THE PHYSIOLOGICAL EFFECTS OF INTRAVENOUS ANAESTHESIA ON MAN

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INTRODUCTION

KEATING noted in 1956 that intravenous anaesthetics cause as many sudden unexplained deaths as did chloroform (1). From recent extensive reviews it appears that estimated death rates from intravenous anaesthetics have been conservative (2, 3, 4). The introduction of new or "better" intravenous agents must therefore be most carefully assessed in the most reliable and valid parameters available for study.

Theory and data recently procured have provided the clinical anaesthetist with some fundamental facts which should form a basis for comparing new agents and for the improved management of intravenous inductions of anaesthesia.

First, and foremost, the effect of premedicant drugs administered to the patient before the intravenous anaesthetic agent must be determined. For this reason, all drugs tested should be given preferably to unpremedicated subjects in order to separate the changes in vasomotor and haemodynamic stability as well as in respiration which occur with premedicant drugs. Clinicians have almost totally ignored or have not included these effects in their studies of changes (5-11).

In addition to theoretical considerations of the intrinsic activity of each drug, the affinity of drugs for various tissues and the effect of drug interaction, it is essential that the anaesthetist also note the physiological age, the state of nutrition and hydration as well as the state of electrolytes in the subjects whom he studies.

To compare the effects of drugs under clinical tests in a group of patients in whom the above factors vary widely is completely invalid. To procure the usual average series of unselected cases may merely add to the variability of the basic conditions and throw in the less common disturbing factors of varying sensitivity.

Other factors of vital concern, particularly with respect to the ultra-short acting intravenous agents, are the phenomena of cumulation, of acute tolerance,

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Supplies of drugs were kindly made available by the following firms sodium thiopental (Pentothal®) by Abbott Laboratories, Montreal, P.Q., thiamylal sodium (Surital®) by Parke, Davis and Company Ltd, Walkerville, Ontario, hexobarbital sodium (Evipal®) by Winthrop Stearns Inc, New York, methitural sodium (Neraval®) by Schering Corporation, Montreal, P.Q., buthalitone sodium (Transithal®) by Poulenc Ltd, Montreal, P.Q., Compound 25398 by Eli Lilly and Company, Indianapolis, Ind., and MRD-125 (Dolitrone®) by the Wm S Merrill Company, Cincinnati, Ohio, U.S.A.

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and perhaps also of tachyphylaxis. Since the intravenous anaesthetics reach a very rapid peak of concentration sequentially in the blood, the brain, and the heart, at a rate which is almost synchronous with the circulation time, and then are rapidly redistributed to the rest of the body, the effect of this initial distribution must be evaluated when several drugs are to be compared. This evaluation is very important, because the cerebral blood flow is maintained even when a state of shock is impending or present. Therefore, the effect of intravenous drugs on the brain will vary in an inverse relationship to the cardiac output. Subsequent injections of a drug under test produce a greater effect on the central nervous system and a lesser effect on the haemodynamics and cannot provide a valid comparison. The cumulative effects or tachyphylaxis further confuse this picture.

As for the phenomenon of *acute tolerance*, Dundee and his associates have shown that the awakening time from intravenous anaesthesia (thiopental) is primarily determined by the initial or acute dose of the intravenous anaesthetic (12).

The physiological effect of intravenous anaesthetic agents on haemodynamics must be considered of primary importance to the clinical anaesthetist, for a large proportion of deaths attributable to inductions of intravenous anaesthetic are caused by both respiratory and cardiovascular depression. The respiratory depression is quite easily supported, while the cardiovascular depression frequently cannot be reversed by vasopressors, by atropine and other supportive measures, especially in elderly or debilitated patients. As many¹ new agents are becoming available, it is essential to evaluate these carefully on healthy subjects prior to employing them in clinical trials. Since the greatest difficulties arise immediately after induction of anaesthesia, the most pertinent information should be obtained *at this time*, rather than after a so-called steady state develops. However these data are procured, the investigator must either account for the gross alterations from the basal state in the patient prepared for an operation or a test study, or clearly evaluate the effect of apprehension or of the narcotic premedication on the parameters being investigated.

One of the reasons for the paucity of data on the haemodynamic effects of anaesthetic agents is the technical difficulty encountered in procuring such information in man. Since a simple method was devised recently, it was deemed important to compare the effects of several intravenous anaesthetics on haemodynamics as well as on respiration of the *same individual subjects*. This comparison provided an integral part of the experimental and clinical evaluations of the newer anaesthetic agents which have been studied (13, 14).

METHOD

For each subject, vital statistics (sex, age, body build, height, weight and body surface area) were measured and noted. Blood volume fractions, venous haematocrit and resting vital signs were recorded. Respiratory and haemodynamic parameters were estimated and calculated from metabolism tables

INTRAVENOUS ANAESTHETICS	
TRANSITHAL Na Buthalitone (Poulenc)	Na-5-Allyl-5-isobutyl-thiobarbiturate
NERAVAL Na Methitural (Schering)	Na-5-(1-Methylbutyl)-5-2(methylthio) ethyl-2 thiobarbiturate
Compound 25398 (Eli Lilly)	Na 1-Methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate
DOLITRONE (Merrill)	5-Ethyl-6-phenyl-M-thiazine-2,4-dione
PENTOTHAL Na Thiopental (Abbott)	Na-5-Ethyl-5-(1-methylbutyl)-2-thiobarbiturate
SURITAL Na Thi amylal (Parke-Davis)	Na-5-Allyl-5(1-methylbutyl)-2-thiobarbiturate
EVIPAL Na Hexobarbital Winthrop-Stearns)	Na N-Methyl-5-cyclohexenyl-5-methyl barbiturate

FIGURE 1 Comparative chemical structure of intravenous anaesthetics.

and from the nomograms of Radford and Jackson (15, 16). These data provided the base line for all changes recorded in the control period and in the acute and delayed test period. Alterations in recorded respiratory and haemodynamic parameters induced by apprehension or anxiety, and by the drugs under study, were then compared.

Data were obtained at weekly intervals from young, healthy, male subjects in a fasting state before and after intravenous administration of thiopental, thiamylal, hexobarbital, buthalitone, methitural, Compound 25398 and Dolitrone (Fig. 1). While the subject was requested to gaze at the ceiling, each freshly prepared drug was administered from a 20 ml. syringe in a 2.5 per cent solution through a 1½" 20-gauge needle at the rate of approximately 15 mg. per second until the eyelids closed involuntarily. Thereupon, an equal dose was injected as rapidly as pressure on the syringe would permit. Arrangement of recording data is shown in Figure 2.

FIGURE 2. Arrangement of respiratory and haemodynamic recording equipment for study of intravenous anaesthetics.

As premedication was not given, it was realized that apprehension was the important factor in altering control values as compared to those of the resting state (17, 18). This could not be avoided even in trained human subjects. No attempt was made to record electroencephalographic levels, as these were virtually "acute" experiments, and in previous studies a grossly erroneous indication of anaesthetic depth and reflex responsiveness during intravenous anaesthesia was observed (13, 19). It was further evident that electroencephalographic levels are not comparable among anaesthetics, even when their route of adminis-

tration or mode of action may be similar. With any anaesthetic drug, if the "depth of anaesthesia" as determined by the electroencephalogram must be known within a reasonably steady blood level, collateral data must be obtained from repeated blood samples or a continuous monitor showing the arterial blood sugar, pO_2 , pCO_2 and cerebral blood flow. Without this data, very wide variation in the blood level of the anaesthetic can exist, without significant alteration in the cortical potentials. Others are now beginning to report similar difficulties (20).

Determinations of blood volume were made on each subject prior to the drug tests, by means of a simple, accurate method which has been developed (21-25). Using human serum albumin iodinated with iodine¹³¹ and radioactive sodium chromate containing chromium⁵¹, plasma volume and red cell volume were determined simultaneously (26, 27). In the first compound, the iodine is firmly bound to the protein and when injected intravenously, there is no transfer of activity to the plasma proteins or to the red cells. Since the albumin is physically and chemically almost identical to the ordinary serum albumin, there is only a slow leakage from the capillary bed. Evans Blue (T1824) diffuses relatively rapidly from the circulating plasma, and repeated determinations within short time intervals are not possible. In the Evans Blue method, lipaemia or haemolysis will cause interference, but since only radioactivity is being measured in the iodine¹³¹ serum albumin method, colour or turbidity is not a problem. When a highly sensitive well-type scintillation counter is used, the dose of radioactivity given to the patient is negligible. With sodium chromate (Na_2CrO_4) incubation with blood allows adsorption of the radioactive chromium⁵¹ by the cells and binding to the globulin in the cells. The calculation of plasma and red cell volume is based on the dilution principle, just as in the Evans Blue method. The general principles of this procedure are as follows:

1. (a) Venous blood (20 ml) from the subject is added to 150 microcuries of chromium⁵¹ and allowed to incubate at room temperature. The subject's labelled cells are later reinjected.

- (b) Iodine¹³¹ labelled albumin is diluted, using sterile containers and sterile saline to an activity level of about 5 microcuries per ml. Then, 5 to 10 microcuries of this dilution are injected intravenously into the subject, the syringe being well flushed with blood before being removed from the vein.

2. Standard dilute solutions are prepared by adding amounts exactly equal to that injected of the iodine¹³¹ and chromium⁵¹ to 4000 ml. and to 500 ml. volumetric flasks respectively and then bringing the solutions to the mark with distilled water.

3. Fifteen minutes after injection of iodine¹³¹ and chromium⁵¹ blood samples are withdrawn from the other arm and added to tubes containing heparin or a dried potassium-ammonium-oxalate mixture.

4. Haematocrit determinations are made on the blood and on an aliquot centrifuged to obtain about 3 ml. of plasma.

5. Then, 2 ml. samples of the standard solutions (2), the subject's blood (3) and plasma (4) are counted in a well-type scintillation counter.

6. After subtraction of background counts, a predicted blood volume may be estimated thus:

$$B V = \frac{\text{Plasma volume}}{1 - (\text{Hct} \times 0.9)}$$

and then may be calculated thus:

$$\text{Red cell volume} = \frac{\text{Counts per min of injected solution/ml}}{\text{Net counts/min./ml}} \times \text{Volume of tagged cells injected}$$

$$\text{Plasma volume} = \frac{\text{Counts/min /ml of standard}}{\text{Counts/min /ml plasma}} \times \text{Volume of standard}$$

Venous haematocrit was determined by centrifuging heparinized blood in Wintrobe tubes.

Normal values by this method in mg/kg. in 25 other subjects were as follows: red cell volume, 22 to 37 (mean 28.5 ± 4), plasma volume, 33 to 60 (mean 43.0 ± 6.8). Total blood volume ranged from 55 to 90. The ratio of body haematocrit to venous haematocrit in 108 estimations was $0.89 \pm .05$ (27).

Arterial and venous blood pressures were measured directly from the brachial artery and the median basilic vein through 5 cm. 18-gauge needles. These needles were connected to Statham strain gauges (Model P 23A) placed at the level of the right auricle, arbitrarily set at 100 mm. above the level of the back as recommended by Lyons and associates (28). These pressures together with lead 2 of the electrocardiogram were recorded continuously on two oscilloscopes with an infinite frequency response. One of these oscilloscopes was set to amplify the complexes. The pressure heads had a frequency response of 185 c.p.s. through a 5 cm. 20-gauge needle. Fry and associates have shown that the technical recording system employed is highly accurate and a stable system for recording pressure data (29). All tracings were photographed for permanent records and subsequent study.

