

case no coils were overlying the stomach, the amount of intestine was greater, and there was the extreme gastric distension which would push the strangulated bowel towards the right lobe of the liver.

The herniation itself presents interesting features which merit consideration—the opening in the lesser omentum and the accessory band of tissue between the gall-bladder and the duodenum. Prof. Blair has given us his opinion of these. The aperture in the lesser omentum is not likely to be congenital; it is more likely to be “acquired.” He has not seen such a congenital defect, nor does he know of any developmental reason why it should occur. In the dissecting-room the lesser omentum is of so delicate a nature that one can imagine it would be readily torn by any hernia spreading within that part of the lesser sac. Indeed, in the anatomy room the lesser omentum is often torn through at the first attempt to pull down the stomach a little in order to explore the region between it and the liver. The band of tissue between the gall-bladder and the duodenum was an unusually well-developed example of the hepato-duodenal fold, which is not infrequently present to a lesser degree and represents a thinned-out part of the lower free border of the ventral mesentery of the fore-gut, which amounts to a prolongation, rather further to the right than usual, of the lesser omentum. The presence of this cystico-duodenal fold of membrane would produce a funnel-shaped approach to the foramen of Winslow and considerably assist an unusually mobile loop of bowel towards the foramen and into the lesser sac. This appears to us a considered and well-founded explanation of the appearances found post mortem.

The appearance of the foramen at the necropsy led one to suspect that perhaps a loop of bowel had been herniated for some time. Such a condition has been described by Schwalbe (1904) in which strangulation did not occur.

In comparison with herniae into the lesser sac, herniation into paraduodenal fossae is relatively common and the literature on such is now quite voluminous.

Summary

A fifth case of this unusual type of herniation is now described. Three abnormal features were present in the abdominal cavity: (1) a well-developed hepato-duodenal fold which had produced a funnel-shaped approach to the lesser sac; (2) a dilated foramen of Winslow; (3) an undue length of mesentery of the small bowel.

We consider that the first and third factors, in association with the normal peristaltic movements, could produce a dilatation of the foramen and so give rise more readily to the herniation which had ruptured through the lesser omentum.

It is a pleasure to us to express our gratitude to Prof. D. Blair, Regius Professor of Anatomy, University of Glasgow, for his co-operation and help, and to Col. M. J. Williamson, M.C., late R.A.M.C., for permission to record this case.

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Hospitals in the Midlands (especially those in Birmingham), children in Yugoslavia and Greece, and youth organizations are among the beneficiaries under the will of Sir Charles Hyde. He has left £10,000 for the benefit of children in Yugoslavia and Greece, and £2,000 each to the Royal Cripples Hospital, Birmingham, and the Coventry and Warwickshire Hospital. A number of hospitals in Birmingham and Worcester will receive £1,000 each, and £3,000 is for the Ophthalmic Hospital at Jerusalem. The Senate of Birmingham University is to receive £20,000 for enlargement of the students' union, and Clifton College a similar sum for scholarships. The residue of the estate is to be divided equally between the University of Birmingham, Queen Elizabeth Hospital, Birmingham, King George's Jubilee Trust, and Dr. Barnardo's Homes.

USE OF METHEDRINE, A NEW BLOOD-PRESSURE-RAISING DRUG, IN SURGICAL OPERATIONS

REPORT OF A CLINICAL STUDY

BY

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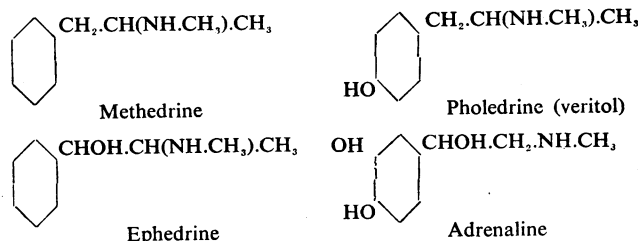
Surgeon to King George Hospital, Ilford, and to the Royal Hospital, Richmond; Assistant Surgeon to the London Homoeopathic Hospital

AND

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During the last ten years one of us (H.D.) has studied the use of pressor agents to counteract the serious falls of blood pressure unaccompanied by severe reduction of blood volume that often occur during major operations. The pressor effects of adrenaline, ephedrine, pholedrine (veritol), and neosynephrin have been recorded, but none of these drugs is effective for more than 30 to 45 minutes, and repeated injections are often necessary. S-methylisothiourea has recently been reported on (Smirk and McGeorge, 1942), but has the disadvantage that it must be injected intravenously. In a search for an effective pressor agent with a sustained action that could be administered by any route under average clinical conditions we examined methedrine.* This is a sympathomimetic drug, and was chosen because of its relation to pholedrine.



