestinal Obstruction.

"ANAESTHESIA FOR ACUTE INTESTINAL OBSTRUCTION"

Reprinted from the British Journal of Anaesthesia, (1950)
Volume 22, pages 131 - 144.

Much of the reasoning in this paper is now outdated, but pages 137 and 140 - 141, of the reprint describe fatalaties following the use of thiopentone, and discuss its uses.

Reprinted from *British Journal of Anæsthesia*, Vol. XXII, No. 3
July 1950

ANÆSTHESIA FOR ACUTE INTESTINAL OBSTRUCTION*

By JOHN W. DUNDEE

ALMOST a century ago John Snow (1853) described 19 cases of operation for strangulated hernia in which the anæsthetic used was chloroform. For the next fifty years ether, in spite of its increasing popularity, was considered to be contra-indicated in these cases (Buxton, 1888) and chloroform remained the drug of choice for acute intestinal obstruction (Hewitt, 1893). The virtue of chloroform in all cases was attributed to the quiet respiration it produced. With the introduction of spinal analgesia, and the discovery of procaine for local infiltration, general anæsthesia was used less and less for seriously ill cases. The opinion is held (James, 1944) that such cases stand a better chance of recovery if a general anæsthetic, no matter how light, is avoided altogether, and regional analgesia is recommended for elderly patients with strangulated hernia (Gillies, 1947). Spinal block will provide the quiet respiration to which chloroform owed its popularity (McGavin, 1911) but deaths have been reported in cases of operation for acute intestinal obstruction in which it has been used (Lake, 1933), due to marked fall in blood-pressure. Where the intercostal muscles are paralysed by high spinal block, expulsion of fluid from the pharynx becomes difficult (Howard-Jones, 1933), and the endotracheal technique with gauze pack or inflated cuff is considered safer (Hewer, 1948) because less

* A Paper read before the Liverpool Society of Anæsthetists, March 26, 1950.

fall in blood-pressure occurs and aspiration of vomitus is avoided.

This is a report of 100 consecutive unselected cases of operation for acute intestinal obstruction, in which all commonly used anæsthetic agents were employed in an attempt to find that which was best suited to all cases.

Figure 1 and Table I show the age distribution and preoperative clinical findings in the series.

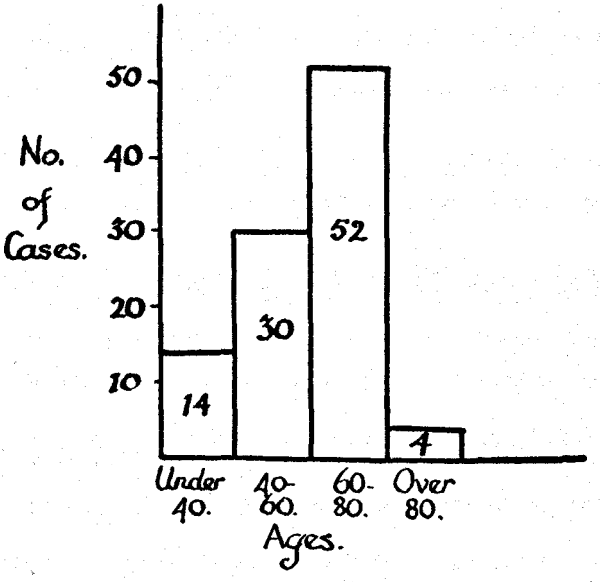

FIG. 1
Diagrammatic representation of the ages of the patients in the present series.

Comments on Table I. Vomiting varied in duration between 12 hours and 6 days, with 48 hours as average.

The incidence of cases with concurrent pulmonary disease was 37 per cent, while 45 per cent had some cardiovascular disease (excluding blood-pressure anomalies) which could be detected clinically; no electrocardiograms were taken.

The high percentage of blood-pressure anomalies is not surprising considering the mean age of the patients in the whole series, 67 years.

TABLE I

Pre-operative conditions of patients

	Per cent
Operations within previous 3 weeks	11
Neoplasms 5 Appendicitis 3	
Ruptured bladder 1 Purely coincidental 2	
Vomiting (50 per cent of these fæculent)	64
Concurrent Pathology	
Pulmonary:	
Chronic bronchitis and emphysema	25
Pulmonary tuberculosis	7
Atelectasis from previous operation	3
Neoplasm of bronchus	1
Pneumokoniosis	1
Cardiovascular:	
Some irregularity in pulse	21
Tachycardia (over 120/min.)	14
Some degree of heart failure (5 of these were cyanosed)	8
Auricular fibrillation	2
Angina of effort	2
Hæmoglobin (estimated in 32 cases) under 65 per cent ...	25
Blood-pressure (recorded in only 50 cases)	
Hypertension (systolic = 100 + age/2 as normal) ...	56
Hypotension (systolic under 100 mm. Hg)	16
Grossly emaciated	20
Blind	4
Diabetes	2

The hæmoglobin figures are misleading since it was estimated only in patients who appeared to be anæmic.

Excluding hypertension, chronic bronchitis and diabetes, 66 of the cases had some concurrent pathology which would have been treated before subjecting them to elective surgery.

In Table II are shown the causes of obstruction.

In Figure 2 is shown the distribution of operating times.

TABLE II

Causes of obstruction

	Per cent		Per cent
Neoplasms	35	Herniæ	33
Adhesions	11	Volvulus	7
Diverticulitis	5	Gall stone ileus	12
Others	7 per cent		

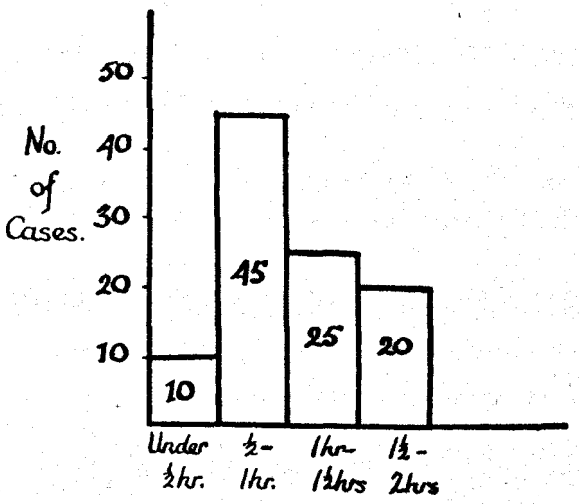

FIG. 2

Diagrammatic representation of the duration of operation in the present series.

The average operating time was 55 minutes. This can partly be explained by the fact that 62 per cent of the operations were performed by registrars and in 36 per cent of the cases the surgeons were relatively inexperienced.

Fæcal vomiting was correlated with a high death-rate. Ten of the total number of deaths occurred among the 32 cases who had this sign. In only three instances could death be attributed to anæsthetic technique.

The 19 per cent mortality (see Table IV) compares closely with the 21 per cent in the series described a century ago by Snow (1853). But it should be remembered that more seriously ill patients than was the case a century ago are now given—what is to them the only hope of recovery —surgical treatment.

TABLE III

Post-operative complications

	Per cent		Per cent
Major Respiratory ...	17	Cardiac Failure	9
Burst Abdomen	8	Thromboses	6
Mental Deterioration ...	4	Uræmia	2
Delayed Chloroform Poisoning		1 per cent	

TABLE IV

Mortality and causes

	Per cent
Deaths within first 10 days	19
Deaths without gaining consciousness	4
Causes of death:	
Peritonitis (8)	45
Pulmonary Embolism (2)	10
Cardiac Failure (2)	10
Atelectasis (2)	10
Others (5)	25

PRE-OPERATIVE PREPARATION

Most of the cases suffered some degree of dehydration due to vomiting. These were assumed to be in a state of salt depletion of the mixed type (Marriott, 1947), varying with the duration and intensity of the vomiting, and attempts were made to correct this in the short time available between admission to hospital and the operation. Patients with a high obstruction, e.g. pyloric stenosis, lose a fluid which is predominantly acid, leading to lowered plasma chloride, a

relative increase in plasma base, and therefore alkalosis; while in regurgitated intestinal contents due to a low obstruction, large quantities of chloride and especially base are lost, which may lead to acidosis. As gastric juice contains 3.3 g. sodium chloride per litre and intestinal contents 5.7 g. sodium chloride per litre (Coller and Maddock, 1940) irrespective of the site of obstruction, normal saline containing 9 g. sodium chloride per litre can correct the loss, and is the fluid generally used. The above authors give a rule for correction of salt imbalance, viz., " For every 100 mg. that the plasma chloride level needs to be raised to normal (560 mg. per cent), give 0.5 g. sodium chloride per kilogram body weight." This may be a very useful rule for non-emergency cases, but in practice the plasma chloride estimation requires skilled laboratory technicians who are rarely available at night, when most cases of intestinal obstruction are admitted. In every case in this series in which it was tried, the operation was over before the plasma chlorides were estimated. Urinary chloride estimation (Fantus, 1936), on the other hand, is a comparatively simple matter, only requiring simple apparatus, and can be done in a few minutes. Interpretation of the results is difficult, because allowance must be made for the concentration of the urine due to vomiting and fluid loss. It must be accepted, however, that cases with complete absence of chloride in the urine are grossly deficient in sodium chloride. No chloride was detected in the urine of 7 out of 10 cases in this series in whom the urinary chlorides were estimated. Fifty per cent of all cases had normal saline intravenously either before or during operation, or both. In cases of prolonged vomiting, one litre of saline was given before operation and in less severe cases it was started during the operation. With this technique the dangers of giving an

excess of salt, e.g. pulmonary œdema, are very small, and it proved very satisfactory in practice. Only when there was complete absence of chloride from the urine was it considered justifiable to postpone operation to allow for intravenous therapy. Correction of the dehydration makes the urinary chloride estimation more reliable post-operatively, and here it was used extensively and normal saline or 5 per cent glucose given as required.

Blood was only given to five cases, in three instances for severe anæmia, and in two cases with gangrene of the gut. This latter is likened to a massive internal hæmorrhage (Boyd, 1947; Illingworth and Dick, 1949) and inadequate transfusion may have been the explanation of two cases of death that occurred. In neither instance was the gangrenous condition diagnosed before operation, and both patients appeared to be reasonably fit. Induction in both cases was with 0.5 g. of 5 per cent thiopentone and in both cases this produced profound anæsthesia from which neither case regained consciousness. Death occurred two hours and eight hours respectively after operation. This prolonged action of thiopentone appears similar to that described by Halford (1943) after the Japanese air-raid on Pearl Harbour in 1941.

Plasma was given in 10 cases, and in most instances it was found to be an effective treatment for shock, where there was no severe blood-loss. In a few cases it was used because blood was not available.

Intravenous digoxin 0.5 mg. was given to 12 cases before or during operation and was very effective in reducing the pulse-rate in severe tachycardia. It was given in cases where the pulse-rate was over 120 per minute; it was not given to patients already digitalised.

Oxygen inhalation pre-operatively was given to several

cases with a view to decreasing the abdominal distension (Macintosh and Mushin, 1946), and in most cases the effect was disappointing, probably due to the short duration of inhalation and inadequate technique of administration. In 2 cases, however, a remarkable decrease in distension occurred after two or three hours of therapy, 6 litres per minute being given by nasal catheter.

ANAESTHETIC TECHNIQUE

Eighty per cent of cases had general anæsthesia, 11 per cent had spinal, and 9 per cent local analgesia.

Spinal. The high incidence (72 per cent) of blood-pressure anomalies, often associated with arteriosclerosis (Evans, 1949), and such factors as cardiac failure and history of angina (Mushin, 1948) made most cases unsuitable for spinal block. Four out of 11 cases had a severe fall of blood-pressure, and 2 of these vomited during handling of the gut. In 1 case of strangulated hernia the mass disappeared following the spinal, necessitating a lower paramedian incision to examine the gut and perform a resection. Death occurred 4 days later from peritonitis. Had the ruptured gangrenous loop of bowel not entered the general peritoneal cavity following the spinal, this patient might have survived.

Local. In all 9 cases a paravertebral block (Labat, 1923) was performed using amethocaine 1: 2,000, procaine 1: 200 and adrenaline 1: 250,000. All the blocks were successful but they were time-consuming and several patients objected to being turned on their side and appeared to be hyper-æsthetic to needle pricks. Three patients requested to be put to sleep. Two cases are worthy of mention; both were very ill patients over 80 years of age with strangulated herniæ. A unilateral block of T 11 to L 12 was sufficient

for repair of the hernia and was probably the only form of anæsthetic which they would have survived.

General. While local and spinal analgesia have the advantage of retaining an active cough-reflex in patients with a full stomach, general anæsthesia has been found to be most acceptable to both surgeon and patient. Two methods are recommended for control of regurgitation of intestinal contents which frequently occurs when consciousness is lost. A full-sized stomach tube can be passed before induction and maintained in position throughout (Guedel, 1937; Galley, 1949; Minnitt and Gillies, 1948) or a Ryle's tube with continuous suction can be relied upon until consciousness is lost when a stomach tube is passed (Hewer, 1948). Both methods were tried. As can be seen from Table V, the use of a stomach tube throughout is the only safe method and it is believed that a Ryle's tube gives a false sense of security.

TABLE V

Control of regurgitation of intestinal contents

1.	Ryle's tube	42 cases
	Regurgitated or vomited	15 cases* (36 per cent)
2.	Stomach tube	20 cases
	Caused trouble	1 case (5 per cent)

* Nine of these during induction.

It was found that pharyngeal suction was very essential during removal of the stomach tube, as it often left a pool of fæculent fluid behind it. Intubation with a cuffed tube under topical analgesia before induction of anæsthesia was tried in a few cases but this was time-consuming and often distressing to the patient.

The use of a stomach tube made endotracheal intubation a necessity, as no face mask was available with an opening for such a tube. Fifty-four out of 80 cases were intubated orally; the presence of a stomach tube did not make intubation any more difficult. A closer watch could be kept on the patient's condition and such things as the intravenous drip attended to without having continually to support the jaw. In two-thirds of the intubated cases a cuffed tube was used. In 3 such cases, who subsequently regurgitated, no fluid was found in the tracheo-bronchial tree on examination (2 at autopsy and 1 at bronchoscopy), whereas 1 case who vomited, when a plain tube was used, subsequently developed a lung abscess. This is in agreement with the accepted view as to the added safety of a cuffed tube.

Anæsthetic Agents. All commonly used agents were tried. The only case to whom chloroform was administered developed jaundice and pernicious vomiting on the third post-operative day, followed by mental confusion. Recovery followed massive doses of glucose and calcium. In obstetrics delayed chloroform poisoning is more frequent in patients with hyperemesis and acidosis, and following vomiting the liver appears to be unduly susceptible to chloroform (Sheehan, 1940). This patient had been vomiting intermittently for 48 hours and had no pre-operative glucose. Likewise, experiences with trichlorethylene have not been at all happy. As has been reported (Hewer, 1942) relaxation could not be guaranteed, and, when the dose was increased, troublesome tachypnœa occurred, necessitating a change to ether.

Apart from the 2 cases previously mentioned, no trouble was encountered with thiopentone as an induction agent, very small doses being required. A $2\frac{1}{2}$ per cent solution was preferred to 5 per cent. In cachectic, anæmic and toxic

patients its effect was generally more prolonged than normally. Towards the end of the series, induction with thiopentone was adopted as a routine as soon as possible after the stomach tube was passed, because this reduced to a minimum the discomfort caused by the large-bore tube. Very few of the cases in whom this method was used remembered the tube being passed, suggesting a brief period of retrograde amnesia. Nitrous oxide—oxygen—ether (or "V.A.M.") or cyclopropane and oxygen were all reliable for maintenance, and the use of curare permitted minimal doses to be used. The closed circuit was preferred to the semi-open technique.

Because of the distended gut, profound muscular relaxation was essential for a proper exploration of the abdomen, and more especially for closure of the peritoneum. In several cases, where muscle relaxants were not used, adequate relaxation could be produced only by a dosage which caused such severe respiratory depression that cyanosis occurred. Relaxants were used in 42 cases (curare in 38, decamethonium iodide in 2, Myanesin in 2), Myanesin was found to be of no value. The average dose of d-tubocurarine chloride to produce good operating conditions was 18 mg. This is a small dose considering the average duration of operation. It was not surprising, however, when it is remembered that the average age of these patients was 67 years, as it is recognized that the elderly require considerably less relaxant drug (Gray, 1947). Cyclopropane was used during closure of the peritoneum in order to avoid giving more curare; it has the advantage of quick excretion and rapid return of cough-reflex.

Pannett's peritoneum forceps (Pannett, 1920) which were used in one hospital were a great help for closure of the peritoneum. Burst abdomen is now attributed to protein

depletion and not to ineffective suturing, but had better relaxation been produced for closure, the high incidence (8 per cent, Table III) of this complication might have been reduced.

During the operation, where there was a fall of blood-pressure due to traction on the mesentery, Methedrine 10–15 mg. intravenously with 10–15 mg. intramuscularly was effective in raising the pressure to normal (Dodd and Prescott, 1943), and in most cases the rise was maintained. No post-operative excitement was seen following its use.

CONCLUSIONS

As with any other procedure, each case must be considered individually, but the following routine is now adopted as the result of experience in this series of cases. A saline drip is set up and $\frac{1}{2}$–1 litre given as required, and 1/100 gr. (0.65 mg.) atropine with or without morphine administered intravenously. If at all possible the patient is anæsthetized on the operating table where Trendelenburg tilt can be adopted when required and suction is available. A liberal amount of liquid paraffin or glycerine is poured over the back of the patient's tongue, and 5 mg. d-tubocurarine chloride given intravenously. While this is having effect a full-sized stomach tube is passed. In tough patients this manœuvre is made much easier by the small dose of curare. Two-and-a-half per cent thiopentone is given slowly into the drip as soon as possible after passage of the stomach tube, to minimize discomfort to the patient, but should be withheld until drainage from the stomach is complete. After inflating the patient with oxygen it may be possible to do an oral intubation with a cuffed tube, but more curare or thiopentone may be required. There need

be no hurry to do this when the stomach tube is in place. After direct union to a closed circuit machine, 1 litre each of nitrous oxide and oxygen is given with minimal ether for maintenance and curare as required. The respiration is always assisted. Cyclopropane is added for closure of the peritoneum, and breaking the table may assist in this. Special care must be taken when removing the stomach tube, and the pharynx should be sucked out after its removal. The endotracheal tube is not removed until the pharyngeal toilet is complete. Atropine 1/50 gr. (1.3 mg.) is given into the drip as the peritoneum is closed, followed by intermittent doses of neostigmine up to a maximum of 5 mg., until there is a normal tidal respiratory excursion.

SUMMARY

Anæsthesia is discussed for 100 unselected consecutive cases of acute intestinal obstruction.

General anæsthesia has proved the most satisfactory method, with a stomach tube and cuffed endotracheal tube to control vomitus.

I wish to express my thanks to Drs. T. Cecil Gray and John B. Hargreaves for their encouragement and advice in preparing this paper, and to the surgeons and registrars of Walton Hospital, Liverpool, and the City and County Hospital, Londonderry, in allowing me to try the various techniques described.

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Chapter 3.

THE EFFECTS OF THIOPENTONE ON THE BODY

A The Onset of Anaesthesia.

(a) Passage through the brain.

(b) Onset of action compared with pentobarbitone.

(c) Effect of enviromental temperature on onset of anaesthesia.

B Liver Function.

C Blood Sugar and Glucose Tolerance.

THE ONSET OF ANAESTHESIA

This work was carried out in association with Drs. Henry L. Price and Eugene H. Connor, at the Hospital of University of Pennsylvania and at Philadelphia General Hospital. It has not yet been submitted for publication, although a paper dealing with the first part will be read at the Annual Meeting of the American Society of Anesthesiologists, November 1956, with subsequent publication in "Anesthesiology".

a. Passage through the brain.

The rate of passage of thiopentone through the brain was studied by simultaneous analysis of the thiopentone content of arterial (brachial) and venous jugular blood. Rapid continuous sampling was done for 2-3 minutes after antecubital injection of a single dose, in patients who were already anaesthetised with a barbiturate and nitrous oxide-oxygen for a superficial operation. At least 20 minutes was allowed to elapse between the previous dose of thiopentone and the experiment.

In some cases two observations were done, and in some pentobarbitone was also studied, but an interval of 20 minutes was always allowed between successive experiments. This was to ensure that the

rate of decline of the blood thiopentone level from the previous dose would not be sufficiently rapid to interfere significantly with the results.

Thiopentone analysis was carried out on whole blood, using the spectrophotometric method described by Brodie, Mark, Papper, Lief, Bernstein & Rovenstine (1950). With the simplification of this method described in pages 295 and 296 of "Thiopentone & other Thiobarbiturates", 95-105% recovery of thiopentone added to whole blood could be obtained repeatedly.

Pentobarbitone analysis was not so simple, for using either the techniques of Jailer & Goldbaum (1946), Goldbaum (1948) or Brodie, Burns, Mark, Lief, Bernstein & Papper (1953), an accuracy of ± 10% was seldom obtained.

Concurrently with this study, observations of arterial blood pressure and tidal volume (and sometimes pH of arterial blood) were made in an attempt to see if the depression of either of the first two could be related to the arterial thiopentone level. This necessitated additional readings, and as a rule the following equipment was used:-

1. Arterial capacitance manometer in R. brachial artery, connected to direct writing apparatus.
2. Needle in L brachial artery with manifold connection for repeated blood sampling.

3. Needle in jugular blood with apparatus for repeated blood sampling.
4. Benedict-Roth spirometer connected to direct writing apparatus.
5. Bipolar lead electroencephalogram (frequently with simultaneous lead 2 electrocardiographic tracings) - "Edin Anesthograph".

Results - During the time the author was associated with this study ten successful experiments using thiopentone and six using pentobarbitone (on ten patients) were carried out. The results obtained in four patients are shown in the following pages.

CASE 1 (a)

Operation: Application of Plaster to Limb.

Anaesthesia: Thiopentone - N_2O - O_2 - Pethidine.

Experiment started at end of operation.

A. 150 mg. Pentobarbitone i.v.

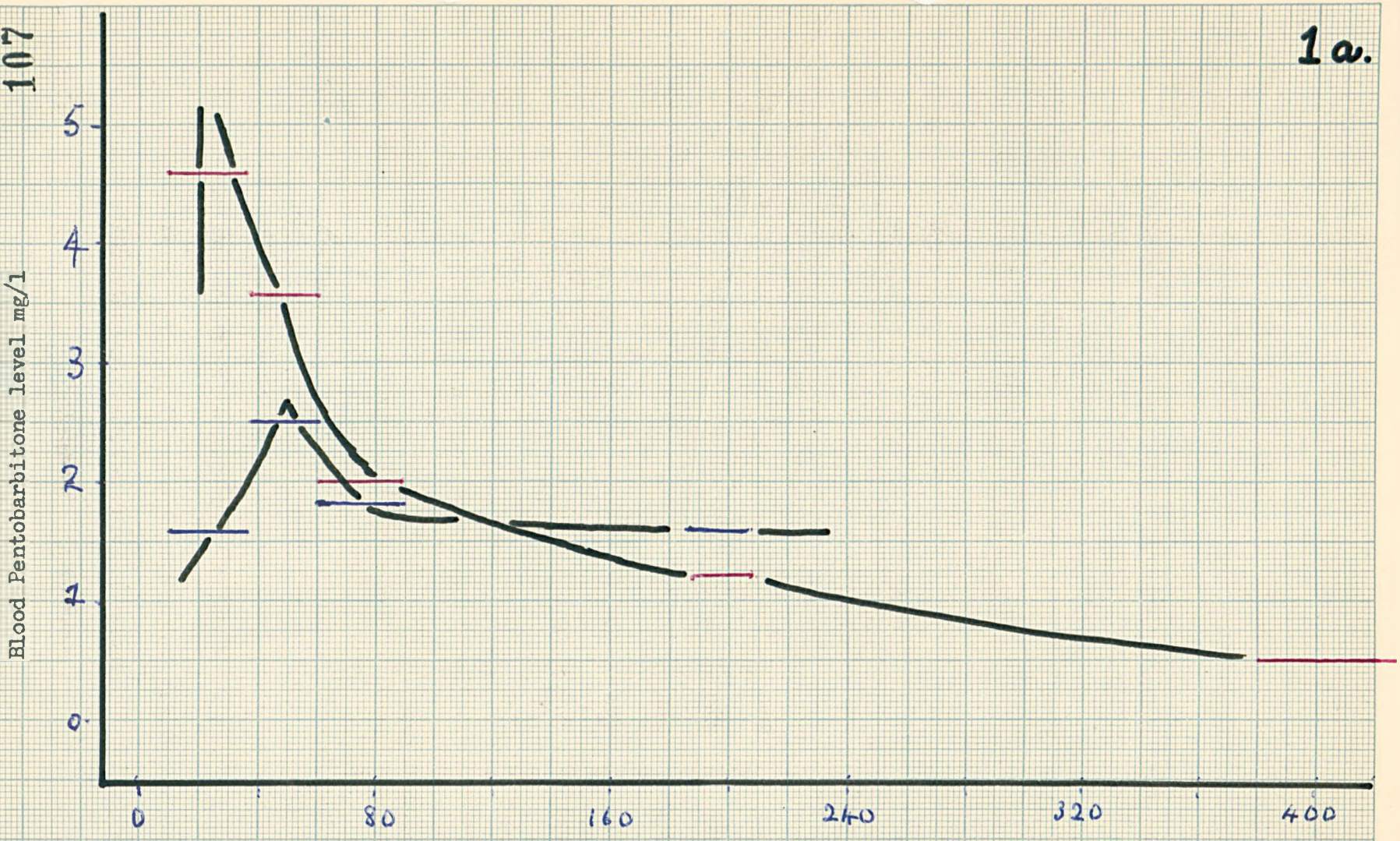
Time from Administration of Pentobarbitone (seconds)	Av.	Blood Pentobarbitone concentration (mg./litre) Arterial	Venous	Heart Rate	Tidal Volume	Arterial Pressure
-20 to -0	-10			82	100%[M]	100%[M]
10 to 35	22	4.6	1.6	84	105%	95%
35 to 60	47	3.6	2.5	78	80%	76%
60 to 89	75	2.0	1.8	78	74%	77%
187 to 210	200	1.2	1.6	80	82%	81%
402 to 420	411	1.0+		82	90%	

Pre-pentobarbitone figures taken as control

[M] Mean Arterial Pressure 85 mm.Hg.

[M] Mean Tidal Volume 460 ccs.

1a.


