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PHARMACOLOGY OF METHYLPENTYNOL AND METHYLPENTYNOL CARBAMATE

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The pharmacology of methylpentynol and methylpentynol carbamate has been studied. The drugs depressed monosynaptic and polysynaptic reflexes, and exerted weak ganglion and neuromuscular blocking actions. They also produced transitory hypotension, and increase of aortic blood flow. Perfusion of the coronary arteries with these drugs led to slowing of the heart, diminished systolic amplitude, dysrhythmias, and increased ccronary flow. Respiration was stimulated with small and depressed with larger doses of both drugs. The two compounds diminished the response of the isolated guinea-pig ileum to drugs acting directly on muscle or through ganglia. The effect of the two substances was likened to that of other central nervous system depressants, particularly to that of ethanol.

The toxicology, hypnotic and anticonvulsive effects of methylpentynol (3-methyl-1-pentyn-3-ol, Oblivon) were described by P'An, Gardocki, Harfenist, and Bavley (1953), Marshall and Vallance (1955) and Gross, Tripod and Meier (1955). Similar studies of these properties of methylpentynol carbamate were made by Halpern (1956), by Halpern and Lehmann (1956) and by Barnes, McCrea, Marshall, Sheahan, and Walsh (1958). Although other pharmacological actions of methylpentynol have received less attention, some have been described by Margolin, Perlman, Villani, and McGavack (1951) and by Gialdroni and Grassi (1952). Quilliam (1955) studied the effect of methylpentynol and other hypnotic drugs on frog skeletal muscle. The present work is concerned with properties of methylpentynol and its carbamate other than anticonvulsant effects.

METHODS

Isolated Tissues.—In all experiments with isolated tissues, the animal was killed by a blow on the head and exsanguination. The tissue was rapidly removed and the dissection completed in cold 0.9% sodium chloride solution.

Kitten Hearts.—The coronary vessels were perfused with oxygenated Locke solution (NaCl, 9 g.; KCl 0.42 g.; $CaCl_2.6H_2O$, 0.472 g.; glucose 2.0 g.; $NaHCO_3$ 0.5 g.; water to 1,000 ml.) at 37° and at a constant pressure head. The Martin-Langendorff technique was used with the apparatus described by Baker (1951). Methylpentynol or methylpentynol carbamate, dissolved in the Locke solution, was injected into the aortic cannula from a Palmer slow injector. Coronary outflow was collected in a funnel draining into a graduated cylinder.

Frog Rectus.—The isolated rectus abdominis muscle of the frog was suspended in a modified Ringer solution (NaCl 6 g.; KCl 0.15 g.; $CaCl_2.6H_2O$ 0.3 g.; $NaHCO_3$ 0.5 g.; water 100 ml.) and bubbled with 5% CO_2 and 95% O_2. Contractures were recorded using a gimbal lever of magnification $\times 9$ giving an effective muscle load of 0.8 g.

Electrically Stimulated Guinea-pig Ileum.—The method of Paton (1955) using coaxial electrical stimulation was employed. The tissue was suspended in a 10 ml. bath of Krebs solution bubbled with 95% O_2 and 5% CO_2 at 35 to 37°. Rectangular pulses of 1.0 msec. duration and of sufficient strength to produce a maximal response to a single shock were applied to the electrodes, the intraluminal electrode being the anode. Contractions were recorded with a pendular auxotonic lever (Paton, 1957a) with a magnification of 8.

Isolated Rat Phrenic Nerve Diaphragm Preparation.—The preparation was set up in the manner described by Bülbring (1946) but with minor modifications. The tissue was suspended in 50 ml. of Tyrode solution bubbled with O_2 at 36 to 37°. Rectangular supramaximal pulses of 0.5 msec. duration were applied to the nerve at a frequency of 6/min. The stimulating electrode consisted of 2 rings of platinum wire 2 mm apart embedded in one end of a polythene tube (5 mm. i.d.). The upper end of the tube was above the surface of the fluid in the bath and the nerve was drawn into the tube (filled with Tyrode solution) by a thread. Muscle contractions were recorded with a semi-isometric lever.