Conditions of Use

Blood pressures and pulse rates were recorded every three to five minutes in 130 operations, many of them major, and in 54 of these the systolic pressure or the pulse pressure dropped sufficiently for the patient to need a pressor agent. Methedrine was used solely in these cases—no other agents or stimulants were given—and was administered when the systolic pressure fell to and remained at 80 mm. or less, or when the pulse pressure was 10 mm. or less; 20 minutes was allowed first for natural recovery. According to Hewer (1943) the systolic pressure during operation should not be allowed to drop below 80 mm. for more than 20 minutes. Methedrine was administered only when the surgeon, anaesthetist, and recorder agreed that the patient's condition required it. If the systolic pressure fell to 60 mm. or less during the operation methedrine was usually given after a few minutes, as such low levels were considered inadequate for the vital processes to be sustained, and if prolonged might lead to surgical shock (McMichael, 1942). The low blood pressure often resulting from spinal anaesthesia is regarded by some as a type of secondary shock (Schubert, 1936). We found that spontaneous recovery from blood pressures as low as 60 mm. did not occur within 1½ hours.

We wish to point out the necessity for the routine determination of blood pressures in all major operations, irrespective of risk, to anticipate and prevent surgical shock. The behaviour of the patient cannot be predicted. We have seen elderly poor-risk patients survive a splenectomy or a complicated gastric resection with hardly any fall in blood pressure, yet young and moderately fit patients have shown a pronounced fall in comparatively minor operations.

* “Methedrine” is the Burroughs Wellcome and Co. trade mark for N-methylamphetamine, the hydrochloride of which was used in this study. The Continental name is pervitin.

Anaesthetics Used

The anaesthetics employed included (a) *spinal*, 1 in 1,500 or 1 in 2,000 nupercaine, alone or supplemented by general anaesthetics, local procaine or amethocaine, or pentothal; (b) *general anaesthetics* such as gas and oxygen, gas-oxygen-ether, open ether, and trichlorethylene; (c) *local anaesthetics* such as procaine or amethocaine, alone or supplemented with the general anaesthetics mentioned above or with pentothal; (d) *intravenous anaesthesia* with pentothal, either alone or with a general anaesthetic.

A fall in blood pressure usually, although not always, occurs after giving a spinal anaesthetic. Pressor agents are often given prophylactically to prevent this, but we preferred to correct the fall if and when it occurred, after allowing 20 minutes for spontaneous recovery, although this does not normally result until sensation is returning (Koster, 1942). If the spinal anaesthetic does not bring about a fall in blood pressure and a pressor agent is administered, the resulting rise in blood pressure causes increased haemorrhage from the operation wound.

Administration and Dosage

Methedrine is effective subcutaneously, intramuscularly, and intravenously. In cases with a profound fall in blood pressure the best results were obtained with a combination of the intravenous and intramuscular routes, the intravenous injection producing an almost instant rise, while the intramuscular injection acted more slowly (in 2 to 10 minutes), but maintained the blood pressure for a considerable time after the intravenous dose had ceased to act. Patients with a low blood pressure often had collapsed veins. In such cases we did not lose time trying to enter them, but gave the methedrine intramuscularly.

A total of 68 injections was given intramuscularly and 17 intravenously; of the latter 14 were given simultaneously with intramuscular injections.