Blood Pentobarbitone level mg/l
5
4
3
2
1
0
0
80
160
240
320
400
Time from injection of pentobarbitone in seconds

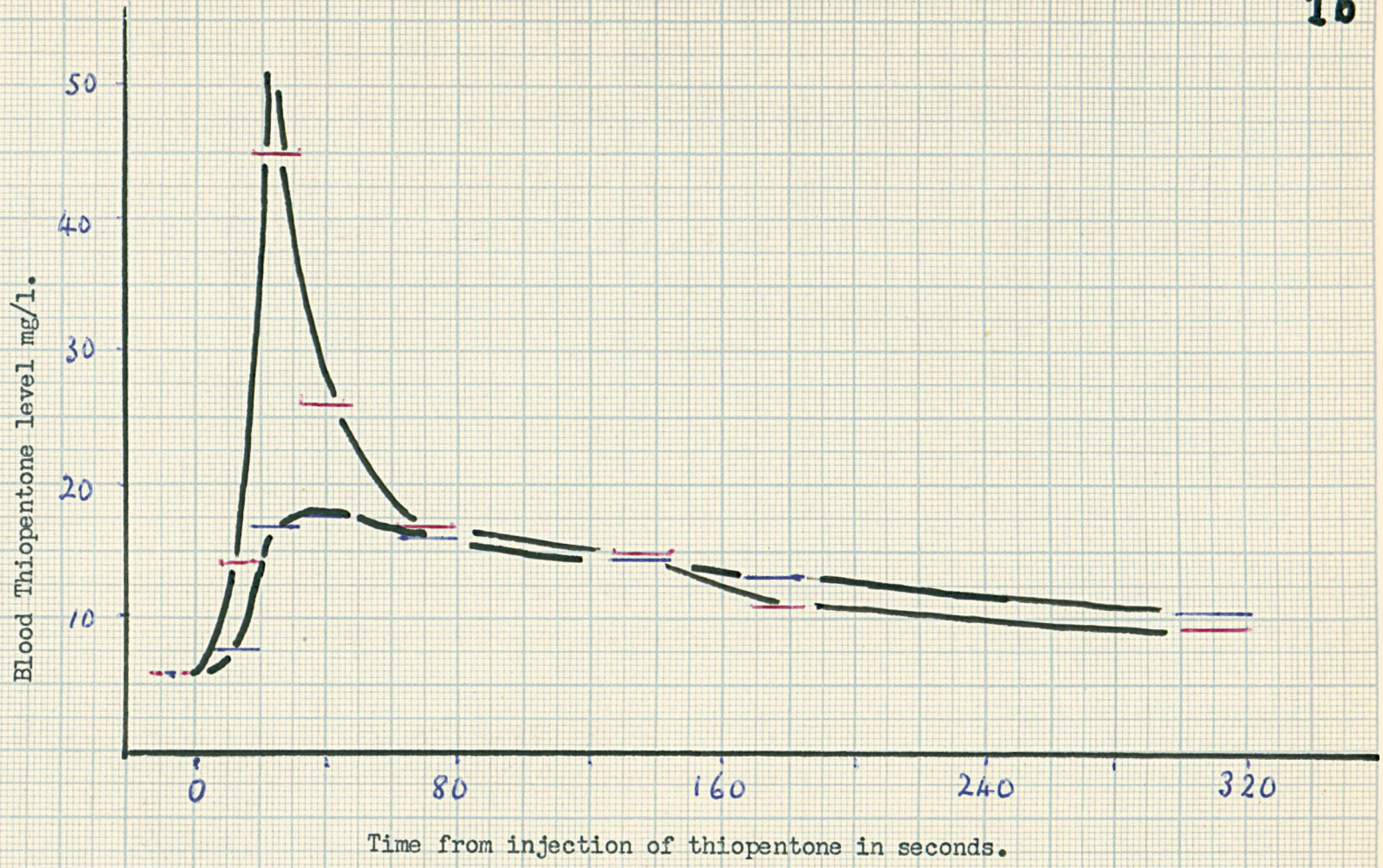
CASE 1 (b)

B - Thiopentone 125 mg. i.v.

Carried out about 20 minutes after A, in the same subject.

Time from Administration of Thiopentone (seconds)	Av.	Blood Thiopentone concentration (mg./litre)		Changes in (percentage)	
		Arterial	Venous	Tidal Volume	Mean Arterial Pressure
-25 to -10	-17	6.74	6.74	100	100
7 to 18	12	14.5	7.6	110	107
18 to 32	25	44.9	16.9	67	100
32 to 46	39	26.4	17.5	55	89
63 to 78	70	17.0	16.2	72	91
107 to 123	116	15.2	14.4	77	90
168 to 183	175	10.8	12.4	84	93
300 to 320	310	9.4	10.1	92	95
	480			100	100

16


Blood Thiopentone level mg/l.
50
40
30
20
10
0
80
160
240
320
Time from injection of thiopentone in seconds.

CASE 2.

Operation: Stripping of Varicose Veins.

Anaesthesia: Spinal (Amethocaine-dextrose)
Thiopentone - N_2O - O_2

Experiment carried out at end of operation
A - 200 mg. thiopentone. B - 100 mg. Thiopentone 25 mins. later.

Time from Administration of Thiopentone (seconds)		Blood Thiopentone (mg./l.)		Mean Arterial B.P.		Heart Rate	Changes in Tidal Volume	pH Arterial Blood
		Art.	Venous	mm. Hg.	%			
(A)								
-20 to 0	-10	11.6	10.7	110	100	68	100	7.32
5 to 14	10	71.0	10.6	110*	100*	69	93	7.34
15 to 45	25	60.0	16.5	99	90	72	0	7.34
45 to 59	52	26.4	22.8	99	90	76	0	7.29
77 to 95	86	18.5	22.4	108	98	77	17	7.24
132 to 154	143	14.7	17.3	112	102	74	72	7.23
203 to 232	218	13.1		112	102	72	97	7.23
(B)								
0				102		70	100	
12 to 19	15	35.0	**	97	96	72	90.8	7.32
30 to 44	37	33.5		-**	-**	73	27.0	7.32
62 to 75	68	18.2		-**	-**	-	55.0	7.32
90 to 104	97	14.4		98	97	72	63.7	7.32
150to 164	157	12.9		100	99	74	94.1	7.32
210to 224	217	12.1		100	99	73	82.0	7.28
	450	10.3		97	96	71	88.5	7.45

* A transient rise in B.P. occurred 11 seconds after injection.

** Failure to obtain readings due to a blocked needle.


70
60
50
40
30
20
10
0
Blood Thiopentone level mg/l.
0
40
80
120
160
200
240
Time from injection of thiopentone in seconds

Case 3 (a).

Operation - Stripping of Varicose Veins
- Coloured male, aged 64.

Anaesthesia - As for Case 2.

Experiment carried out at end of operation.

A 125 mg Thiopentone

Time from Administration of Thiopentone (seconds)	Av.	Blood Thiopentone Concentration (mg/l) A	V	Mean Arterial B.P. mm Hg	%	Heart Rate	Tidal Volume %	Resp. Rate
- 10 to 0	-5	0.36	0.43	117	100	57	100	20
10 to 34	22	5.17	0.79	125	105	70	145	15
37 to 50	44	2.37	1.80	120	103	70	65	20
50 to 80	65	1.51	1.44	117	100	70	46	20
140 to 165	150	1.07		114	97	78	72	19
240 to 265	252	0.76	0.97	105	92	60	80	19
	360			100	89	60	85	18

Case 3 (b)

B Pentobarbitone 150 mg.

Time from Administration of Pentobarbitone (seconds)	Av.	Blood Pentobarbitone Concentration (mg/l)		Mean Arterial B.P.		Heart Rate	Tidal Volume	Resp. Rate
		Art.	Ven.	mm Hg	%		%	
- 2 to - 9	-15	0.4	0.5	120	100	55	100	18
9 to 22	16	4.5	1.5	135	112	68	135	18
30 to 48	32	2.6	2.8	127	98	73	106	18
48 to 70	54	1.8	1.8	120	100	69	62	19
95 to 115	105	1.1	1.3	120	100	64	76	18
180 to 200	190	0.9	0.9	117	98	64	65	18
310 to 332	321	0.7	0.9	110	92	57	76	19
465 to 485	475	0.7	0.8	117	98	57	85	18

Case 4.

White male, 185 lb, aged 48 years.

Operation - Herniorrhaphy

Anaesthesia - Spinal and thiopentone

Experiment carried out at end of operation.

Thiopentone 150 mg I.V.

Time from Administration of Thiopentone (seconds)	Av	Blood Thiopentone level mg/l		Mean Arterial B.P.		Tidal Volume %	Resp. Rate
		A	V	mm Hg	%	Control	
-25 to - 5	-15	.85	.89	117	100	100	19
20 to 44	32	9.25	2.30	130	111	58	
44 to 74	59	3.02	2.38	123	105	0	0
74 to 106	90	2.16	2.21	110	94	52	23
186 to 218	202	1.46	1.71	107	91	85	20
326 to 355	339	1.45	1.52	97	82	103	20

The steep early fall in arterial thiopentone level is similar to that described by Brodie et al. (1950) and Brodie (1952). Jugular venous content of the drug rose slowly and usually exceeded the arterial content within 80-120 seconds after injection. Despite the fact that the clinical onset of anaesthesia with pentobarbitone is slightly slower than with thiopentone, these studies did not show a more rapid rate of equilibration with the latter drug. Ideally carotid drug levels should have been estimated instead of brachial arterial levels, but this error existed with both drugs.

In addition to the well known early respiratory stimulation, occurring 10-12 seconds after injection, a transient rise in arterial blood pressure was almost always detected at the same time. This stimulation occurred before the cerebral effects of the drug could be detected on the EEG tracing, suggesting that it is due to a reflex mediated through the carotid sinus.

Using large doses of thiopentone, once equilibrium had been achieved, it was possible to obtain a direct relation between the depression of the mean arterial blood pressure and the blood thiopentone level. This relationship only held in individual patients, and

different subjects showed a wide variation in their susceptibility to the depressant effects of the drug.

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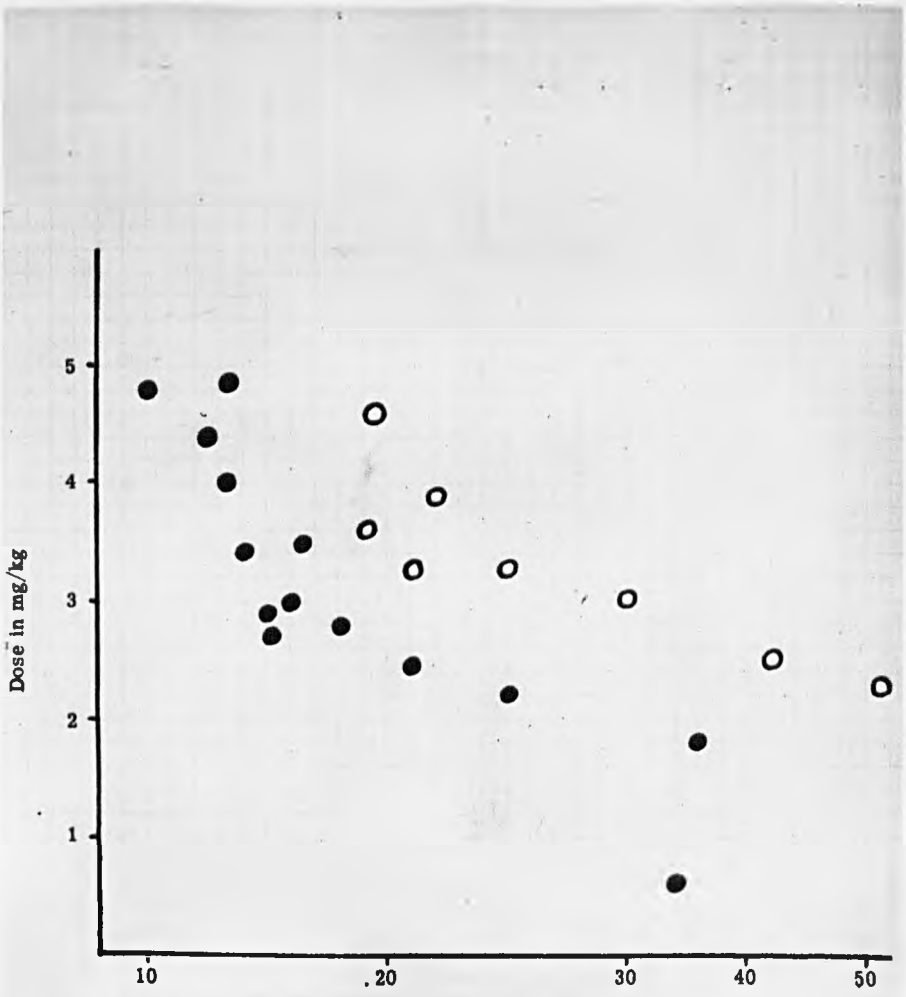
b. Comparison of Onset of action of Thiopentone and Pentobarbitone.

Ay a constant environmental temperature (the significance of which will be described in the next section), the onset of electroencephalographic levels 1 & 2 was timed from the time of rapid administration of varying doses of these drugs in conscious unpremedicated fit subjects. All injections were given in the antecubital fossa.

The results show conclusively that anaesthesia is achieved more rapidly with thiopentone than with pentobarbitone. A few of the typical tracings obtained are shown.

During this study a search was made for an end-point which could be used clinically in a large number of patients. It was found that the patients stopped counting about one-third of the way between the onset of EEG levels 1 & 2. This was a fairly reliable finding in most patients, and, in the next study was used to indicate the onset of anaesthesia.

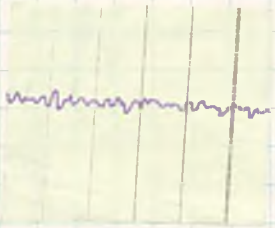


● - Thiopentone

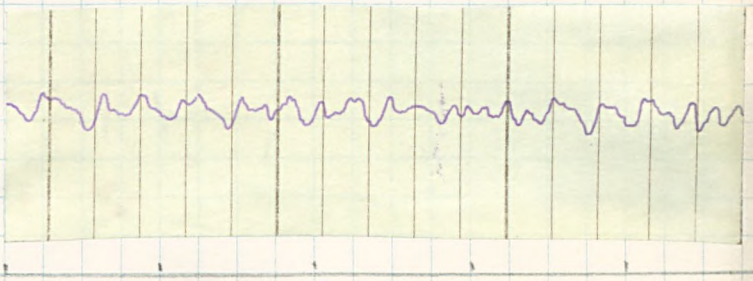
○ - Pentobarbitone

Typical Electroencephalographic tracings obtained before and after the administration of THIOPENTONE in three subjects.

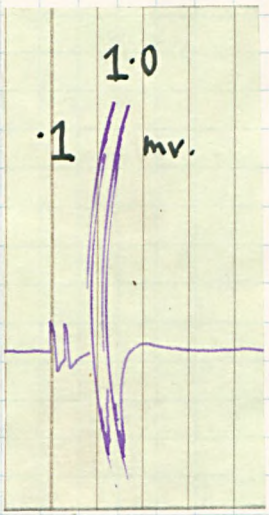
Conscious Control



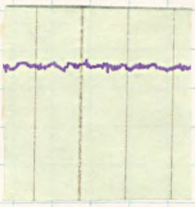
Level 2



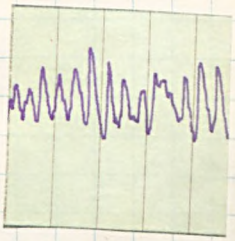
Time in seconds

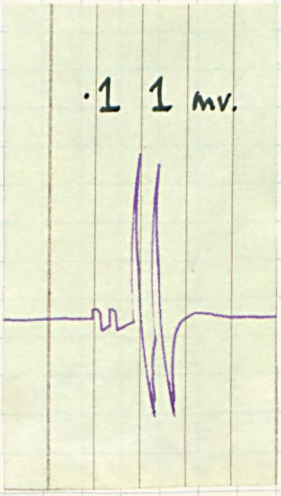


Control

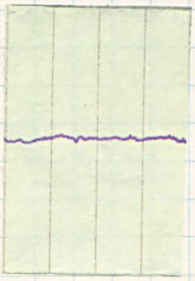


Level 2

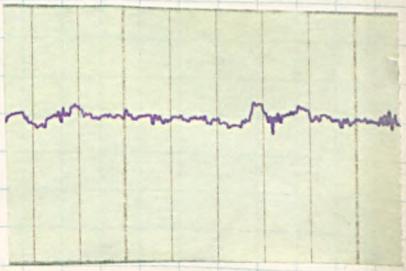




Control



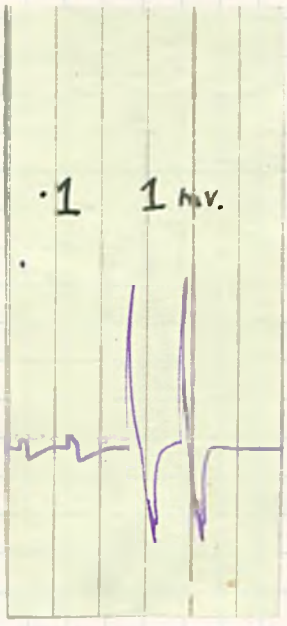
Level 1 - 2

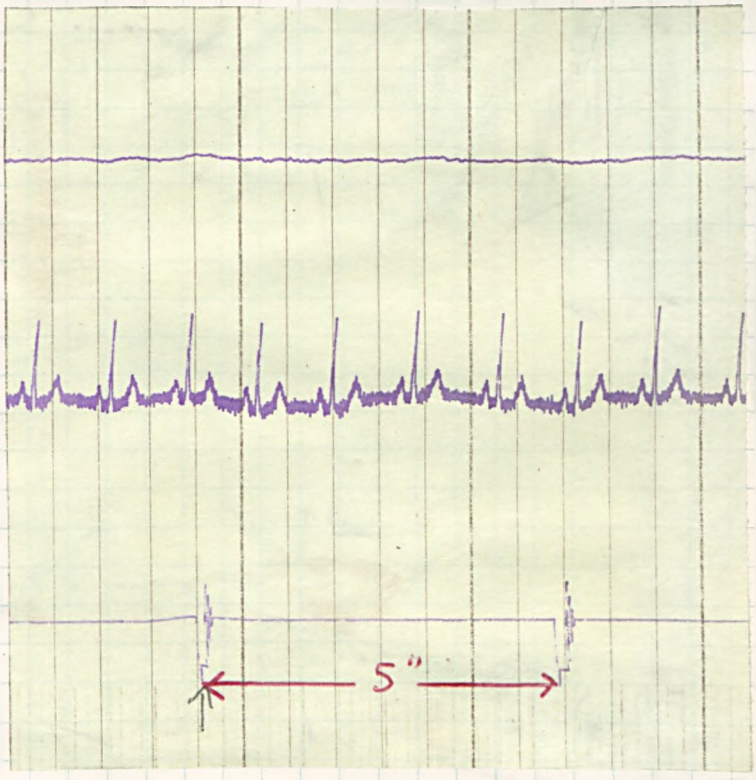


Time in seconds

Electroencephalographic (upper trace) and Electrocardiographic (lower trace) patterns recorded in one subject before and after the administration of 250 mg THIOPENTONE

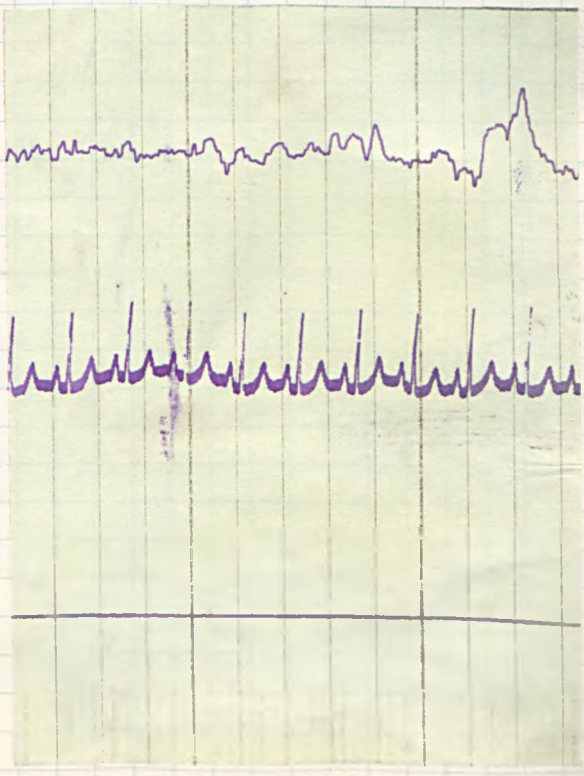
Conscious Control





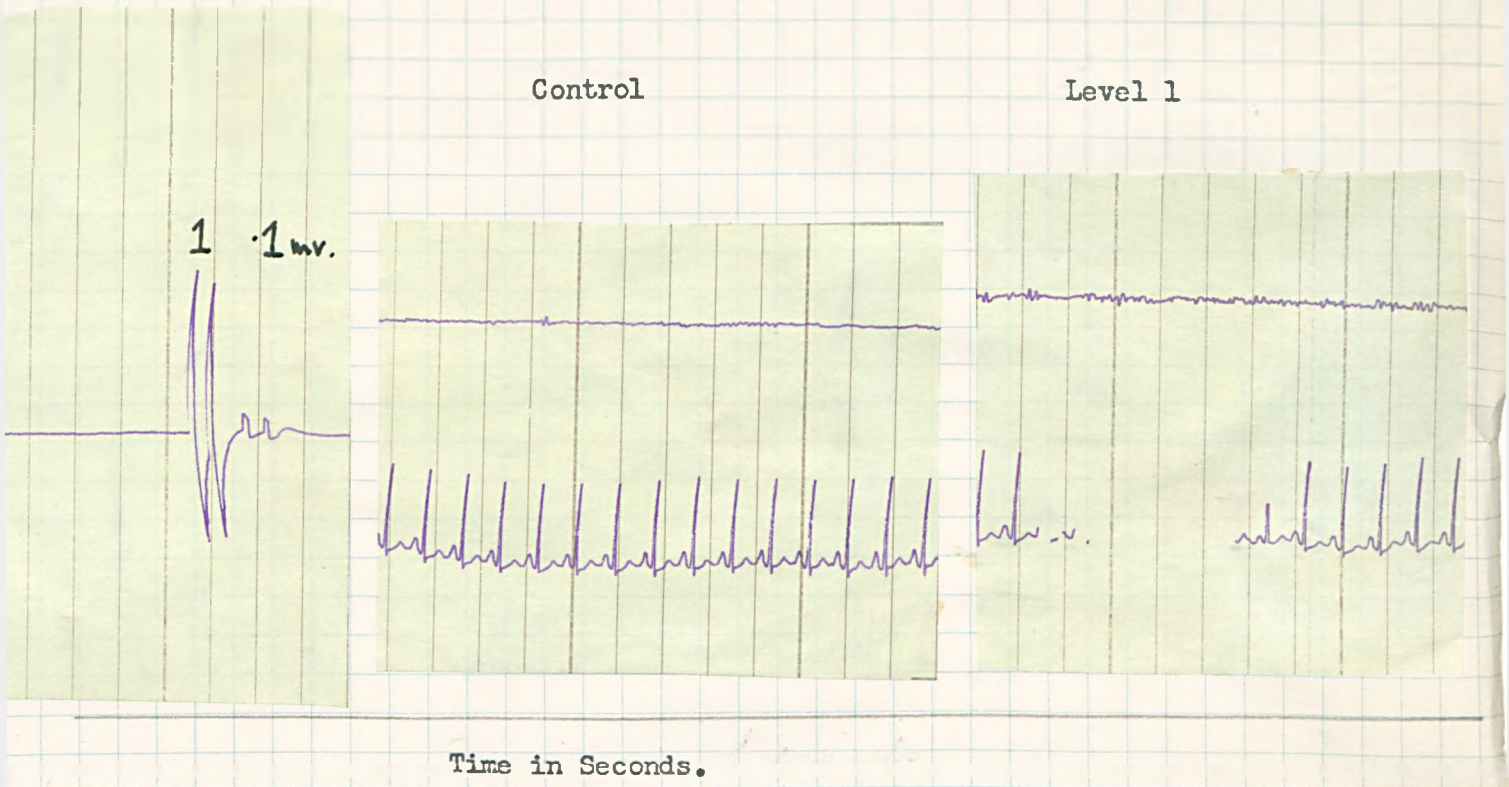
Level 2

(note tachycardia following thiopentone)

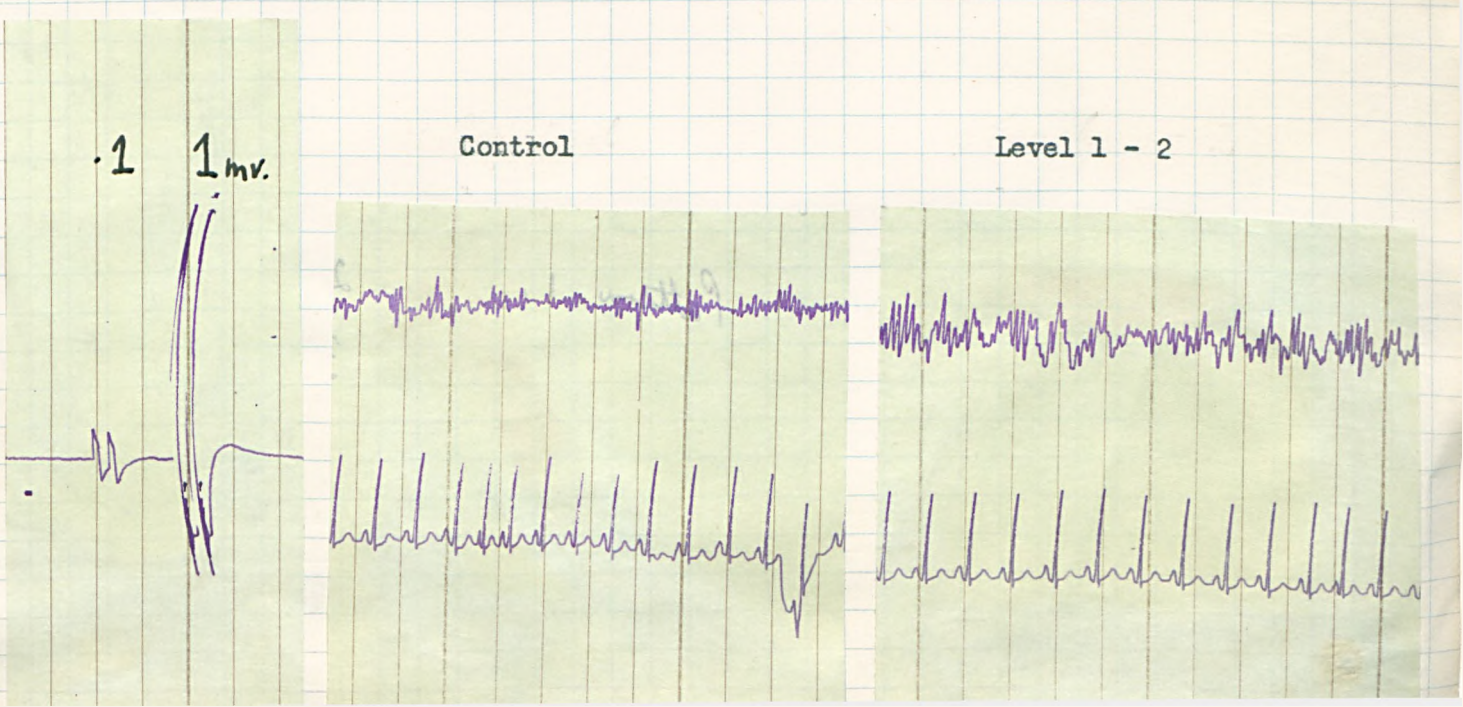


Electroencephalographic (and electrocardiographic) patterns before and after PENTOBARBITONE in two subjects.

Changes were generally less marked than after thiopentone, and onset of any particular pattern was less well defined.



Time in Seconds.



c. Effect of Environmental Temperature on the onset of anaesthesia.

It was attempted to confirm the more rapid onset of action of thiopentone, as compared with pentobarbitone, on a large number of fit subjects, using the time when the patient stopped counting as indicative of the onset of anaesthesia.

This was done with a blind technique, the nature of the drug not being known to the investigator. It was surprising to find that 50 investigations with each drug did not, on first analysis, confirm the EEG finding. However, the observations were made at two hospitals, and when the findings at each hospital were studied separately, in each group thiopentone invariably exerted its anaesthetic effect before pentobarbitone.