The mean pulse rate, mean venous pressure, mean systolic and diastolic blood pressure and mean pulse pressures were computed from the average of all pulse rates and arterial and venous blood pressures measured on the tracings for each subject. These measurements were made in a representative three-minute period when other data were recorded (cardiac output, oxygen consumption, respiration rate and tidal volume) before and immediately after the injection of the test drugs and again for five to thirty minutes during the awakening period when blood pressure, pulse rate and respiration had stabilized somewhat. From the tracings the mean arterial blood pressure was computed thus: mean arterial blood pressure = mean diastolic B.P. + $1/3$ (mean systolic B.P. - mean diastolic B.P.). It was found that this calculation provides essentially the same values as that determined by planimetry of the pulse waves.

Cardiac output Cardiac output was measured by the recording of radioactivity transients at the precordium by the external body counting of iodine¹³¹ as described by Veall and associates in 1954 and by Huff and associates in 1955 (30, 31). The technique described by the latter authors was followed exactly. A collimator with a diameter of $3/4$ inch was used on a thyroid counter. The detector was placed over the skin between the first and second ribs at the left

parasternal line. The scintillation counter was connected to a count-rate meter and a Varian strip-chart recorder. For each determination 75 microcuries of Rihsa® in a small volume (1 ml.) were injected directly into the same median basilic vein in a single continuous motion at a rate not exceeding one second for the entire injection. The needle and vein were then flushed with normal saline. The uptake of Rihsa® was recorded until an equilibrium counting rate was observed on the calibrated recording chart. The initial fall in intensity of radioactivity following the first rise was extrapolated exponentially to the base line. The area under this curve was measured accurately by planimetry in square inches using a "Paragon" Compensating Polar Planimeter. The cardiac output in blood volumes per minute was then equal to:

$$\frac{\text{Height (in) of equilibrium value} \times \text{record speed (in/min)}}{\text{Area (in}^2 \text{ of extrapolated curve)}}$$

The cardiac output in litres per minute was then determined from this estimation multiplied by the total blood volume which was determined initially. Theoretical considerations of this method will be amplified in the discussion. As estimations were made at weekly intervals, potassium iodide was prescribed to be taken by the subjects for a few days before and after each test, in order to prevent uptake of the radioactive iodine by the thyroid.

From the recorded determinations the following estimations were made:

1. *Mean circulation time (MCT)* was measured objectively by a method which would include the transit time through the heart and lungs (32, 33). This parameter is determined on the curve for cardiac output by measuring the first moment (or the centre of gravity) of the extrapolated curve. By definition

$$MCT = \frac{\int_{T_1}^{\infty} ct \, dt}{\int_{T_1}^{\infty} c \, dt}$$

(Cyvin's formula) (34). In practice this is done by summing the products C_1T_1 , C_2T_2 , C_3T_3 , C_nT_n and dividing this value by the sum of C_1 , C_2 , C_3 and C_n as described by Hamilton in 1932 (35). This method is cumbersome and does not significantly increase the accuracy of that time measurement from the moment of starting injection of Rihsa into the median basilic vein (x) until the peak activity is recorded over the precordium (y), that is, on Figure 3 the xy time interval is very nearly equal to the time interval from "a" to the projection of the centre of gravity of the exponentially extrapolated curve on the abscissa. XY is very nearly equal to "ac" because the time concentration curve is skewed to the right (to the left on the recording). In six tracings checked at random, the mean difference between these two methods was less than 0.3 seconds. With mean circulation times observed in this study lying for the most part between 10 and 15 seconds, the error is relatively small compared to any subjective methods (< 3 per cent).

Another simple method for determining the mean circulation time in radio-cardiographic work is employed by Shipley (36). The extrapolated curves are traced on index card paper, cutting out the enclosed area and finding the centre

FIGURE 3. The *cardiac output* is derived from the area ($A + B$) in square inches under the primary circulation tracing caused by the injected Rhisa, and extrapolated exponentially from point b to the base line in order to exclude the recirculation curve (bF). The final dilution of Rhisa is represented by the height C_f (inches). This height is multiplied by the paper speed (8 inches per minute), and the product divided by the area, which is measured by planimetry. The derived figure represents the cardiac output in blood volumes per minute. The latter figure is multiplied by the total blood volume, previously determined (see Fig. 4 or example). The *mean circulation time* is derived from the same tracing either by measuring the time xy in seconds (from moment of injection to moment of peak radioactivity), or the time interval from a to the projection of the centre of gravity of the primary extrapolated tracing on to the abscissa. The latter may be found empirically or mathematically (see text).

of gravity by balancing the cut-out on a knife edge. The errors by these two empirical methods (xy measure and balancing) are no greater than making multiple measurements on the curve and applying mathematics.

$$2. \text{ Cardiac Index (CI)} = \frac{\text{Cardiac output (litres/min.)}}{\text{Body surface area}}$$

$$3. (a) \text{ Stroke Volume (SV)} = \frac{\text{Cardiac output (litres/min.)}}{\text{Mean pulse rate/min.}}$$

$$(b) \text{ Stroke Index (SI)} = \frac{\text{Stroke volume}}{\text{Body surface area (BSA)}}$$

4. *Total peripheral resistance (TPR)* was estimated by the over-all resistance formula of Apiera (37) in which *TPR* in dynes/sec./cm.⁵ equals

$$\frac{\text{Mean arterial B.P. (mmg Hg)} \times 1332}{\text{Cardiac output in ml /sec}}$$

or

$$\frac{\text{Mean arterial B.P. (mm Hg)} \times 80}{\text{Cardiac output in litres}}.$$

Differences greater than 20 per cent in the above parameters were taken as significant (38).

5. *Cardiac power or left ventricular work (LVW)* was estimated as recommended by Remington and Hamilton (39) according to the formula:

$$\text{LVW in kg metres/min} = \frac{13.5 \times \text{cardiac output (L/min)} \times \text{mean arterial B.P. (mm Hg)}}{1000}$$

This formula assumes that the specific gravity of blood is slightly greater than unity. Differences greater than 30 per cent are taken as significant.

6. The *intrathoracic blood volume index (ITBVI)* was derived from the formula:

$$\frac{\text{Mean circulation time} \times \text{cardiac output}}{60 \times \text{BSA}}$$

A change greater than 15 per cent is considered to be significant (38, 40-44).

7. *Oxygen consumption* was measured on the respiration tracings recorded on a respirometer known as a Pulmotest¹. This instrument was calibrated with oxygen so that a one centimetre rise in the slope indicated utilization of 300 ml. of oxygen. Paper speed on this recorder was 30 mm. per minute. This instrument is ordinarily employed as a recording bronchspirometer and was used in this study for oxygen consumption measurements by filling one bell with oxygen and allowing the oxygen to leak across to the other bell (filled with room air) via an electro-magnetic solenoid which is activated by the tidal volume. This instrument was connected to the patient via a short piece of corrugated tubing and a well-fitting face mask selected previously (as in Fig. 1). The same fitted mask was used for each subject during all the studies.

RESULTS

The mean resting vital signs for each subject, together with the cardio-respiratory parameters derived from metabolic rate tables, the ventilation standards for use in artificial respiration described by Radford, and the cardiac output from the nomogram devised by Jackson, are summarized in Table I. The vital statistics, the blood volume and fractions and the mean control vital signs, together with the cardio-respiratory parameters obtained prior to administration of the intravenous anaesthetics, are summarized in Table II. The data obtained for each subject with each drug are tabulated in Tables III to IX.

¹Made by J. H. Becker in Delft, Holland

TABLE I

MEAN RESTING VITAL SIGNS AND PREDICTED CARDIO-RESPIRATORY PARAMETERS

	AB	LC	WH	NK	DS	EB	PB	AL	MEANS
Systolic Blood Pressure	112	121	110	125	106	119	110	111	114
Diastolic Blood Pressure	70	70	60	62	70	70	70	70	68
Pulse Pressure	42	51	50	63	36	49	40	41	46
Mean Blood Pressure	84	87	77	83	82	86	83	84	83
Pulse Rate	68	71	62	68	69	72	66	73	69
Respiration Rate	18	18	18	16	18	16	18	18	17.5
Tidal Volume**	380	420	400	500	370	560	350	390	420
Minute Volume**	6.84	7.85	7.20	8.00	6.65	8.98	6.30	6.82	7.30
Oxygen Consumption*	262	284	268	300	264	328	248	270	277
Circulation Time	15.5	14.6	11.8	10.6	11.9	16.7	14.2	11.2	13.3
Cardiac Output ⁺	4.6	5.1	4.8	5.5	4.5	5.1	4.4	4.6	4.82
Index	2.55	2.52	2.60	2.62	2.42	2.22	2.63	2.35	2.48
Stroke Volume ⁺	68	72	78	81	65	71	67	63	70
Index	38	35	42	39	35	31	40	32	36
Total Peripheral Resistance	1460	1370	1283	1203	1446	1346	1510	1462	1380
Left Ventricular Work	5.2	6.0	4.9	6.2	5.0	5.9	4.9	5.2	5.4
Intrathoracic Blood Volume	1.19	1.24	0.95	0.98	0.90	1.42	1.04	0.86	1.09

* Calculated from the Mayo Foundation Studies of 1936 modified to permit determination at "present age"

** Predicted from Nomogram of Radford

+ Predicted from Nomogram of Jackson

Statistical analysis of these data is summarized in Tables X to XVI. The mean respiratory and haemodynamic effects of each intravenous anaesthetic are summarized in Tables XVII and XVIII respectively. Figures 4-8 show selected tracings which illustrate the typical effects observed.

The significant alteration with each drug is described below, first with regard to the acute effect, the changes from the resting and control values, and then the effects after the acute changes have passed (during "waking up" period).

Thiopental. Apnoea lasted approximately 30 seconds with the mean dose of 442 mg./M². Oxygen consumption and BMR decreased approximately 30 per cent in all subjects ($P < .01$). This effect persisted until the subject recovered. The change was accompanied by a 16 per cent rise in pulse rate, a 17 per cent fall in the mean blood pressure and a 23 per cent fall in the venous pressure. There was no significant alteration in the mean circulation time or cardiac output. Peripheral resistance and left ventricular work showed an inconsistent decrease. These changes indicated that a substantial quantity of the circulating blood volume was probably shifted to the capillary or venous side of the circulation.

During recovery, the depression of tidal volume was compensated for adequately by a rise in the respiration rate. The pulse rate compensated for the fall in blood pressure.