Other Methods.—The cats were anaesthetized with chloralose (80 mg./kg.) after induction by ethyl chloride and ether. In some experiments, spinal cats were prepared by the method of Kosterlitz, Krayer, and Matallana (1955) or by pithing. Rabbits were anaesthetized with urethane (1 g./kg., 25% solution). Rectal temperatures were maintained at 38°. When methylpentynol or its carbamate was injected intraperitoneally into guinea-pigs, the carotid artery was usually cannulated during the anaesthesia produced by the drug, 5 ml. blood was withdrawn and laked with distilled water, and the brain was then removed. If, however, the anaesthetic effect of the drug was insufficient, the animal was given ethyl chloride and ether before carotid cannulation. Because of the volatility of methylpentynol, blood and tissue samples were stored in sealed tubes until required for estimation.

Blood Pressure.—Recordings were made from the left carotid artery on a kymograph using a mercury manometer connected to a siliconed glass cannula filled with heparin-saline.

Blood Flow.—The density flowmeter described by Dawes, Mott, and Vane (1953) was connected in series with the lower abdominal aorta below the renal vessels.

Respiration.—The apparatus described by Paton (1949) was used for cats and rabbits. In man, the volume of respiratory expired air was measured by an integrating motor pneumotachograph (Wolff, 1958), % O_2 and CO_2 composition being determined by the method of Scholander (1947).

Neuromuscular Transmission.—The tension of the twitch of the tibialis anterior muscle of the cat (and in one experiment of both tibialis and soleus muscles) was recorded with an isometric steel myograph, the preparation being mounted on the Brown-Schuster myograph stand. The sciatic nerve was tied centrally, above the point of stimulation and above the point of entry of its blood supply. The muscle was excited by slightly supramaximal shocks at a frequency of about 6/min. applied to the sciatic nerve through shielded platinum electrodes. In some experiments, the muscle was tetanized with shocks at a rate of 50/sec. for a duration of 1 sec. in every 12 sec. Intravenous injections were made either into a femoral or jugular cannula. Retrograde arterial injections were given into the contralateral common iliac artery which was ligatured just below the cannula. Infusions were given by a Palmer slow injector.

Nictitating Membrane.—Records were made of the contracture of the nictitating membrane (after enucleation of the eyeball) in response to stimulation of the preganglionic or postganglionic portions of the cervical sympathetic trunk which had been separated from the vagus and cut centrally. Platinum wire electrodes were applied to the nerve to be stimulated by supramaximal rectangular pulses of 0.5 msec. duration at a frequency of 10/sec., either continuously or for 30 sec. periods at regular intervals. Infusions were made into the right femoral vein and retrograde arterial injections into the stump of the ipsilateral lingual artery. In another experiment, the responses of both nictitating membranes were recorded. The isotonic levers were adjusted so that equal shortening gave equal movements of the writing point. The loading weight was 4.0 g. and the magnification seven-fold. The same parameters of stimulation were used although the stimulating circuits on the two sides were independent. The animal was artificially ventilated and the chest opened by splitting the sternum. The drugs were injected into the right internal mammary artery with the distal aorta occluded during continuous stimulation of the right preganglionic and the left postganglionic cervical sympathetic trunks. In this way the effects of arterial injection to both nictitating membrane preparations could be studied simultaneously.

Suprarenal Gland. — The blood pressure of eviscerated pithed cats was recorded. The peripheral end of the sectioned nerve to the left suprarenal gland was stimulated with rectangular pulses of 0.5 msec. duration and of 20 volts at a frequency of 10/sec. for 30 sec. which resulted in maximum output of sympathetic amines (Marley and Paton 1958, unpublished observations). Injections of methylpentynol or its carbamate into the right femoral vein were made 45 sec. prior to the period of stimulation.

Knee Jerk.—The jerk was elicited by a solenoid tapping the quadriceps tendon of a cat every 5 sec. and recorded on a kymograph by a lever attached to the ankle by a thread.

Stomach Contraction Following Vagal Stimulation. —In cats, the oesophageal and pyloro-duodenal junctions were tied. The stomach was cannulated on the greater curvature, washed out and filled with 60 ml. of saline and movements were recorded on a smoked paper. Both vagi were stimulated in the neck by supramaximal rectangular pulses of 0.5 msec. duration at a frequency of 5/sec. for 60 sec. which gave maximal contraction of the stomach (Burge and Vane, 1958).

Gastric Secretion Induced by Histamine.—Cats were deprived of food, but not water, from the previous evening as Black, Fisher, and Smith (1958) have shown that histamine-induced secretion may decline and even cease in animals fed shortly before the experiment. Under chloralose anaesthesia, the abdomen was opened in the midline, the pyloro-duodenal junction occluded (leaving the pancreatico-duodenal arteries intact) and a glass cannula tied into the body of the stomach near the greater curvature. The abdominal wound was closed around the cannula and the animal turned on its side. The oesophagus was also tied off to prevent drainage of saliva and mucus into the stomach, the vagi being left intact. The stomach was then washed out with warm saline and the juice collected in graduated centrifuge tubes. Histamine acid phosphate (15 μg. base/min.) was

infused from a Palmer slow injector connected to the right femoral vein. The animals were given artificial respiration throughout the experiment to minimize respiratory variation.