It was thought that the different environmental temperatures in the anaesthetic rooms of the two hospitals might explain the findings. During July and August 1955, the temperatures in Philadelphia General Hospital (non-air conditioned) ranged from 96 to 102° F. (35.6 to 39° C.), while in the Hospital of the University of Pennsylvania the temperature

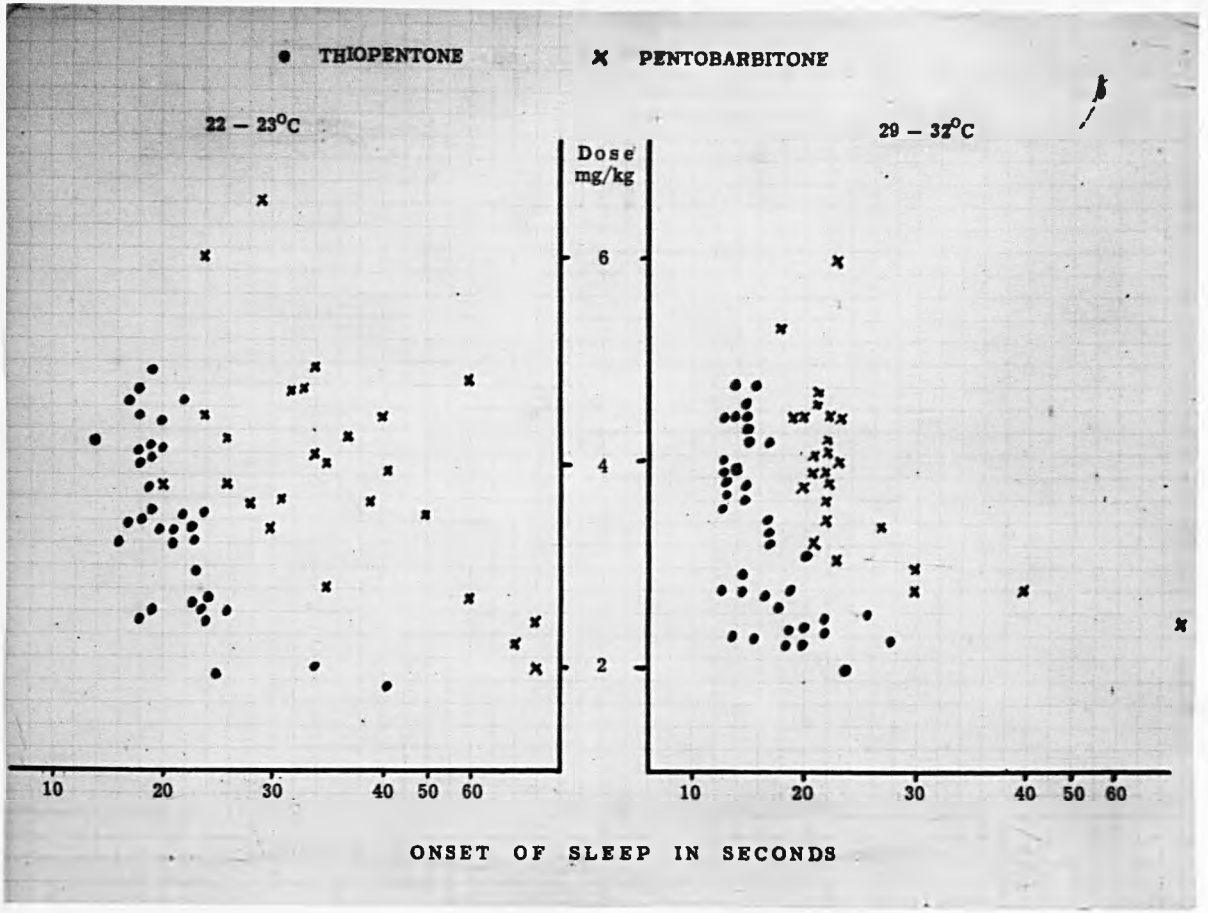
remained constant about 72 to 74° F. (22° C.). The actual pre-operative rectal temperatures of the patients in different hospitals did not vary significantly. At a later date, when air-conditioning was installed in the former hospital, it was possible to exclude any of the possible difference in the type of patients at the two hospitals as a cause of the difference in time of onset of anaesthesia.

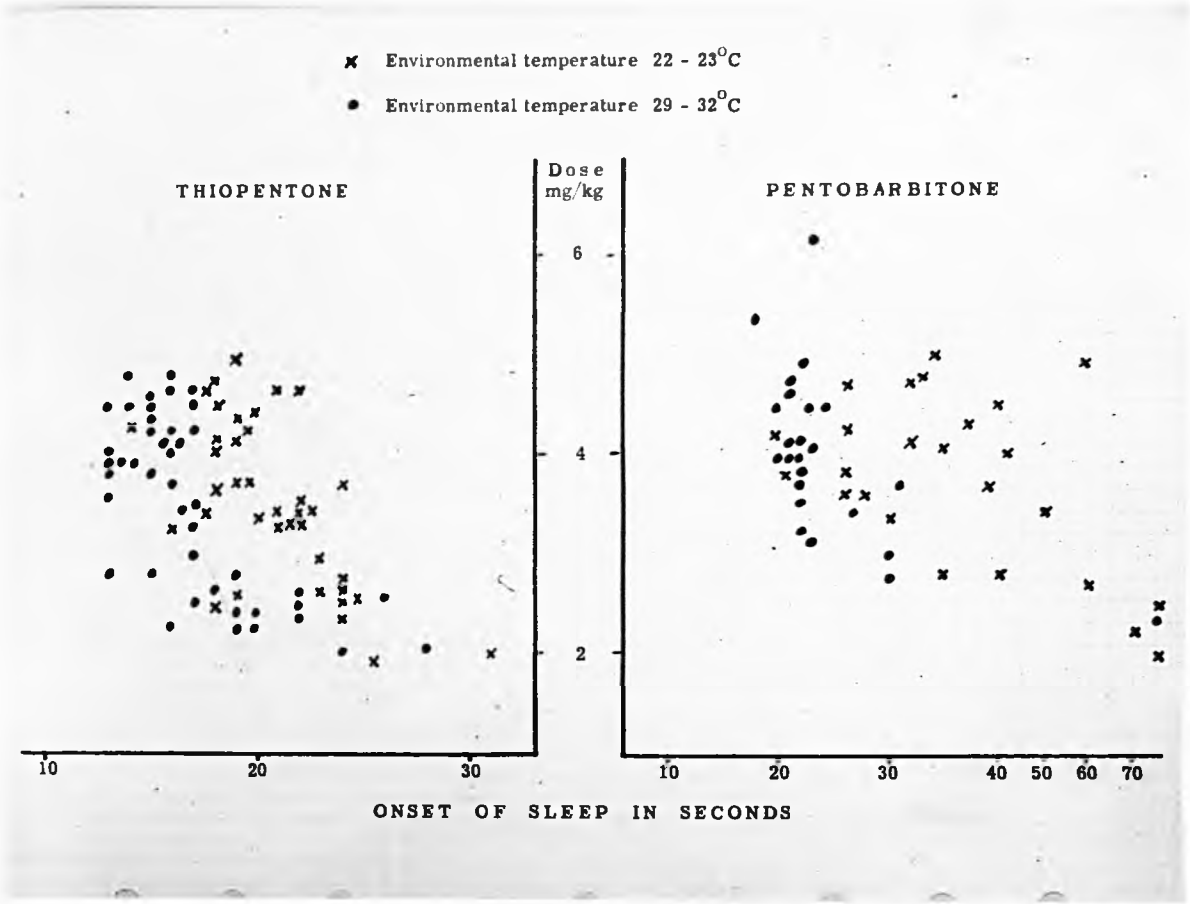
In the graphs on the next few pages are shown the results obtained in this study. These show:-

(a). At any given environmental temperature, the onset of action of thiopentone is more rapid than with pentobarbitone.

(b). With either drug, the onset of anaesthesia is appreciably faster at the higher environmental temperatures.

(c). When a dose of either drug exceeding 3.5 mg/kg was used, it was found that the time of onset was fairly constant under any given circumstances. Analysis of the findings with doses of 3.5 mg/kg and over, show that the difference of time of onset with the two drugs and the effects of environmental temperature are both statistically significant.


● THIOPENTONE
× PENTOBARBITONE
22 – 23°C
29 – 32°C
Dose mg/kg
6
4
2
10
20
30
40
50
60
ONSET OF SLEEP IN SECONDS


Environmental temperature 22 - 23°C
Environmental temperature 29 - 32°C
THIOPENTONE
Dose mg/kg
PENTOBARBITONE
6
4
2
10
20
30
10
20
30
40
50
60
70
ONSET OF SLEEP IN SECONDS

Time of Onset of Anaesthesia with Doses of Thiopentone and Pentobarbitone greater than 3.5 mg/kg.

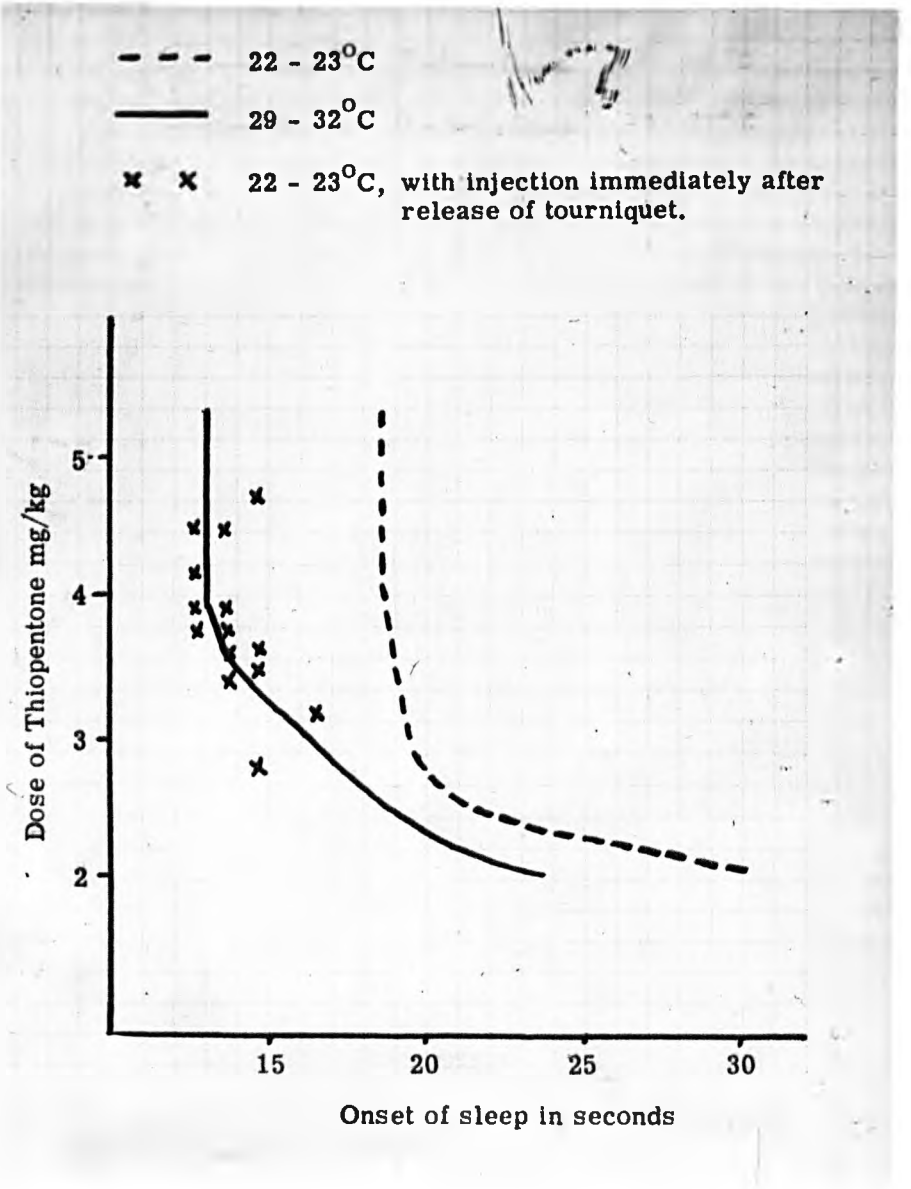
Room Temperature	Drug	No. of Cases	Average Time in seconds
22 - 23°C	Thiopentone	22	19.7 ± 0.90
	Pemtobarbitone	17	33.2 ± 3.10
29 - 32°C	Thiopentone	22	14.9 ± 0.67
	Pentobarbitone	17	21.3 ± 1.64

There is a significant difference between the time of onset of anaesthesia with thiopentone and pentobarbitone at 22 - 23°C ($t = 6.08$) and at 29 - 32°C ($t = 5.12$) and also between the time of onset of anaesthesia with thiopentone ($t = 6.12$) and pentobarbitone ($t = 5.00$) at the different enviromental temperatures.

On close examination of the results in the previous graphs, it can be seen that with high environmental temperatures there is less scatter of readings than at low temperatures. This may be due to the presence of maximum vasodilatation at 36 to 39° C., as compared with varying degrees of dilatation at 22° C.

The possibility of vasodilatation explaining the previous findings was explored by producing marked vasodilatation of the one limb only, at low environmental temperatures (using a sphygmomanometer cuff inflated to beyond the systolic blood pressure of one minute and then released), and injecting the thiopentone into this limb.

The graph on the next page shows that by this manoeuvre, the onset of anaesthesia at low environmental temperatures could be approximated to that obtained at the higher temperatures. This suggests that the findings can be explained on the basis of more marked vasodilatation in the limb used for injection, with resultant more rapid arrival of the drug at the brain, in the patients exposed to the higher temperatures.


22 - 23°C
29 - 32°C
22 - 23°C, with injection immediately after release of tourniquet.
Dose of Thiopentone mg/kg
5
4
3
2
15
20
25
30
Onset of sleep in seconds

The Effects of Thiopentone on the Body.

(b) Liver Function.

"THIOPENTONE AS A FACTOR IN THE PRODUCTION OF LIVER DYSFUNCTION"

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THIOPENTONE AS A FACTOR IN THE PRODUCTION OF LIVER DYSFUNCTION

by

JOHN W. DUNDEE

ALTRINCHAM

JOHN SHERRATT AND SON

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THIOPENTONE AS A FACTOR IN THE PRODUCTION OF LIVER DYSFUNCTION

BY

JOHN W. DUNDEE

Department of Anaesthesia, University of Liverpool

AFTER a long controversy there is now abundant evidence to show that the liver is the main site of detoxication of thiopentone. This applies both to animals (Walker and Wynn Parry, 1949; Gould and Shideman, 1952; Shideman, Gould, Winters, Peterson and Wilner, 1953; Meyers and Peoples, 1954) and man (Shideman, Kelly, Lee, Lovell and Adams, 1949; Dundee, 1952). Furthermore it is now established that detoxication of thiopentone is a slow process, only 10–15 per cent of the drug in the body being metabolized per hour (Brodie, Mark, Papper, Lief, Bernstein and Rovenstine, 1950; Brodie, Bernstein and Mark, 1952). One might expect the drug to have a toxic action on the liver, but there is no definite evidence for this in man.

Richards and Appel (1941) have shown that hepatic impairment follows the use of thiopentone in animals. The smaller the animal the more marked was the effect of the drug on the liver. Walton, Uhl, Egner and Livingstone (1950) found that small doses of thiopentone were mildly toxic to both the normal and damaged liver of the dog, but this effect was due to hypoxia and could be overcome by adequate ventilation with oxygen. Doses of 20 mg./kg. given twice daily to normal dogs for periods of 2–3 weeks caused a mild depression of hepatic function, as judged by prothrombin time and serum bilirubin level, with complete return to normal four days after the last injection of thiopentone (Walton, Saldamando and Egner, 1951). In contradistinction to the effects of small doses, adequate oxygenation did not reduce the toxicity of repeated large doses of thiopentone.

Pohle (1948), using a battery of liver function tests found that liver impairment occurred in 50 per cent of cases after operation. Its occurrence was unrelated to the anaesthetic agent used, and the effects of thiopentone did not differ from those of chloroform. Unfortunately, the doses of barbiturate used were not recorded. The patients he studied were in poor general condition before operation and he suggested that their nutritional state and the occurrence of hypoxia after operation were the important factors in the aetiology of liver damage. Fairlie, Barso, French, Jones and Beecher (1951) examined the effects of anaesthetics (excluding thiopentone) and also found no significant difference in the effects of the various agents on the liver.

Carraway (1939), using the hippuric acid excretion test, found no alteration in liver function after thiopentone in 100 cases. Many of these patients were

jaundiced or had liver damage before operation. Using the same test, Boyce and McFetridge (1938a) found that ether, ethylene and spinal analgesia all had a marked effect on liver function for the first seven days after operation. The hippuric acid excretion test, urobilinogen metabolism, and blood sugar levels were examined by Mordvinova (1948) before and after thiopentone anaesthesia in 80 cases. The detoxicating function was significantly lowered in 17 patients, pigment metabolism was upset in 31 cases and blood sugar levels were abnormal in 17 cases. Recovery to normal took as long as two weeks in some instances. A much quoted case, reported by Vaizey (1928), describes the occurrence of jaundice following thiopentone, but the evidence incriminating the drug is not very convincing.

It can be seen from the above that there is no agreement as to the hepato-toxic properties of thiopentone. In this paper the effects of large and small doses of the drug on liver function are reported in 464 patients. No comparison is made between the effects of thiopentone and other anaesthetic agents. The urinary excretion of urobilinogen has been used to detect hepatic dysfunction in this series. Because of the pitfalls in the use and interpretation of the results of this test the metabolism of urobilinogen and factors influencing it will first be described in detail.

UROBILINOGEN EXCRETION

Normal Excretion.

Bilirubin that enters the intestine in the bile undergoes reduction by bacteria to form stercobilinogen (urobilinogen). A part of this is excreted in the faeces as urobilin. The remainder is reabsorbed into the portal circulation, passes through the liver and is almost completely re-excreted in the bile. Any urobilinogen which may escape into the circulation is excreted by the kidneys. Normally no urobilinogen (or a mere trace) appears in the urine.

Factors Influencing Excretion.

1. *Increased production of bilirubin.*

(*a*) Extravasation of blood. Elton (1931, 1950) has shown that "post-operative latent jaundice" occurs following contusions, fractures, lacerations, operation incisions, etc. An excess of bilirubin is formed and released into the blood stream to be excreted by the liver. Even though liver function is normal, it is unable to re-excrete the excess pigment absorbed from the intestine, and urobilinogen appears in the urine.

(*b*) Opinions vary as to whether the products of intravascular haemolysis are converted to urobilinogen. Harrison (1947) lists excessive haemolysis as a cause of urobilinuria. Fairley (1941) states that methaemoglobin occurs in the plasma following intravascular haemolysis and is excreted mostly as faecal porphyrin.

(*c*) Pernicious Anaemia.

2. *Liver Dysfunction.* Failure of the liver to re-excrete the absorbed urobilinogen results in an increase in the amount of absorbed urobilinogen excreted by the kidneys. Glynn (1949) considers a rise in urinary urobilinogen to be a sensitive test of liver function, frequently preceding any demonstrable retention of bile pigment in parenchymatous hepatitis. In a correlation of morphological liver changes and clinical tests Popper, Steigmann and Szanto (1949) found that an increase in urinary urobilinogen excretion bore closer relation to the results of liver biopsy than any of the other liver function tests investigated. The test is of no value in assessing the degree of liver damage present. They conclude that a positive cephalin-cholesterol flocculation test together with an increased urinary urobilinogen excretion indicates liver cell damage, while negative results do not exclude it in the presence of biliary obstruction.

3. *Obstruction of the common bile duct.* At first there is an accumulation of urobilinogen in the blood with resultant excretion in the urine. This can only occur for a short time after obstruction of the flow of bile, and is due to absorption of the pigment remaining in the intestine from the period prior to the obstruction. After this pigment has been removed urinary urobilinogen excretion completely ceases.

4. *Constipation* offers increased opportunity for absorption of urobilinogen from the large intestine with a consequent increase in urinary excretion.

5. *Most fevers* are accompanied by an increased urinary excretion of urobilinogen, probably due to temporary cloudy swelling of the liver.

METHOD OF INVESTIGATION

From the preceding discussion it can be seen that urobilinogen excretion in the urine cannot be utilized to assess the effect of anaesthetic agents on liver function in man unless the drugs be administered to volunteer subjects who undergo no operative procedures. The absorption of extravasated blood and post-operative consti-

pation or pyrexia are factors which of themselves could increase excretion of the pigment irrespective of liver function.

However, it can be used to compare the effects of different agents, or different doses of the same agent, in subjects undergoing the same operative procedure. In a large enough series of cases it can be hoped that the effect of the operative procedure and its sequelae will be the same with each agent under study. This is the basis of the present investigation.

The concentration of urobilinogen in the urine was measured for three days after operation in two series of cases. In one series thiopentone was the main narcotic, supplemented by nitrous oxide, muscle relaxants or minimal doses of other agents as required. In the other cases thiopentone was used only for induction of anaesthesia and followed by the usual doses of other agents. Details of the patients, operations and anaesthetic techniques in each series are shown in table I. This shows that both series are comparable with the exception of the anaesthetic agents. Since age may be a factor in making the liver more susceptible to the effects of thiopentone, the age distribution of each series is shown in greater detail in figure 1. This shows no appreciable difference between the patients to whom thiopentone was administered as the main anaesthetic agent and those who received it only for the induction of anaesthesia.

In each operation group both series of cases were from the same surgical unit in the same hospital. This ensured the same pre-operative preparation, the same premedication: morphine 1/6 gr. (10 mg.) and atropine 1/100 gr. (0.65 mg.) were given to each patient. The same post-operative routine was followed for all patients having the same operation. No patients were included who received any intravenous infusions or transfusions during operation, or in whom there was any prolonged (10 mins.) blood pressure fall. There was no restriction of analgesics or sedatives after operation, each patient receiving the routine drug for the ward. Any patient who developed a pyrexia (over 99.5°F.) or any other complication during the first three days after operation was excluded from the series. The majority of anaesthetics were personally administered.

It was originally proposed to do a quantitative estimation of urobilinogen on 24-hour specimens of urine for the first three days after operation. The loss of one sample of urine meant that the case had to be discarded and in the patients listed in table I, the concentration of urobilinogen was estimated in one sample of urine voided as near as possible to 20, 44 and 68 hours after operation using the technique described by Harrison (1947).

It will be noted that urobilinogen estimations were not carried out as a routine before operation. This was done in the early cases, but it soon became obvious that abnormal concentrations did not appear during the first 24 hours after operation. This can be accounted for by the time taken for absorption and re-excretion of the pigment. Any pre-operative abnormality was detected in the 24-hour specimen of urine. Patients who showed an excess of urobilinogen on the first post-operative day were excluded from the series.

As has been mentioned previously, there is some doubt as to whether intra-

TABLE I

Details of 464 patients, nature and duration of operations and anaesthetic techniques, in whom urinary urobilinogen concentration was measured for three days after operation.

A. 232 cases in which thiopentone was the main anaesthetic agent.

B. 232 cases in which thiopentone was only used for induction of anaesthesia.

	DETAILS OF PATIENTS										DETAILS OF ANAESTHETICS															
											Gaseous supplements				Volatile supplements								Muscle relaxants					
		Average age (years)		Sex distribution				Average duration of operations (mins.)		Average dose of thiopentone (G)	Nitrous oxide		Cyclopropane		Diethyl-ether		Trichlor-ethylene		Methyl-n-propyl ether		Pethidine		d-Tubocurarine chloride		Gallamine triethiodide		Suxamethonium	
				Males		Females																					
Operations	No. of cases in each series	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Dilatation and curettage ...	84	38.0	34.0	—	—	84	84	15.3	15.1	1.08	0.42	77	57	2	24	0	49	1	1	2	11	0	0	—	—	—	—	—	—
Inguinal hernia repair ...	44	44.7	42.4	36	32	8	12	60.8	48.1	1.47	0.46	44	37	0	7	2	30	2	6	0	0	2	2	13	8	26	9	4	2
Varicose vein ligation ...	18	35.9	35.9	11	12	7	6	56.7	56.6	1.36	0.48	17	15	0	1	0	9	2	6	0	2	1	5	—	—	—	—	—	—
Appendicectomy	15	33.5	35.7	9	11	6	4	33.0	30.0	1.02	0.44	15	13	0	2	1	3	0	2	—	—	—	—	2	1	8	3	4	0
Lumbar sympathectomy	13	44.9	45.1	7	5	6	8	67.7	63.5	0.87	0.52	13	12	0	1	0	1	—	—	—	—	1	6	11	13	2	0	—	—
Plastic operations	11	41.7	31.8	5	3	6	8	45.5	37.3	1.10	0.42	11	11	0	0	0	4	3	7	—	—	1	2	—	—	4	4	2	3
Haemorrhoidectomy ...	11	41.1	43.2	8	8	3	3	25.0	23.6	1.08	0.49	11	11	0	0	2	10	1	1	—	—	—	—	—	—	8	3	1	1
For hydrocele	10	46.5	40.1	10	10	—	—	44.0	52.0	1.03	0.46	10	9	0	1	—	5	2	5	—	—	1	2	—	—	—	—	—	—
Hysterectomy	9	46.8	47.6	—	—	9	9	65.0	77.8	1.19	0.46	9	9	0	0	1	9	—	—	—	—	2	1	6	8	3	1	—	—
Thyroidectomy	8	37.1	35.0	2	2	6	6	48.0	75.6	0.99	0.38	8	8	0	0	1	5	1	3	0	1	1	2	—	—	4	1	3	3
Incisional hernia repair ...	6	49.3	48.8	6	6	0	0	100.8	85.0	1.23	0.40	5	4	1	2	0	5	0	1	—	—	3	2	6	6	6	6	—	—
Meniscectomy	3	32.7	47.7	3	3	0	0	40.0	26.7	1.75	0.43	3	3	0	0	0	1	0	1	—	—	0	1	—	—	—	—	—	—
Totals	232	40.4	38.3	97	92	135	140	40.0	37.7	1.17	0.44	223	189	3	38	7	137	12	33	2	14	12	23	32	30	61	27	14	9

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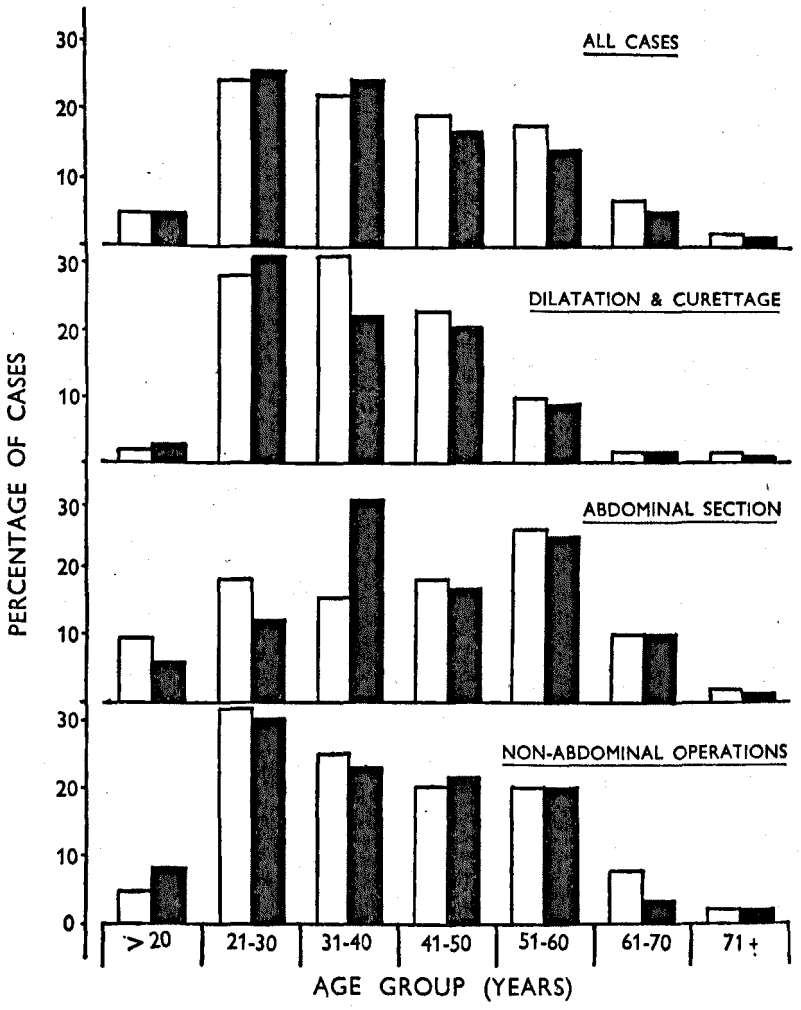

FIG. 1

Histograms showing the age distribution in the two series of patients described in test.