TABLE II
MEAN VALUES OF CARDIO-RESPIRATORY PARAMETERS—CONTROL STUDIES

Subject	Sex	Age	Build	Ht. cm.	Wt. Kg.	BSA sq.m.	Respiration Rate /min.	Tidal Volume ml.	Minute Volume litres	Oxygen Consumption ml.	Metabolic Rate	Mean Pulse Rate /min	Mean Blood Pressure mm. Hg.	Mean Venous Pressure cm. H ₂ O	Plasma Volume litres & ml/kg	Red Cell Volume litres & ml/kg	Total Bd. Vol. litres & ml/kg	Body Haematocrit	Venous Haematocrit	BH/VH	Mean Circulation Time sec.	Cardiac Output and Index litres	Stroke Volume and Index litres	Total Peripheral Resistance dynes/cm ²	Left Ventricular Work kgM/min	Intrathoracic Blood Volume & Index litres
1 AB	M	22	Medium	175	68	1.80	16	560	9.0	316	+21	88	91	10.4	3.38 50	2.25 33	5.63 83	40.0	44.5	.90	15.5	6.1 3.4	70 39	1180 1180	7.5 7.5	1.78 .99
2 LC	M	25	Medium	183	80	2.01	14	630	8.8	375	+33	93	91	11.2	3.56 44	2.62 39	6.18 77	42.4	47.1	.90	14.8	5.9 2.9	64 32	1230 1230	7.2 7.2	1.92 .96
3 WH	M	23	Lean	175	74	1.85	16	510	8.1	313	+17	94	98	11.3	3.21 43	2.25 31	5.46 74	41.2	45.8	.90	11.8	6.3 3.4	67 36	1240 1240	8.3 8.3	1.84 1.0
4 NK	M	23	Heavy	183	89	2.10	17	590	10.0	389	+30	110	92	11.9	3.66 41	2.58 29	6.24 70	41.4	46.0	.90	10.6	7.7 3.7	70 33	955 955	9.5 9.5	2.34 1.12
5 DS	M	23	Lean	183	66	1.86	18	570	10.2	325	+22	98	80	9.8	4.10 62	3.00 45	7.10 107	42.3	47.0	.90	11.9	7.0 3.7	72 39	915 915	7.5 7.5	2.70 1.45
6 EB	M	23	Heavy	191	102	2.31	11	810	8.9	341	+4	80	89	7.4	4.23 41	3.12 31	7.35 72	42.5	47.2	.90	16.7	5.3 2.2	66 29	1340 1340	6.4 6.4	2.87 1.24
7 PB	M	22	Lean	175	60	1.67	13	620	8.0	365	+48	80	80	11.6	3.74 62	2.54 42	6.28 104	40.9	45.0	.91	14.2	5.3 3.2	66 39	1210 1210	5.7 5.7	2.19 1.63
8 AL	M	31	Lean	188	72	1.96	12	820	9.8	377	+39	104	93	8.8	3.65 51	2.58 36	6.23 87	41.4	46.0	.90	11.2	5.7 2.9	55 28	1300 1300	7.2 7.2	1.92 .98
Means		24		182	76	1.94	14	640	9.1	352	+31	93	90	10.3	3.70 49	2.61 34.9	6.18 84.2	41.4	46.0	.90	13.3	6.2 3.2	66.2 34.4	1171 1171	7.4 7.4	2.20 1.17

TABLE III
PENTOTHAL: ACUTE EFFECTS

	Dose mg.	O ₂	BMR	R _E /min	P _E mm. Hg.	V _E cm. H ₂ O	T _E sec.	CO (P) litres	CO (R) litres	CO (P) litres	CO (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec./cm ⁵	TPR (R)	LW (P) Kg./M/min	LW (R)	(R) litres
1	c	280	+7	94	100	12.3-13.6	14.5	6.5	7.9	3.6	4.4	39	46	1230	1008	8.8	10.7	1.06
	472	200	-16	116	70	10.2	13.1	7.5	10.2	4.2	5.7	38	49	748	548	7.1	9.6	1.25
	% Difference	-28.6	-23	23	-30	-22	-10	+15	29	17	30	-3	+7	-39	-46	-19	-10	+18
2	c	390	+38	100	88	10.2-12.3	12.2	7.5	9.9	3.8	4.9	37	49	940	712	8.9	11.8	1.00
	498	270	-4	116	72	8.2	8.8	7.6	9.9	3.8	4.9	34	41	757	582	7.4	9.6	.73
	% Difference	-31	-42	16	-18	-27	-28	1	0	0	0	-8	-16	-20	-32	-17	-19	-27
3	c	300	+12	115	93	9.5-16.3	8.8	6.8	10.4	3.7	5.6	32	4.9	1092	715	8.5	13.1	1.11
	433	190	-29	125	70	5.4	12.6	8.5	9.8	4.6	5.3	37	42	658	572	8.0	9.2	1.11
	% Difference	-37	-41	9	-25	-58	43	25	-6	24	-5	13	-14	-40	-20	-6	-30	0
4	c	380	+27	120	73	-PT	9.8	8.3	13.7	3.9	6.5	34	54	704	425	8.2	13.5	1.16
	333	260	-16	105	54	-PT	10.8	7.9	11.8	3.8	5.6	37	53	546	361	5.8	8.6	1.11
	% Difference	-32	-43	-13	-26		10	-5	-14	-3	-14	9	-2	-22	-15	-29	-36	-5
5	c	315	+20	100	90	10.2-12.3	12.2	7.7	14.9	4.2	8.0	39	80	935	483	9.4	18.1	0.98
	323	240	-9	120	83	8.2	12.6	7.8	18.4	4.2	9.9	36	82	853	361	8.7	20.6	2.08
	% Difference	-24	-29	20	-8	-27	3	1	24	0	24	-8	3	-9	-25	-7	14	112
6	c	315	-4	70	90	6.8	13.6	4.2	9.6	1.8	4.2	25	58	1715	750	5.1	11.6	0.94
	260*	240	-27	90	90	6.8	13.1	5.2	6.6	2.3	2.9	25	32	1384	1088	6.3	8.0	0.63
	% Difference	-24	-23	29	0	0	-4	24	-31	28	-31	0	-46	-19	45	24	-31	-33
7	c	330	+34	77	83	10.2-11.0	15.9	5.1	13.2	3.1	7.9	40	61	1300	504	5.7	14.8	1.82
	598	250	+1	100	72	3.4	14.0	7.0	9.4	4.2	5.5	42	51	822	613	6.8	9.1	1.32
	% Difference	-24	-33	30	-13	-7	-12	37	-29	36	-30	5	-16	-37	22	19	-39	-28

*** Sleep dose +20%**

PT = poor tracing

TABLE IV

SURITAL: ACUTE EFFECTS

Dose mg.	O ₂ ml.	BMR	E _g /min.	E _{mm. Hg}	E _{cm. H₂O}	E _{sec.}	CO (p) litres	CO (R) litres	CO (p) litres	CO (R) litres	SI (p) ml.	SI (R) ml.	TPR (p) dynes-sec/cm ⁵	TPR (R) Kg. M/min.	LW (R)	litres	
1 c 445 % Difference	340 190 -44	+30 -27 -57	88 100 14	87 77 -12	-PT	15.5 12.2 -21	6.2 7.9 27	5.6 6.8 21	3.4 4.3 27	3.1 3.8 21	40 44 10	35 38 9	1180 780 -34	1240 928 -25	7.3 8.2 12	6.6 7.2 9	0.81 0.77 -5
2 c 398 % Difference	360 280 -22	+21 -1 -29	86 110 28	93 73 -22	11-13.6 2.7 -78	17.3 16.8 -3	5.1 8.0 57	6.2 6.8 7	2.6 3.9 57	3.1 3.4 9	29 36 24	46 31 33	1455 730 -50	1200 856 -29	6.4 7.9 23	7.8 6.7 -14	0.89 0.95 7
3 c 486 % Difference	340 260 -24	+27 -3 -30	85 90 6	103 80 -22	13.6-20 11.6 -31	13.1 16.4 25	6.4 7.5 17	7.1 6.6 -7	3.5 4.1 17	3.8 3.6 -5	41 45 10	45 39 -13	1286 854 -37	1160 968 -17	8.9 8.1 -9	9.9 7.1 -28	0.84 0.98 17
4 c 381 % Difference	370 300 -23	+24 0 -24	105 120 14	83 73 -12	-PT	10.8 10.8 0	7.2 8.7 21	10.0 10.6 6	3.4 4.1 21	4.8 5.1 6	32 35 9	45 42 -7	924 672 -27	664 545 -18	8.1 8.6 6	11.2 10.4 -7	0.86 0.91 6
5 c 323 % Difference	330 300 -9	+25 +14 -11	100 110 10	77 80 4	8.2-13.6 5.5 -50	10.3 10.3 0	7.9 6.8 -14	12.8 17.0 33	4.3 3.7 -14	6.9 9.1 32	42 33 -21	69 83 20	778 940 21	480 376 -22	8.2 7.3 -11	13.3 18.3 38	1.18 1.57 33
6 c 217* % Difference	310 250 -19	-5 -24 -19	90 105 17	73 77 6	8.2 5.5 -33	22 15.4 -30	6.5 7.1 9	8.8 6.6 -25	2.8 3.1 9	3.8 2.9 -24	32 29 -9	42 27 -36	900 867 -4	664 928 40	6.4 7.4 16	8.7 6.9 -21	1.39 0.74 -47
7 c 415 % Difference	400 315 -21	+62 +28 -34	88 96 9	82 70 -10	11-19 12.3 -18	PT	5.7 6.4 12		3.4 3.8 12		39 40 3		1150 874 -24		6.3 6.0 -5		

PT = poor tracing

* Sleep dose +20%

TABLE V

EVAL: ACUTE EFFECTS

Dose mg.	O ₂ C ml.	BMR	E g/min.	E mm. Hg	E cm. H ₂ O	E sec.	(P) litres	(R) litres	(P) ml.	(R) ml.	(P) dynes-sec/cm ⁵	(R) Kg./M/min.	(P) LW	(R) LW	(P) litres
1															
c	315	+20	90	90	9.5-11	14.5	6.7	6.8	3.7	3.8	1056	8.1	8.3	0.92	
556	310	+18	120	87	5.5	13.6	8.5	9.0	4.7	5.0	800	10.0	10.6	1.16	
% Difference	-2	-2	33	-3	-53	-6	27	32	27	31.6	-24	24	28	26	
2															
c	330	+17	95	97	.11	13.1	6.1	6.8	3.0	3.4	1207	8.0	8.9	0.74	
472	325	+15	115	77	12.9	10.8	8.7	5.7	4.3	2.8	700	9.0	5.9	0.52	
% Difference	-2	-2	21	21	17	-18	43	-16	43	-18	-42	13	-34	-30	
3															
c	325	+21	80	97	6.8-7.5	11.2	5.2	7.1	2.8	3.8	1490	6.8	9.8	0.72	
514	280	+5	100	83	6.8	13.6	6.6	13.6	3.6	7.3	1005	7.4	15.4	1.66	
% Difference	-14	-6	25	14	-5	21	27	92	29	92	-33	9	57	131	
4															
c	320	+7	120	107	PT	9.8	9.4	15.4	4.5	7.4	911	13.6	22.3	1.21	
417	400	+33	130	83	PT	8.4	8.2	14.3	3.9	6.8	819	9.2	16.0	0.96	
% Difference	25	+26	8	22		-14	-13	-8	-13	-8	-10	-32	-28	-21	
5															
c	330	+25	100	83	11-13.6	14.5	8.7	13.4	4.7	7.2	764	9.7	15.0	1.74	
538	290	+10	125	77	8.2	15.9	9.2	17.0	5.0	9.2	669	9.5	17.6	2.42	
% Difference	-12	-15	25	-7	-33	10	6	27	6	28	-12	-2	17	39	
6															
c	360	+10	72	90	6.8-9.6	23.8	4.0	9.5	1.7	4.2	1795	4.9	11.5	1.63	
260*	290	-11	105	83	6.8	19.7	5.9	8.8	2.6	3.8	1125	6.6	9.9	1.25	
% Difference	-19	-21	46	-8	-17	-17	48	-7	53	-10	-37	35	-14	-23	
7															
c	350	+42	80	77	17-30	PT	5.3		3.2		616	5.5			
598	300	+22	110	70	16.3		7.0		4.2		800	6.6			
% Difference	-14	-20	38	9	-31		32		31		30	20			

Sleep dose +20%

PT = poor tracing

TABLE VI
TRANSITIONAL: ACUTE EFFECTS.