Single Doses.—The dose for a single intramuscular injection of methedrine varied from 15 to 30 mg., and for a single intravenous injection from 10 to 20 mg. The dose depended upon the patient's condition. In 44 out of 54 cases studied—i.e., 81%—a single injection was sufficient to restore the blood pressure to normal limits. In *minor operations* (e.g., for hernia or varicose veins), if the systolic pressure dropped to 90 mm. and the pulse pressure to 15 to 10 mm. or less, an intramuscular

40 mm. or less, from 15 to 20 mg. of methedrine was given intramuscularly and 15 to 20 mg. intravenously. Only two patients received the maximum single dose of 20 mg. i.m. plus 20 mg. i.v. Patients with a low blood pressure need larger doses. We would emphasize that each case must be critically evaluated in the light of the patient's condition, age, and physique as well as the blood pressure and respiration.

Multiple Injections.—In 10 of our cases more than one injection was given, although subsequent experience revealed that the first dose was too low in 4 of these, leaving 6 who really required more than one injection. At least 20 minutes was allowed for the first injection to exert its full effect before giving another. Seven patients required two injections to restore the blood pressure to normal, although in 4 of these the initial dosage was experimental and too cautious, leaving 3 who actually needed a second injection. In 3 cases three injections were necessary to raise the blood pressure to normal levels; one of these was a mastectomy, in which three small doses were given deliberately to minimize the risk of haemorrhage from the large traumatized area.

Although the maximum single dose of methedrine given was a combined injection of 20 mg. intramuscularly and 20 mg. intravenously (i.e., a total of 40 mg.), the maximum total dosage received by any one patient was 75 mg., given in three injections over a period of 1½ hours. Other patients received total doses of 70, 65, 55, and 50 mg. respectively. No untoward effects were observed in these patients, and with one exception, in which post-operative vomiting occurred, they all made an uneventful recovery.

Time taken for Methedrine to Act

Intravenously.—After an intravenous injection the blood pressure began to rise almost at once—certainly within a minute. The time taken for the blood pressure to reach its maximum value depended on the dose and varied considerably from individual to individual. The shortest time was 2 minutes and the longest 10 minutes in the cases studied, with an average of 5½ minutes.

Intramuscularly.—An intramuscular dose of 15 to 30 mg. of methedrine produced a measurable rise of blood pressure in from 2 to 10 minutes (one case took 15 minutes), with an average of 4 minutes. The maximum rise in blood pressure after an intramuscular injection was reached in from 4 to

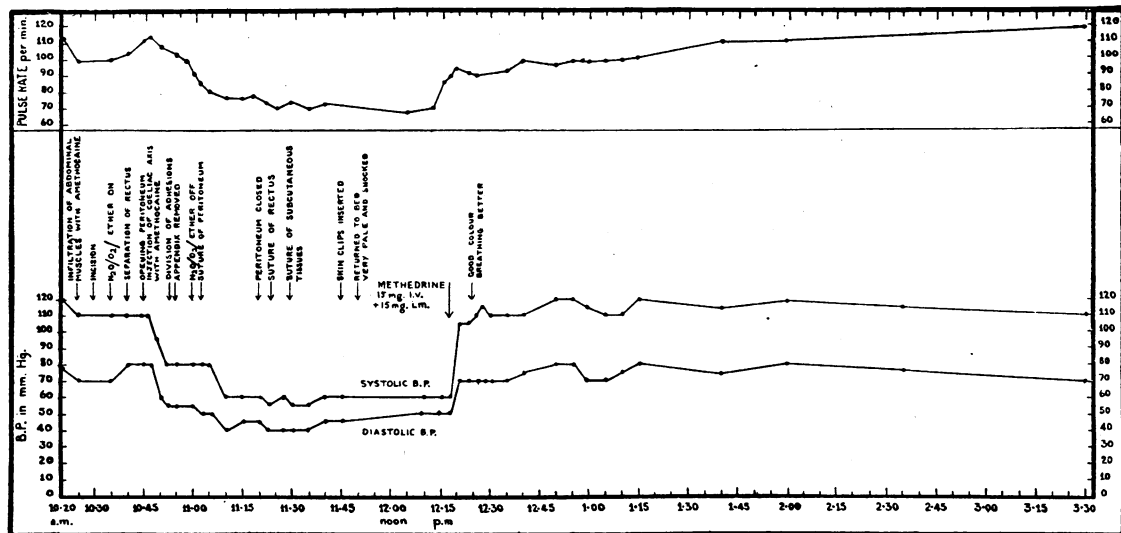


FIG. 1.—Effect of combined intramuscular and intravenous injection of methedrine on blood pressure and pulse rate after a laparotomy in which the blood pressure fell to 60 mm. Hg and showed no sign of natural recovery.