□ patients who received large doses of thiopentone.

■ patients to whom the drug was given only for induction of anaesthesia.

vascular haemolysis results in an increased urinary excretion of urobilinogen. To ascertain what part intravascular haemolysis played in the results obtained its presence was looked for in 40 cases. These include both patients with normal and excess urinary urobilinogen excretion and those receiving large and small doses of thiopentone.

The method used for detection of intravascular haemolysis is based on the observation that the presence of carbonic anhydrase in the urine indicates intravascular destruction of erythrocytes (Robinson, 1950). Where extravascular haemolysis has occurred the erythrocytes are destroyed within the cells of the reticulo-endothelial system and their

carbonic anhydrase is also destroyed. The technique for detection of carbonic anhydrase in the urine described by Robinson (1950) was used in the present investigation.

RESULTS

There is some difference of opinion as to whether the presence of urobilinogen in the urine, detectable in dilutions of 1 in 15, is abnormal. Its presence to a dilution of 1 : 20 is definitely abnormal. In table II results are recorded as follows:

± possibly increased excretion of urobilinogen. This includes cases in whom it was detected in the urine in a dilution of 1 : 15 on either the second or third post-operative day.

\+ definitely increased excretion of urobilinogen, its presence in the urine to a dilution of 1 : 20 on both the second and third days after operation.

Table II shows that there was a statistically significant increase in urinary urobilinogen excretion after operation in cases who received large doses of thiopentone as compared with those in whom the drug was used only for induction of anaesthesia. This applied to all the operation groups when its presence to a dilution of 1 : 15 was accepted as abnormal. With the alternative interpretation of results the difference is not significant in the patients

TABLE II

Post-operative excretion of urobilinogen in 464 cases, half of whom received thiopentone as the main anaesthetic agent; in the remaining half it was used only as an induction agent.

\+ *signifies that urinary urobilinogen was detected in a dilution of greater than 1 in 20 in the second and third post-operative days.*

± *signifies that urinary urobilinogen was detected in a dilution of greater than 1 in 15 in either the second or the third post-operative days.*

p *probability of difference in urinary urobilinogen excretion between the two series having occurred by chance.*

Operation	No. of cases in each series	Post-operative urobilinogen excretion: Thiopentone as main agent — Number of cases +	±	−	Thiopentone for induction only — Number of cases +	±	−	Difference between series: + χ^2	+ p	± χ^2	± p
Dilatation and curettage	84	20	44	40	5	6	78	259.2	<.001	47.9	<.001
Inguinal hernia repair	44	28	36	8	7	9	35	101.8	<.001	74.9	<.001
Varicose vein ligation	18	5	14	4	0	1	17	178.9	<.001	26.4	<.001
Appendicectomy	15	7	12	3	4	4	11	21.8	<.001	3.1	<.05 > .
Lumbar sympathectomy	13	8	10	3	3	3	10	23.3	<.001	10.4	<.01
Plastic operations	11	7	10	1	1	1	10	89.1	<.001	39.6	<.001
Haemorrhoidectomy	11	8	11	0	3	4	7	17.3	<.001	11.5	<.001
For hydrocele	10	8	8	2	0	0	10	70.4	<.001	70.4	<.001
Hysterectomy	9	6	7	2	0	0	9	54.4	<.001	40.0	<.001
Thyroidectomy	8	4	8	0	2	2	6	24.0	<.001	2.7	<.2 > .
Incisional hernia repair	6	3	4	2	0	0	6	18.7	<.001	10.7	<.01
Meniscectomy	3	1	2	1	0	0	3	5.3	<.05	1.3	<.3 > .
TOTALS	232	105	166	66	25	30	202	708.1	<.001	286.9	<.001

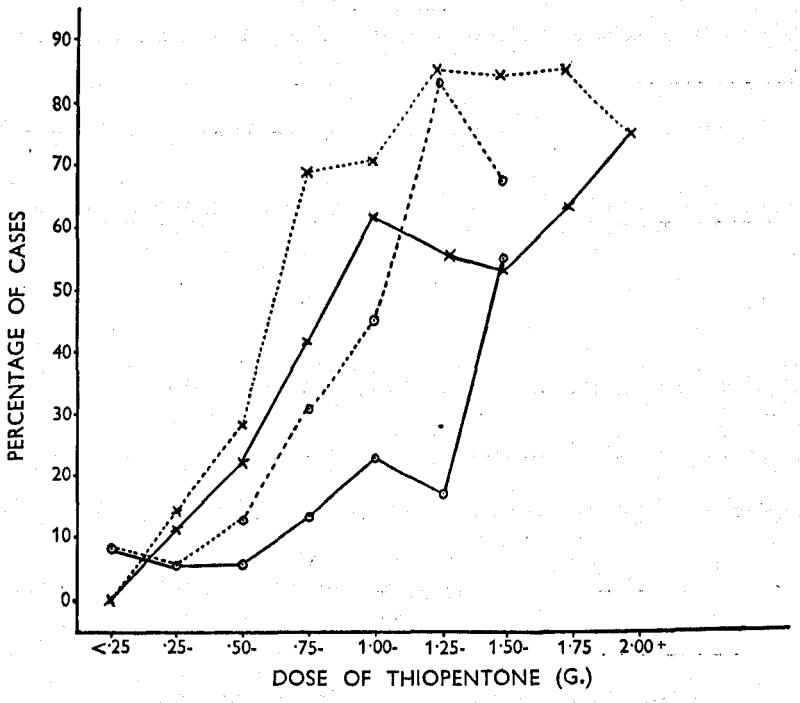

FIG. 2

Correlation between the incidence of hepatic dysfunction and dose of thiopentone administered.

O patients undergoing dilatation and uterine curettage.
X abdominal operations.
... possible liver impairment (urobilinogen excretion ±).
— definite liver impairment (urobilinogen excretion +).

undergoing thyroidectomy and menisectomy. However, it is significant when the series is analyzed as a whole.

In only one operation group were there sufficient cases to correlate the incidence of increased urinary urobilinogen excretion to the dose of thiopentone. The results in 168 patients undergoing dilatation and uterine curettage are shown in figure 2. To confirm these findings a similar correlation is made in a group comprising all operations in which the peritoneal cavity is opened (88 inguinal hernia repairs, 30 appendicectomies, 18 hysterectomies, and 12 repairs of incisional herniae). In both series there is a relationship between the dosage of thiopentone and the incidence of increased urinary excretion of urobilinogen after operation. As might be expected, the over-all incidence is higher in patients after abdominal operations, but irrespective of the procedure the incidence is high in all patients who received 750 mg. thiopentone.

In table III an attempt is made to correlate the incidence of increased urinary urobilinogen excretion with the nature and type of operations and the use of muscle relaxants. The minimal disturbance of metabolism occurred in the

TABLE III

Incidence of increased urinary excretion of urobilinogen related to nature and type of operation and the use of muscle relaxants.

	All cases		Cases receiving large doses of thiopentone	
	+	±	+	±
	Percentage of cases			
Individual operations				
Dilatation and curettage	15.1	25.2	23.8	52.4
Inguinal hernia repair	40.0	51.1	63.6	81.8
Varicose vein ligation	14.0	42.0	28.0	77.8
Appendicectomy	36.7	53.3	46.7	80.0
Lumbar sympathectomy	42.5	50.5	61.5	77.0
Plastic operations	36.4	50.0	62.7	91.0
Haemorrhoidectomy	50.0	64.1	72.8	100.0
For hydrocele	40.0	40.0	80.0	80.0
Hysterectomy	33.3	38.8	66.7	77.8
Thyroidectomy	37.5	62.5	50.0	100.0
Nature of operation				
Abdominal operations	41.0	54.6	57.1	76.7
Surface operations	28.0	36.0	50.0	84.0
Operations in which muscle relaxants could be used				
Relaxants used	40.1	56.7	60.4	82.2
Relaxants not used	36.4	43.0	70.0	84.6

patients undergoing dilatation of cervix and uterine curettage, while the greatest excretion of pigment followed the operations of haemorrhoidectomy and thyroidectomy. On the whole, operations on the surface of the body are followed by a smaller urinary excretion of urobilinogen than cases where the peritoneal cavity is opened.

There is no relationship between the use of muscle relaxants in anaesthesia and the excretion of urobilinogen in the urine after operation.

The results of examination of the urine for carbonic anhydrase are shown in table IV, and analyzed in table V. There seems to be no relationship between the presence of this enzyme in the urine and urinary excretion of urobilinogen. The deduced occurrence of intravascular haemolysis is likewise unrelated to whether thiopentone was the main anaesthetic agent employed or whether its use was reserved only for induction of anaesthesia. There are not sufficient cases to permit conclusions about the effect of the various operations, but the results suggest that the duration of the operation (irrespective of its nature) may be an important factor in the occurrence of intravascular haemolysis.

DISCUSSION

The above findings show conclusively that the use of large doses of thiopentone results in an impairment of the ability of the liver to deal with the urobilinogen absorbed from the gut. The results give no guide to the severity of the hepatic dysfunction, but only show the incidence of its occurrence. The percentage of patients showing evidence of liver damage is fairly closely related to the dose of thiopentone administered.

At some operations there is more extra-

TABLE IV

Details of 40 cases in whom urine was examined for the presence of carbonic anhydrase on the first three days after operation

Operation	No. of cases	Average dose of thiopentone (6)	Supplementary agents (No. of cases)				Urobilinogen in urine after operation		No. of cases with carbonic anhydrase in urine
			Nitrous oxide	Ether	Trichlorethylene	Muscle relaxants	+	±	
Dilatation and curettage	3	0.95	3				0	0	0
	6	1.10	3				4	6	0
	3	0.45	3	2	1		0	1	0
Repair of inguinal hernia	3	1.35	3			3	1	2	2
	4	0.50	4	4	0	4	0	0	0
	2	1.50	1			1	0	0	0
	1	0.25	1		1	1	1	1	0
Varicose vein ligation	1	1.30	1				1	1	1
	2	1.00	2		1		0	0	1
	3	0.62	3	1	2		1	2	0
	2	0.40	2	2	1		0	0	1
Haemorrhoidectomy	5	1.10	5		2	4	5	5	0
	1	1.00	1			1	0	0	0
	3	0.35	3	3		1	2	3	1
	1	0.45	1		1	1	0	0	0

TABLE V

Analysis of the results of the estimation of carbonic anhydrase in urine. Findings are related to:

(a) *presence of urobilinogen in urine;* (c) *nature of operation;*

(b) *dose of thiopentone used;* (d) *duration of operation.*

		No. of cases	No. showing carbonic anhydrase in urine	Percentage of cases showing evidence of intramuscular haemolysis
Urobilinogen in urine	+	15	3	20
	±	21	4	19
	0	19	3	16
Anaesthetic agents				
Thiopentone as main		20	4	20
Thiopentone for induction		20	3	15
Operation				
Dilatation and curettage		12	0	0
Repair of hernia		10	3	30
Varicose vein ligation		8	3	37
Haemorrhoidectomy		10	1	10
Duration of operation				
Less than 30 minutes		21	0	0
½–1 hour		14	3	21
1–1½ hours		4	3	75
Longer than 1½ hours		1	1	100

vasation of blood than at others, and following these the liver has to excrete a larger amount of the breakdown products of bilirubin. This is reflected in the findings of table III, where the percentage of abdominal cases showing an excessive urinary excretion of urobilinogen was greater than for surface operations. Following dilatation of the cervix and uterine curettage, where there is very little extravasation of blood, there was the lowest incidence of excessive urinary output of urobilinogen, irrespective of the anaesthetic agent used.

Many factors, other than the anaesthetic agent, may adversely affect the liver function during operation. As regards the nature of the operation, upper abdominal section has the most deleterious effects (Morrison, 1943; Engstrand and Friberg, 1945; Tagnon, Robbins and Nicholas, 1948; Zamcheck, Chalmers, and Davidson, 1949). The longer the duration of the operation, the more likely is liver damage to occur (Coleman, 1938). Chronic sepsis, pulmonary tuberculosis (Coleman, 1938), thyrotoxicosis (Boyce and McFetridge, 1938b), intestinal obstruction (Cole and Elam, 1932), advanced carcinoma and severe burns (Hugill, 1950), all cause impairment of liver function. Complications during convalescence likewise increase the risk of hepatic damage.

Among the factors associated with anaesthesia, hypoxia has the most profound effect on the liver (Rich and Resnick, 1926). Falls in blood pressure during operation adversely affect the liver by producing anoxia (Schmidt, Unruh and Chesky, 1942). The early stages of shock may not be manifested by a fall in blood pressure at a time when hypoxia of internal organs, such as the liver and kidneys, has already taken place (Richards, 1944).

These considerations reveal that there are many factors outside the control of the anaesthetist which may have harmful effects on the liver. By avoidance of hypoxia, correction of falls in blood pressure, and the use of minimal doses of non-toxic drugs, he can do much to reduce the effects of the anaesthetic on the liver. The latter has been made possible by the introduction of muscle relaxants. The use of these is frequently combined with intermittent doses of thiopentone and nitrous oxide. With this technique it is unusual to require doses of thiopentone in the order of those shown in table I in the patients in whom it was the main narcotic agent. When the dose of thiopentone exceeds 750 mg., it has been shown in figure 2 that the incidence of hepatic dysfunction following its use is high. Likewise the same figure shows that its use as an induction agent only followed by minimal doses of ether, trichlorethylene, cyclopropane or pethidine appreciably diminishes the risk of liver damage.

This may not be of great importance in routine elective operations where post-operative complications are not likely to occur. One rarely, if ever, hears of a post-operative death being attributed to liver failure. Be this as it may, the results of this investigation show that the use of large doses of thiopentone is an extra hazard for the patient. Minimal doses should always be employed in known cases of hepatic dysfunction or in patients suffering from such diseases as thyrotoxicosis, acute intestinal obstruction, pulmonary tuberculosis, or where a fall in blood pressure during operation is expected.

SUMMARY

The literature on the effects of thiopentone on liver function is reviewed. There is no general agreement as to the hepatotoxic properties of this drug.

The metabolism of urobilinogen and factors affecting it are discussed. The significance of an increased output of urobilinogen as an indication of hepatic dysfunction is reviewed.

Urinary excretion of urobilinogen was measured for three days after operation in 464 patients. The patients are divided into two equally balanced series, each of 232 cases. In one series thiopentone was used as the main narcotic and in the other its use was reserved for induction of anaesthesia. Evidence of intravascular haemolysis was looked for in 40 cases drawn from both series of cases.

The results obtained were analyzed in relation to the dose of thiopentone, nature and type of operation, and the use of muscle relaxants.

Liver dysfunction occurs in an appreciable number of patients when doses of thiopentone exceeding 750 mg. are administered. The incidence of hepatic damage is related to the dose of barbiturate given. It is considered unwise to use large doses of thiopentone in patients who show any evidence of liver damage, or for operations where any factors which may cause it are liable to occur.

ACKNOWLEDGMENTS

I am indebted to Dr. T. Black, Pathologist, Liverpool Royal Infirmary, for his encouragement and help in this investigation and for providing laboratory facilities for urine analysis in the early cases. My thanks are also due to Professors C. A. Wells and T. N. A. Jeffcoate, who allowed me to carry out the investigation for patients under their care.

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The Effects of Thiopentone on the Body.

(c) Blood Sugar and Glucose Tolerance.

"EFFECT OF THIOPENTONE ON BLOOD SUGAR AND GLUCOSE TOLERANCE"

Copy of paper submitted for publication to the British Journal of Pharmacology and Chemotherapy.

Subsequent studies (as yet incomplete) on this subject reveal a slight, but no statistically significant rise in blood sugar, during operation in patients given promethazine 25 mg and atropine 0.6 mg as pre-operative medication, and anaesthetized with thiopentone - nitrous oxide-oxygen. The same applies to the use of other thiobarbiturates - thiamylal, buthalitone, Inactin and methurital (Neraval).

The use of thiopentone for induction of anaesthesia, followed by nitrous oxide-pethidine and occasional small increments of thiopentone as required has also been studied. It was thought that the respiratory depression which can accompany this technique, might have led to a hyperglycaemia from CO_2 retention, but this was not found, in fact there was less alteration in the blood sugar level than after large doses of thiopentone-nitrous oxide-oxygen. Studies of arterial blood pH and p CO_2 did not confirm the expected carbon dioxide retention. Elam and

Brown (1956) have measured CO_2 production during the use of pethidine and found a decrease as compared with the basal rate and as compared with the findings during the intermittent use of thiopentone. In one patient they found that depression of the respiratory rate from 17.2/min to 8.4/min actually decreased alveolar CO_2 tension from 39.0 mm Hg to 36.0 mm Hg.

The effect of thiopentone narcosis on the rise in blood sugar that accompanies the continuous infusion of 5% dextrose has also been studied. It would appear from preliminary results that neither thiopentone-nitrous oxide-oxygen, or thiopentone-d-tubocurarine chloride -nitrous oxide-oxygen have any appreciable effect on the hyperglycaemic response. This finding can be reconciled with those in the previous paper on the difference in dosage of thiopentone and, more likely, on the smaller amounts of glucose presented to the liver for deposition. (In the experiments being conducted at present, glucose is infused at the rate of 100 ml of 5% solution (5g) per 30 minutes).

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Effect of Thiopentone on Blood Sugar and Glucose Tolerance

by

John W. Dundee

M.D., F.F.A.R.C.S., D.A.

Department of Anaesthesia
University of Liverpool

Attention has recently been drawn by Hunter and Greenberg (1954) and Merivale and Hunter (1954) to the abnormal blood sugar response to glucose that occurs in patients who are receiving large doses of sedative and hypnotic drugs, particularly barbiturates. All types of glucose tolerance curves have been reported, and as yet, no really satisfactory explanation for the abnormalities has been found.

Similar disturbances in glucose metabolism have been reported by Booker and his associates (1946, 1949) in dogs following thiopentone administration. In animals on normal diets liver glycogen was found to be progressively depleted during long anaesthesia, and the administration of glucose prior to the induction of anaesthesia produced hyperglycaemia and glycosuria. Even animals whose livers were depleted of carbohydrate by starvation, before the administration of thiopentone, were unable to convert glucose to glycogen and remained hyperglycaemic. Intermediate metabolism of carbohydrates were also depressed by prolonged thiopentone anaesthesia, as shown by a rise in the blood lactic acid content. All these changes could be mitigated by the use of small doses of insulin, if given along with or immediately following the administration of the thiopentone. Other workers (Blackberg and Hrubetz, 1937; Hrubetz and Blackberg, 1938; Richards and Appel, 1941), have also reported finding

a mild hyperglycaemia during thiopentone anaesthesia in animals.

No significant changes in blood sugar were noted during thiopentone anaesthesia in man by Carraway (1939) or by Sessoms, Watts, Chase and Andrews (1955). Other workers (Cameron, 1937; Thomas, 1938; Marshall, 1939; Ruth et al., 1939.), found a transitory slight hyperglycaemia returning to normal within a few hours of return of consciousness. Sessoms et al., (1939) found that patients receiving thiopentone - nitrous oxide - oxygen behave in a similar manner to those receiving thiopentone alone. It has also been noted by Bass, Watts and Chase (1955) that ether hyperglycaemia is inhibited by induction with thiopentone.

Stern, Papper, Bueding and Rovenstine (1945) have studied glucose tolerance in three subjects who were anaesthetised for 45 to 60 minutes with thiopentone. They found that the intravenous administration of 1.5 g of 50 per cent glucose produced a greater rise in blood sugar than when the same amount was administered in the conscious state. Their findings suggest a similarity in behaviour of glucose tolerance in man and dogs during thiopentone anaesthesia. However, these observations are open to criticism in that all three subjects were admitted to hospital with acute alcoholism, since hyperglycaemia responses are also found in chronic alcoholics (Bowman, Wortis, Orenstein and Goldfarb, 1939).

This paper describes observations made in man on blood sugar

changes during thiopentone anaesthesia with an without operation. Changes in the glucose tolerance curve produced by thiopentone have also been studied in healthy subjects. A preliminary mention of some of this work has appeared elsewhere (Dundee, 1956).

METHOD

This study was carried out on eight healthy adult volunteer subjects (6 males, 2 females), aged 23 - 51 years. These were admitted to hospital for ligation of varicose veins. Observations were made as follows:-

(a) Blood sugar determinations at 30 minute intervals, during prolonged administration of thiopentone.

(b) Blood sugar determinations at 10 - 20 minute intervals during operation for ligation of veins. Anaesthesia was with thiopentone - nitrous oxide - oxygen and morphine 10 mg with atropine 0.6 mg, was given as pre-operative medication.

(c) Glucose tolerance test, no anaesthesia; 50 g glucose in 150 ml water was given by mouth and blood samples drawn at approximately 30, 50, 70, 100 and 130 minutes thereafter (six subjects).

(d) Glucose tolerance test under thiopentone anaesthesia. Glucose given as above and anaesthesia induced ten minutes later and continued for a period of 100 - 270 minutes. This was done on the same six subjects as in (c).

All patients had fasted for 3 - 4 hours before each procedure save (b), when the time from the last meal varied from 4 - 11 hours.

The blood sample for the control blood sugar reading was withdrawn immediately before the administration of the thiopentone in (a) and (b) and before the glucose in (c) and (d). The order in which the above investigations were carried out varied in each case, but the interval between each administration of thiopentone was always longer than one week. The normal response to glucose (c) was estimated at different times depending on circumstances, (on two occasions on the day before operation; in three subjects during the second week after operation and once about six weeks after the patient had left hospital).

All anaesthetics were given personally and all administrations were smooth throughout with no marked respiratory depression or hypotension. As far as possible the same dose of thiopentone was given on each occasion, but on no instance was the amount of drug given more than appeared necessary to maintain the desired degree of narcosis. It was found that the doses of thiopentone which, following pre-operative medication and combined with six litres nitrous oxide and two litres oxygen per minute, produced satisfactory operating conditions, if given alone were sufficient to produce light narcosis with the occasional return of the corneal reflex. There were no untoward sequelae following any of the anaesthetics and convalescence after operation was uneventful, in all cases.

Blood sugar estimations were carried out by the method described by Folin and Wu (1920), using venous blood from the forearm. For

repeated withdrawals of blood and injections of thiopentone the Mitchell self-sealing needle (Mitchell, 1952) proved very useful.

RESULTS

Table 1 gives the average blood sugar readings and doses of thiopentone given in investigation (a) when no operation was carried out or other drugs given. At no time was the increase in blood sugar level significantly different from the control reading.

The average effects on vlood sugar of thiopentone-nitrous oxide-oxygen, after pre-operative morphine and atropine in subjects undergoing non-abdominal surgery are shown in Table 2. These show a significant increase in glucose content of the blood samples drawn between 5 and 50 minutes after induction of anaesthesia. The rise in blood sugar is not very great and its magnitude is decreased if one allows for a possible error of $\pm$ 5 mg/100 ml in the technique of estimation. However, despite this, the rise in blood sugar immediately after the induction of anaesthesia was significantly greater, ($p < 0.01$) than occurred in the same subjects after thiopentone alone.

Figure 1 shows the average results in the six patients in whom all four investigations were carried out. The blood sugar readings with and without operation are essentially the same as in tables 1 and 2 and require no further comment. This figure shows that thiopentone

Volunteers

Time in minutes	No. of observations	Average dose of thiopentone mg	mg/kg	Average blood sugar (mg/100 ml)	Average deviation from control
Control	8			84	
20 - 40	8	769 (450 - 1750)	10.7	85	+ 0.8 ± 4.0
50 - 70	8	850 (700 - 1750)	16.1	84	0
80 - 100	6	1228 (825 - 2000)	19.5	83	+ 1.7 ± 1.8
110 - 130	6	1560 (900 - 2800)	23.8	80	- 1.7 ± 1.4
140 - 160	5	1700 (1000 - 2800)	26.7	82	0
200 - 220	4	2212 (1200 - 3400)	30.1	80	- 2.5 ± 1.6
230 - 250	4	2306 (1325 - 3400)	35.2	81	- 1.2 ± 1.2
260 +	3	1967 (1400 - 2900)	30.4	80	0

Table 1

Average blood sugar readings in 8 subjects who received thiopentone in doses stated above but who were not subjected to any operation.

Fig 1.

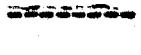
Figure 1

Average Blood Sugar Readings on Six Subjects

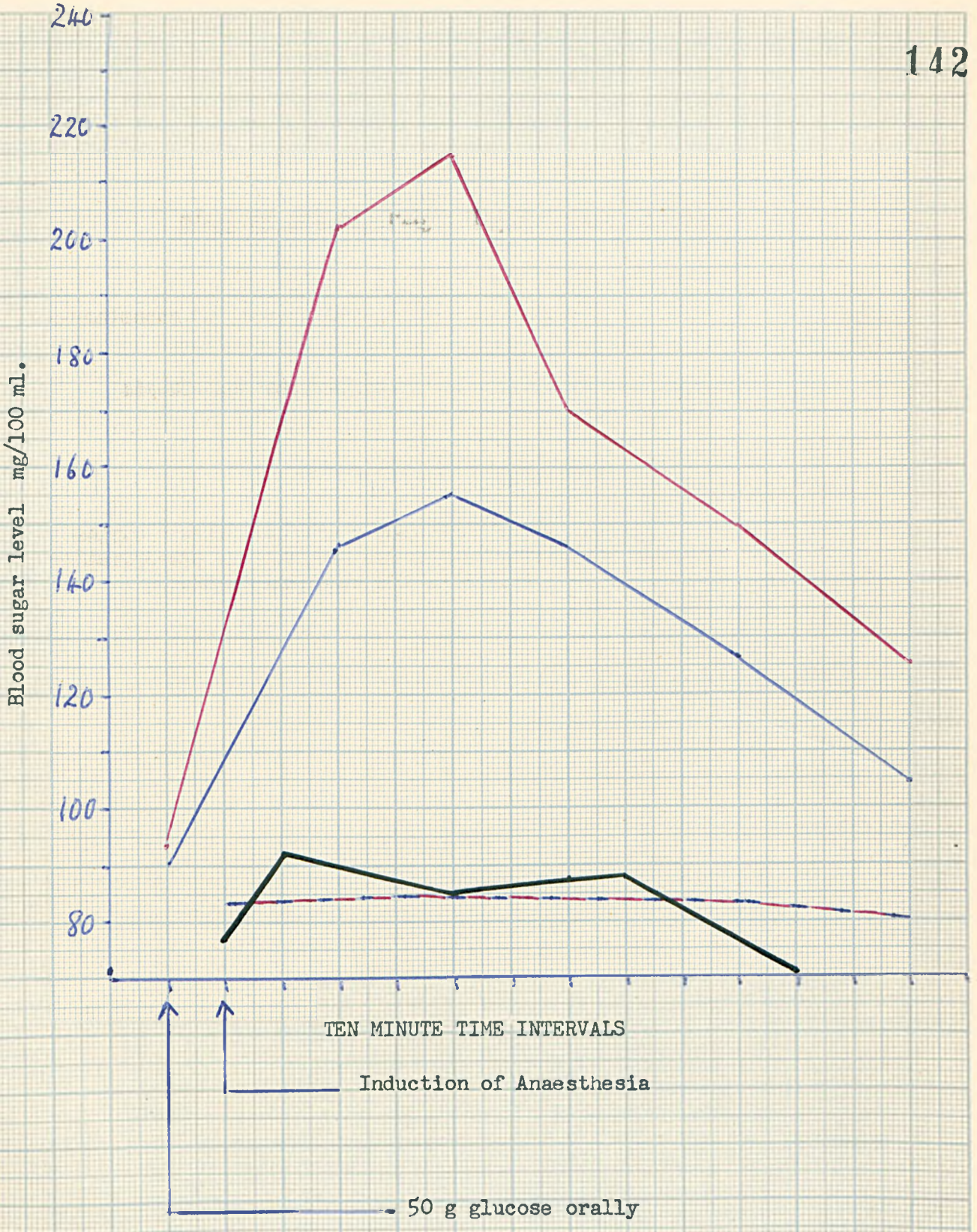
(~~upper curve~~) glucose tolerance test, no anaesthesia

glucose tolerance test, thiopentone anaesthesia

thiopentone anaesthesia alone



(~~lower curve~~) thiopentone - nitrous oxide - oxygen anaesthesia : atropine and morphine as pre-operative medication. Operation for varicose veins.