Estimate of Acute Toxicity.—Male and female albino mice of Schofield strain were employed weighing about 15 g. Food and water were not withheld prior to the experiment and the drugs were injected intraperitoneally. It was not possible to give the doses in equal concentrations because of the different solubility of the two drugs. The methylpentynol was injected in concentrations of 40 mg./ml. in 0.9% saline, the carbamate in a concentration of 20 mg./ml. in slightly warm saline.

Measurement of Dissociation Constants.—Solutions were made up using distilled water which had been boiled and allowed to cool in an atmosphere of nitrogen. 5.0 ml. of a 1.0 mg./ml. solution of either methylpentynol or the carbamate was pipetted into a tube and 1.0 ml. of 0.1 N-HCl added to bring the *p*H below 2.0. The electrodes of a Pye *p*H meter, connected to an ink recorder, were lowered into the solution, together with two lengths of syringe needle tubing. Nitrogen was bubbled through one of these at a rate to give adequate stirring, the other being connected to a micrometer syringe containing 5 N-NaOH (carbonate free). The syringe piston was advanced at a constant rate by a velodyne motor, the speed adjusted to deliver 0.02 ml. of alkali/min. As the *p*H of the solution was continuously recorded by the pen writer on moving paper, the titration curve was drawn directly. Neither methylpentynol nor methylpentynol carbamate was found to dissociate.

Oil/Water Partition Coefficient.—Olive oil B.P. was shaken with a buffer solution of *p*H 7.0 to remove any acidity. The emulsion was separated by centrifugation and the oil then washed in a similar manner with distilled water. Methylpentynol (5.0 mg.) or methylpentynol carbamate (5.0 mg.), in the form of a 1.0 mg./ml. solution in distilled water, was added to 5.0 ml. of olive oil, treated as above, or to 5.0 ml. of oleyl alcohol, and shaken mechanically for 60 and 120 and 240 min. at room temperature. The emulsion was then separated by centrifugation in capped tubes and an aliquot from both the water and the oil phases distilled as described below for estimation of the drugs, the carbamate being hydrolysed with 5.0 ml. 3N-NaOH which gave a mean recovery of 80% added material. Methylpentynol carbamate may be hydrolysed using alkali when dissolved in distilled water, olive oil or oleyl alcohol, but acid hydrolysis must be used if the drug has to be distilled from body fluids or tissues. The $C_{olive\ oil}/C_{water}$ was in all cases 1/1. The $C_{oleyl\ alcohol}/C_{water}$ was 2.2/1. for methylpentynol after 1 hr., rising to 2.6/1. after 4 hr. shaking; that for the carbamate 2.8/1. at 1 hr., and 3.8/1. after 4 hr.

Estimation of Methylpentynol or Methylpentynol Carbamate.—Methylpentynol or its carbamate was estimated by the method of Perlman, Sutter and Johnson (1953) as modified by Marley and Vane (1958). Methylpentynol, or methylpentynol carbamate after previous treatment with 2 to 3 ml. of 3N sulphuric acid, was distilled from the specimen into N/40 ammoniacal silver nitrate in which methylpentynol combined quantitatively with silver to form a precipitate. After centrifugation, the supernatant fluid was decanted and the silver remaining in solution was titrated with N/40 potassium thiocyanate. Standard curves were obtained for both drugs by adding them directly to N/40 ammoniacal silver nitrate, centrifuging and titrating the silver remaining in solution with N/40 potassium thiocyanate. The mean recovery of methylpentynol from cat blood was 95% and of methylpentynol carbamate 65%. The accuracy of the method was within 0.01 mg. for methylpentynol, but for the carbamate concentrations in blood or tissue recovery experimental results have been corrected for a 65% recovery, then given to the nearest 0.05 mg./g. or ml.