Dose mg.	O ₂ ml.	BMR	E _g /min.	E _A mm. Hg	E _A cm. H ₂ O	E _U sec.	CO (P) litres	CO (R) litres	D (P) litres	D (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec/cm ⁵	TPR (R) cm ⁵	W (P) Kg.	W (R) M/min.	LBV (R) litres
1 c 556 % Difference	300 300 0	+15 +15 0	94 106 9	87 73 -16	16.3-19 10.2 -42	16.4 14.0 -15	6.6 7.6 15	5.6 7.9 41	3.7 4.2 14	3.1 4.4 42	39 40 3	33 41 24	1053 759 -28	1240 757 -39	7.8 7.5 -4	6.6 7.8 18	0.85 1.02 20
2 c 898 % Difference	420 390 -1	+48 +38 -10	100 104 4	80 63 -21	8.2 8.2 0	13.1 12.2 -7	8.0 8.0 0	9.9 9.3 -6	4.0 4.0 0	4.9 4.6 -6	40 38 -5	49 44 -10	800 628 -22	648 542 -16	8.6 6.8 -21	10.7 7.9 -26	1.07 0.94 -12
3 c 540 % Difference	290 190 -35	+9 -29 -38	90 110 22	83 90 8	13.6-19 12.2 -25	9.8 8.4 -14	7.2 8.3 15	11.4 7.6 -33	3.9 4.5 15	6.2 4.1 -34	43 41 -5	68 37 -46	923 867 -6	582 944 62	8.1 10.1 25	12.8 9.3 -27	1.00 0.58 -42
4 c 476 % Difference	420 300 -29	+40 0 -40	120 110 -8	107 83 -22	PT PT 0	11.7 11.7 0	9.4 7.3 -22	11.8 11.8 0	4.8 3.5 -27	5.6 5.6 0	38 31 -18	47 51 9	912 910 0	734 562 -23	7.5 8.2 9	17.1 13.2 -23	1.10 1.10 0
5 c 753 % Difference	320 310 -3	+22 +18 -4	95 110 16	70 57 -19	11 11 0	11.2 PT PT	6.3 8.5 35	14.9	3.4 4.6 35	8.0	36 42 17	85	888 535 -40	336	6.0 6.5 8	14.1	1.50
6 c 433* % Difference	365 270 -26	+12 -17 -29	90 100 11	93 87 -7	8.2 5.5 -33	14.0 13.6 -3	5.0 7.1 42	11.8 7.4 -37	2.2 3.1 41	5.1 3.2 -37	24 31 54	57 32 -44	1484 980 -34	631 836 33	6 8 32	14.8 8.7 -41	1.19 0.73 -39
8 c 920 % Difference	380 270 -29	+41 0 -41	106 124 17	93 67 -28	10-12.3 8.2 -3	10.3 10.8 5	5.9 7.0 19	10.6 7.5 -29	3.0 3.6 20	5.4 3.8 -30	28 29 4	52 31 -40	1260 806 -36	700 7.4 2	7.4 6.3 -15	13.3 6.8 -49	0.93 0.69 -26

* Sleep dose +20% PT= poor tracing

TABLE VII
NERAVAL: ACUTE EFFECTS

	Dose M^2 mg.	O_2C ml.	BMR	P^E /min.	A^E mm. Hg	V^E cm. H_2O	T^E sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	(P) SI ml.	(R) SI ml.	TPR (P) dynes-sec/cm ⁵	TPR (R) dynes-sec/cm ⁵	LVW (P) Kg. M/min.	LVW (R) Kg. M/min.	ITBVI (R) litres
1	c 264*	320 280	+22 +7	88 88	93 87	8.2-11 5.5	14.5 PT	5.3 6.1	8.5	3.0 3.4	4.8	33 39	53 L	1400 1140	872	6.7 7.2	10.7	1.14
% Difference		-13	-15	0	-7	-43		15		-13		18		-19		8		
2	c 398	390 310	+38 +8	88 100	83 60	13.6 11	19.2 14.5	5.7 7.3	7.4 7.4	2.8 3.6	3.7 3.7	33 36	42 37	1222 658	898 648	6.4 5.9	8.3 6.0	1.18 0.89
% Difference		-21	-30	14	-28	-19	-25	28	0	29	0	9	-12	-46	-28	-8	-28	-25
3	c 378	305 240	+14 -10	118 104	100 90	17-20 13.6	13.6 16.4	8.2 7.9	9.3 13.1	4.4 4.3	5.0 7.1	38 41	43 68	978 912	856 548	11.1 9.6	12.5 15.9	1.14 1.93
% Difference		-21	-24	-12	-10	-27	21	-4	41	-2	42	8	58	-7	-36	-14	27	69
4	c 405	420 310	+40 +4	100 110	93 73	10.2-13.6 6.8	11.2 10.8	6.0 7.8	14.6 6.2	2.9 3.7	6.9 3.0	29 34	70 27	1240 740	510 944	7.5 7.7	18.3 6.1	1.30 0.53
% Difference		-26	-36	10	-22	-57	-4	30	-58	28	-57	17	-61	-40	85	3	-67	-59
5	c 376	330 320	+25 +22	110 95	78 64	10 6.8	10.3 10.8	8.9 6.7	PT	4.8 3.6		44 38		702 766		7.7 5.8		
% Difference		-3	-3	-14	-18	-32	5	-25		-25		-14		9		-25		
6	c 433	300 250	-8 -24	75 104	97 83	6.8 9.6	14.5 11.2	4.9 6.9	9.6 10.1	2.2 3.0	4.2 4.4	28 29	56 42	1582 963	808 656	6.4 7.7	12.6 11.3	1.00 0.82
% Difference		-17	-16	39	-14	-41	-23	41	5	36	5	4	-25	-39	-19	20	-10	-18
8	c 510	360 220	+34 -18	110 95	93 70	9.6 4.1	12.2 11.2	6.1 5.9	11.8 9.4	3.1 3.0	6.0 4.8	28 32	47 50	1220 950	630 596	7.7 5.6	14.8 8.9	1.22 0.90
% Difference		-39	-52	-14	-25	-57	-8	-3	-20	-3	-20	14	6	-22	-5	-27	-40	-26

* Sleep dose

PT = poor tracing

TABLE VIII

COMPOUND 25398: ACUTE EFFECTS

Dose mg.	Q ₂ ml.	BMR	R _E /min.	P _E mm. Hg	S _E cm. H ₂ O	U _E sec.	CO (a) litres	CO (b) litres	CO (c) litres	SI (a) ml.	SI (b) ml.	SI (c) ml.	TPR (P) dynes-sec /cm ⁵	TPR (R) /cm ⁵	LWT (P) Kg./min.	LWT (R) /min.	ITBVI (R) litres
1 c 278 % Difference	340 270 -21	+30 +3 -27	90 120 33	83 67 -19	6.8-9.5 3.4 -58	16.8 13.6 -19	7.7 9.6 25	8.5 7.3 -14	4.3 5.3 23	4.7 4.1 -13	48 46 -4	52 34 -35	888 559 -37	782 726 -7	8.6 8.7 1	9.5 6.6 -31	1.32 0.92 -30
2 c 224 % Difference	375 230 -39	+34 -18 -52	100 135 35	100 93 -7	11-13.6 9.5 -25	12.6 11.7 -7	6.8 7.9 16	9.9 6.8 -31	3.4 4.0 18	5.0 3.4 -32	34 30 -12	49 38 -22	1175 944 -20	808 1096 36	9.2 9.9 8	13.4 8.5 -37	1.04 0.66 -37
3 c 270 % Difference	315 275 -13	+18 +3 -15	90 130 44	100 83 -17	11-16.3 8.2 -40	14 10.8 -23	6.3 8.4 33	9.0 10.4 16	3.4 4.5 32	4.9 5.6 14	38 36 -5	54 43 -20	1268 790 -38	888 638 -28	8.5 9.9 17	12.1 11.7 -3	1.14 1.01 -11
4 c 238 % Difference	390 370 -5	+30 +24 -6	116 132 14	83 83 0	13.6-15 10.2 -29	9.8 14.5 48	7.5 8.5 13	15.0 8.1 -46	3.7 4.1 11	7.2 3.9 -46	31 31 0	62 29 -53	885 781 -12	442 818 85	8.4 9.5 13	16.8 9.1 -46	1.17 0.93 -21
5 c 242 % Difference	300 260 -13	+14 -1 -15	100 150 50	73 77 6	PT PT	10.3 10.8 5	7.2 8.4 17	14.9 9.9 -34	3.9 4.5 15	8.0 5.3 -34	39 30 -23	80 35 -56	812 735 -10	432 624 44	7.1 8.7 23	14.7 10.3 -30	1.37 0.96 -30
6 c 217 % Difference	370 350 -5	+13 +7 -6	84 100 19	80 77 -4	PT PT	14.5 14.0 -3	6.8 7.7 13	11.7 8.8 -25	2.9 3.3 14	5.1 3.8 -26	35 33 -6	60 38 -37	941 802 -15	546 700 28	7.3 8.0 10	12.6 9.2 -27	1.22 0.89 -27
7 c 300 % Difference	380 250 -34	+54 +1 -53	76 120 58	77 60 -22	8.2 2.7 -67	12.6 13.6 8	5.1 8.7 71	6.3 8.2 30	3.1 5.2 68	3.8 4.8 26	40 44 10	50 41 -18	1208 552 -54	976 586 -40	5.3 7.0 32	6.6 6.6 0	0.79 1.11 41

* Sleep dose + 20%

PT = poor tracing

TABLE IX
DOLITRONE: ACUTE EFFECTS

No. mg.	O ₂ ml.	BMR	E _g /min.	E _a mm. Hg	E _{sp} cm. H ₂ O	E _{ct} sec.	CO		O ₂		(d) IS ml.	(s) IS ml.	(R) IS ml.	TPR (P) dynes-sec/cm ⁵	TPR (R)	LW (P) Kg./M/min	LW (R)	litres
							(d) CO litres	(s) CO litres	(d) O ₂ litres	(s) O ₂ litres								
1 e 445 % Difference	315 300 -5	+20 +15 -5	75 110 47	90 87 -3	9.5-11 8.2 -20	16.4 15.0 -9	4.1 5.5 34	5.6 5.1 -9	2.3 3.2 39	3.1 2.8 -10	31 28 -10	42 26 -38	1760 1265 -28	1288 1570 22	5.0 6.4 28	6.8 4.5 -34	0.85 0.71 -17	
2 c 498	360 300 -17	+28 +6 -22	85 110 29	90 67 -26	13.6 11 -19	15.0 10.3 -31	4.6 6.5 41	6.2 6.2 0	2.3 3.2 39	3.1 3.1 0	27 30 11	36 28 -22	1562 825 -47	1460 864 -26	5.6 5.1 -9	7.9 5.6 -29	0.77 0.53 -31	
3 c 541 % Difference	315 290 -8	+18 +9 -9	94 130 38	93 90 -3	8.9-10.2 6.8 -29	12.2 9.8 -20	7.3 9.3 27	9.3 7.1 -24	3.9 5.0 28	5.0 3.8 -24	44 41 -7	48 30 -38	1012 775 -23	800 1012 27	9.2 11.3 23	11.7 8.6 -27	1.02 0.63 -38	
4 c 357 % Difference	420 350 -17	+40 +18 -22	100 130 30	97 97 0	PT PT	11.2 12.2 9	6.5 8.4 29	12.4 10.6 -15	3.1 4.0 29	5.9 5.1 -14	31 31 0	59 39 -34	1192 925 -22	624 732 17	8.5 11.3 33	16.2 13.5 -17	1.10 1.03 -6	
5 c 538 % Difference	320 260 -19	+22 -1 -23	85 120 41	93 70 -25	8.2-10.2 11 20	14.5 14.0 -3	5.2 8.0 54	14.9 9.9 -34	2.8 4.3 54	8.0 5.3 -34	32 36 13	95 44 -54	1248 788 -37	500 566 13	6.4 7.6 19	18.7 9.4 -50	1.93 1.24 -36	
6 c 380* % Difference	370 330 -11	+13 +1 -12	75 105 40	97 93 -4	PT PT	14.5 12.2 -16	5.2 6.3 21	12.4 5.2 -58	2.3 2.7 17	5.4 2.3 -57	28 26 -7	72 22 -69	1490 1210 -19	624 656 5	6.8 7.9 16	16.2 6.5 -60	1.30 0.46 -65	
7 c 510 % Difference	390 260 -33	+44 -3 -47	100 128 28	93 70 -25	6.8-8.9 3.4 -57	9.8 8.8 -10	6.0 8.5 42	9.4 8.7 -7	3.1 4.3 39	4.8 4.4 -8	31 34 10	48 35 -27	1270 658 -48	792 644 -19	7.5 8.0 7	11.8 8.2 -31	0.78 0.62 -21	
8 c 520 % Difference	300 215 -28	+9 -22 -31	83 135 63	100 80 -20	11 8.2 -26	PT 9.4 -	6.0 11.0 83	10.0 -	3.1 5.7 84	5.2 -	37 43 16.0	38 -	1332 582 56	640 -	8.1 11.9 47	10.8 -	0.82 -	