240
220
200
180
160
140
120
100
80
Blood sugar level mg/100 ml.
TEN MINUTE TIME INTERVALS
Induction of Anaesthesia
50 g glucose orally

Time in minutes	No. of observations	Average dose of thiopentone		Average blood sugar (mg/100 ml)	Average deviation from control
		mg	mg/kg		
Control	8			77	
5 - 15	8	950 (500 - 1400)	13.6	92	+ 25.3 ± 4.0
20 - 35	8	1170 (850 - 1700)	16.4	85	+ 8.3 ± 3.6
50 - 70	7	1143 (1000 - 1700)	16.2	88	+ 10.6 ± 4.7
80 - 100 (awake)	8	1350 (1000 - 1700)	19.5	75	- 1.8 ± 0.8

Table 2

Details of average blood sugar readings and doses of thiopentone in 8 subjects who were operated on for varicose veins under thiopentone - nitrous oxide - oxygen anaesthesia.

produces a marked effect on the blood sugar response to the oral administration of 50 g glucose. The hyperglycaemic responses produced by thiopentone was consistant in all cases and an analysis of the average increases in blood sugar (Table 3) shows the effect of thiopentone to be statistically significant. Urine samples collected in three subjects reduced Benedict's solution after the administration of thiopentone, while this only occurred in one of the three subjects when they did not receive an anaesthetic.

DISCUSSION

Despite the small number of subjects used in this study, since these volunteers were willing to submit to repeated administrations of thiopentone, it is hoped that the results will be more valuable than would be obtained from a larger number of subjects, each having only one investigation. One cannot be certain from the few results in table 1, that thiopentone alone has no effect on blood sugar, but a comparison of tables 1 and 2 show that the combination of thiopentone with either morphine, atropine, nitrous oxide or operative stress produces a temporary mild hypoglycaemia.

The work of Sessoms et al., (1955) shows that, in the absence of hypoxia, nitrous oxide was not the cause of the hyperglycaemia. Factors other than the anaesthetic agents can cause a rise in blood sugar and these have recently been exhautively reveiwed by Foster and

Average deviation of blood sugar level (1 mg/100 ml) from control value.

Time after administration of glucose (minutes).	No Anaesthesia (A)	Thiopentone (B)	Difference (A - B)	"t" value
30	+ 48 ± 7.5 (18 - 100)	+ 110 ± 10.8 (80 - 140)	62 ± 13.4	4.7
50	+ 65 ± 9.7 (30 - 100)	+ 125 ± 9.2 (90 - 140)	60 ± 15.0	4.0
70	+ 57 ± 10.6 (40 - 80)	+ 78 ± 9.3 (40 - 110)	21 ± 14.5	1.5
100	+ 27 ± 5.3 (10 - 50)	+ 52 ± 4.1 (35 - 80)	25 ± 6.8	3.7
130	+ 7 ± 1.9 (0 - 20)	+ 35 ± 7.6 (0 - 60)	28 ± 8.0	3.5

Table 3.

Average increase in blood sugar after 50 g glucose by mouth in 6 subjects with and without thiopentone anaesthesia.

Francis (1955). Morphine, despite its depressant effect on the central nervous system may raise blood sugar and can act as a stressor (Selye, 1950). Atropine has been shown by several workers to block insulin secretion produced by vagal stimulation (Portis, 1950; Portis and Zitman, 1943). However, Bass et al., (1953) and Goodman and Gilman (1955) consider the effects of therapeutic doses of morphine and atropine to be negligible. The alarm reaction, described by Selye (1950) as part of the body's response to stress, following the initial trauma of surgery may have caused a transient rise in blood sugar, produced by liberation of adrenaline. If marked apprehension had been present before induction of anaesthesia the control blood sugar reading in table 2 should have been raised, whereas it was lower than before any of the other investigations.

A more likely explanation for the rise in blood sugar during operation is the combined respiratory depressant effects of thiopentone and morphine, which Eckenhoff and his colleagues (Eckenhoff et al, 1954, 1955; Helrich et al, 1956) have shown to be much more marked than that produced by thiopentone alone. Hypercarbia and hypoxia can both raise the blood sugar level; in fact, these are the reasons given by Goodman and Gilman (1955) for the hyperglycaemia that follws large doses of morphine.

Save for the report of Sessoms et al., (1955) sufficient data on dosage of thiopentone and nature of operations etc., is not given to

allow the results of this investigation to be compared with those of other workers. Sessoms found an insignificant drop in the blood sugar levels of patients undergoing dilatation of the cervix and cutterage of the uterus under thiopentone alone or under thiopentone-nitrous oxide-oxygen anaesthesia. The operations are comparable in that in neither case did they involve the peritoneal cavity or autonomic nervous system. Although the doses of drugs used as pre-operative medication are not given in Sessom's paper, they are unlikely to have differed greatly from those given before operation in this study. However, the average doses of thiopentone given by Sessoms et al., were 675 (575 - 800) mg, when the drug was given alone and 463.8 (300 - 750) mg when it was combined with nitrous oxide-oxygen. The latter figure is approximately half that used for the first 5 to 15 minutes in the operated patients in this study (table 2) and the consequently greater degree of respiratory depression is the most probable explanation for the different results obtained.

The altered glucose tolerance in patients receiving thiopentone (Figure 1; table 3) is in full agreement with the findings of Booker (1946) in dogs and Stern et al., (1945) in man. It has been shown (Booker, 1946; Booker, French and Milano, 1949) that intermediate metabolism of carbohydrates is also interfered with by thiopentone, and these workers consider the depression of the glycogenolytic - glycogenic activity of the liver by thiopentone to be indirect evidence of the

role of this organ in its metabolism. The hepatic detoxication of thiopentone is now proven beyond all reasonable doubt (Shideman, Kelly and Adams, 1947; Shideman, Kelly, Lee, Lovell and Adams, 1949; Walker, Wyan and Parry, 1949; Dundee, 1952; Meyers and Peoples, 1954) and it seems more likely that this is a manifestation of the hepatic toxicity of large doses of thiopentone, since the author (1955) has shown that similar doses interfere with other functions of the liver.

SUMMARY

1. Thiopentone anaesthesia alone produces no appreciable effect on the blood sugar levels in man.
2. Slight hyperglycaemia was observed when thiopentone - nitrous oxide-oxygen anaesthesia, following morphine and atropine as pre-operative medication, was used as anaesthesia for operations on varicose veins.
3. The rise in blood sugar during operation differed significantly from that produced by the anaesthetic alone, and may be secondary to respiratory depression from the morphine - thiopentone combination.
4. Thiopentone markedly depresses the ability of the body to deal with an extra load of glucose.

5. The depression in glucose tolerance is thought to be a manifestation of the hepatotoxic effect of large doses of thiopentone.

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Chapter 4.

MISCELLANEOUS

(a) Clinical use of Thiopentone.

(b) Thiamylal.

(c) Solutions of Barbiturates

(d) Use in Experimental Animals.

Miscellaneous.

(a) Clinical Use of Thiopentone.

"USES AND ABUSES OF THIOPENTONE"

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THE USES AND ABUSES OF THIOPENTONE

(abridged)

by

JOHN W. DUNDEE

M.D., F.F.A.R.C.S.

Lecturer in Anaesthesia,
University of Liverpool.

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29th October, 1954.

"It is not the fault of the drugs and the methods concerned that a syringe and a hollow needle are no susceptible to clinical abuse."

(Gillespie, 1950).

Thiopentone has been described in such varying terms as 'a godsend' and 'too dangerous a drug for routine use'. Published figures show that in some centres in America it is used in between one quarter to one half of all anaesthetics. In Britain thiopentone is more popular and it is safe to say that an intravenous thiobarbiturate is used for the induction of anaesthesia in more than three quarters of all cases. In view of Gillespie's statement and our ever increasing knowledge of the action of thiopentone it is timely to consider some of the uses and abuses of this commonly used drug.

Uses

Adriani (1946) has admirably outlined the occasions when thiopentone should be used in anaesthesia.

1. As an anaesthetic for very brief surgical procedures or induction of anaesthesia.

2. Basal narcotic to supplement nitrous oxide or other more powerful drugs in low concentrations, or in combination with analgesics.
3. Anti-convulsant.
4. In hypnotic doses combined with spinal or local anaesthesia.

In as far as the word 'anaesthesia', as conceived by Oliver Wendell Holmes, refers to loss of sensation, thiopentone is a satisfactory anaesthetic. Today the more commonly accepted meaning of this word is a state which will permit surgical procedures to be performed without any reaction from, or any dangers to the patient. While thiopentone is one of the best hypnotic drugs known, by modern standards it is an unsatisfactory anaesthetic agent when used alone. It possesses very little analgesic power and the margin between the dose required for relaxation and that which will result in apnoea is very small.

Abuses

Many of the complications which have followed the administration of thiopentone can be attributed to the terms 'short-acting' or 'ultra-short-acting' by which it is referred to in most of the standard books on anaesthesia or pharmacology. A short period of narcosis generally follows the administration of small doses, but large doses may be followed by prolonged sleep. It is slowly broken down in the

body and a cumulative effect is evident if a dose is repeated within thirty hours. Impairment of mental activity often persists for many hours after the administration of thiopentone and the deleterious effects on the cardiovascular system or the liver may last for an even longer period of time. A more descriptive term for thiopentone would be 'rapidly-acting diffusible' barbiturate.

Only under very special circumstances should thiopentone be used as the sole anaesthetic except for very minor procedures. No one would use it alone for such major procedures as gastric resection or the repair of herniae, but it is not uncommon to find it being the sole agent for systoscopic examinations taking half an hour or more. More anaesthetic is required where the stimulus is strong, e.g. during distension of the bladder, or where profound relaxation is required as in reduction and plastering a fracture. Large doses are often followed by delayed recovery. The patient may appear to be lightly anaesthetised when the stimulus is present, but on return to the ward may lapse into deep unconsciousness with the dangers of the tongue falling back and causing respiratory obstruction.

Thiopentone is a direct cardiac depressant and while the intact healthy cardiovascular system can accomodate itself to the effects of small doses one has no way of telling whether the damaged myocardium can stand up to large amounts. The effects on the cardio-

vascular system depend, among other factors, on the absolute concentration of the drug in the blood stream. While rapid injection produces a short period of good relaxation, the high concentration of the drug has a profound effect on the blood pressure, and cardiovascular system in general. The safety of thiopentone is decreased enormously by a rapid rate of injection.

Insufficient use is made of dilute solutions (2 - 2½%). With a dilute solution the rate of injection cannot be so quick, the drug will be more diluted in the blood stream and the effects on the heart will be less. It is interesting to note that so severe damage to a limb has been reported following the intra-arterial injection of a 2.5 per cent solution of thiopentone. This does not mean that the precautions taken to avoid this catastrophe when using 5 per cent solutions should be relaxed with the more dilute solutions. Less severe damage is also likely to follow the extravenous injection of dilute solution of thiopentone.

Judged by views expressed in the literature there seems to be an improper understanding of the contraindications to the use of thiopentone and the factors which render patients sensitive to the drug. In table 1 are listed the contraindications which appear most frequently in 28 publications on the drug during the past 10 years. In all 29 conditions were listed in which at least one writer advised against the use of thiopentone. One author lists idiosycrasy to the

Contraindication	No. of Appearences in Literature		
	Absolute	Relative	Total
Myocardial weakness	16	4	20
Liver dysfunction	14	5	19
Factors interfering with airway	16	2	18
Gross respiratory disease with dyspnoea	15	3	18
Oedema of glottis	16	1	17
Shock	9	77	16
Renal disease	9	4	13
Respiratory obstruction	9	2	10
Children under 10	5	4	9
Feeble elderly patients	5	4	9
Severe anaemia	8	1	9
Sepsis	3	3	6
Diabetes	2	4	6
Advanced malignant disease	3	2	55

Table 1.

Contraindication to thiopentone reported in 28 publications during the past 10 years.

drug as a contraindication to its use, but fails to mention how this condition can be detected before the induction of anaesthesia.

It is not a very great exaggeration to say that the absence of suitable veins is the main contraindication to the use of thiopentone. It is better avoided in patients suffering from porphyria in Addison's disease, or in severe uraemia. Most of the conditions listed in table 1 render patients sensitive to thiopentone, but it can be safely administered in reduced dosage. Another series can be grouped under 'inadequate airway', whether this is present before induction of anaesthesia or is liable to occur during the operation. These conditions or procedures are no more a contraindication to the use of thiopentone than to any other general anaesthetic agent. If a good airway is established before the induction of anaesthesia or steps are taken to see that it will remain patent during the operation, then thiopentone can be administered with safety. As an example of this is the report by Williams and Guribruck (1943) of twenty administrations of the drug to patients suffering from Ludwig's angina in which no fatalities attributed to its use occurred. Where the subject was using the necessary respiratory muscles, an endotracheal tube was passed under topical anaesthesia or a tracheotomy was performed before the induction of anaesthesia.

Liver or kidney dysfunction are the next most commonly

mentioned contraindication to the use of thiopentone. Recovery from small doses occurs by diffusion to non-nervous tissues and is independent of the liver, but with large doses the detoxicating mechanism is important in recovery and prolonged narcosis may occur in the presence of severe hepatic dysfunction. Apart from this, it is not advisable to adminster large doses of a hepatotoxic agent to a patient with an already damaged liver. The kidney only excreted minute doses of unchanged thiopentone and there is no evidence that its breakdown products, whose excretion may be impaired in kidney disease, have any narcotic properties. However, uraemia which is a common accompaniment of renal disease is one of the most important factors met in clinical practice which prolongs narcosis with thiopentone.

Myocardial weakness in a relative contraindication to the use of thiopentone. In severe cases it is better to avoid the use of the drug if possible, but where necessary small doses of a dilute solution can be injected slowly. In this type of case the maximum use should be made of non-toxic adjuvants, especially nitrous oxide-oxygen and relaxants.

The ineffective use of nitrous-oxide-oxygen as an adjuvant to thiopentone is only too common. One frequently sees it serving only as a vehicle for carrying a volatile supplementary agent, and playing no major part in the anaesthetic sequence. By using a close fitting

face mask or a cuffed endotracheal tube with high flows of the gas immediately after the induction of anaesthesia a large concentration of nitrous oxide in the blood is soon obtained with a corresponding reduction in thiopentone requirements. Pre-oxygenation before the administration of thiopentone also makes any subsequent administrations of nitrous oxide-oxygen more effective earlier, it also permits a longer period of repiratory obstruction should any unforseen accident occur during the induction period.

There is no justification of the use of thiopentone in outpatients if the patients are allowed to leave hospital unaccompanied. Return of consciousness does not mean that the powers of thought and reasoning are normal, subjects may perform automatic actions, such as walking along a quiet street, but when confronted with a situation which requires a certain amount of quick thinking, such as crossing a busy street, an accident may happen. Further complications may arise from the presence of a period of retrograde amnesia which often follows the use of thiopentone.

The mixing of thiopentone with muscle relaxants and especially the continued use of dilute solutions of this mixture is a practice which is without any scientific basis. The two types of drugs are broken down by different means and conditions which render patients sensitive to thiopentone often cause resistance to relxants. In this

case an overdose of narcotic can be very easily given. At different periods during an operation either more relaxation or deeper narcosis is needed and with the use of thiopentone-relaxant mixtures one cannot be produced without the other.

Mixtures of thiopentone and analeptics are likewise not advised. With Lundy's (1935) mixture of thiopentone and nikethamide one is administering two myocardial depressants to prevent respiratory depression from one of them. Lockett's suggestion of mixing thiopentone with d-oxyephedine (Methedrine) also seems unwise, since the latter drug does not raise the blood pressure by the opposite means to which thiopentone lowers it.

The safe administration of thiopentone necessitates a proper appreciation of the pathological conditions which result in sensitivity to it. In anaesthetic practice shock, anaemia and uraemia are the most important clinical entities in this respect. One has only to recall Halford's (1943) report of its indiscriminate use at Pearl Harbour to appreciate the sensitivity that occurs in shock patients. An 'ideal form of euthanasia' was the most complimentary description that he could give to the use of intravenous anaesthesia. Later and more extensive reports from all over the world have since shown that given slowly in minimal doses, thiopentone is a safe agent for shocked patients.

Severe anaemia prolongs thiopentone narcosis (fig. 1) this effect being particularly marked when the haemoglobin level is less than 60 per cent of normal (Haldaine standard).

The duration of narcosis is particularly sensitive to alterations in the blood urea level (fig. 2). With a severe degree of uraemia extremely small amounts of thiopentone will lead to prolonged sleep, and the drug is better avoided.

Other conditions which result in decreased tolerance to thiopentone include maleria (where anaemia and liver dysfunction may both be present), malnutrition, myasthenia gravis and intestinal obstruction. Where the drug is used to control the convulsions which follow overdose of a local anaesthetic, the dosage should be kept to a minimum to avoid prolonged narcosis. Whether this is solely due to the thiopentone is open to question.

In conclusion it is interesting to see how thiopentone stands in relation to the requirements of a perfect anaesthetic as outlined by Morrin at the annual meeting of the British Medical Association in 1933, the year before its discovery.

1. Administration should be accomplished without discomfort to either the young or old patient and without complicated apparatus - this can be done with thiopentone, but to use the drug without means of inflating the chest or controlling the airway is asking for trouble.

2. Induction must be agreeable and the anaesthetic should not have any deleterious effects on the respiration or circulation - thiopentone is both a respiratory depressant and myocardial poison although these effects can be minimised by proper administration.

3. Blood pressure should be maintained at a normal level throughout - one cannot guarantee this, but again the method of administration is of prime importance.

4. Elimination should be rapid without producing harmful effects on the hepatic, renal or pulmonary tissues - clinically thiopentone is short acting after small doses but pharmacologically it is long acting, irrespective of the dose.

5. The anaesthetic effect should be induced gradually and it should be at all times under control - this depends on the method of administration.

6. In addition to securing sensory paralysis, complete muscular relaxation should be rapidly and safely obtained. To attempt this with thiopentone is to increase its toxicity out of proportion to the advantages gained.

The writer in 1933 concludes - "The perfect anaesthetic awaits discovery ..... the anaesthetist has welcomed the products of the analytical chemist with faith and hope". We shall never find the ideal anaesthetic combination. However, we owe a lot to the analytical chemist for producing a drug, which, if its limitations are appreciated and if it is handled properly can be one of the safest agents available today.

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INTRA-ARTERIAL INJECTION OF THIOPENTONE

from Correspondence:- British Medical Journal, (1953). 1, 402.

Sir,

Your correspondent J. N. Fell (January 10th, 1953, p. 96) once again shows the ease with which thiopentone can be injected into an artery. His case is interesting in that all the recognised precautions were taken to avoid this accident. A similar condition must have existed in a published case in which a saline drip was inserted into an artery about two inches above the wrist on the radical side of the forearm, (Brit. J. Anaesth., (1952). 24, 149). The way in which the classical picture can be masked by the use of a Gordh needle and other factors is illustrated by the following case.

A primipara came to the theatre for caesarian section, having been in labour for abour 24 hours. She was very distressed and restless as pains were occurring every few minutes. With difficulty her arm was secured to an arm board and a Gordh needle inserted into a 'vein' at the distal end of the antecubital fossa. Because of the constant movement of the patient palpation of the area before insertion of the needle was inadequate and the amount of pressure applied to the limb could easily have obliterated any arterial

pulsation. Once the needle was inserted it was securely strapped down to both arm and arm board.

Injections were given through the Gordh needle of 0.65 mg atropine and 5 mg d-tubocurarine chloride. These were followed by 5 - 6 ml normal saline. When the patient was towelled up ready for the skin incision a further 12 mg d-tubocurarine chloride followed by 250 mg 2½% thiopentone were injected. The patient immediately cried out and tried to wrench her arm from the arm board. These signs were interpreted as being due to either another labour pain or a suffocating feeling following the injection of the relaxant. Anaesthesia was continued with light cyclopropane until the baby was delivered and then with deeper cyclopropane. During the course of the operation which was uneventful, 0.5 mg ergometrine, 0.65 mg atropine and 2 mg neostigmine were all given through the Gordh needle. Between each successive injection 5 - 6 ml normal saline were injected.

It was only when the operation was completed and the strapping removed from the Gordh needle that the pulsations became apparent. The diaphragm of the needle was removed and bright red blood spurted from it. The needle was removed and a pressure bandage applied. A new interpretation was now given to the cry during induction of anaesthesia and a brachial plexus block was performed with 1% procaine. A large volume of this solution was used and 10 - 20 ml

deposited well back on the first rib. The purpose of this was to try to include the stellate ganglion with the brachial plexus block, its sucess being signified by appearence of a Horner's syndrome. No other treatment was given save the substitution of Omnopon for morphine as postoperative analgesia. Other than complaining of a tingling sensation in the arm on waking up, (presumably due to brachial plexus block wearing off), the patient made an eneventful recovery.

Although the conditions under which venepuncture was performed in this patient were extremely difficult, there would have been no justification for inadequate palpitation should anything have happened as the result of the intra-arterial injection. That complications did not arise can presumably be attributed to the dilute solution of thiopentone, the injections of saline, the peripheral vasodilatation due to the cyclopropane, and possibly the effects of the combined brachial plexus and stellate ganglion blocks. The therapeutic value of procaine was not known at the time when this case occurred. Recent work on peripheral vascular diseased (Edwards, J. W. L., Jones, N. B., McConnell, R. B., Pemberton, H. S. and Watson, D. C. (1952). Brit. med. J., 2, 808) has suggested that intra-arterial papaverine, 40 mg in 20 ml saline could be added to the treatmsnt of these cases with benefit. This can be done easily into the subclavian artery during block of the medial trunks of the brachial plexus.

This case illustrates how the cardinal signs of intra-arterial injection of thiopentone can be masked by a) the use of a Gordh needle securely strapped to the arm, and b) the previous use of a relaxant drug, on the onset of labour pain being taken for an explanation for the distressing pain which follows such an injection.

I am, etc.,

Liverpool. John W. Dundee

Miscellaneous.

(b) Thiamylal.

"A CLINICAL TRIAL OF THIAMYLAL AS AN INTRAVENOUS ANAESTHETIC IN 1750 CASES".

(published jointly with Dr. J. E. Riding)

Reprinted from the British Journal of Anaesthesia, (1955).

27, pages 382 - 388.

The findings with this drug in man, are in agreement with the observations on its cumulative action, as compared with thiopentone, in animals (see page).

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A CLINICAL TRIAL OF THIAMYLAL AS AN INTRAVENOUS ANAESTHETIC IN 1,750 CASES

BY

JOHN W. DUNDEE AND J. E. RIDING

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Brit. J. Anaesth. (1955), **27**, 381

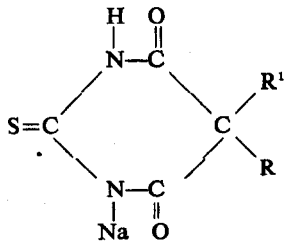
A CLINICAL TRIAL OF THIAMYLAL AS AN INTRAVENOUS ANAESTHETIC IN 1,750 CASES

BY

JOHN W. DUNDEE AND J. E. RIDING

Department of Anaesthesia, University of Liverpool

THIAMYLAL is one of the group of rapidly-acting thiobarbiturates which was described by Tabern and Volwiler in 1935. It bears the same chemical relationship to quinalbarbitone (Seconal) as thiopentone bears to pentobarbitone (Nembutal). The chemical structure of the two drugs is shown below:



	R	R¹
Thiopentone	—CH(CH₃)—C₃H₇	—CH₂.CH₃
Thiamylal	—CH(CH₃)—C₃H₇	—CH₂.CH=CH₂

It can be seen that thiamylal is the sodium salt of 5-allyl-5′-(1-methyl butyl) -2 thiobarbituric acid.

Dornette (1954) has reviewed the development of the drug, the pharmacological properties of which were first investigated by Wyngaarden, Woods, Ridley and Seevers in 1949. Its use in clinical anaesthesia has been the subject of numerous American reports within the last five years, the most extensive being that of Lund (1954), whose experience at that time extended to more than 15,000 cases. Thiamylal is not commercially available in this country and the only report of its use is that of Barran and Wylie who described a small series of cases in which the drug was referred to as thioquinalbarbitone.

From the published reports it appears that thiamylal offers certain advantages over thiopentone which warrant further study. Over a period of about one year thiamylal was used by the authors as a routine drug in place of thiopentone, the precautions applicable to the latter drug being observed. This paper is a report of its use in 1,750 cases.

CLINICAL MATERIAL

Table I shows the nature of the operations for which thiamylal was used. The ages of the patients and the duration of the procedures are given in figures 1 and 2. The use of thiamylal as a main narcotic refers to its use as sole agent or combined with nitrous oxide and in some cases with an intravenous analgesic. It will be seen that the drug has been used in most types of operative procedures. In the age group 0–10 years there are few patients because the authors have few opportunities to anaesthetize children. Its rectal use as a basal narcotic has not been studied.

TABLE I

Nature of Operations.

Nature of operation	Thiamylal as main narcotic	Thiamylal for induction only	Total
Abdominal surgery			
Herniae	73	10	83
Gall bladder and pancreas	15	1	16
Gastric	51	3	54
Appendix	51	10	61
Prostate	20	1	21
Colon and Rectum	13	5	18
Renal	8	1	9
Miscellaneous	14	2	16
Thoracic surgery			
Thoracoplasty	21	0	21
Lung resections	46	0	46
Miscellaneous	20	0	20
Gynaecology			
Major	32	15	47
Minor	11	175	186
Neurosurgery	13	23	36
Orthopaedics			
Major	0	28	28
Minor	30	96	126
Endoscopy			
Bronchoscopy	104	0	104
Cystoscopy	86	58	144
Oesophagoscopy	20	0	20
Electroconvulsive therapy	307	0	307
Sympathetic nervous system	9	2	11
Thyroidectomy	0	11	11
Caesarean section	19	2	21
Intra-oral and Dental	9	9	18
Ophthalmic	0	5	5
Minor rectal surgery	20	41	61
Miscellaneous			
Varicose veins	33	30	63
Testes and scrotum	4	21	25
Breasts	2	23	25
Spine and back	11	8	19
Bladder and penis	2	7	9
Others	58	61	119
Total	1102	648	1750

TABLE II

Anaesthetic combinations.