injection of from 15 to 20 mg. was given; this was increased to 25 mg. if the systolic pressure fell to 80 mm. or below. Intravenous injection is not necessary in these cases. In *major operations* in which the blood pressure fell below 80 mm. the dosage of methedrine was from 25 to 30 mg., given either intramuscularly in a single dose or as a combined injection of from 10 to 15 mg. intravenously and 15 to 20 mg. intramuscularly. When the systolic blood pressure fell to 60 to

38 minutes, with an average of 18 minutes. In the 10 cases studied second intramuscular doses reached their maximum effect in from 5 to 20 minutes, with an average of 15 minutes.

Duration of Action of Methedrine

The duration of action of an intravenous dose of methedrine is variable. It may last for half an hour or for several hours. A carefully calculated intramuscular dose or a combined intra-

muscular-intravenous dose produces an effect which lasts for many hours. In 44 out of the 54 cases a single intramuscular injection or combined intramuscular-intravenous injection permanently restored the systolic pressure to its pre-operative level or to within 90% of it. This pressure was sustained, with small variations, throughout the operation and for recorded periods of from half an hour to over 48 hours afterwards. Nine cases required more than one injection to raise the blood pressure to normal values; in all of these the effect was sustained throughout the operation and for several hours afterwards. In only 1 of the 54 cases did the methedrine fail to restore and maintain the systolic blood pressure above 100 mm.

Evaluation of Pressor Effect of Methedrine

Systolic Pressure.—We have been impressed by the effective and sustained pressor action of methedrine. Omitting the first

case, in which the dosage and mode of administration were largely a question of trial and error, only one case failed to respond to the drug. In 97% of the cases the blood pressure was restored to normal levels in a period varying from 2 to 18 minutes. The general effect of a carefully calculated injection, given by the combined intravenous-intramuscular route, on a patient with a systolic blood pressure that has fallen from normal levels to between 80 and 40 mm. is as follows. A measurable rise in systolic pressure occurs in 1 minute, reaches a maximum in a period varying from 5 to 15 minutes, and is sustained over a period of several hours after the operation (see Fig. 1). There is no precipitate rise and fall such as occurs with pressor agents like adrenaline and ephedrine (Dodd, 1940). The blood-pressure curve is of a plateau and not a peak type. After an intramuscular injection (Fig. 2) the rise in blood pressure is not so rapid, but the maximum pressure is of the same order as after an intravenous injection, and the action is usually more prolonged.

The maximum systolic pressure after the injection rarely rises much above the pre-operative value unless an overdose is given. In only 3 of our cases did it rise more than 30 mm. above this value. The blood pressure quickly settled down to the pre-operative level or within 90% of it. The average systolic blood pressure of our 54 patients just before operation was 137 mm. The average systolic pressure of these patients when the methedrine was given was 66 mm., which rose to an average maximum of 135 mm. in an average time of 18 minutes. The average figure to which it finally settled, measured at periods of from half an hour to 48 hours after operation, was 124 mm. This corresponds to a permanent rise to an average of 91% of the pre-operative level. Repeated observation of the blood pressure over periods of several hours after operation showed that this level was maintained.

Diastolic Pressure.—The average diastolic pressure just before administering methedrine was 52 mm.; after the drug was given it rose and was sustained at an average value of 84 mm. The corresponding figures for the average pulse pressures were 14 and 40 mm. respectively.

Pulse Rate.—The effect of the methedrine on the pulse rate was variable. Generally there was an increase of 15 beats to the minute on the average, although in 6 patients there was a fall of an average of 12 beats per minute. In 3 cases the pulse rate was unaffected. After administering methedrine to collapsed and pulseless patients the pulse soon became full and bounding.

Respiration.—This was not systematically recorded, but an increase in the rate and depth of respiration was noted in many patients.

Repeated Doses.—Repeated injections were effective, but the best response was obtained by a carefully selected adequate dose given in one injection rather than in divided doses. Small repeated doses are unsatisfactory.