* Sleep dose + 20% PT = poor tracing

TABLE X

PENTOTHAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-33	8.8	3.3	-10	.01
Mean Pulse Rate	+16	14.6	5.6	+2.9	.05
Mean Arterial Pressure	-17	10.8	4.1	-4.3	.01
Mean Venous Pressure	-23	20.3	8.3	-2.8	.05
Mean Circulation Time	+5	22.4	8.5	+0.6	ns
Cardiac Output (Predicted)	+14	15.8	6.0	+2.4	ns
Cardiac Output (Recorded)	-4	23.3	8.9	-.4	ns
Cardiac Index (Predicted)	+14	15.5	5.9	+2.5	.05
Cardiac Index (Recorded)	-4	23.9	9.0	-.4	ns
Stroke Index (Predicted)	+1	8.0	3.0	+4	ns
Stroke Index (Recorded)	-12	17.5	6.6	-1.8	ns
Total Peripheral Resistance (Predicted)	-26	12.1	4.6	-5.8	.01
Total Peripheral Resistance (Recorded)	-10	32.4	12.2	-.8	ns
Left Ventricular Work (Predicted)	-5	19.8	7.5	-.7	ns
Left Ventricular Work (Recorded)	-21	18.5	7.0	-3.1	.05
Intrathoracic Blood Volume Index (Recorded)	+5	50.9	19.2	+3	ns

ns = not significant

TABLE XI

SURITAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-29	14.6	5.5	-5.3	.01
Mean Pulse Rate	+14	7.2	2.7	+5.1	.01
Mean Arterial Pressure	-7	13.1	5.0	-1.4	ns
Mean Venous Pressure	-42	23.1	10.3	-4.1	.05
Mean Circulation Time	-5	19.3	7.9	-.6	ns
Cardiac Output (Predicted)	+19	+21.3	8.1	+2.3	ns
Cardiac Output (Recorded)	+6	20.4	8.3	+7	ns
Cardiac Index (Predicted)	+19	20.6	7.8	+2.4	.05
Cardiac Index (Recorded)	+6	19.8	8.1	+9	ns
Stroke Index (Predicted)	+4	14.9	5.6	+6	ns
Stroke Index (Recorded)	-10	22.2	9.1	-1.1	ns
Total Peripheral Resistance (Predicted)	-22	23.3	8.8	-2.5	.05
Total Peripheral Resistance (Recorded)	-12	25.6	10.5	-1.1	ns
Left Ventricular Work (Predicted)	+5	13.3	5.0	+9	ns
Left Ventricular Work (Recorded)	-4	24.0	9.8	-.4	ns
Intrathoracic Blood Volume Index (Recorded)	+2	27.0	11.0	+.2	ns

ns = not significant

TABLE XII

EVIPAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-6	16.1	6.1	-9	ns
Mean Pulse Rate	+28	12.2	4.6	+6.1	.01
Mean Arterial Pressure	-12	7.2	2.7	-4.5	.01
Mean Venous Pressure	-17	27.2	11.1	-1.6	ns
Mean Circulation Time	-4	16.1	6.6	-6	ns
Cardiac Output (Predicted)	+24	21.1	7.8	+3.1	.05
Cardiac Output (Recorded)	+20	36.9	15.1	+1.3	ns
Cardiac Index (Predicted)	+24	22.3	8.4	+3.0	.05
Cardiac Index (Recorded)	+20	41.1	16.8	+1.2	ns
Stroke Index (Predicted)	-2	12.1	4.6	-4	ns
Stroke Index (Recorded)	+2	38.2	15.6	+2.0	ns
Total Peripheral Resistance (Predicted)	-19	24.6	9.3	-2.0	ns
Total Peripheral Resistance (Recorded)	-21	19.7	8.0	-2.6	.05
Left Ventricular Work (Predicted)	+9	21.8	8.2	+1.1	ns
Left Ventricular Work (Recorded)	+4	35.6	14.5	+3	ns
Intrathoracic Blood Volume Index (Recorded)	+20	61.0	24.9	+8	ns

ns = not significant

TABLE XIII

TRANSITHAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-23	17.1	6.7	-3.4	.05
Mean Pulse Rate	+10	10.0	3.8	+2.6	.05
Mean Arterial Pressure	-15	12.2	4.6	-3.2	.05
Mean Venous Pressure	-17	18.1	7.6	-2.3	ns
Mean Circulation Time	-6	7.8	3.2	-1.8	ns
Cardiac Output (Predicted)	+15	21.4	8.1	+1.8	ns
Cardiac Output (Recorded)	-11	29.6	12.1	-9	ns
Cardiac Index (Predicted)	+15	22.7	8.6	+1.6	ns
Cardiac Index (Recorded)	-11	30.0	12.2	-9	ns
Stroke Index (Predicted)	+6	23.8	9.0	+6	ns
Stroke Index (Recorded)	-18	29.9	12.2	-1.5	ns
Total Peripheral Resistance (Predicted)	-14	15.3	5.8	-4.1	.01
Total Peripheral Resistance (Recorded)	+3	38.0	15.5	+2	ns
Left Ventricular Work (Predicted)	+5	19.5	7.4	+7	ns
Left Ventricular Work (Recorded)	-25	23.3	9.5	-2.6	.05
Intrathoracic Blood Volume Index (Recorded)	-17	23.9	9.8	-1.7	ns

ns = not significant

TABLE XIV

NERAVAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-25	16.2	6.1	-4.1	.01
Mean Pulse Rate	+3	19.2	7.3	+5	ns
Mean Arterial Pressure	-17	7.7	2.9	-6.0	.01
Mean Venous Pressure	-39	14.6	5.5	-7.2	.01
Mean Circulation Time	-6	17.1	7.0	0.8	ns
Cardiac Output (Predicted)	+12	23.3	8.8	+1.3	ns
Cardiac Output (Recorded)	-6	36.6	16.2	-4	ns
Cardiac Index (Predicted)	+11	20.0	8.3	+1.3	ns
Cardiac Index (Recorded)	-6	36.1	16.1	-4	ns
Stroke Index (Predicted)	+8	10.9	4.1	+2.0	ns
Stroke Index (Recorded)	-7	43.9	19.6	-3	ns
Total Peripheral Resistance (Predicted)	-23	20.0	7.6	-3.1	.05
Total Peripheral Resistance (Recorded)	-6	49.2	22.0	-0.03	ns
Left Ventricular Work (Predicted)	-6	17.4	6.6	0.9	ns
Left Ventricular Work (Recorded)	-23	35.0	15.7	-1.5	ns
Intrathoracic Blood Volume (Index (Recorded))	-12	48.1	21.5	-5	ns

ns = not significant

TABLE XV

COMPOUND 25398: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher Value	Probability
Metabolic Rate	-25	20.1	7.6	+3.3	.05
Mean Pulse Rate	+36	16.0	6.0	+6.0	.01
Mean Arterial Pressure	-9	10.5	4.0	-2.3	ns
Mean Venous Pressure	-43	19.0	8.0	-5.1	.01
Mean Circulation Time	+1	23.5	8.9	+1	ns
Cardiac Output (Predicted)	+27	20.6	7.8	+3.4	.05
Cardiac Output (Recorded)	-15	27.8	10.5	-1.4	ns
Cardiac Index (Predicted)	+26	22.0	8.3	+3.1	.05
Cardiac Index (Recorded)	-16	31.3	11.8	-1.3	ns
Stroke Index (Predicted)	-6	10.2	3.9	-1.5	ns
Stroke Index (Recorded)	-34	15.6	5.9	-5.8	.01
Total Peripheral Resistance (Predicted)	-26	16.9	6.4	-4.1	.01
Total Peripheral Resistance (Recorded)	+17	44.2	16.7	+1.0	ns
Left Ventricular Work (Predicted)	+15	10.2	3.9	+3.8	.01
Left Ventricular Work (Recorded)	-25	17.0	6.4	-3.9	.01
Intrathoracic Blood Volume Index (Recorded)	-16	26.4	10.0	-1.6	ns

ns = not significant

TABLE XVI
DOLITRONE: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-21	13.4	4.7	-4.6	.01
Mean Pulse Rate	+39	11.5	4.1	+9.6	.01
Mean Arterial Pressure	-13	11.5	4.1	-3.2	.05
Mean Venous Pressure	-22	24.5	10.0	-2.2	NS
Mean Circulation Time	-11	12.7	4.8	-2.4	NS
Cardiac Output (Predicted)	+41	19.7	7.0	+5.9	.01
Cardiac Output (Recorded)	-21	19.8	7.5	-2.8	.05
Cardiac Index (Predicted)	+41	20.3	7.2	+5.7	.01
Cardiac Index (Recorded)	-21	19.5	7.4	-2.8	.05
Stroke Index (Predicted)	+3	10.3	3.6	+ .9	NS
Stroke Index (Recorded)	-40	16.2	6.1	-6.6	.01
Total Peripheral Resistance (Predicted)	-35	14.0	4.9	-7.2	.01
Total Peripheral Resistance (Recorded)	+4	20.5	7.7	+ .5	NS
Left Ventricular Work (Predicted)	+20	16.9	6.0	+3.4	.05
Left Ventricular Work (Recorded)	-35	14.7	5.6	-6.3	.01
Intrathoracic Blood Volume Index (Recorded)	-30	19.0	7.1	-4.3	.01

ns = not significant

Thiamylal. The alterations in respiratory and haemodynamic parameters observed with this drug were similar to those for thiopental. The differences observed may be explained by the somewhat smaller doses of thiamylal administered, and may substantiate early clinical impressions of slightly greater potency of thiamylal with cardio-respiratory effects similar to those of thiopental.

In comparing the predicted changes with the recorded experimental data for both thiopental and thiamylal there is a depressed response by the heart, a lesser fall in total peripheral resistance and a greater fall in left ventricular work. These are indicative of cardiac depression by both thiopental and thiamylal at the dose level employed. However, the depression was not reflected in any significant fall in cardiac output.

Hexobarbital. The mean period of apnoea with this drug was 7 seconds with the mean dose of 517 mg./M². There was virtually no depression of the respiration or the metabolic rate. The pulse rate rose 28 per cent while the mean arterial pressure fell 12 per cent. The mean venous pressure tended to fall, but this was not consistent. Cardiodynamic parameters changed in the

TABLE XVII
SUMMARY OF MEAN CHANGES IN RESPIRATION WITH INTRAVENOUS ANAESTHETICS

	Time	2x Sleep dose, mg/M ²		BMR	R.R.	% Diff	T.V.	% Diff	M.V.	% Diff
PENTOTHAL (7 subjects)	R				17.5		420		7.3	
	C			+19	14	-20	640	+52	9.0	+23
	A	442	32"	-33	24	+37	360	-14	8.6	+18
SURITAL (7 subjects)	R				17.5		420		7.3	
	C			+27	14	-20	620	+48	8.7	+19
	A	402	23"	-29	20	+14	330	-21	6.6	-10
EVIPAL (7 subjects)	R				17.5		420		7.3	
	C			+21	14	-20	610	+45	8.6	+18
	A	517	7"	-6	21	+20	420	0	8.8	+21
TRANSITAL (7 subjects)	R				17.5		420		7.3	
	C			+28	15	-14	620	+48	9.3	+27
	A	637	12"	-23	20	+14	360	-14	7.2	-1
NERAVAL (7 subjects)	R				17.5		420		7.3	
	C			+24	15	-14	640	+52	9.6	+31
	A	432	6"	-25	18	+3	330	-21	6.0	-18
LILLY 25398 (7 subjects)	R				17.5		420		7.3	
	C			+28	16	-9	570	+36	9.6	+31
	A	273	82"	-25	18	+3	300	-29	6.9	-5
DOLITRONE (8 subjects)	R				17.5		420		7.3	
	C			+24	14	-20	660	+57	9.1	+25
	A	512	8"	-21	22	+26	390	-7	8.6	+18

R = Resting C = Control Study A = Period of Apnoea in seconds
T = Mean during 10 - 15 minutes after acute changes have stabilized
BMR = Basal metabolic rate RR = Respiration Rate
TV = Tidal Volume MV = Minute Volume

direction predicted showing a tendency to increased cardiac output and decreased total peripheral resistance without significant alteration in the left ventricular work. On the whole, hexobarbital had far less effect on either respiration or haemodynamics than thiopental and thiamylal for the corresponding anaesthetic state.