For injection and infusion, pure methylpentynol was dissolved in 0.9% saline. The methylpentynol carbamate was also dissolved in slightly warmed saline for infusion experiments (up to 20 mg./ml.) but, for some single injections, had to be dissolved in 65% aqueous propylene glycol in order to minimize the volume. When comparing the effects of the two drugs, they were injected in the same dilution, since it is known (Mellanby, 1919) that dilute solutions of alcohol have less physiological effect than strong solutions containing the same amount of alcohol. For the infusion experiments in man, the methylpentynol was dissolved in dextrose solution (5.0 g. methylpentynol and 5.0 g. dextrose in 100 ml. distilled water). The two drugs conformed to the following analytical standards. *Methylpentynol:* the refractive index was between 1.4305 to 1.4315 at 21°, and not less than 90% of the substance distilled between 118° and 123°. It contained no more than 10 p.p.m. of lead, 1 p.p.m. of arsenic, and there was no more than 0.05% of residue. *Methylpentynol carbamate:* this contained not less than 96.0% and not more than the equivalent of 101.1% of $C_7H_{11}O_2N$. The freezing point was not less than 51.5° and the melting point about 52°. It contained no more than 5 p.p.m. of arsenic, 20 p.p.m. of lead, and no more than 0.1% sulphated ash.

Drugs Used.—Adrenaline bitartrate, noradrenaline bitartrate, histamine acid phosphate, acetylcholine chloride, atropine sulphate, physostigmine sulphate, nicotine hydrogen tartrate, decamethonium iodide, barium chloride and gallamine triethiodide. Weights refer to the base in the instances of adrenaline, noradrenaline and histamine and to the salts of all the other compounds.

RESULTS

Acute Toxicity.—The number of deaths and the number of mice which remained asleep 24 hr. after intraperitoneal injection of either methylpentynol or methylpentynol carbamate are

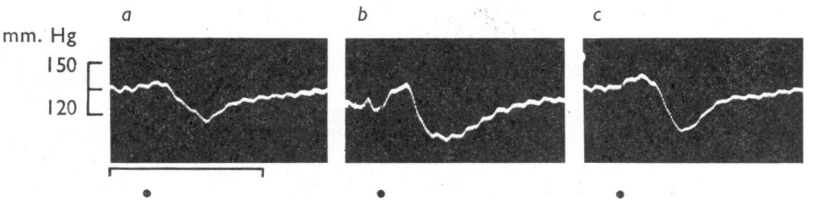

FIG. 1.—Blood pressure of a cat (2.5 kg., chloralose anaesthesia). Intravenous injections in (*a*) of 50 mg. of methylpentynol, in (*b*) of 1 μg. of histamine, and in (*c*) of 50 mg. of methylpentynol carbamate. Time, 30 sec.

shown in Table I. The approximate LD50 from the combined results for both sexes was 320 mg./kg. for the carbamate and 550 mg./kg. for methylpentynol yielding an equipotent molar activity of 2.5 for methylpentynol carbamate compared to 1 for methylpentynol. Allowing for the small numbers of animals employed, there was no significant difference between the sexes in their susceptibility to the drugs. Attention is drawn to the number of animals still asleep 24 hr. after drug administration.

TABLE I

TOXICITY OF METHYLPENTYNOL AND METHYLPENTYNOL CARBAMATE

Number of male or female mice dead (D) or asleep (S) 24 hr. after the intraperitoneal injection of methylpentynol or methylpentynol carbamate in the doses stipulated. 10 mice used with each dose.

Drug	Dose (mg./kg.)	Male		Female	
		D	S	D	S
Methylpentynol	400	0	0	1	2
	467	3	5	0	0
	533	4	2	5	3
	600	7	2	6	1
	800	10	—	10	—
Methylpentynol carbamate	267	1	2	3	2
	300	4	3	4	5
	333	5	3	5	1
	367	6	4	5	5
	400	7	1	9	1

Blood Pressure.—Four experiments were done. Single intravenous doses of 25 mg. or greater of either drug were followed by an immediate and transitory fall of blood pressure without bradycardia, an effect which was seen in anaesthetized, spinal, or pithed animals. The response to a single intravenous injection of 50 mg. of methylpentynol matched and followed the same time course as that to 1 μg. of histamine, the hypotension being slightly less than that due to the injection of 50 mg. of methylpentynol carbamate. Recovery occurred in approximately 30 sec. (Fig. 1). Intravenous infusion of either drug caused a prolonged hypotension (Figs. 4 and 5).