A. Thiamylal as main narcotic combined with:		B. Thiamylal for induction of anaesthesia followed by:	
Suxamethonium and oxygen	399	N_2O—O_2—trichlorethylene	305
N_2O—O_2 long acting relaxant	302	N_2O—O_2—ether	152
N_2O—O_2	142	Cyclopropane and oxygen	84
Used as sole agent	98	N_2O—O_2—trichlorethylene ± analgesic	73
N_2O—O_2—analgesic ± relaxant	66	N_2O—O_2—ether—relaxant	30
N_2O—O_2—suxamethonium	53	Cyclopropane—oxygen—relaxant	4
Gallamine triethiodide and oxygen	30		
Spinal analgesic	12		
Total	1102	Total	648

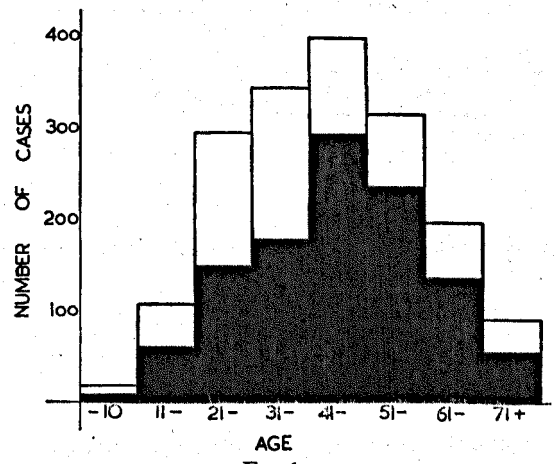


FIG. 1

Age distribution of cases

Thiamylal as sole narcotic.

Thiamylal for induction of anaesthesia only.

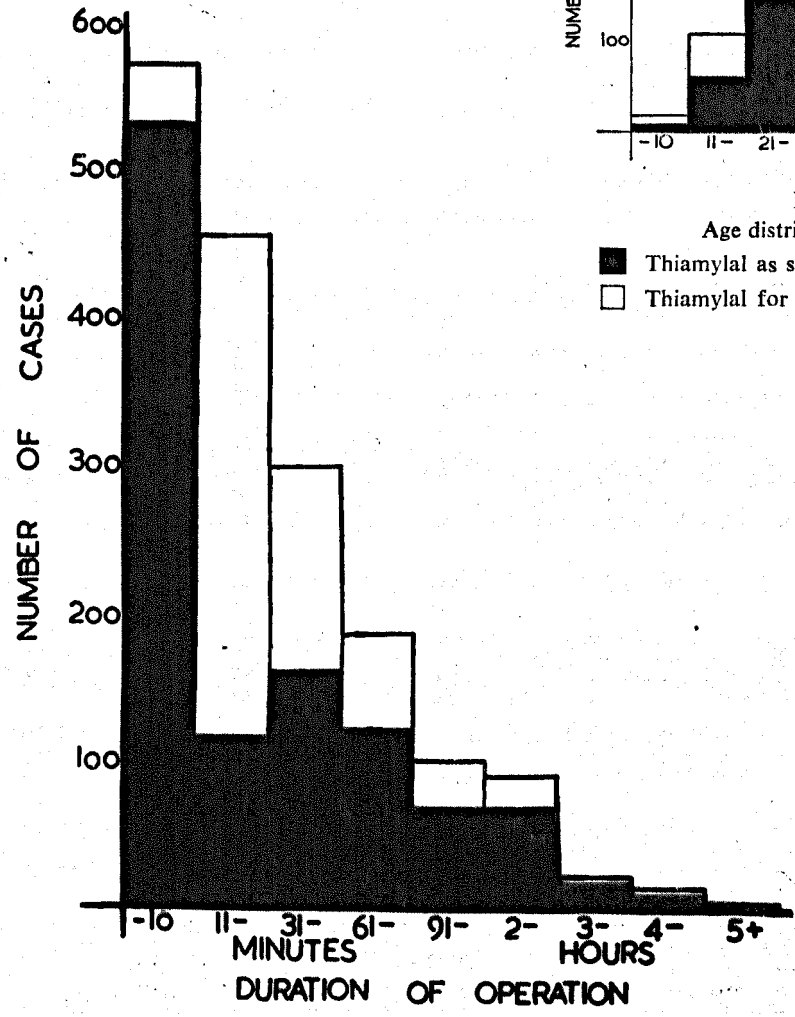


FIG. 2

Duration of operations

Thiamylal as sole narcotic.

Thiamylal for induction of anaesthesia only.

Table II lists the anaesthetic combinations with which thiamylal has been used, and it can be seen that this includes most recognized techniques. The drug was administered in a 2–5 and 5 per cent solution and in 40 cases (to be described in detail later) in a 0.4 per cent continuous drip.

CLINICAL RESULTS

Thiamylal is a rapidly effective agent for the induction of anaesthesia, which, from the patient's point of view, is as pleasant as thiopentone. There is no doubt that the drug is slightly more potent than thiopentone, as judged from the dose required to induce sleep. Supplementary agents were introduced with the same ease as after thiopentone, and respiratory depression seemed to be of the same order as that seen with other thiobarbiturates. No case of laryngospasm was seen following the induction of anaesthesia and no case of prolonged apnoea was encountered, attributable to the use of the drug. Comments cannot be offered on its tissue-irritant properties as gross extravenous injection did not occur in this series. The impression was gained that, with equipotent doses, recovery was more rapid from thiamylal than from thiopentone. Because of the multiplicity of factors involved in postanaesthetic vomiting, this was not studied. This applies also to postoperative respiratory complications.

In cases where blood pressure readings were taken during operation, the changes were similar to those seen after the use of comparable doses of thiopentone. No prolonged hypotension was encountered for which thiamylal could be held responsible. In 17 patients electrocardiographic studies during the induction and maintenance of anaesthesia showed no abnormality.

In our experience all the variations in response to thiopentone which are seen in certain pathological states such as shock and uraemia apply equally to thiamylal. A marked degree of resistance was encountered in only one patient, and this person had an acquired tolerance to opiates and similar drugs.

COMPARISON WITH THIOPENTONE

It appears to us that thiamylal differs from thiopentone mainly in its greater potency (fig. 3) and shorter action of

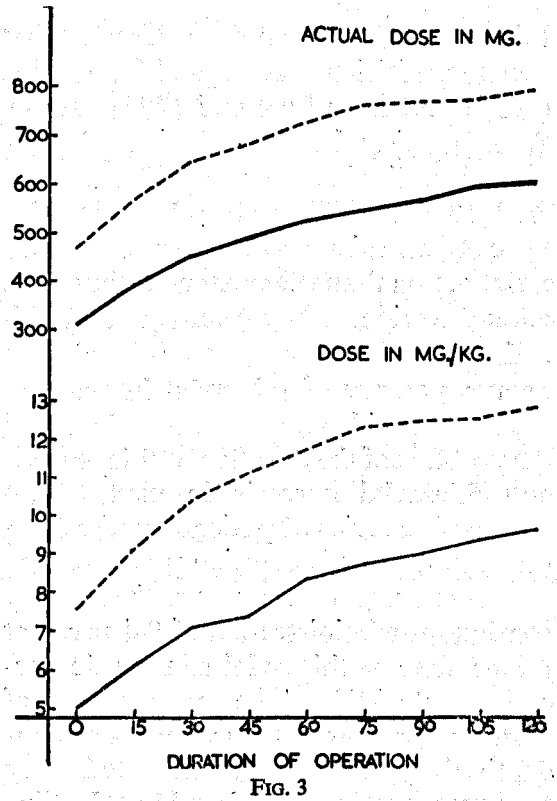


FIG. 3

Average doses of thiopentone and thiamylal required to produce anaesthesia in two comparable series of abdominal cases, in which the anaesthetic technique thiobarbiturate-relaxant-nitrous oxide-oxygen was used
- - - Thiopentone. —— Thiamylal.

TABLE III

Details of cases in which the requirements of thiopentone and thiamylal were analysed in detail.

	Thiopentone	Thiamylal
Number of cases	40	40
Average age (years)	45.1 ± 2.1	43.9 ± 2.2
Average weight (kg)	64.3 ± 0.97	66.8 ± 1.64
Sex incidence		
Males	28	27
Females	12	13
Nature of operations		
Varicose vein ligation	23	23
Urethral endoscopy	7	7
Prostatectomy (supplementary to spinal analgesia)	6	6
Transurethral prostatectomy	2	2
Pelvic floor repair (supplementary to local analgesia)	1	1
Bilateral inguinal hernia (supplementary to local analgesia)	1	1

equipotent doses. There also seems to be less tendency to laryngospasm than after thiopentone. These differences were first noted by Helrich, Papper and Rovenstine (1950) and later by Lund (1951, 1954), Wall (1951) and Philips (1953). Experimental studies in animals by Wyngaarden *et al* (1949) and Swanson and Chen (1953) have shown thiamylal to have less cumulative action than thiopentone on repeated administration. Wyngaarden and his colleagues have also established the greater potency of thiamylal in the dog.

It was decided to investigate in detail the problem of the duration of thiopentone and thiamylal narcosis in man. Two comparable series of patients, undergoing the same types of operation performed by the same surgeons were anaesthetized by continuous administration of 0.4 per cent thiopentone or thiamylal as the sole narcotic (table III). The average dose of each drug required to produce a similar depth of anaesthesia was calculated every 5 minutes and is shown in table IV. The depth was the lightest possible sufficient to obtund reflex and muscular response to surgical stimuli. In table V these results are expressed as mg/kg and reveal that, on the average, a significantly larger dose of thiopentone was required during the first 45 minutes of anaesthesia. The failure to find a statistically significant difference between the total doses of the two drugs at 60 minutes is in agreement with the hypothesis that thiamylal has a shorter action than thiopentone. The more cumulative agent (thiopentone) will require less incrementation than the less cumulative thiamylal.

TABLE IV

Comparison of average actual requirements of thiopentone and thiamylal.

Time	Average dose mg		S.E. (difference)
	Thiopentone	Thiamylal	
Induction	490 ± 36.7	363 ± 98.9	± 105
5 mins.	599	504	
10 mins.	697	592	
15 mins.	764 ± 19.1	699 ± 119.1	± 120
20 mins.	817	703	
25 mins.	879	770	
30 mins.	920 ± 36.8	816 ± 133.9	± 139
35 mins.	966	861	
40 mins.	1000	893	
45 mins.	1042 ± 26.2	921 ± 153.0	± 155
50 mins.	1073	969	
55 mins.	1095	990	
60 mins.	1109 ± 19.1	1013 ± 147.0	± 148

As a comparison between the cumulative action of the two drugs the supplementary doses required during fifteen-minute periods was compared (table VI). In this case allowance has to be made for the greater potency of thiamylal and doses of the latter were multiplied by a "correction factor". This was obtained by dividing the initial dose of thiopentone (mg/kg) by the initial dose of thiamylal (mg/kg). In three out of the four periods in which the supplementary dosage of the two drugs is compared on the above basis, a statistically significant difference was obtained.

Since it has been shown by Brodie (1952) that acute tolerance occurs to thiobarbiturates, and that the requirements during anaesthesia bear some relationship to the initial dose, in table VII the ratio of the total dose to the induction dose was compared at 5-minute intervals for each drug. This shows that the incrementation required to maintain a constant level of narcosis with thiamylal was significantly greater than that required for thiopentone. This clearly indicates that in these cases recovery after thiamylal was more rapid than after equipotent doses of thiopentone.

TABLE V

Comparison of average doses of thiopentone and thiamylal in mg/kg

	Average dose mg/kg		S.E. (difference)
	Thiopentone	Thiamylal	
Induction	7.70 ± 0.31	5.59 ± 0.23	0.441*
5 mins.	9.14	7.70	
10 mins.	10.77	9.06	
15 mins.	11.76 ± 0.36	10.27 ± 0.44	0.634*
20 mins.	12.54	11.12	
25 mins.	13.48	11.75	
30 mins.	14.11 ± 0.44	12.46 ± 0.45	0.822*
35 mins.	14.79	13.16	
40 mins.	15.30	13.67	
45 mins.	15.87 ± 0.47	14.15 ± 0.54	0.798*
50 mins.	16.32	14.72	
55 mins.	16.62	15.21	
60 mins.	16.81 ± 0.52	15.31 ± 0.68	0.962

*Represents a statistically significant difference between the doses of the two drugs

TABLE VI

Difference between supplementary doses of thiopentone and thiamylal in mg/kg required every 15 minutes.

Time interval (mins.)	Thiopentone (mg/kg)	Thiamylal (mg/kg)		S.E.† (difference)
		Actual dose	Corrected dose*	
1–15	4.06 ± 0.302	4.68	6.11 ± 0.394	0.496‡
16–30	2.35 ± 0.097	2.18	2.84 ± 0.233	0.243‡
31–45	1.76 ± 0.169	1.70	2.22 ± 0.180	0.247
46–60	0.94 ± 0.005	1.16	1.51 ± 0.190	0.190‡

* Corrected dose = actual dose × 1.305.

† Difference was calculated between actual dose of thiopentone and correlated dose of thiamylal.

‡ Represents significant difference between two drugs.

TABLE VII

Comparison of the average ratio of total dose of thiopentone and thiamylal administered at times shown to the induction dose.

	Ratio of total dose administered to induction dose		S.E. (difference)
	Thiopentone	Thiamylal	
0 mins.	1.0	1.0	
5 mins.	1.22	1.39	
10 mins.	1.42	1.64	
15 mins.	1.56 ± 0.051	1.84 ± 0.110	0.141*
20 mins.	1.67	1.94	
25 mins.	1.79	2.12	
30 mins.	1.88 ± 0.093	2.25 ± 0.083	0.134*
35 mins.	1.97	2.37	
40 mins.	2.04	2.46	
45 mins.	2.13 ± 0.107	2.54 ± 0.178	0.199*
50 mins.	2.19	2.67	
55 mins.	2.23	2.73	
60 mins.	2.26 ± 0.124	2.79 ± 0.163	0.125*

* Signifies a statistically significant difference between the ratio for the two drugs.

SUMMARY

On the basis of its use in 1,750 cases we believe that thiamylal is a safe intravenous anaesthetic, in many respects similar to thiopentone, but of slightly greater potency and with less tendency to cumulation.

ACKNOWLEDGMENTS

We are indebted to Dr. Robert Hodgkinson of the Department of Clinical Research, Parke Davis & Company, for generous supplies of thiamylal (Surital) and for his help during this clinical trial.

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MADE AND PRINTED IN GREAT BRITAIN

Miscellaneous.

(c) Solutions of Barbiturates.

"SOLUTIONS OF BARBITURATES USED IN ANAESTHESIA"

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SOLUTIONS OF BARBITURATES USED IN ANÆSTHESIA

BY JOHN W. DUNDEE, M.D., F.F.A.R.C.S.
DEPARTMENT OF ANÆSTHESIA, UNIVERSITY OF LIVERPOOL

REPORTED investigations of the variation in response to barbiturates have all been concerned with factors which increase or decrease tolerance to the drug. Requirements of thiopentone observed clinically have been recorded in actual doses or in mg./kg. To date no doubt has been thrown on the accuracy of the solutions as prepared by the anæsthetist.

During spectrophotometric estimation of plasma thiopentone, one set of results threw doubt on the strength of a so-called 5% solution of thiopentone, which was prepared for intravenous use in the usual manner. This led to an investigation of the accuracy of the strengths of solutions as prepared for clinical use. This paper reports the result of an analysis of over 500 thiobarbiturate solutions taken at random from anæsthetic rooms and operating theatres. Specimens were taken from syringes, ampoules or multidose bottles; the number of hospitals involved and the number of anæsthetists by whom the solutions were prepared was as large as practicable.

Studies were also carried out to try and find if any one of the proprietary brands of barbiturates used in anæsthesia possessed properties which might help in the preparation of more accurate solutions. These included checking on the weight of the contents of the ampoules and comparing their solubility.

Variations in percentage of solutions

Thiopentone, thialbarbitone and thioquinalbarbitone were the drugs studied. Random supplies of solution were compared against known standards in the spectrophotometer.

Standard solutions were prepared in strengths of 2.5, 4, 5 and 6 mg./litre for thiopentone and thioquinalbarbitone and in double these strengths for thialbarbitone. The observation of Brodie et al[1] that optical density is proportional to the concentration of solution was confirmed on several occasions.

Unknown solutions were diluted 1 : 10,000, transferred to quartz cells and the optical density determined at 288 μ in a Beckman or Unicam spectrophotometer (Fig. 1). For a blank solution, 0.06% w/v sodium carbonate was similarly diluted, for thiopentone and thioquinalbarbitone, triple distilled water being employed for thialbarbitone.

Once this method was perfected the error was very small (±2.5%), and gave more consistent results than could be obtained using the Spekka absorptiometer.

Where the solutions were made up to be used in a strength other than 5% (as with thialbarbitone) the results were suitably corrected. The average percentages (w/v) are given in Table I, the scatter being shown diagrammatically in Fig. 2. These both reveal an appreciable deviation from 5%. The scatter is largest in the case of thialbarbitone (Coefficient of Variation=46.61) and least with thioquinalbarbitone (Coefficient of Variation=17.70), thiopentone being intermediate (Coefficient of Variation=28.63).

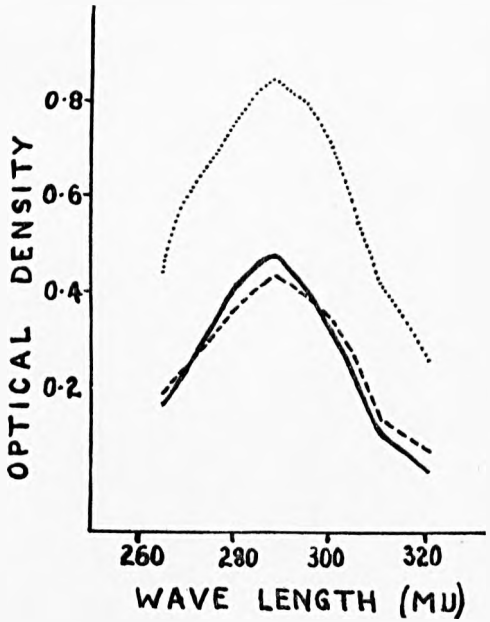

FIG. 1.—The absorption spectra of aqueous solutions (approx. 5 mg./litre) of
——— thiopentone
····· thialbarbitone
- - - - - - - thioquinalbarbitone

TABLE I

Results of estimation of percentage (w/v) of 507 samples of thiobarbiturates, collected at random from solutions for clinical use.

Drug	No. of Estimations	Average	Range	S.D.
Thiopentone	383	4.889±0.095	3.86—7.40	1.40
Thialbarbitone	81	5.828±0.302	3.40—7.00	2.72
Thioquinalbarbitone	43	4.860±0.131	4.00—5.85	0.86
Total	507	5.047±0.022	3.40—7.40	0.50

The deviation from the intended percentage of solution could be due to many factors, *e.g.* spilling water, loss of barbiturate in the top of the ampoule, incorrect weight of drugs in the ampoules, or inadequate mixing. This latter was found to be very important as solutions taken from the top of ampoules tended to be weaker than those from the bottom. Dilution of solutions to a weaker strength than could be prepared in the ampoules as in the case of 2½% thiopentone or 5% thialbarbitone, was also a potent cause of inaccuracy.

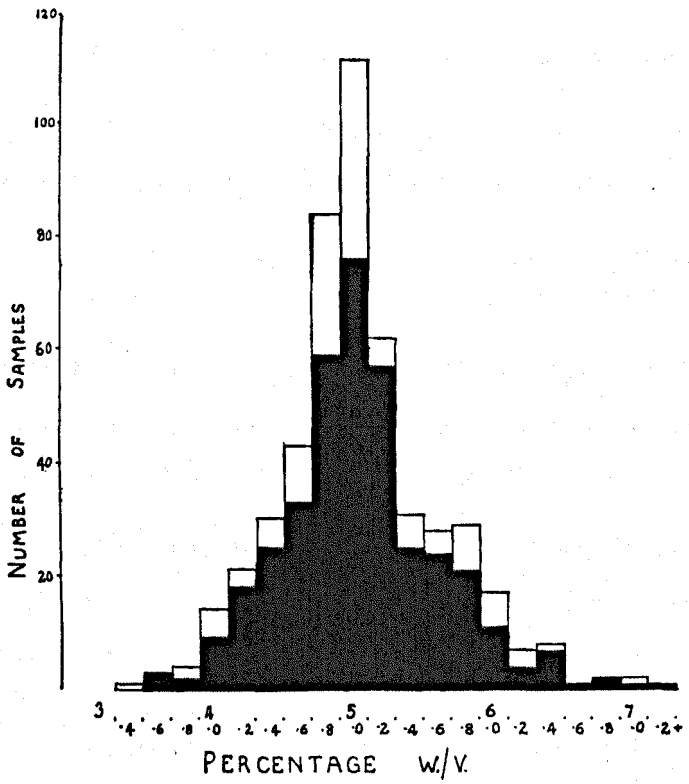

FIG. 2.—Histogram showing scatter in the percentage (w/v) of various random samples of thiobarbiturates. Shaded area represents thiopentone and the non-shaded area thialbarbitone and thioquinalbarbitone.

Contents of Ampoules

The actual amount of barbiturate in the ampoule was checked for each drug and for the different makes of several of these. Hexobarbitone was included in this and in subsequent investigations.

Ten 1 g. ampoules of each drug were weighed, their contents removed, the glass washed several times, dried and re-weighed. The average results obtained are shown in Table II. Since there was, of necessity, some slight loss of glass during the opening of the

ampoules, all these readings were within the range of normal. Faulty filling of ampoules is thus excluded as a causative factor in the variation in percentages of solutions.

TABLE II

Results of analysis of average contents of the ampoules of various barbiturates and thiobarbiturates used in anæsthesia, and percentage of drug wasted in the top of the ampoules.

Drug	Proprietary Names	Average amount of drug in grammes found in 1 g. ampoule	Average percentage of drug remaining in top of ampoule after removal
Thiopentone	Intraval Pentothal ———	1.002 1.024 1.008	0.83 1.15 0.20
Thialbarbitone	Kemithal	1.000	2.40
Thioquinalbarbitone	Surital	0.992	0.50
Hexobarbitone	Evipan ——— Cyclonal	1.030 1.052 0.991	0.90 1.15 —

A similar procedure was adopted for measuring the average amount of barbiturate remaining in the top of ampoules after opening (and hence discarded). The findings are also shown in Table II, and except in the case of thialbarbitone this cannot be called a serious source of error when preparing solutions for intravenous injection.

Comparative solubility of different preparations

Considering it is not unusual to find an appreciable amount of solid material remaining in the bottom of the ampoule after the anæsthetic is removed, the question of relative solubility of the different preparations that are, or recently have been, available in this country was studied. An experiment was designed with this end in view.

One gramme ampoules (where available) were used for the test. The appropriate amount of water was run into each ampoule at a fixed rate and from a constant height. Exactly half of the contents was withdrawn into a pipette every two minutes and allowed to run back into the ampoule. During this mixing process the same precautions were observed so that the amount of turbulence would be constant. The contents of the pipette were never blown back into the ampoule; not only would this vary the rate of flow, but it was found that the carbon dioxide of expired air was sufficient to precipitate the free acid and interfere with the solubility.

The time was noted from the end of adding the water until the last solid particle of drug disappeared. This was referred to as the " solubility time ".

Table III shows the average of ten experiments with each drug studied. A method of comparison is adopted by expressing the solubility time as a relationship of the average obtained for intraval and pentothal.

TABLE III

Comparison of the rates of solubility of various thiobarbiturates and barbiturates used in anæsthesia, and of different strengths of solution of the same barbiturate.

Drug	Proprietary Name	Percentage Solution w/v	Solubility Time Average	Time (mins.) Range	Relationship to average of Intraval and Pentothal
Thiopentone	Intraval	5	9.40	7.75—12.50	—
	Pentothal	5	9.28	7.00—12.00	—
	———	5	12.51	9.00—15.00	1.34
Thialbarbitone	Kemithal	10	37.03	26.00—47.00	3.95
	Kemithal	5	11.43	8.75—14.00	1.22
Thioquinalbarbitone	Surital				
	bottles	5	5.68	3.50—7.50	0.61
	ampoules	5	6.60	5.00—12.00	0.70
Hexobarbitone	Evipan	10	18.87	10.50—33.75	2.00
	Evipan	5	10.64	6.25—14.25	1.14
	———	10	9.40	6.00—16.00	1.06
	Cyclonal	10	5.00	4.00— 6.00	0.53

While this experiment leaves much to be desired from the point of view of accuracy, nevertheless, it gives some idea of how easily different drugs will dissolve under clinical conditions. Dealing first with the strengths of solution advocated by the manufacturers we see that in the case of thiopentone the results obtained show no difference between intraval and pentothal, but that manufactured by Boots Pure Drug Co. appears to be less soluble.

Thialbarbitone (10% solution) is by far the most difficult drug to dissolve, thioquinalbarbitone being the easiest. It would appear from these findings that the variation in percentage of solution of thiobarbiturates is related to the solubility. Thialbarbitone, the most difficult to dissolve, is the one in which was found the greatest scatter of readings for the percentage of the drug in a random selection of solutions. The opposite applies to thioquinalbarbitone.

Findings were very variable in the case of hexobarbitone—not only with different proprietary brands, but with different ampoules of the same make. As far as is known, hexobarbitone is very little used in this country, and for this reason many of the ampoules used were old. This may have some bearing on the results, as the temperature at which different ones were stored may have varied.

The 10% solution of thialbarbitone having been found the most difficult to dissolve, a study was made of the drug in 5% solution. Half the contents of ten 2 g. ampoules was removed, and the above process carried out using 20 ml. water. The solubility times obtained put the drug more on a par with thiopentone (Table III). With such a 5% solution the great deviation between the actual and expected percentage of the drug would be greatly diminished. Whether this is

of sufficient importance to induce the makers to market 20 ml. ampoules containing 1 g. of thialbarbitone is very much open to question.

Of all the thiobarbiturates in current use, it has been found that thioquinalbarbitone is the most satisfactory from the point of view of solubility. Particularly noticeable is the fact that it is easier to dissolve when supplied in bottles than in ampoules. This is due to the large surface area of drug coming in contact with the water. Under clinical conditions, when it is necessary to fill a syringe in a hurry, this packing has proved most valuable as it can be shaken vigorously without fear of spilling the contents. While this latter applies to the 5 g. packs of intraval and pentothal, the time saved with these is not so great as with Surital. The multidose packs of thiopentone only hold 100 ml. water, whereas with Surital 50 ml. can be added to 1 g. if desired.

Summary

A random sample of solutions of three thiobarbiturates has been studied and the variation in percentage from that intended is recorded.

Variations in the contents of the ampoule cannot be incriminated as a cause of these variations, but in the case of one drug the amount which is wasted in the top of the ampoule may be a factor.

The different rates of solubility of various drugs is reported, and commented on.

Acknowledgements

I am indebted to Dr. W. H. H. Andrews of the Liverpool School of Tropical Medicine for putting a spectrophotometer at my disposal. The solutions of thioquinalbarbitone (Surital) studied were part of a supply of the drug from Messrs. Parke, Davis and Co. for clinical trial. Supplies of pure drugs for preparations of standard solutions and solubility experiments were by courtesy of Pharmaceutical Specialities (May and Baker) Ltd., Abbott Laboratories, Imperial Chemical (Pharmaceuticals) Ltd., Bayer Products Ltd. and Parke, Davis and Co. My thanks are also due to Mrs. U. M. Todd for her technical assistance, and to Miss M. Garrett for her help with the statistics.

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Miscellaneous.

(d) Use in Experimental Animals.

"A METHOD FOR DETERMINING THE DURATION OF THIOPENTONE NARCOSIS IN THE DOG".