Buthalitone. The mean period of apnoea was 12 seconds with the mean dose of 637 mg./M². This was followed by a slight depression of respiration during the period of action of this drug. There was a significant fall in the metabolic rate (23 per cent). The pulse rate rose 10 per cent while the mean arterial pressure fell 15 per cent. This was accompanied by an inconsistent fall in mean venous pressure. Cardiodynamic alterations were inconsistent but tended towards a slight fall in cardiac output without any significant change in the total peripheral resistance. However, the left ventricular work decreased by 25 per cent. In the parameters studied, this drug has an effect which is not unlike that of hexobarbital, except for the greater apparent effect on the heart.

Methitural. Although the potency of this drug is similar to that of thiopental and one-third greater than that of buthalitone, according to the dose adminis-

TABLE XVIII

SUMMARY OF MEAN HAEMODYNAMIC EFFECTS WITH INTRAVENOUS ANAESTHETICS

DRUG		SBP	% Diff.	DBP	% Diff.	BP _m	% Diff.	PP _m	% Diff.	PR _m	% Diff.
PENTOTHAL (7 subjects)	R	114		68		83		46		69	
	C	119	+ 4.4	72	+ 5.9	82	- 1.2	47	+ 2.2	85	+23
	A	97	-15	62	- 8.8	74	-10.8	35	-24	111	+61
	T	98	-14	60	-17.7	73	-12	40	-13	96	+39
SURITAL (7 subjects)	R	114		68		83		46		69	
	C	121	+ 6.1	72	+ 5.9	88	+ 6	49	+ 6.5	93	+35
	A	103	- 9.7	62	- 8.8	76	- 8.4	41	-11	104	+51
	T	103	- 9.7	63	- 7.4	76	- 8.4	40	-13	103	+49
EVIPAL (7 subjects)	R	114		68		83		46		69	
	C	137	+20.2	75	+10.3	96	+15.7	62	+35	95	+37
	A	107	- 6.1	66	- 3	80	- 3.6	41	-11	115	+66
	T	115	+ 1	63	- 7.4	80	- 3.6	52	+13	116	+68
TRANSITAL (7 subjects)	R	114		68		83		46		69	
	C	126	+10.5	68	0	87	+ 4.8	58	+26	100	+45
	A	102	- 9.7	61	-10.3	75	- 9.7	42	- 8.7	109	+58
	T	105	- 8.6	61	-10.3	76	- 8.4	44	- 4.3	109	+58
NERAVAL (7 subjects)	R	114		68		83		46		69	
	C	119	+ 4.4	75	+10.3	90	+ 8.4	44	- 4.3	88	+28
	A	102	-10.5	61	-10.3	75	- 9.7	41	-11	100	+45
	T	103	-10	62	-10.3	75	- 9.7	41	-11	87	+26
Lilly 25398 (7 subjects)	R	114		68		83		46		69	
	C	124	+ 8.8	70	+ 3	88	+ 6	54	+18	99	+43
	A	103	- 9.7	64	- 5.9	77	- 7.2	39	-15	126	+83
	T	105	- 8.6	72	+ 5.9	83	0	33	-28	129	+87
DOLITRONE (8 subjects)	R	114		68		83		46		69	
	C	121	+ 6.1	78	+14.7	92	+10.8	43	- 6.5	88	+28
	A	105	- 8.6	70	+ 3	82	- 1.2	35	-24	121	+75
	T	116	+ 1.8	80	+17.7	92	+10.8	36	-22	111	+61

R = resting SBP = Systolic Blood Pressure PP_m = Mean Pulse Pressure
 C = control study DBP = Diastolic Blood Pressure PR_m = Mean Pulse Rate
 A = acute effect BP_m = Mean Blood Pressure
 T = mean during 10 - 15 minutes after acute changes have stabilized.

tered (432 mg./M²), all changes observed in these experiments were in the same direction and of the same order of magnitude as seen with buthalitone.

Compound 25398. The mean period of apnoea was 82 seconds with mean dose of 273 mg./M². Metabolic rate fell 25 per cent. Pulse rate rose 36 per cent

FIGURE 4. Tracing from a typical experiment showing simultaneous determinations of haemodynamic and respiratory parameters: *upper* shows arterial and venous pressure (ECG is too compressed in copy); *middle* shows respiration and oxygen consumption; *lower* shows cardiac output. "A" represents beginning of injection of drug. "B" represents beginning of injection of second sleep dose and "C" is end of injection. "C O" and "D" represent the control and test injections of Rhisa for the cardiac output estimation. On the respiration tracing the sloping line represents the oxygen consumption, which is noted before and after the injections. Method of computing the cardiac output is shown on the recording from the count-rate meter and Varian recorder.

while mean arterial blood pressure fell 9 per cent. There was a consistent fall in the mean venous pressure of 43 per cent. Cardiac output fell inconsistently to 15 per cent below resting levels while total peripheral resistance rose inconsistently to 17 per cent above resting levels. There was a 25 per cent fall in left ventricular work. These observed changes place this compound in the same class as thiopental and thiamylal, but with greater potency and greater depression of cardio-respiratory dynamics.

Dolitrone. The mean period of apnoea lasted 8 seconds with the mean dose of 512 mg./M², while metabolism was reduced 21 per cent. Pulse rate rose 39 per cent; mean arterial pressure fell 13 per cent. There was an inconsistent fall in the mean venous pressure of 22 per cent. There was a consistent fall in the cardiac output of approximately 20 per cent while the total peripheral

FIGURE 5. Haemodynamic response to thiopental, thiamylal and hexobarbital by a double dose. Note the rise in venous pressure preceding the start of injection, and then a fall to below the control level. Note the persistent depression in arterial blood pressure after the initial acute fall, which is greatest with hexobarbital and least with thiopental.

resistance tended to rise slightly. Left ventricular work decreased by 35 per cent.

The potency of this drug approximated that of hexobarbital very closely. Respiratory effects of this drug were also very similar to those seen with hexobarbital and buthaliton. However, the cardiodynamic depression by this drug was much greater than with both hexobarbital and buthalitone.

DISCUSSION

Blood Volume and Cardiac Output

The determination of total blood volume and cardiac output are critical values in this study. It is essential therefore to elaborate on their accuracy. It has been shown that "complete mixing" of an injected tracer substance such as Rihsa for determination of plasma volume occurs in the range of 4 to 15 minutes and that mixing times are discrete from the disappearance slope in most subjects (45, 46, 47). In this study a single 15-minute sample was taken in these normal subjects and was assumed to have complete mixing so that plasma volume would be calculated accurately. The determination of red cell volume by radioactive chromium is also a highly accurate determination according to Sterling and Gray.

FIGURE 6 Haemodynamic response to thiamylal, methitural and Dolitrone. Note depression of arterial pressure for all three and marked fall in venous pressure with thiamylal and Dolitrone

(22). The simultaneous measurement of plasma volume, red cell volume and venous haematocrit in the eight normal subjects in this study showed an almost constant ratio of body haematocrit to the venous haematocrit (0.90). These observations agree very closely with those of Hicks and associates (48) and those found in another study (27).

The determination of cardiac output by the injection method is based on the measurement of the varying concentration of the injected material as it passes through the heart. If a small volume of highly concentrated material is injected into the inflow tract, the average dilution of the material coming out from the heart will be a direct indication of the volume passing through the heart and causing this dilution. The measurement of the change of concentration during a definite interval permits the output to be expressed as volume of flow per unit time, as measured on a recorded cardiac dilution curve (45).

The main advantage of using iodine¹³¹ tagged serum albumin is that this concentration may be determined by gamma-ray assay. A continuous sampling of concentration without sample preparation may then be made, since the absorption in the blood or tissue is negligible. This obviates the laborious system of withdrawing arterial blood samples and assaying the samples, and makes

FIGURE 7. Respiratory and haemodynamic response to Cpd 25398 (Lilly) (double the sleep dose administered in a 2.5% solution). Note long period of apnoea and marked depression of respiration, arterial blood pressure and pulse pressure accompanied by marked tachypnoea and tachycardia.

accurate timing of the dilution curve more easily obtainable. Since all critical time measurements were made primarily within sixty seconds (including the time from the moment injection started), and the loss of serum albumin from the vascular system is not more than about 3 per cent for the first ten minutes following injection, the method is entirely satisfactory for precise measurement of the period being studied and has a high order of accuracy compared to the dye injection method (49, 50).

Because the injected material is diluted very rapidly, it is necessary to employ a detector of the highest sensitivity. A highly collimated crystal detector (scintillation counter) with high sensitivity to gamma radiation is therefore essential for these estimations. Such a detector must be directed over the area of the chest where the least interference from other blood flows is located, namely the first left interspace of the chest, adjacent to the sternum (51). The dilution curve or the change in concentration of the diluted material in the blood is recorded by a scaler and counting rate-computer combination and inscribed automatically by a direct writing recorder. A fast response time-counting rate meter is also satisfactory, but the scaler-computer combination eliminates the memory effect of the rate meter and allows a lower counting rate and dose to be used. Successful repeated measurements can be made with 25 to 75 microcuries (52, 53, 54).

The dilution curve has the same general form as that seen with Evans Blue dye. There is characteristically a rapid initial rise as the bulk of the radioactivity passes the counter site, followed by a steep fall to a partially super-

FIGURE 8 Typical respiration tracings obtained with hexobarbital and Dolitrone. Note the similarity in response with these two agents

imposed small recirculation curve. To correct for the recirculation effect, the curve is extrapolated exponentially from the point *b* (Fig. 2). Since the same total injected material (*I*) must come out of the heart as was injected into the inflow tract, this quantity of injected material must be equal to the product of the flow rate (*F*) multiplied by the concentration of the tagged material (*c*) in the blood integrated over the entire time of the primary circulation. This is represented by the equation:

$$I = \int_0^{\infty} F c dt$$

and if *F*, the flow rate or cardiac output, is constant,

$$I = \int_0^{\infty} F c dt, \quad \text{where } \int_0^{\infty}$$

represents the area under the primary circulation curve and the extrapolation line. This area is equivalent to area *A* and area *B* shown in Figure 2. Since the injection dose *I* is equivalent to the final dilution *C_f* multiplied by the volume *V*, the expression for the cardiac output is: $F = C_f V / (A + B)$.

Much has been reported on the accuracy of cardiac output determinations

by the direct Fick method and by the dye injection method of Hamilton. Any new method must agree closely with these to have experimental validity. In 1949, Prinzmetal initiated the new approach to the subject by radiocardiography (55). A technique was later developed by Veall and associates (1954) and Huff and associates (1955), for estimating cardiac output by external body-counting of iodine¹³¹ following a single injection, using a well-collimated and shielded scintillation detector placed over a fixed site for recording a time concentration curve (30, 31). From this, calculation of cardiac output by a modification of the Hamilton dye method has proved to be reliable. Comparison of external body-counting of iodine¹³¹ with the direct Fick method in men and in dogs by Huff and associates showed no statistically significant difference. MacIntyre has confirmed the accuracy of the radiocardiography method (47), and Huff is extending this work by employing multiple detectors (56).