Heart.—In two experiments, the perfusion of the coronary system of the isolated kitten heart (Fig. 2) with methylpentynol or its carbamate led initially to a slowing of the heart, a decrease in amplitude of ventricular systole, the appearance of occasional extrasystoles, followed by their

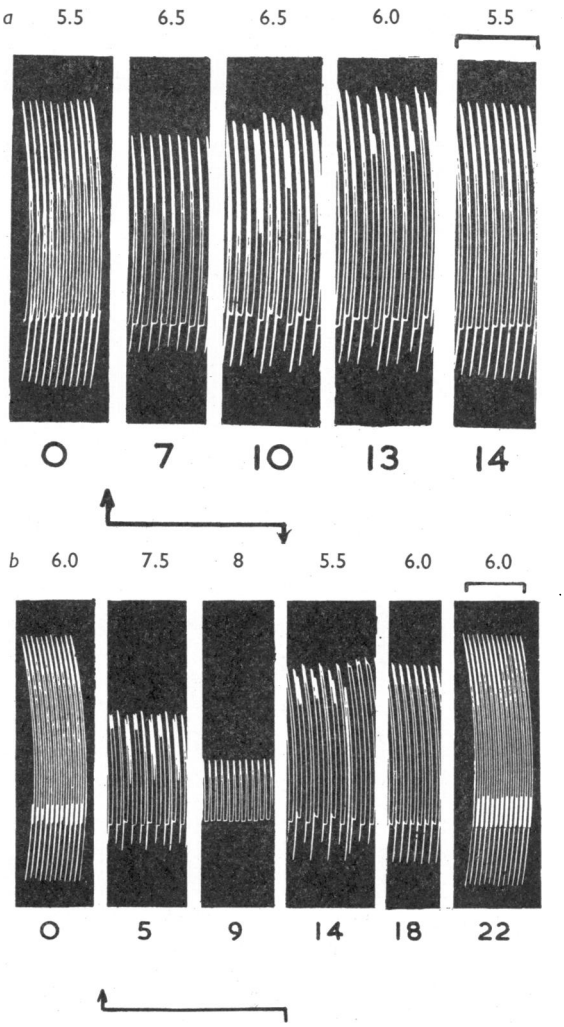

FIG. 2.—(*a*) Isolated kitten heart preparation. The numerals below indicate the time in min. at which records were taken after adding methylpentynol (0.5 mg./min.) to the perfusion fluid for 10 min. The numerals above indicate coronary flow in ml./min. Systole, upwards. Time, 5 sec. (*b*) Isolated kitten heart preparation. Recordings as in (*a*) but perfusion with 1 mg./min. of methylpentynol carbamate for 10 min.