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A METHOD FOR DETERMINING THE DURATION OF THIOPENTONE NARCOSIS IN THE DOG

By JOHN W. DUNDEE

Department of Anæsthesia, University of Liverpool

MOST of the experimental work on the duration of thiopentone narcosis under varying conditions has been done on small animals, e.g. rabbits or guinea pigs. The return of the righting reflex, when the animal assumes its normal position, has been taken as the end point in most of the recorded experiments on dogs. This end point is reported in most instances to have been very definite and often appeared very suddenly (Paulson, Lundy and Essex, 1949). A method of determining the duration of thiopentone narcosis in the dog is described in this paper; it is compared with other possible methods, and the significance of any results obtained with it are discussed.

METHOD

The maximal tolerated dose of thiopentone in the dog is between 35 mg./kg. (Werner and Pratt, 1936) and 45 mg./kg. (Gruhitz, Dox, Rowe and Dodd, 1937), while the minimal anæsthetic dose is about 10 mg./kg. (Gruhitz et al., 1937). Wright (1947) recommends doses of between 20 and 30 mg./kg. for anæsthesia lasting about 5 minutes. In practice I have found that doses of between 15 and 25 mg./kg. have proved very satisfactory. The animal remains anæsthetized long enough to enable different signs to be observed, yet ultimate recovery is never so long

delayed as to prevent observations on a number of dogs from being carried out on the same day.

A well-marked excitement stage occurs with thiopentone in the dog if the rate of injection is too slow. This may result in dislodgement of the needle from the vein, reinsertion being practically impossible until the animal quietens. It is essential in any experiments designed to measure the duration of narcosis that the rate of injection of the drug be constant. This can easily be achieved by using a "closed vein" technique and a concentrated (10 per cent) solution of thiopentone. Duration of anæsthesia is then measured from the time when the tourniquet on the limb is released. Injection into the jugular vein (Gruhitz et al., 1937) cannot be carried out with this technique, but in a personal series of about 200 injections it was found that dogs weighing 9–15 kg. had sufficiently large veins in the forelegs to permit numerous injections to be made. Wright (1947) has pointed out that the anæsthesia resulting from rapid injection of thiopentone is alarmingly abrupt in onset and followed by considerable shock. This has not been observed using doses of 15–25 mg./kg.; there has always been a brief period of apnoea, but even with 30 mg./kg. this did not last for more than one minute.

During this series of cases it was observed that in animals, in whom, for any reason, the thiopentone was given in divided doses, the duration of narcosis was much more prolonged than if it had been given in one injection. Even a pause of 10 seconds, to enable a needle to be reinserted into a vein, upset the readings. This is difficult to explain save on the grounds of acute tolerance to the drug. The central nervous system may respond to the initial peak concentration of the drug, and the plasma level at which awakening occurs may be related to this concentration (Brodie, 1952). Whatever may be the explanation, any

trouble during injection is an indication that the experiment should be abandoned for a further 48 hours.

In spite of observations to the contrary (Adams, 1944), acquired tolerance to thiopentone has been observed in the dog. Thrice weekly injection of the same dose was found to reduce significantly the duration of narcosis by the end of the third week, but the tolerance disappeared after a rest for one week. In practice twice weekly injections for 3 weeks out of 4 had no significant effect on the duration of narcosis. Tolerance to one barbiturate will result in tolerance to others (Green and Koppanyi, 1944). This has been observed in the case of thiopentone, hexobarbitone and thialbarbitone. However, cumulative effects of thiopentone became manifest when injections were repeated at intervals of 36 hours or less (Dundee, 1953). To be certain of avoiding this an interval of not less than 48 hours should elapse between successive injections of the drug.

A series of well defined end points can be observed in the dog as follows.

1. *Return of the corneal reflex.* This reflex does not disappear until about 20 seconds after the tourniquet is released, and care must be taken lest these two phases be confused.
2. *Spontaneous return of blinking.*
3. *Head raising.*
4. *Sitting up*: defined as the point where the dog raises its shoulders from the ground.
5. *Standing*: defined as the moment when the animal first stands unsupported on all four limbs.

For an accurate comparison of these on different occasions the surroundings of the animals should be the same at each injection, e.g. noises may cause the head to be raised sooner, a slippery floor may prolong the time of the last observation, etc.

The method advocated uses the average of the times of appearance of the above 5 signs (measured from release of the tourniquet) as the duration of anæsthesia.

RESULTS

A statistical analysis of figures obtained from 16 injections of 16.3 mg./kg. thiopentone in one dog are shown in table I. Attention was paid to all the points mentioned in regard to the injection, control of surroundings, etc. The

TABLE I

Showing average results obtained from 16 observations on one dog using various end points, following 16.3 mg. thiopentone per kg. body weight.

End point	Average time (secs.)	Range (secs.)	Standard deviation	Coefficient of variation
Return of corneal reflex	50.3	20–105	22	43.7
Blinking	125	40–285	39.5	31.6
Head raising	260	140–390	55.8	21.4
Sitting	331	240–470	76.5	23.1
Standing	516	420–720	93.5	18.1
Average of above ...	259	185–332	40.3	15.5

times taken for the return of the corneal reflex and appearance of blinking are too variable to be of any value. The other three end points, although much less variable, do not give results as constant as are obtained using the average time of all five. There is very little to choose between this and using the return of standing as the sole end point, but it would seem to reflect better changes in the course of anæsthesia, rather than showing the time of ultimate recovery.

Table II shows results obtained with 4–6 injections in 9 other dogs using this method and two comparable results for thialbarbitone and hexobarbitone. Even with only 4 injections the coefficient of variation did not exceed 12.4.

It is necessary to establish the "normal sleeping time" for a fixed dose of thiopentone before subjecting a dog to

TABLE II

Showing results obtained in 11 series of experiments using method referred to in text to determine duration of barbiturate narcosis, comprising 4–6 administrations of each dose

Dose of thiopentone mg./kg.	No. of observations	Average duration of narcosis (secs.)	Range	Standard deviation	Coefficient of variation
14.0	6	310	268–350	36.0	11.6
15.8	5	398	360–451	44.0	11.1
15.8	5	475	414–582	46.3	9.7
16.0	5	652	607–750	58.3	8.9
17.0	5	453	426–484	22.4	4.9
21.0	6	526	462–593	58.2	11.1
22.0	4	618	588–660	26.5	4.8
27.0	4	991	946–1050	45.7	4.6
30.0	4	2215	2080–2758	275	12.4
26.0(K)	5	191	171–233	21.5	11.2
36.2(E)	4	1014	920–1092	100	9.8

K=Thialbarbiturate (Kemithal) used.
E=Hexobarbitone (Evipan) used.

any procedure which will alter its response to thiopentone. Tables I and II show that, using the method described, this can be accomplished by 4–6 injections of the same dose of the drug. The duration of narcosis obtained following any one injection should be well within the range of "average ± 20 per cent". For the duration of narcosis under different conditions to differ significantly from the normal, an allowance must be made for this variation. Preliminary results indicate that this method is equally applicable to any of the other ultra-short-acting barbiturates in common use.

As in humans, the duration of anæsthesia produced by thiopentone in the dog is not constant in the same animal from day to day. Tables I and II indicate that even more variable are the results obtained with the same dose in different dogs. There would appear to be no grounds for comparing the duration of narcosis in one dog with that of

another dog who received the same dose per kilogram body weight.

SUMMARY

1. The difficulties encountered in assessing the duration of thiopentone narcosis in the dog are discussed.

2. A method is described using the average times required for return of 5 different end points.

3. The significance of any results obtained using this method are discussed.

ACKNOWLEDGEMENTS

My thanks are due to Pharmaceutical Specialists (May and Baker) Ltd. for generous supplies of thiopentone.

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Appendix 1

Additional data on "Acute Tolerance to Thiopentone in Man".
(see page 8)

This appendix describes one typical case in detail and shows examples of method used in the statistical analysis.

Some additional data, not contained in the original paper is included. This data confirms the findings of the published paper, but adds no additional information.

A reprint of the relevant paper is included in the Appendix.

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ACUTE TOLERANCE TO THIOPENTONE IN MAN

BY

JOHN W. DUNDEE, HENRY L. PRICE, AND ROBERT D. DRIPPS

ALTRINCHAM

JOHN SHERRATT AND SON

Brit. J. Anaesth. (1956), **28**, 344

ACUTE TOLERANCE TO THIOPENTONE IN MAN

BY

JOHN W. DUNDEE, HENRY L. PRICE, AND ROBERT D. DRIPPS

From the Department of Anesthesiology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

ONE of us (J.W.D.) noted that although much smaller doses of thiopentone were given to patients at the Hospital of the University of Pennsylvania than at most centres in the British Isles, recovery of consciousness appeared to be equally prompt in all cases. To test the accuracy of this observation anaesthesia records from various hospitals in Liverpool were compared with those of the Philadelphia institution.

CLINICAL DATA

The anaesthesia technique compared was the intermittent administration of thiopentone, combined with nitrous oxide-oxygen, using the semi-open circuit at flow ratios of 4.5 : 1.5 or 6 : 2 litres per minute. No cases were included who received a volatile anaesthetic agent, a muscle relaxant or an intravenously administered analgesic. Records dealing only with surface operations were selected. The minimum duration of the procedures was 70 minutes, so that dosage figures for at least one hour of surgical anaesthesia were available for analysis.

Selection of cases was limited to patients of good physical condition under the age of 55 and suffering from no pathological condition other than that which necessitated the operation. The premedication consisted of 10 mg (1/6 grain) morphine for all patients combined with either 0.6 mg (1/100 grain) atropine or 0.4 mg (1/150 grain) scopolamine. Approximately one-third of the administrations in each country were by consultant anaesthetists, the remainder being given by residents or registrars with varying degrees of experience.

Table I gives details of the patients from each centre. The average total amount of thiopentone administered at 15-minute intervals is shown in figure 1. Irrespective of whether the actual dose in mg or the dose expressed in mg/kg is compared the British patients received approximately twice as much thiobarbiturate as the Americans for any given duration of anaesthesia. The average 30-minute requirements are significantly different by recognized statistical tests ($p<0.01$).

The possibility of factors peculiar to to the two different hospital groups being involved in this difference in requirements of thiopentone was excluded by a small series of 27 cases anaesthetized at the Hospital of the University of Pennsylvania with double its average induction dose (7.84 mg/kg thiopentone). The average total amount of thiopentone administered to these patients at the end of 30 minutes of anaesthesia was 14.9 mg/kg, which

TABLE I

Details of patients and nature of operations in a series of cases from America and Britain in whom thiopentone requirements were studied, together with the average induction and 30-minute dosage of the drug in each series.

Series	Hospital of the University of Pennsylvania	United Liverpool Hospitals
Number of cases	120	100
Average age (years)	40.0	44.8
Average weight (kg)	60.1	60.0
Nature of operations: for varicose veins	96	72
for plastic surgery	24	28
Average induction dose of thiopentone	212 mg 2.5 mg/kg	500 mg 8.3 mg/kg
Average dose administered at end of 30 minutes ...	411 ± 10.8 mg 7.0 ± 0.18 mg/kg	905 ± 22.0 mg 15.1 ± 0.13 mg/kg

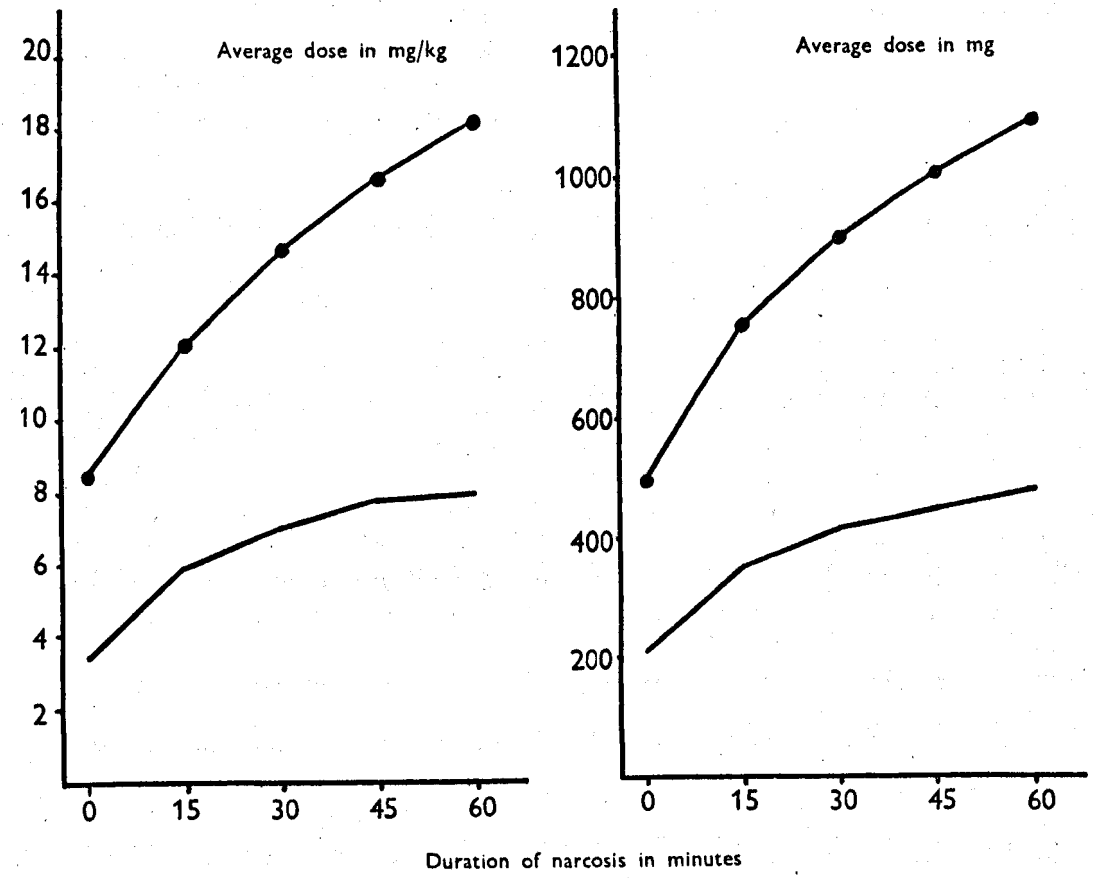

FIG. 1

Comparison of the average doses of thiopentone required during anaesthesia in two series of patients referred to in the text.

——— Hospital of the University of Pennsylvania.

●——● United Liverpool Hospitals.

compares closely with the figures (15.1 mg/kg) for the British patients. Conversely, Dundee (1955a) has described 21 patients, anaesthetized in Britain in whom the initial and 30-minute requirements of thiopentone were similar to those used in the Philadelphia hospital (2.4 and 4.6 mg/kg respectively). The awakening time for both groups was the same.

DISCUSSION

Since the return of consciousness was thought to be equally prompt in all patients studied, the possibility existed that either the thiopentone was removed more rapidly from the central nervous system in the British patients or that these subjects awakened with a higher brain content of the drug.

The pharmacologically active concentration of thiopentone in the blood depends on the degree of binding of the drug to the plasma proteins. This varies with the albumin content and the pH of the blood and also with the concentration of thiopentone (Goldbaum and Smith, 1954). The former two factors are unlikely to vary widely in the essentially normal patients studied. With increasing barbiturate concentration the percentage of the bound drug diminishes, although the total amount increases. Thus the patients who received the large amounts of thiopentone will have proportionately more free drug per mg/kg injected than those receiving the smaller doses, and the observed differences in dosage cannot be explained by differences in plasma binding.

In 1952 Brodie showed that the plasma concentrations at the time of orientation following small total doses of thiopentone were lower than the corresponding levels following larger total doses. The amounts of thiopentone given by Brodie (22–65 mg/kg) were well above those used in clinical anaesthesia, but if his findings apply with total doses varying from 5 to 18 mg/kg, they would throw light on why the return of consciousness in the British patients was as prompt as in those anaesthetized in the United States. However, they do not explain why the increment doses required in the British series of cases was approximately double those of the American series (fig. 1).

The higher induction doses of thiopentone administered to the British patients may be the important factor in determining why these patients required larger increments of the drug to maintain anaesthesia, since the greater initial brain concentration of thiobarbiturate may result in increased tolerance to supplementary doses of the drug. When the increment doses required every 15 minutes are compared with the initial dose (fig. 2), it can be seen that the ratio is the same for both series of cases. This suggests that, within the range of dosage of this study, the greater the initial dose of thiopentone the greater will be the increments of drug required to maintain surgical anaesthesia.

EXPERIMENTAL DATA

This hypothesis was investigated by a study of blood thiopentone levels at recovery in a series of 119 patients anaesthetized with single doses or intermittent injections of thiopentone, combined in the latter case with nitrous oxide-oxygen. Atropine 0.4–0.6 mg (1/150–1/100 grain) was the only drug given prior to anaesthesia.

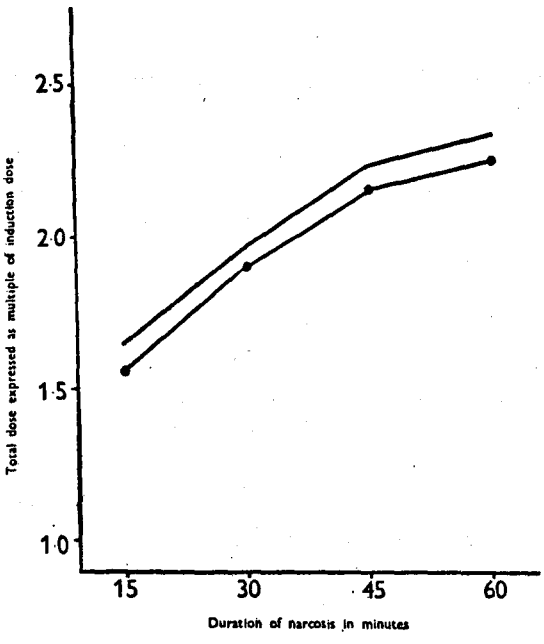

FIG. 2

Comparison of ratio of total dose of thiopentone required during anaesthesia to the induction dose in same series of patients.
——— Hospital of the University of Pennsylvania.
●———● United Liverpool Hospitals.

The subjects were fit female adults within the weight range of 110–160 pounds (50–73 kg), with ages varying from 16 to 44 years. All patients had a pre-operative haemoglobin of 11 g per cent or over. The operations were either minor gynaecological procedures or body surface operations such as plastic surgery. It was felt that the degree of pain following these was so little as not to act as a stimulus and hasten recovery from anaesthesia. The occurrence of hypotension, severe blood loss, or hypoxia excluded cases from this study.

The exact moment of return to consciousness is difficult to define and in the early cases several endpoints were used. From these the moment when the patient would open her eyes in response to a command was selected as being the most reliable. Blood was drawn slowly over a period of 30 to 60 seconds so that the average blood thiopentone level for the period immediately following the return of consciousness could be determined. In order to be certain that the patients were awakening from the effects of thiopentone and not because of elimination of nitrous oxide no patient was included in whom the desired endpoint was elicited within five minutes of withdrawal of the inhalation agent.

It has been shown by Price and Conner (1956) that two minutes after rapid intravenous injection of thiopentone the brachial arterial and jugular venous blood levels of the drug differ little and thereafter decline in a parallel manner. This does not necessarily apply to venous blood drawn from the forearm or anticubital fossa, as some thiopentone may diffuse into the muscles and fat of the limb. In an attempt to obtain samples which would give readings similar to those of jugular venous or arterial blood the veins on the dorsum of the hand or around the wrist were used whenever possible.

Thiopentone determinations were carried out on whole heparinized blood using the technique described by Brodie et al. (1950) for plasma. Where possible several samples were drawn before and after recovery from anaesthesia and these revealed that the decline in blood barbiturate concentration was rarely more than 1 mg/litre during the period from five minutes before to five minutes after the return of consciousness. Thus, if the assessment of the endpoint was not accurate, the degree of error was not gross.

Figure 3 shows the blood levels at awakening in 15 patients who received varying single doses of thiopentone. There is a significant ($p<0.01$) relationship between the dosage and the blood thiopentone level at recovery (correlation coefficient (r) $= +0.74$).

Thus Brodie's observations are applicable for single injections of thiopentone within the range of dosage used in clinical anaesthesia. However, these findings do not indicate whether the initial dose of the drug, the total dose, or the duration of anaesthesia is the important factor in determining the blood level of thiopentone at which consciousness will return following intermittent injections of this substance.

Figure 4 shows the blood thiopentone levels at awakening in 72 cases, to whom the drug was administered for periods not exceeding 20 minutes and in whom the total duration of anaesthesia did not exceed 40 minutes. This reveals a striking relationship ($r = +0.88$; $p<0.01$) between the blood thiopentone level at awakening and the induction dose of the drug, and no significant relationship between the blood level and total ($r = +0.20$; $0.05<p<0.10$) or increment doses ($r = -0.06$; $0.50<p<0.60$). Within the limits of the duration of administration and anaesthesia set out above, the following regression equation applies:

$$\text{Blood thiopentone level at awakening in mg/litre} = 1.88 \times (\text{induction dose of thiopentone in mg/kg}) + 0.45.$$

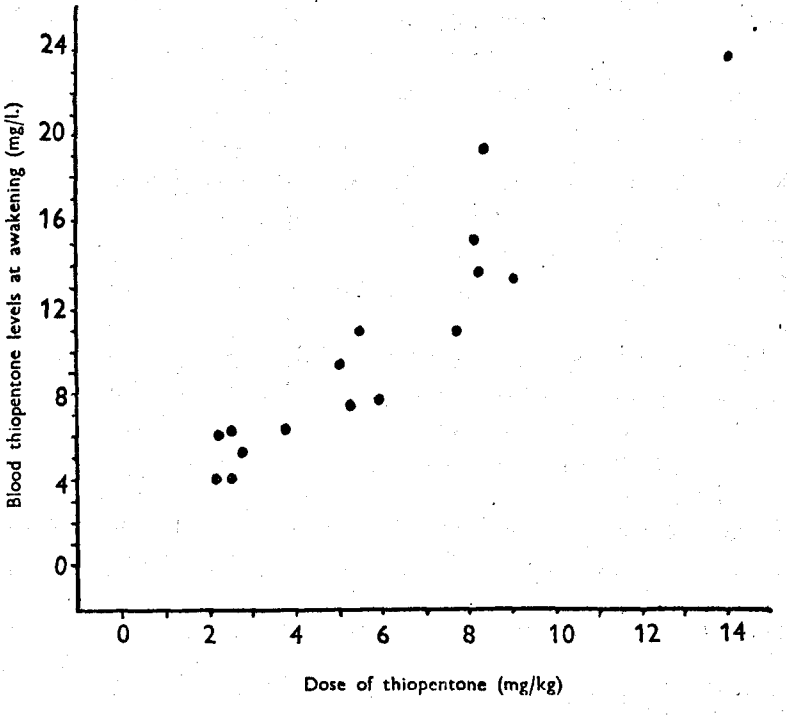

FIG. 3
Blood thiopentone levels at awakening in 15 patients who received single injections of the drug.

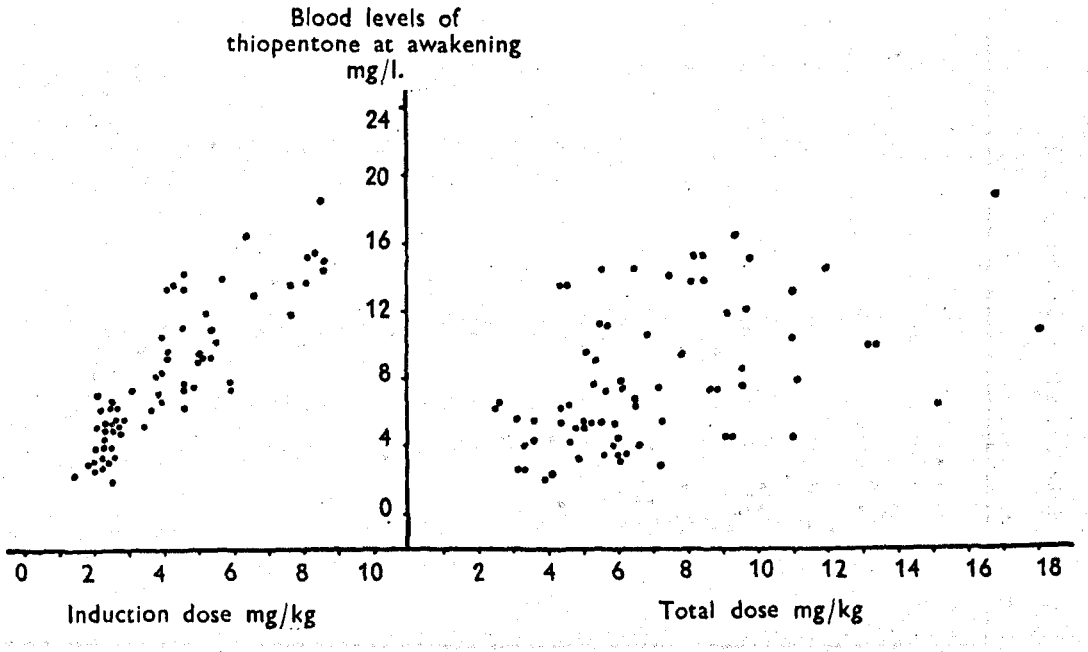

FIG. 4

Relationship between the blood thiopentone levels at awakening and the induction and total doses of the drug in 72 patients who were anaesthetized by intermittent injection of thiopentone. In these subjects the duration of administration did not exceed 20 minutes and the total period of unconsciousness was 40 minutes or less.

If the limitations of duration of anaesthesia and unconsciousness set out above were exceeded, it was found that the blood thiopentone level at awakening was dependent on both the initial ($r = +0.18$; $0.10 < p < 0.20$) and total ($r = +0.25$; $0.10 < p < 0.20$) doses of the drug, although the degree of correlation with either of of these factors was not great.

The part played by the total dose in determining the blood thiopentone levels at recovery was investigated in 58 patients. These received an initial dose varying only from 2.25 to 2.75 mg/kg, with a wide variation in the total amounts administered. No time limit was placed on the duration of the administration (1–58 minutes) or the total period of anaesthesia (2–105 minutes). The results, shown in figure 5, reveal that with total doses up to three times the induction dose the blood thiopentone level at recovery was fairly constant. Above this limit there was a gradual but inconsistent increase in the blood thiopentone levels at recovery from anaesthesia. Analysis of these data (table II) shows that, despite the wide scatter of readings, the increase in blood thiopentone levels at awakening is statistically significant.

In the patients receiving intermittent injections of thiopentone, no relationship could be found between the blood thiopentone levels at awakening and the duration of anaesthesia, although such a relationship did exist after a single injection of the drug.