Reactions

Apart from extrasystoles no abnormal clinical findings were observed in patients who were given methedrine in the correct dosage. Extrasystoles were noted in 3 patients; these were also observed under anaesthesia when methedrine had not been given. In normal persons methedrine acts as a cortical stimulant (Golla *et al.*, 1940), but this effect was not observed in our patients, being presumably annulled by the premedication, the anaesthetic, and the post-operative morphine that they received. Three patients out of 54 became excited or delirious post-operatively, but we consider this incidence to be within normal.

When one of us received 70 mg. of methedrine intramuscularly in divided doses over five hours the systolic blood pressure rose from 130 to 180 mm., and vomiting, cortical stimulation, persistent tachycardia, and severe palpitations were experienced. The acute symptoms lasted 24 hours and the tachycardia and

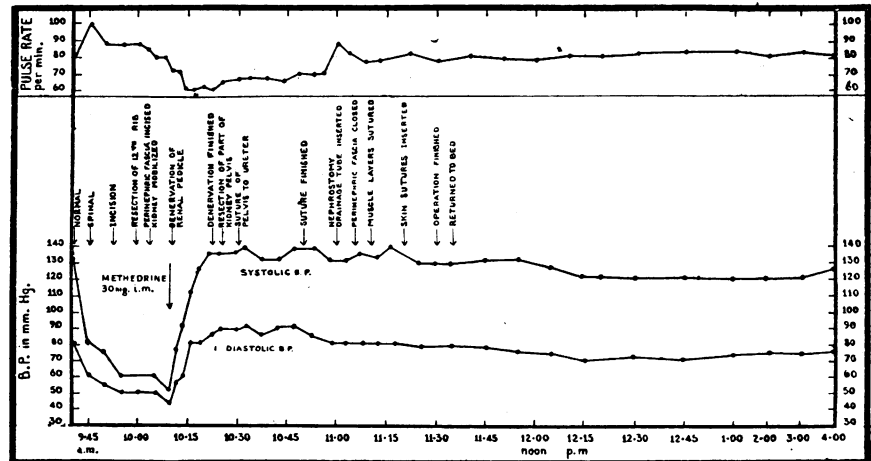


FIG. 2.—Effect of intramuscular injection of methedrine on blood pressure and pulse rate during operation for renal sympathectomy, pyeloplasty, and nephrostomy.

palpitations for several days. We would therefore suggest caution in giving total doses of more than, say, 60 mg. of methedrine, although this dose appears to be well tolerated by patients with a low blood pressure. Pressor agents are potent drugs and must always be used with caution; they should never be given without reading the blood pressure before each injection. Overdosage may be disastrous in a patient with cardiovascular disease or hyperthyroidism.

Electrocardiograms

These were taken in 3 patients, two of whom received the maximum single dose of 40 mg. No significant permanent changes were observed. In one case we observed a shortened RST segment in lead II, iso-electric waves in lead I, and upward displacement of the ST segment in leads II and III. These changes were transient, and we attach no significance to them. An E.C.G. of one of us taken 24 hours after the administration of 70 mg. of methedrine was normal. It must be remembered that anaesthetics, surgical trauma, and many drugs used in emergencies produce temporary changes in the E.C.G. (Kurtz *et al.*, 1936; Brechling and Hansen, 1939; Graybiel and White, 1941; Hartwell *et al.*, 1942).

Comparison with other Pressor Agents

One of us (Dodd, 1939, 1940, 1942) has had the opportunity of comparing clinically the pressor effects of methedrine with those of adrenaline, ephedrine, and pholedrine (veritol). We consider that the pressor effect of methedrine is superior to that of these drugs because: (a) it does not produce a precipitate rise and fall of blood pressure; (b) the blood pressure is restored to and maintained at its pre-operative level or within 90% of it for several hours, not for 30 to 45 minutes; (c) one injection is usually enough.