The probability of random variations in the cardiac output greater than 5 per cent with a standard deviation of 7 per cent in seven cases is less than 5 per cent ($P = <.05$). This is approximately the same order of significance reported for the Fick method. A consistent difference of 15 per cent is therefore the least change that can be considered to be a significant physiological effect. In this order of significance only consistent changes greater than 20 per cent may be considered as physiological or pharmacological effects or the stroke volume and other parameters derived from the cardiac output. In the tabulated data (Tables X-XVI), the P value for significant changes only are shown. Otherwise, no significance (ns) is recorded.

Reviewing mainly the data obtained on cardiac output with each drug and each individual, it is evident that major changes did occur, but these were more often not consistently in the same direction. Van Harreveld and Shadle have also noted such changes in haemodynamics by barbiturates and point out that the great complication is produced in the normal circulation by the activity of circulatory reflexes and hormonal mechanisms which affect a number of parameters of the circulatory apparatus simultaneously (57). The analysis of such changes may therefore become very difficult. It is essential, especially in the study of the regulating mechanism of the circulation, to record simultaneously as large a number of dependent variables as possible. These give a more reliable clue to major parameters affected, and the direction of such change. It will be possible only in rare instances to draw conclusions about the mechanisms of circulatory effects from the changes of a single dependent variable like the cardiac output.

Arterial Blood Pressure

With few exceptions, every drug that was studied in these experiments caused an initial sharp fall in blood pressure which lasted at least a few minutes. This fall was followed by a gradual rise to a lesser depressed level, where it remained until the subject was fully conscious. The initial fall may be considered as primary depression of vasomotor tone, followed rapidly, in most instances, by partial reflex restoration. However, persistent mild depression lasted beyond the time the subject was awake, indicating that some depressant is probably

present in the circulation in active concentration. This alteration is well known in clinical anaesthesia (58).

Venous Blood Pressure

The determination of venous pressure has been a neglected aspect of haemodynamic effects of anaesthetic drugs even though its role in surgical shock has been suggested frequently. Moon found that fall in venous pressure, which persists, precedes the fall in arterial blood pressure that is a characteristic of traumatic or haemorrhagic shock—both in experimental studies and in clinical situations (59). Although venous distension is seen after the administration of vasodilator drugs, it is not accompanied by a decrease in circulating blood volume (27). However, it is seen also with many anaesthetic agents (especially diethyl ether), and particularly with the intravenous anaesthetics, as observed in this study, and then it is accompanied by a considerable fall in venous pressure. Such a fall is most likely indicative of a reduced circulating blood volume (60). The fall in arterial blood pressure and the rise in pulse rate which accompany or follow this fall in venous pressure can probably be taken as indicative of a significant fall in the circulating blood volume to a level which may produce hypoxia to the heart and other vital organs (brain, liver, kidney).

Although these changes in arterial and venous pressure were well tolerated by the healthy subjects in this study, a critical disturbance is often evident in the patient who is in poor general health. Because venous pressure is usually found to be at its lowest level when a patient is in the supine position, a great fall from this level assumes greater significance and should not be ignored as a sign of advancing shock. The venous pressure changes observed in this study are therefore highly significant and probably symptomatic of a derangement of haemodynamics which is less obviously indicated by arterial hypotension, by tachycardia and by an occasional minor electrocardiographic alteration.

It was of interest to observe a sudden significant rise in the venous pressure in most experiments immediately upon the subject becoming aware that drug injection was about to begin. This reaction is clearly evidence of the effect of anxiety on venous pressure. The rise may be seen in Figures 5, 6 and 7, and is shown on the tables by the range of venous pressures in the control record.

Heart Rate and Electrocardiogram

There was invariably a marked increase in heart rate above the resting and control levels with all the drugs. This effect was most apparent with Dolitron, Compound 25398 and hexobarbital. However, no gross disturbances of the PQRST complexes were evident with any of the drugs. Although continuous electrocardiographic recordings were taken throughout this study, it was known that they would be inadequate for estimating the degree of myocardial depression produced by barbiturates, since severe depression of contractile function usually does not lead to any remarkable electrocardiographic changes.

In animal studies, Daniels and associates observed that heart failure induced by barbiturates alone is primarily the result of their negative inotropic action. However, suppression of autonomic rhythmicity and conduction is responsible

for cardiac arrest when contractility is preserved by norepinephrine infusion, and under these circumstances arrest occurs when excitability is relatively unimpaired. They stated that the ability of noradrenaline and isoproterenol to antagonize barbiturate intoxication is probably the result of cardiac stimulation and could not be attributed to peripheral vasoconstriction. They observed further that when these drugs fail to antagonize cardiac depression induced by barbiturates, there is atrio-ventricular block and suppression of sinus pacemaker activity (61).

From the work of Brodie and associates (62) it is evident that the degree of impairment of cardiovascular function is initially determined by the concentration in the blood of the intravenous anaesthetic, and that the metabolic inactivation is not sufficiently rapid to affect the results significantly at the rates of administration employed clinically. This statement unquestionably applies in a similar, but distinguishable degree, to each of the drugs tested in this study.

Since clinical limitations must be respected, we always turn to *animal data* for guidance and infer the sequence of changes which may occur in man (63-72). In this respect, it is unfortunate that only a few of the small number of clinical studies (20, 38) that have been reported were carefully controlled by limiting the drugs administered (73, 74, 75).

The cardiovascular lethal dose of thiopental occurs in dogs with approximately 160 mg. per kg. when this agent is infused at the rate of 75 mg per kg per minute (64). Variation in the extent of redistribution of thiopental into fat may account for some of the variations in the cardiovascular lethal doses at different infusion rates. This probably applies also to different concentrations of injected drugs. The sequence of events leading to cardiovascular failure in continuous infusion experiments have been worked out in the dog. The following sequence is seen consistently. onset of hypotension soon after infusion is started, progressing rapidly to severe hypotension as the infusion continues. The rate of injection influences the rate of collapse and at critical rates irreversible cardiovascular collapse occurs in spite of artificial respiration. The compensatory tachycardia is not sufficient to compensate for hypotension. The heart rate begins to fall rapidly in the terminal stages. T-wave flattening is the earliest significant electrocardiograph change, then further flattening and depression of the ST segment occurs. *These may not appear until very low blood pressures are reached.* Daniels pointed out that barbiturates in quantities not much larger than those producing respiratory arrest, produced marked hypotension in the dog even when hypoxia is prevented (61). Employing a "mathematical model of the circulation" Van Harreveld and Shadle demonstrated that the heart is the primary site of cardiovascular depression due to barbiturates rather than any central or peripheral vasodilating effect (57). If myocardial depression is the principal mechanism whereby cardiovascular function is impaired during barbiturate intoxication, it seems reasonable that much smaller doses of barbiturate may affect cardiac function adversely under appropriate circumstances. This could explain the brief episodes of hypotension often seen with small intravenous doses of barbiturates in intact dogs or in patients. The transitory nature of such effects are attributed to compensatory mechanisms, which are present

until reflex nervous activity is eliminated. However, a study of anaesthetic doses of pentobarbital in dogs attributes hypotensive effects to peripheral vaso-dilatation with *no decrease in cardiac output* (67). In a study of thiopental anaesthesia in man, a decreased cardiac output with peripheral vasoconstriction and pooling of blood but with *no change in arterial pressure* was observed. The data from this study confuse the question somewhat since the patients received premedication with therapeutic doses of opiates, the thiopental was administered in a dilute drip, and electroencephalographic levels rather than actual drug doses were primarily considered. Administration by a dilute drip technique permits compensatory mechanisms to come into play and usually prevents the appearance of acute changes in haemodynamics until very large doses have been administered. The consistent decreases in cardiac output seen by these experimenters therefore is difficult to explain, unless they actually administered very large doses of thiopental, or their patients had impaired cardiac function which was not detected preoperatively. In addition, a potentiating depressant effect on the heart by drug combinations was not ruled out (75).

That anaesthetic levels of thiopental actually do depress cardiac function, *if compensatory changes cannot occur*, has been shown with the heart-lung preparation by Price and Helrich. They demonstrated that changes in slope of the curve relating cardiac output to right arterial pressure caused by thiopental may be used as an index of cardiac depression (76). In the studies of Daniel, despite the infusion of epinephrine in animals, anaesthetic doses of thiopental still impaired cardiac function (61).

From work with animals it seems evident that doses of intravenous barbiturates which produced respiratory arrest for more than a brief period directly depress cardiac function. Artificial respiration and stimulation of the central nervous system as by amphetamine alone does not counteract this effect. Therefore, cardiac stimulants such as sympathomimetic amines and the catecholamines would seem to be indicated in animals.

In applying such information to man it is important to realize that it is essential to limit the use of the short-acting barbiturates to the "sleep dose" with the drug *which does not cause more than a few seconds of apnoea*. It would be best to employ an agent which produces hypnosis and some analgesia entirely without apnoea and employ supplementary anaesthetic drugs if greater analgesia and muscle relaxation are necessary for the operative procedure. In this way, cardiovascular function may be preserved in an optimal way without the need for supportive drugs.

Since extensive comparative data in humans are lacking for the newer short-acting barbiturates, one must begin with such data as reported in this study and compare them with reports on animal studies and human studies of the individual drugs. From these one must attempt to infer those data which are applicable to man. Thereafter, clinical data must be collected carefully, with documented notes on relative potency, duration of sleep for various dose levels, rate and concentration of drug administration, rate of onset of sleep and rate of recovery (77). The latter must be related to valid criteria, such as response to name, lucidity, absence of diplopia and dizziness, and ability to concentrate

mentally. Since repeated doses may be necessary under clinical circumstances, note must be made of "acute" tolerance, cumulation or tachyphylaxis. The degrees of respiratory depression and cardiac acceleration are vital parameters to the clinical anaesthetist and must be diligently recorded. Cardiac arrhythmias, such as ectopic beats and bigeminal rhythm, are easily missed, but these must be carefully sought. Of importance also is the incidence of vagus-like reflexes such as coughing, hiccoughing, sneezing and laryngeal spasm. The protective effect of premedication with belladonna derivatives or a specified technique of anaesthetic induction on these undesirable reactions or reflexes should be sought and clarified. Last but not least, the incidence of inflammatory reactions in the veins must be carefully observed, as must neuromuscular responses to these drugs (twitching, shivering and involuntary spastic movements). Even if an agent fulfils all the desirable anaesthetic criteria, rigidity or twitching in a patient frequently suggests acute hypoxia or toxic reactions in the nervous system and is most undesirable, even if analgesia and hypnosis are optimal.