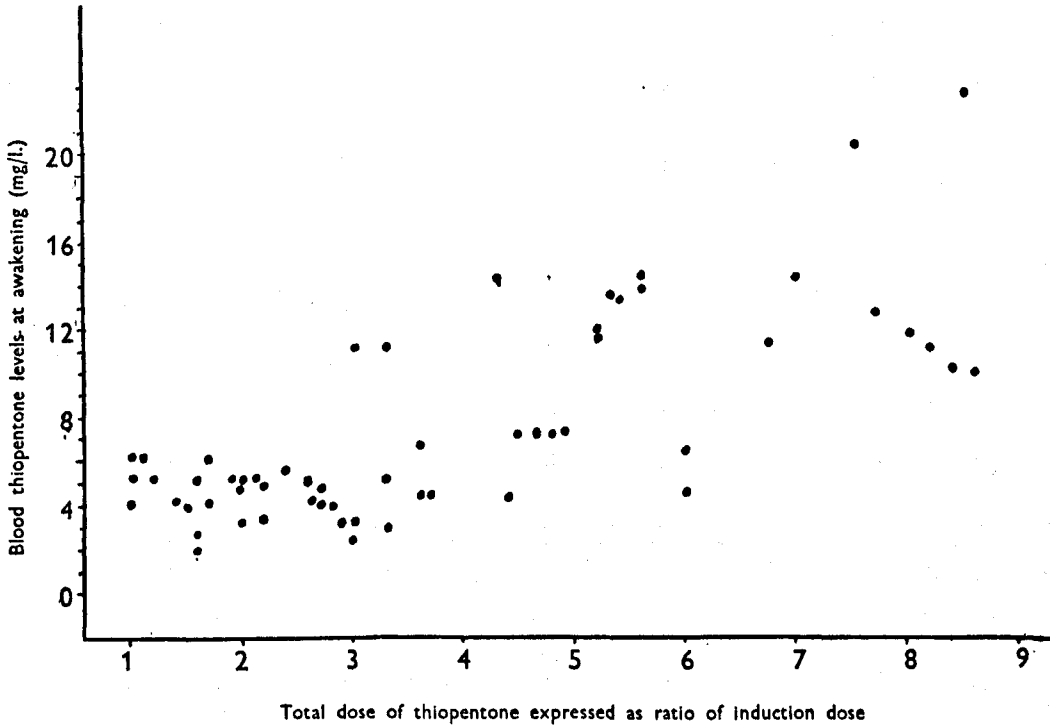

FIG. 5

Blood thiopentone levels at awakening in 58 subjects who received intermittent injections of thiopentone following an induction dose of 2.25–2.75 mg/kg related to the total dose administered (expressed as a ratio of the induction dose).

TABLE II

Analysis of blood levels of thiopentone on return of consciousness, related to total dose administered in patients receiving a constant induction dose of 2.25–2.75 mg/kg. Using "students" t test, each of the above average blood levels differs significantly from the others, the values for t being A-B 14.9, A-C 7.2, B-C 3.2.

	Ratio of total dose to induction dose	Number of observations	Average blood level on recovery (mg/litre)
A	Under 3	30	4.73 ± 0.152
B	3–6	19	8.20 ± 0.330
C	Over 6	9	12.56 ± 2.253

DISCUSSION

These observations show that there is a wide variation in the blood thiopentone levels at which normal patients awake from the doses of the drug used in clinical anaesthesia. The blood thiopentone level thus is not a reliable guide to the depth of anaesthesia. Contrary to the view expressed by Harris (1951) the degree of anaesthetic depression does not depend on the concentration of thiopentone in the circulating blood.

Brodie (1952) has suggested that the response of the central nervous system to thiopentone appears to depend on either the peak concentration or on the time of exposure of the tissues to the drug. From our results one can state that, with total doses of thiopentone not exceeding three times the induction dose, this latter determines the blood level at which patients

will awaken. With total doses exceeding three times the initial dose, the total amount of thiopentone administered also seems to be an important factor.

Our data suggests that the peak thiopentone concentration reached in the brain, whether this be attained during the induction or maintenance of anaesthesia, determines the blood level at which a patient will awaken from anaesthesia. With small total doses (relative to the initial dose) this peak is most likely to be reached during the induction period, while with the larger total doses, this peak concentration may be exceeded by one of the late supplementary injections. The greater the magnitude of the incremental doses, the more likely is this to occur, and the scatter in blood levels in figure 5 may be due to the variation in the size of the supplementary doses.

With the intermittent administration of thiopentone the time of exposure of the nervous system to thiopentone is not a factor *per se*, in determining blood levels at awakening.

The phenomenon of adaptation of the central nervous system to the narcotic effects of thiopentone has been called "acute tolerance", a term first used by Schmidt and Livingstone (1933) to describe the effects of morphine on the circulation. In contrast to chronically acquired tolerance, acute tolerance appears to develop rapidly after a single dose of drug. This is shown in figure 1, by the higher increment doses required to maintain anaesthesia in subjects induced with a large dose of the drug. Brodie (1952) has stated that adaptation of the central nervous system to the narcotic effects of thiopentone is not persistent and may last for less than one week. Apart from the fact that subjects have been shown to awaken at approximately the same blood level on three or four occasions within one hour, after repeated injections of thiopentone, our study throws no light on the duration of the effects of acute tolerance to thiopentone.

The agreement between the results of the dosage studies and the observations on blood thiopentone levels at awakening show that an unnecessarily large amount of thiopentone appears to have been used in the British cases. Unfortunately, it was not possible to compare the effects of such doses on the cardiovascular, respiratory or other systems with those produced by the smaller doses in the American series. However, as with all anaesthetic agents, it would seem desirable to administer the smallest amount of drug necessary to produce satisfactory operating conditions. Price and Helrich (1955) have found a linear relationship between the percentage reduction of the functional efficiency of the dog heart-lung preparation and the concentration of thiopentone to which it is exposed. Large doses also have a deleterious effect on liver function, the degree of impairment being roughly proportional to the total amount of thiopentone administered (Dundee, 1955b). There is as yet no evidence to suggest that acute tolerance develops to the effects of thiopentone on structures other than the central nervous system.

For these reasons it is suggested that the induction of anaesthesia should be accomplished with smaller doses of thiopentone than are currently in use in many centres in Britain. The initial injection, which can be given slowly, should not be

more than that required to produce sleep. Supplementary doses during the maintenance of anaesthesia should be kept to a minimum, except where momentarily deep anaesthesia is required. By these means the maximum concentration of the drug in the brain will be kept low and since this appears to govern the blood thiopentone concentration at which patients awake from anaesthesia, the total requirements of the drug should be appreciably reduced.

SUMMARY AND CONCLUSIONS

An analysis of average doses of thiopentone used in combination with nitrous oxide-oxygen to produce surgical anaesthesia was carried out in comparable series of patients anaesthetized at the Hospital of the University of Pennsylvania and at various hospitals in Liverpool. It was found that, for any given period of anaesthesia, the British anaesthetists administered approximately twice as much thiopentone as their American counterparts. Recovery appeared to be equally prompt in each centre.

Irrespective of the initial dose of thiopentone, a constant relationship was found between the total dose and the initial dose of the drug at any given duration of anaesthesia. Within the dosage range used in clinical anaesthesia, a linear relationship was found to exist between the blood thiopentone level at which patients awaken from a single injection of the drug and the amount injected.

Where the total dose of thiopentone did not exceed three times the induction dose, there was a striking relationship between the latter and the blood thiopentone levels at which patients awaken from anaesthesia, but no correlation could be found between the blood thiopentone levels at awakening and the total dose of the drug. When this range of dosage is exceeded, the total dose also played a part in determining the blood thiopentone level at which patients recover.

The above findings can be reconciled by the hypothesis that acute tolerance to the depressant effects of thiopentone on the central nervous system develops rapidly, the degree of adaptation being proportional to the peak concentration of thiopentone in the brain, whether this occurs during the induction of anaesthesia or following a supplementary dose of the drug.

The clinical application of these findings are discussed.

ACKNOWLEDGMENT

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Typical case report in whom blood thiopentone level at awakening (after intermittent injection of the drug) was estimated.

Data Included

(a) Copy of original anaesthesia record chart.

(b) Figures obtained during analyses of blood samples.

PRE-OPERATIVE

SURGICAL CLINICAL DIAGNOSIS.....

Anesthetic history, teeth and mouth, vital capacity, laboratory and X-ray data, heart disease, functional capacity, arrhythmia, shock, upper respiratory infection, pulmonary disease, cough, asthma, psychic state, increased intra-cranial pressure, CNS disease, neurological signs and symptoms, gastro-intestinal disease, nausea and/or vomiting, genito-urinary disease, diabetes, obesity, thyroid disease, cachexia, dehydration, blood dyscrasia, drug allergy or alcohol addiction.

PHYSICAL STATUS 1234

POST-OPERATIVE

RESP.
Airway
Anoxia
Laryng. Edema
Tracheitis
Atelect. or Pneum.

CIRC.
Shock
Hemorrhage
Thrombi or Emboli
Cardiac. Compl.

C.N.S.
Agitation
Consciousness
Psychosis
Paresthesia
Paralysis
Headache (Type)
Backache

G-I.
Nausea or Emesis
Distention
Liver Damage

G.U.
Anuria
Retention
Kidney Damage

METAB.
Thyroid Crisis
Tetany

OB.
Post-Part. Hem.
Condition of Baby

SUMMARY:

Seen within 24 hours: Yes.....No.....

No. of days followed post-operatively.....

_____Anestheti

Form No. 514 20M 10-49

ANESTHESIA RECORD—HOSPITAL UNIVERSITY OF PENNSYLVANIA

Date 19th Aug 55

Ward K

INDUCTION: (S) U.

TAP: No.

Paresthesia

Name

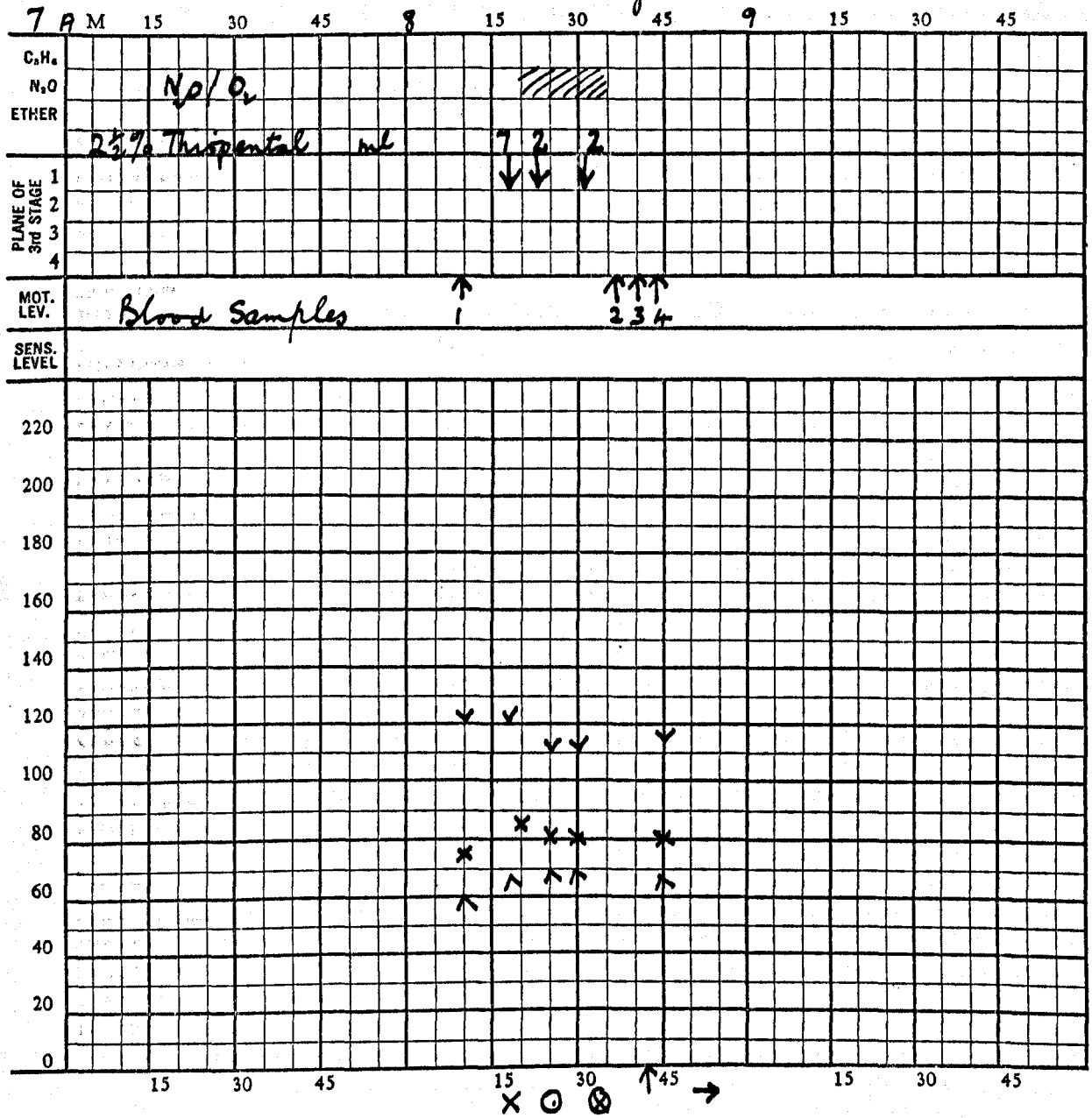
Address

Age 31 Ht. 5'6" Wt. 126 Hb 12·2 Recent Meal 0 Bl. Type

Premedication Atropine 0·6 mg Time 6·30 AM

AIRWAY:

Endotracheal: Natural



MAINTENANCE:

× = Induction

⊙ Op^n. Commenced

⊗ Op^n. completed

↑ Awake.

→ To room

Agents: 2½% Thiopental 275 mg I.V. : No : O2 6 : 2 : semiclosed

Tech.:

Operation D & C.

Surgeons

Anesthetists Instr.

Position Lithotomy Sponge Count Correct, Nurse

Reflexes recovered. Time 8-40 AM Retch — Emesis — TBT — Excit.: M.S. —

FLUIDS

P. S. S.

Gluc. 5% 200

Blood

Plasma

Total 200

Spectrophotometric Readings (Beckman)

Wave length 305 mu

Specimen	Optical Density				Blood Thiopentone mg/litre
	1	2	Average	Corrected	
Reagent	.032	.034	.033		
1. Blood blank	.103	.103	.103		
2.	.178	.178	.178	.075	
	.178	.178	.178	.075	5.66
3.	.168	.176	.172	.069	
	.172	.174	.173	.069	5.27
4.	.168	.166	.167	.064	
	.168	.168	.168	.065	5.10
Standard Deviation	.668	.672	.670	.637	50

Solution

Blood thiopentone levels at awakening (mg/litre) in 15 patients who received varying single doses of thiopentone (mg/kg).

(Figure 3 of paper)

and calculations of statistical relationship between these factors.

No	Dose (mg/Kg) x	Blood level at awakening (mg/l) y.	x^2	y^2	x − (mean of x) A	y − (mean of y) B	A × B
1	8·1	15·1	65·61	228·01	+ 2·5	+ 5·0	+ 12·50
2	5·9	7·9	34·81	62·41	+ 0·3	− 2·2	− 0·66
3	8·2	19·4	67·24	376·36	+ 2·6	+ 9·3	+ 24·18
4	7·7	11·0	59·29	121·00	+ 2·1	+ 0·9	+ 1·89
5	8·1	13·8	65·61	190·44	+ 2·5	+ 3·7	+ 9·25
6	2·5	6·4	6·25	40·96	− 3·1	− 3·7	+ 11·47
7	2·5	4·0	6·25	16·00	− 3·1	− 5·9	+ 18·29
8	2·7	5·3	7·29	28·09	− 2·9	− 4·8	+ 13·92
9	2·2	6·2	4·84	38·44	− 3·4	− 3·9	+ 13·26
10	5·0	9·4	25·00	88·36	− 0·6	− 0·7	+ 0·42
11	14·3	23·6	204·49	556·96	+ 8·7	+ 13·5	+ 117·45
12	5·4	11·0	29·16	121·00	− 0·2	+ 0·9	− 0·18
13	3·7	6·2	13·69	38·44	− 1·9	− 3·9	+ 7·41
14	2·2	4·0	4·84	16·00	− 3·4	− 6·1	+ 20·74
15	5·2	7·6	27·04	57·76	− 0·4	− 2·5	+ 1·00
Total	83·9	151·9	621·41	1980·23			+ 250·94
Av	5·6	10·12	41·45	132·01			+ 16·69

Standard Deviations

Dose of Thiopentone (mg/kg)

Average = 5.6

Sum of squares = 621.41

$$\frac{621.41}{n-1} = \frac{621.41}{14} = 44.40$$

$$\text{S.D.} = \sqrt{44.40 - (5.6)^2} = \sqrt{13.04}$$

$$= 3.61$$

Blood Thiopentone Level at Awakening

Average = 10.12

Sum of squares = 1980.23

$$\frac{1980.23}{n-1} = \frac{1980.23}{14} = 141.44$$

$$\text{S.D.} = \sqrt{141.44 - (10.12)^2} = \sqrt{39.03}$$

$$= 6.25$$

Correlation Coefficient

$$\frac{\text{Average } A \times B}{(\text{S.D. } x) \times (\text{S.D. } y)} = \frac{16.69}{3.61 \times 6.25}$$

$$= + 0.74$$

Significance $p < 0.1$

Regression Equation

Blood level at awakening (mg/litre) - 10.12

$$= 0.74 \times \frac{6.25}{3.61} \times \left[\text{Dose of thiopentone (mg/kg)} - 5.6\right]$$

Blood thiopentone level at awakening (in mg/litre)

= 1.28 (Dose of thiopentone in mg/kg) + 2.95

Dose (mg/kg)	2 - 3	5 - 6	8 - 9
Number of observations	5	4	5
Average duration of sleep	3.6 mins.	8.2 mins.	15.6 mins.
Average blood thiopentone level on recovery	5.2 ± 0.50 mg/litre	8.0 ± 0.79 mg/litre	14.6 ± 1.25 mg/litre

Table 3. Average duration of narcosis and average blood thiopentone levels on recovery at three dosage levels in subjects receiving a single injection of thiopentone.

This table confirms the findings of Figure 3 of paper. As it does not add any additional information to the discussion, it was not included in the paper.

Data of 72 cases (figure 4 of paper) giving details of:-

A = Initial dose of thiopentone (mg/kg)

B = Total dose of thiopentone (mg/kg)

C = Blood thiopentone levels at awakening (mg/litre)

and calculations of statistical relationship between these figures.

No	Initial dose of Thiopentone mg / kg	Total dose of Thiopentone mg / kg	Blood level at awakening mg / L.
1	2·2	6·0	4·5
2	2·2	3·3	3·3
3	4·6	9·6	7·5
4	2·5	3·9	2·0
5	2·4	4·8	5·0
6	5·2	9·7	12·0
7	2·6	5·6	3·5
8	4·5	5·5	11·1
9	2·3	5·0	5·0
10	2·7	4·6	6·4
11	2·3	3·6	5·7
12	3·7	4·4	6·2
13	5·5	11·0	10·2
14	4·4	9·6	8·5
15	2·2	3·5	5·2
16	5·7	7·5	14·0
17	2·1	5·9	4·0
18	2·7	4·6	4·1
19	4·6	5·5	14·4
20	6·6	11·0	13·0
21	4·6	6·5	6·4
22	3·4	5·9	5·2
23	3·9	6·5	6·8
24	8·6	12·0	14·4
25	3·1	6·2	7·4
26	4·6	6·5	14·5
27	5·9	7·3	7·3
28	3·8	8·6	7·2
29	2·0	3·3	2·7
30	4·8	5·3	7·6
31	2·4	4·8	3·3
32	5·3	7·8	9·3
33	3·9	6·8	10·6
34	3·8	8·6	7·2
35	2·0	3·3	2·7
36	2·0	6·0	3·2
37	2·6	5·0	5·3
38	4·3	13·2	9·8

	A	B	C
No	Initial dose of Thiopentone mg / kg.	Total dose of Thiopentone mg / kg	Blood Thiop. level at awakening mg / l.
39	4·1	4·4	13·5
40	8·5	16·9	18·6
41	4·6	11·2	7·8
42	8·3	21·3	9·3
43	5·3	8·3	15·1
44	5·4	5·6	11·0
45	2·7	3·1	5·3
46	6·3	9·4	16·9
47	5·9	6·1	7·9
48	4·6	5·5	10·2
49	5·0	5·2	9·3
50	2·7	5·5	5·3
51	8·1	8·3	6·3
52	2·7	7·3	13·8
53	7·7	15·2	11·9
54	2·5	8·0	7·1
55	7·7	9·2	2·4
56	2·1	5·7	6·3
57	1·4	4·1	2·4
58	2·5	2·7	6·3
59	4·1	4·4	13·5
60	8·1	8·3	15·1
61	4·4	13·2	9·8
62	2·9	9·3	4·5
63	2·6	5·0	5·3
64	2·0	6·0	3·2
65	8·1	9·7	15·0
66	3·5	11·0	4·4
67	2·5	6·6	4·0
68	2·2	7·2	2·9
69	2·7	9·1	5·3
70	2·2	2·5	6·2
71	2·2	4·4	5·3
72	5·0	5·4	9·2
Av	4·03	7·19	8·03

Standard Deviations

A = Initial dose of Thiopentone

Average = 4.03

Sum of squares = 1415.68

Average of above = 19.66

S.D. = $\sqrt{19.66 - (4.03)^2}$

= 1.84

B = Total Dose of Thiopentone

Average = 7.19

Sum of squares = 3203.85

Average of above = 44.50

S.D. = $\sqrt{44.50 - (7.19)^2}$

= 2.70

C = Blood Thiopentone Levels at Awakening.

Average = 8.03

Sum of suares = 5759.51

Average of above = 80.00

S.D. = $\sqrt{80.00 - (8.03)^2}$

= 3.94

Relation of Blood Thiopentone levels at Awakening to Initial Dose of Thiopentone

Sum of (A - Average A) X (C - Average C) = + 499.64

Average of " " = + 6.245

$$\text{Correlation Coefficient} = \frac{+ 6.245}{1.84 \times 3.94} = + 0.88$$

Regression Equation

[Blood Thiopentone level at awakening (mg/litre)] - 8.03

= 0.88 x (3.94 ÷ 1.84) X

[Induction dose of Thiopentone (mg/kg)] - 4.03

Blood Thiopentone level at awakening (mg/litre) =

1.88 (Induction dose of thiopentone in mg/kg) + 0.45

Significance

$$t = \frac{0.88}{\sqrt{1 - (0.88)^2}} \times \sqrt{72 - 2} = 16.0$$

p 0.01

Relation of Blood Thiopentone levels at Awakening to Total Dose of Thiopentone

Sum of (B - Average B) x (C - Average C) = + 385.4

Average " " = + 5.35

$$\text{Correlation Coefficient} = \frac{+ 5.35}{2.70 \times 3.94} = + 0.500$$

Significance

$$t = \frac{0.500}{\sqrt{1 - (0.50)^2}} \times \sqrt{72 - 2} = 3.59$$

$p < 0.10 > 0.05$

Because of low significance the Regression Equation was not calculated.

Relationship of Increment Dose (i.e. Total Dose less Induction Dose) of Thiopentone to Blood Thiopentone levels at Awakening.

Average increment dose = 3.1 mg/kg

S.D. = 2.95

Sum of (Increment dose - average increment dose) X (C - Average C) = 48.14

Average = - 0.66

$$\text{Correlation Coefficient} = \frac{-0.66}{2.95 \times 3.94} = -.056$$

$$t = \frac{0.56}{\sqrt{1 - (0.56)^2}} \times \sqrt{72 - 2} = 0.570$$

$p = < .6 \quad > .5$

Details of 25 cases who received a constant total dose of thiopentone varying from 10 - 11 mg/kg with varying induction doses.

Correlation of induction dose with blood thiopentone level at awakening.

This information is drawn from cases in the paper, but was not included in the publication.

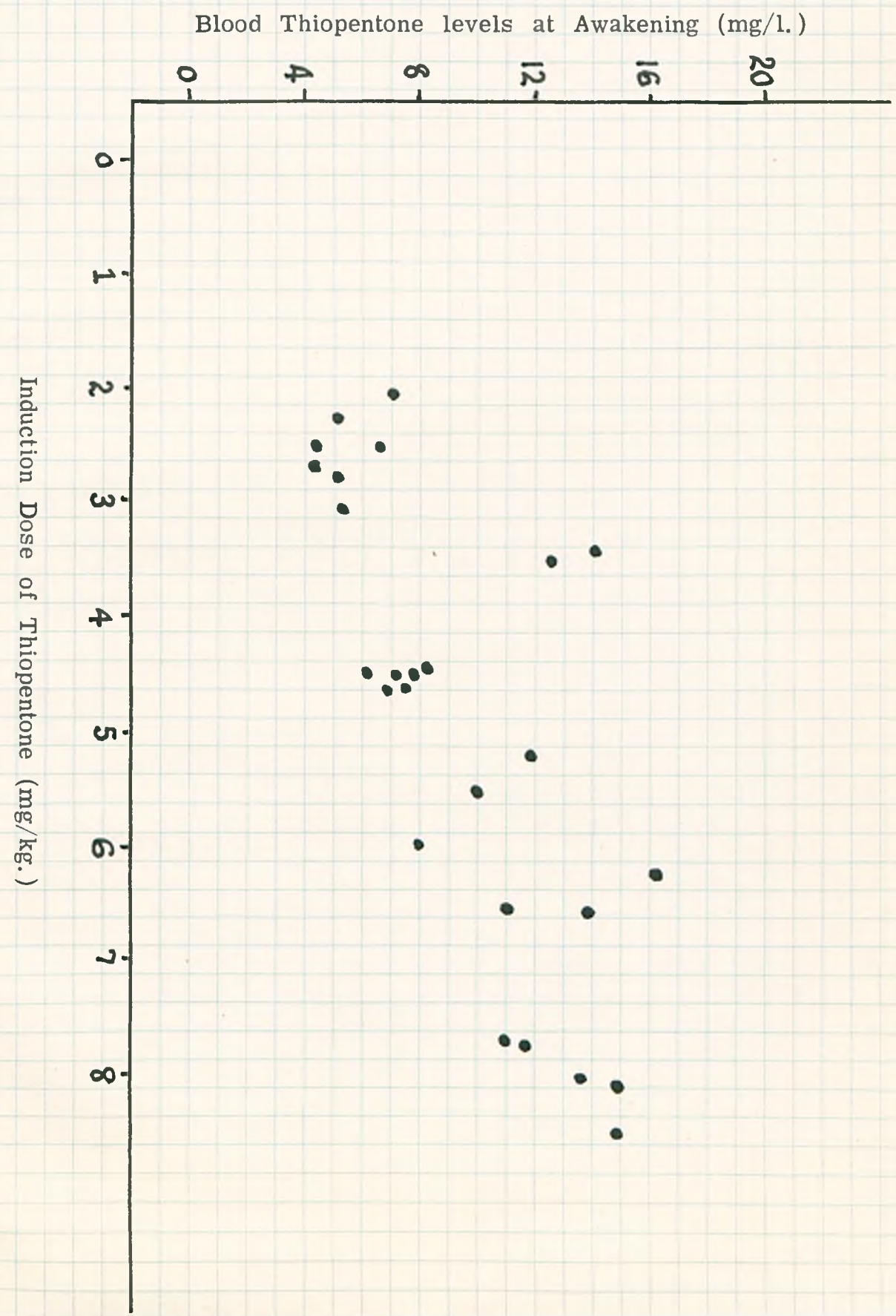
It is presented as additional evidence of the part played by the induction dose of thiopentone in determining the blood level at awakening. In only 4 of the cases did the ratio of total dose to induction dose exceed 4 : 1. If these are excluded from the series the graph becomes more linear and the significance increase.

Initial dose of Thiopentone mg/Kg	Blood thiopentone level at awakening mg/litre
5·2	12·0
5·5	10·2
4·4	8·5
2·0	9·3
6·6	13·0
8·6	14·0
4·4	6·2
4·6	7·8
6·6	11·1
6·3	16·3
7·7	11·0
8·1	13·8
2·5	11·5
2·7	5·3
2·2	7·5
4·5	7·8
6·0	9·1
3·5	11·8
2·5	6·8
3·1	5·3
4·6	7·5
7·7	11·9
8·1	15·0
2·6	4·5
3·4	14·4
Av 4·94	10·06.

Correlation Coefficient + 0·463

t 2·52

p $< 0.05 > 0.02$


Blood Thiopentone levels at Awakening (mg/l.)
0
4
8
12
16
20
Induction Dose of Thiopentone (mg/kg.)
0
1
2
3
4
5
6
7
8

Same data as in previous graph, but excluding 4 cases in whom total dose was more than 4 times greater than the induction dose.