We have not had the opportunity of testing neosynephrin and paredrine, two sympathomimetic pressor drugs recently used in America during operations under spinal anaesthesia. The duration of action of a single dose of neosynephrin is only half to three-quarters of an hour, and several injections (from

two to six) are sometimes necessary to raise and maintain the blood pressure during the course of operations under spinal anaesthesia (Johnson, 1937; Lorhan and Oliverio, 1938; Bittrich, 1939; Brunner and de Takats, 1939; Silvers and Leonard, 1940; Lorhan and Lalich, 1940). The initial rise in blood pressure due to the drug may also be excessive, and the bradycardia which it causes has resulted in partial heart-block (Brunner and de Takats, 1939). Paredrine may also produce an excessive rise in blood pressure—e.g., to 250 mm. systolic (Loman *et al.*, 1939; Altschule and Gilman, 1939).

It would thus seem that methedrine is the most valuable of the drugs so far tested for counteracting the serious falls in blood pressure that often occur in surgical operations. The 54 cases of the series under review are summarized in the table below.

Summary of Cases showing Effect of Methedrine on Blood Pressure

No.	Operation	Dose in mg.*	Pre-operative B.P.	Lowes B.P.	Max. B.P. after Methedrine	Final B.P. in Ward
1	Excision of rectum	3 x 10 i.m.	150/90	0	120/70	?
2	Laparotomy	+2 x 10 i.v.	120/75	70/50	125/80	110/65
3	"	15 i.v. + 15 i.m.	120/80	60/50	115/70	110/70
4	Gastro-enterostomy	10 i.v. + 15 i.m.	120/80	70/55	120/85	105/70
5	Cholecystectomy	30 i.m. + 15 i.v. + 10 i.m.	150/90	50/45	150/100	150/85
6	"	20 i.v. + 20 i.m.	130/80	60/55	150/80	115/65
7	"	"	"	"	"	"
8	+gastroctomy	15 i.m. + 15 i.v.	140/80	40/30	140/80	120/80
9	Hernia	20 i.v. + 20 i.m.	160/90	60/50	180/100	135/85
10	"	10 + 15 i.v.	130/70	60/50	145/90	110/70
11	"	15 i.v. + 15 i.m.	140/80	50/40	135/75	130/70
12	"	25 i.m.	140/90	70/60	130/80	125/75
13	"	20 + 20 i.m.	150/100	80/70	140/80	130/70
14	"	25 i.m.	180/90	60/50	150/80	150/80
15	"	20 i.m.	140/80	90/70	140/85	140/90
16	"	20 i.m.	180/100	70/60	160/105	130/80
17	Hydrocele	25 i.m.	120/80	75/55	180/100	120/80
18	Orchidectomy	20 i.m.	100/70	90/80	130/90	100/70
19	Varicose veins	15 i.m.	140/70	95/85	140/80	135/80
20	"	15 i.m.	120/70	100/90	135/70	120/70
21	"	20 i.m.	130/90	85/75	140/100	130/90
22	"	20 i.m.	140/100	95/85	190/130	140/100
23	Torek?	20 i.m.	120/70	70/60	120/70	120/70
24	Steinach II	20 i.m.	220/150	55/50	145/75	130/75
25	Cholecystectomy	25 i.m.	110/60	70/50	130/70	130/80
26	"	30 + 15 i.m.	135/95	0	125/80	120/80
27	"	20 i.m.	140/70	65/35	120/60	120/75
28	"	25 + 15 + 25 i.m.	140/100	50/40	105/85	100/70
29	"	20 i.m.	170/110	110/85	170/100	170/100
30	Amputation Cervical sympathectomy	15 i.m.	120/70	80/60	120/70	110/70
31	"	30 i.m.	120/70	70/55	130/80	120/65
32	"	25 i.m.	120/70	50/40	120/60	115/75
33	Excision of rectum	10 i.m.	120/80	90/75	120/60	115/75
34	Haemorrhoids	20 i.m.	160/95	50/40	150/80	140/80
35	Pilonidal sinus	30 i.m.	120/80	90/75	100/60	100/60
36	Thyroidectomy	10 i.m.	120/80	90/60	110/60	110/60
37	Hysterectomy	30 i.m.	150/90	90/60	240/150	150/90
38	Laparotomy	30 i.m.	120/70	0	150/90	120/70
39	"	25 i.m.	130/85	50/40	110/70	110/70
40	Ureter?	25 i.m.	110/70	70/65	110/75	110/75
41	Bladder	30 i.m.	140/70	100/80	120/70	120/70
42	Mastectomy	3 x 15 i.m.	120/90	0	120/80	115/80
43	Kidney	30 + 20 i.m.	125/80	35/30	125/90	125/90
44	"	30 + 30 + 15 i.m.	115/80	65/60	90/65	90/70
45	"	30 i.m.	130/80	55/45	140/90	128/78
46	"	30 i.m.	130/80	65/45	135/75	120/80
47	Varicose veins	20 i.m.	140/100	95/85	160/100	140/100
48	"	15 i.m. + 15 i.v.	130/80	55/40	145/90	125/70
49	Hernia	25 i.m.	125/80	70/65	150/80	125/80
50	Excision of rectum	30 + 20 i.m. + 20 i.v.	110/70	70/65	115/75	115/75
51	Gastrostomy	20 i.m.	150/90	95/80	150/80	140/85
52	Gastro-jejunostomy	25 i.m.	110/65	80/60	130/75	110/65
53	Laparotomy	25 i.m.	120/80	80/65	135/80	120/80
54	Gastro-jejunostomy	10 i.v. + 20 i.m.	110/80	70/55	125/85	100/70
	Hernia	20 i.v.	120/75	0	120/80	118/80