The data from this study indicate that as far as duration of sleep is concerned for double the sleep dose, the drugs may be divided into two classes: those with over 30 minutes of sleep and more than 20 seconds of apnoea on induction; and those with less than 20 minutes of sleep and less than 10 seconds of apnoea. This division is most evident when the duration of apnoea and sleep are computed on an equal dose basis (Table XIX). In the first group, Compound 25398 is by far the most potent hypnotic, and has the marked disadvantage of causing a prolonged period of apnoea, hypotension and tachycardia. There is essentially no difference between thiopental and thiamylal, although the latter is a somewhat more potent hypnotic, without prolonging the period of sleep, and produces less apnoea on the basis of equal dose administration. The second group of drugs consists of methitural, Dolitrone, hexobarbital and buthalitone. Methi-

TABLE XIX
ANAESTHETIC EFFECT OF INTRAVENOUS ANAESTHETICS
(Calculated on the basis of 500 mg./M² of body surface area)

DRUGS	Duration of Apnea seconds	Duration of Sleep minutes	2 x Sleep Dose mg.
LILLY 25398	150	42	273
SURITAL	29	33	402
PENTOTHAL	36	34	442
NERAVAL	7	19	432
DOLITRONE	8	12	512
EVIPAL	7	12	517
TRANSITHAL	9	5	637

tural is the most potent of this group and is very similar to thiopental with respect to the double sleep dose. However, the duration of hypnosis is only approximately 60 per cent of that for thiopental, whereas the period of apnoea is the shortest seen in the whole group with respect to both duration of sleep and the double sleep dose. It would appear from the above findings that methitural has particular advantages over the other three drugs in that group, if hypnotic potency is desired for short operative procedures, while very short procedures would be best carried out under buthalitone as originally suggested by Weese (69); and Dolitrone has the one advantage of having a definite analgesic effect of its own (13). However, both buthalitone and Dolitrone have a disturbing side effect (twitching or spontaneous movements) which is difficult to tolerate, and Dolitrone has a higher incidence of venous irritation than the other agents (13). Compared to thiopental methitural produces less cardiac acceleration, but the same degree of hypotension, and more vagal-type reactions (coughing, sneezing and hiccoughing) on induction. In animals, a far greater incidence of cardiac arrhythmias (ectopic beats and bigeminal rhythm) is seen with methitural. Arrhythmias may become evident in clinical anaesthesia with methitural when specifically sought, unless premedication with belladonna derivatives adequately prevent their occurrence. No tolerance or cumulative action for thiopental (25 mg./kg.) and methitural (45 mg./kg.) after daily administration for 30 days has been reported (70). There is probably also no tolerance or cumulative action for the other drugs studied.

All the drugs significantly depressed oxygen consumption except hexobarbital, with the greatest decrease produced by thiopental, and the least by Dolitrone. This effect is common to all anaesthetics in varying degree (78). The pulse rate was significantly increased by all the drugs except methitural, with the greatest increase by Dolitrone (39 per cent) and Compound 25398 (36 per cent) and the least by buthalitone (10 per cent). All the drugs depressed the blood pressure

TABLE XX
SUMMARY OF SIGNIFICANT MEAN PERCENTAGE CHANGES IN HAEMODYNAMICS AND
METABOLISM DURING ACUTE STUDY

	Pentothal	Surital	Evipal	Transithal	Neraval	Lilly 25398	Dolitrone
Metabolic Rate	-33	-29	-6	-23	-25	-25	-21
Mean Pulse Rate	+16	+14	+28	+10	+3	+36	+39
Mean Arterial Pressure	-17	-7	-12	-15	-17	-9	-13
Mean Venous Pressure	-23	-42	-17	-17	-39	-43	-22

to a degree which did not vary greatly among the seven agents. Venous pressure was also reduced by all the drugs by at least 15 per cent, with the least changes observed with hexobarbital and buthalitone (Table XX). None of these changes approached the degree of disturbance which is observed with high spinal anaesthesia (79, 80).

SUMMARY AND CONCLUSIONS

The problems of comparing several anaesthetics are reviewed with particular reference to the effects of premedication, the intrinsic activity of drugs and their affinity for certain tissues and the effect of multiple drug interaction. The physiological and pathological states of those patients who are used as subjects of such studies are essential factors to be clearly determined. The effects of acute tolerance, cumulation and tachyphylaxis were also cited as factors to be considered.

A controlled study of respiratory and haemodynamic parameters was carried out on eight young healthy male subjects in order to determine the principal and statistically significant effects of thiopental, thiamylal, hexobarbital, buthalitone, methitural, Compound 25398 and Dolitrone.

Resting vital signs were initially obtained as well as other vital statistics. Basal metabolism and cardio-respiratory parameters were determined from nomograms related to the resting values. These data provided the base line for all control and experimental data. Plasma volume and red cell volume were initially determined simultaneously with radioactive iodinated human serum albumin (I^{131}) and radioactive chromium⁵¹, employing the dilution principle. These were checked against venous haematocrit determinations.

Respiration data were obtained on a recording spirometer which also recorded oxygen consumption. Cardiovascular data (arterial and venous blood pressure) were recorded via intra-arterial and intravenous needles attached to Statham strain gauges, oscilloscopes and a photographic recorder. The pulse rate and electrocardiogram (lead 2) were also recorded on this system. The cardiac output was estimated by external body-counting of I^{131} following single injections of Rihsa, using a shielded scintillation detector directed over a fixed site on the chest where tissue circulation was minimal, in order to measure primarily the blood flow in the aortic arch. Mean circulation time and cardiac output were derived from measurements on the recordings, and stroke volume, total peripheral resistance, left ventricular work and intrathoracic blood volume were computed from the above data.

All data were analysed for mean alterations, and statistical significance was computed to determine the probability (P value) of random variation by the method of the Fisher t -test.

The accuracy of the technical procedures employed was reviewed, with particular reference to the newer methods for estimating blood volume, cardiac output and mean circulation time, and was found to compare reliably with that of tried and recognized methods. The limitations of clinical studies were also discussed, and data from animal studies were reviewed with a view to supplementing information on the toxicity and cumulative effects of these drugs.

A conservative evaluation of the results was essential in this study since it was assumed that deviations of values were normally distributed, and that the study dealt essentially with the healthiest type of subjects one ever encounters in clinical practice. The authors also felt, as noted by Johnson and Van Harreveld, that so many factors are involved in cardio-respiratory regulation, both before and during anaesthesia, that one must be extremely cautious in stating which factor is primarily involved in a change. One must therefore avoid conclusions from individual changes and base critical evaluation on consistent and statistically significant changes in a "homogenous" group, and then perhaps apply these data to an individual.

From the experiments, the seven intravenous anaesthetics studied could be divided into two main groups: those that produced a prolonged depression of respiration and circulation; and those that produced a brief depression of these parameters. Compound 25398, thiamylal and thiopental belong to the first group, while methitural, Dolitrone, hexobarbital and buthalitone belong to the second. All the drugs except hexobarbital depressed oxygen consumption. Tachycardia was a significant finding with all the drugs except methitural and acute hypotension (arterial and venous) was a consistent finding with all the drugs. Considering all the parameters, myocardial depression was induced by the first group, but this was not consistently manifested by a decrease in the cardiac output.

From this investigation, it is difficult to choose among the agents and state which disturbs human physiology to the least extent while providing clinically adequate hypnosis. It is only possible to state the advantage of a particular agent with reference to a specific patient, a specific type of operation and a specific clinical situation. On this basis, extensive clinical experience with one agent is probably the most reliable method of managing most situations, for then the problem comes down to a matter of dosage, concentration of the drug, and rate of its administration.

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RÉSUMÉ

Nous avons étudié les problèmes que pose la comparaison de plusieurs anesthésiques en prêtant une attention particulière aux effets de la prémédication, à l'activité intrinsèques des médicaments et à leur affinité pour certains tissus, puis, enfin, à l'effet de l'interaction de plusieurs médicaments. Il nous faut donner des précisions sur la condition physio-pathologique des malades chez qui on a

employé ces médicaments pour les étudier. Nous avons également mentionné comme facteurs non négligeables, la tolérance aigue, l'accumulation et la tachyphylaxie.

Nous avons fait, chez huit jeunes sujets mâles en santé, une étude, avec contrôles, des paramètres respiratoires et hémodynamiques pour tabuler les effets principaux et les effets présentant un intérêt statistique sur le thiopental, le thiamylal, l'hexobarbital, le buthalitone, le methitural, le composé 25398 et le dolitrone.

Nous avons d'abord cherché les signes vitaux à l'état de repos de même que d'autres statistiques vitales. Le métabolisme de base et les paramètres cardio-respiratoires ont été tirés des nomogrammes donnant les valeurs à l'état de repos. Ces résultats nous ont fourni les bases pour les données de contrôle et expérimentales. Les volumes plasmatique et globulaire ont été recherchés simultanément au début avec le sérum albumine humain iodé radioactif (I^{131}) et le chromium radioactif⁵¹ en employant le principe de dilution. Ces deux résultats ont été comparés aux déterminations de l'hématocrite sur le sang veineux.

Au sujet de la respiration, les données ont été obtenues au moyen d'un spiromètre enregistreur renseignant également sur la consommation d'oxygène. Les renseignements sur le système cardiovasculaire (pression artérielle et veineuse) ont été obtenus et enregistrés au moyen d'aiguilles placées dans les artères et dans les veines et reliées au manomètres Statham, aux oscilloscopes et à un enregistreur photographique.

Le rythme cardiaque et l'électrocardiogramme (en deuxième dérivation) ont également été enregistrés sur le même système. Le débit cardiaque a été évalué de l'extérieur de l'organisme en repérant l' I^{131} , après une seule injection de Rihsa, et en promenant un détecteur à champ scintillant au-dessus d'un endroit précis sur le thorax où la circulation tissulaire est réduite de façon à obtenir principalement le débit sanguin de la crosse aortique. La moyenne du temps de circulation et le débit cardiaque ont été obtenus de ces enregistrements, et le débit systolique, la résistance périphérique totale, le travail du ventricule gauche et le volume de sang intrathoracique ont été calculés d'après ces données.

Tous les résultats ont été analysés pour trouver la moyenne des modifications et la signification statistique a été calculée pour obtenir la probabilité (la valeur P) de variation isolée par la méthode de Fisher.

Nous avons contrôlé la précision des techniques employées, plus particulièrement les techniques nouvelles pour mesurer le volume sanguin, le débit cardiaque et la moyenne du temps de circulation et nous pouvons affirmer que les résultats sont comparables à ceux obtenus par d'autres techniques éprouvées et reconnues. Nous avons également discuté des limites des études cliniques et les résultats des études faites sur l'animal ont été étudiés dans le but d'obtenir des renseignements additionnels sur la toxicité et les effets cumulatifs de ces médicaments.

Dans cette étude, il était essentiel d'avoir une évaluation conservatrice des résultats car nous présumons que la déviation des résultats était répartie normalement et que l'étude a été faite sur des sujets les plus en santé qu'on puisse trouver en clinique. Les auteurs ont également eu la conviction, comme l'affirment Johnson et Van Harreveld, qu'il y a tellement de facteurs impliqués dans

le maintien de l'équilibre cardiorespiratoire, aussi bien avant que pendant l'anesthésie, qu'il faut être très prudent avant d'affirmer que tel ou tel facteur est primitivement responsable d'un changement. Conséquemment, il faut éviter de conclure d'après des changements individuels et baser une évaluation critique sur des changements considérables et d'importance statistique observés sur un groupe homogène et après, peut-être, comparer ces données à l'individu.

D'après ces expériences, on peut diviser en deux groupes les sept agents anesthésiques étudiés, il s'agit d'agents administrés par voie endoveineuse: ceux qui ont entraîné une dépression prolongée de la respiration et de la circulation et ceux qui ont entraîné une brève dépression sur ces paramètres. Le composé 25398, le thiamylal et thiopental appartiennent au premier groupe, tandis que le methitural, le dolitrone, l'hexobarbital et le buthalitone appartiennent au dernier groupe. Tous ces médicaments diminuent la consommation d'oxygène à l'exception de l'hexobarbital. On a observé une tachycardie importante à la suite de l'administration de tous ces médicaments à l'exception du méthitural et une hypotension marquée (artérielle et veineuse) à la suite de l'administration de chacun de ces médicaments. En analysant tous les résultats, on note que les médicaments du premier groupe ont causé une dépression myocardique mais elle n'a pas toujours été accompagnée d'une diminution du débit cardiaque.

Après cette enquête, il demeure difficile d'affirmer lequel de ces agents cause le moins de changement dans la physiologie humaine tout en procurant une hypnose adéquate cliniquement. Il nous est possible tout au plus de mentionner la supériorité d'un agent en particulier pour tel ou tel malade, ou encore pour telle sorte d'opération ou pour une situation clinique particulière. En se basant sur ces faits, nous pouvons affirmer qu'une longue expérience clinique avec un agent demeure probablement le facteur le plus sûr pour contrôler toutes les éventualités, car le problème se résume à une question de dosage, de dilution de médicament et de vitesse d'administration.

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