We have not had the opportunity of using methedrine in cases of traumatic shock, but we think that the outstanding properties of the drug make it worthy of trial in such cases, particularly in those which fail to respond to measures designed to increase the blood volume.

Summary

Out of 130 observed operations 54 patients were found suffering from an unduly low systolic or pulse pressure and some degree of impending surgical shock. The capacity of methedrine to meet the needs of these patients has been studied under average general hospital operating conditions. Anaesthetics included all those in common use.

Under these conditions methedrine has been found to be an effective blood-pressure-raising drug with a prolonged action.

The effective dose is from 15 to 30 mg. intramuscularly, or 10 to 20 mg. intravenously plus a depot dose of 10 to 20 g. intramuscularly.

In 97% of the cases the systolic pressure was restored to normal levels in a period varying from 2 to 18 minutes. The systolic pressure was raised from an average of 66 mm. to an average maximum of 135 mm., and settled to an average minimum of 124 mm. This last figure corresponds to 91% of the average pre-operative value (137 mm.). There is no abnormally high rise if the dose is carefully calculated. One injection was adequate in 81% of patients; repeated injections were given in 17%; 1 case (2%) did not respond.

The blood pressure was maintained throughout operation and for several hours after.

Reasons are given for considering methedrine to be superior to adrenaline, ephedrine, pholedrine, neosynephrin, and paredrine for counteracting serious falls of blood pressure in surgical operations.

We wish to thank Drs. M. Griffiths, Hunt, Fraser Simpson, and Barnes for their help and co-operation in this study.

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TETRACHLORETHANE POISONING

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Tetrachlorethane (C₂H₂Cl₄) is a colourless mobile liquid with an odour resembling that of carbon tetrachloride and chloroform. It is non-inflammable, and the commercial product has a boiling-point varying from 140 to 150° C. and a specific gravity of from 1600 to 1602 (Browning, 1937). It is a solvent for cellulose acetate and nitrate, bitumen, waxes, resins, pitch, tar, sulphur, rubber, and oils.

This substance is sold under various trade names, such as "westron," "alanol," "emaillet" (Browning, 1937), and "cellon" (Willcox, 1915). It is issued to the Army as "silk-cleansing fluid" for the purpose of cleaning the silk of duplicators (Hepple, 1927; Elliott, 1933). Corry's white fly fumigant, which is stocked by most nurserymen and seedsmen for sale in small quantities, is composed of nearly pure tetrachlorethane. Its sale is not controlled by the Dangerous Drugs Acts, 1920-32, and though not commonly stocked by retail chemists it may be bought from some at the price of 2s. a pint.

Commercial Uses

During the early stages of the war of 1914-18 tetrachlorethane was extensively used, both in this country and on the Continent, as a constituent of the solution employed to treat aeroplane fabric so as to render the wings of aircraft impervious to air and moisture. In July, 1916, its use for this purpose was prohibited, as by that time 70 cases of jaundice with 12 deaths had occurred as a direct result of inhalation of the vapour (Willcox, 1915), and a substitute of a non-toxic nature was