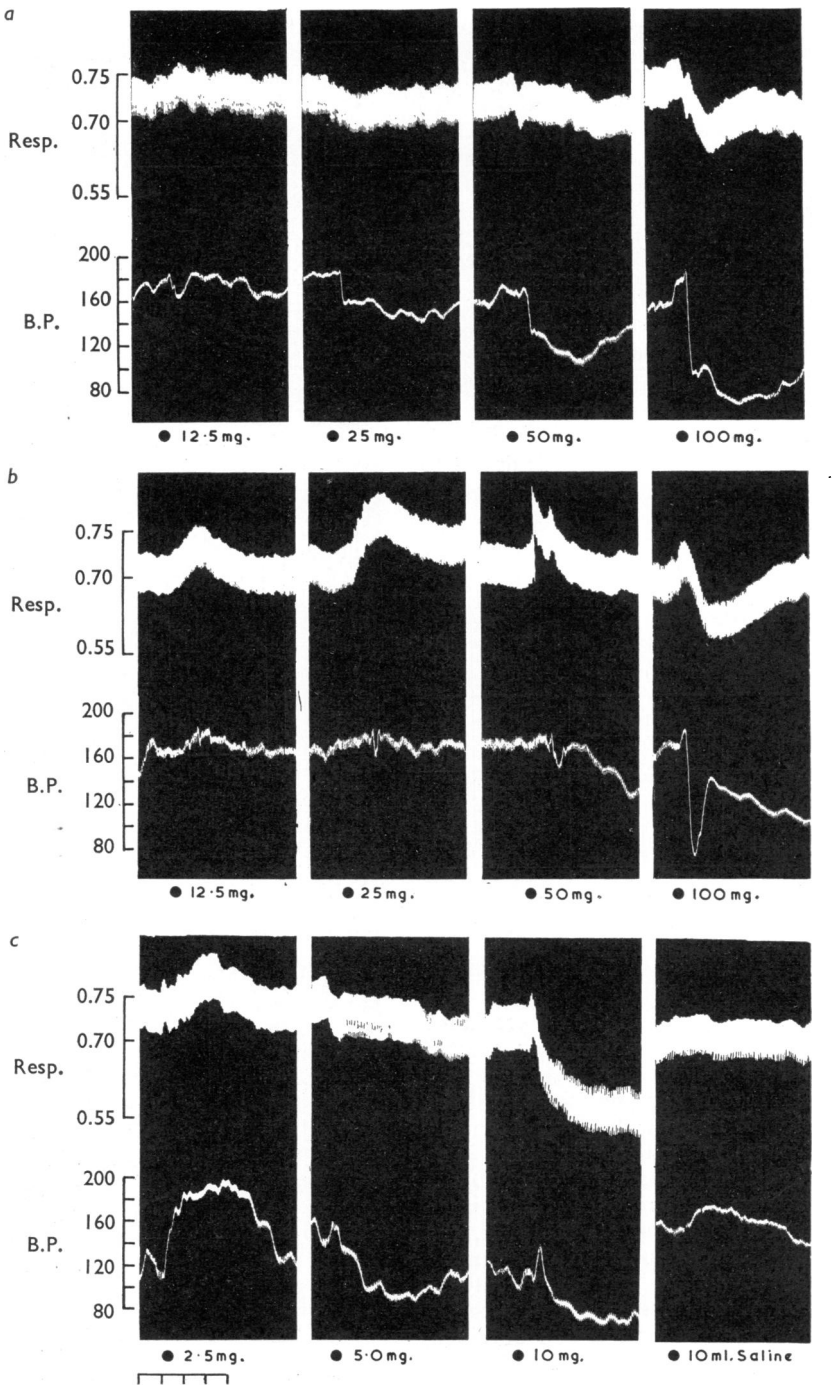

FIG. 3.—Records of respiration (**Resp.**) and blood pressure (**B.P.**) in a cat (2.5 kg., chloralose anaesthesia). Respiration scale, min. vol. in l., blood pressure scale mm. Hg. Responses after single intravenous injections of (*a*) methylpentynol, (*b*) methylpentynol carbamate, and (*c*) sodium pentobarbitone (dose in mg.) and, in lowest right-hand record, 10 ml. saline. Time, min.

regular occurrence after every fourth, third, or second beat. At this stage, the ventricular response might return to a normal regular rate but with a marked reduction of systolic amplitude (Fig. 2*b*). During recovery, these phenomena recurred but in reverse order. Coronary flow was increased by between 15 and 30% during perfusion of the drugs.

These responses arose with a perfusion concentration for methylpentynol of 5 mg. in 58 ml. (1/1,160 solution) and for methylpentynol carbamate of 10 mg. in 75 ml. (1/750 solution).

Blood Flow in the Hind Limbs of the Cat.—In one experiment, the injection of either methylpentynol or its carbamate into the arterial system produced vasodilatation, similar increases of blood flow occurring with 6 mg. of pentobarbitone sodium, 10 mg. of methylpentynol carbamate, and 12 mg. of methylpentynol. Vasoconstriction was never seen.

Respiration

Single Injections.—In four experiments, all but the smallest doses of both drugs were respiratory depressants. Thus the intravenous injection of 5 mg./kg. (total 12.5 mg.) or 10 mg./kg. (total 25 mg.) of either drug had no effect on respiration or produced slight increase of the respiratory rate and minute volume (Fig. 3). Doses in excess of 20 mg./kg. led to a reduction of minute volume, falling from about 725 ml. with 40 mg./kg. (total 100 mg.) of methylpentynol carbamate to about 600 ml./min., and with the same dose of methylpentynol from 750 ml. to just less than 700 ml./min., full recovery taking some 15 min. The diminution of minute volume was associated with a fall of blood pressure. A small increase of respiratory minute volume was seen with the intravenous injection of 1 mg./kg. of sodium pentobarbitone, but a marked reduction of minute volume followed the administration of 4 mg./kg. of sodium pentobarbitone, the fall being from 700 to 550 ml. air/min.

Infusions.—Considerably greater depression of respiration occurred in two cats during infusions of either drug (Figs. 4 and 5). Thus after the infusion of 1,940 mg. methylpentynol in 76 min. (blood concentration, 1.25 mg./ml. of methylpentynol) the respiratory minute volume had fallen from about 0.5 to about 0.1 l. The infusion of 1,800 mg. of methylpentynol carbamate in 105 min. led to complete arrest of respiration (corrected blood concentration of the carbamate, 0.5 mg./ml.). There was a reduced response to preganglionic stimulation of the nictitating membrane. There was also a 60% reduction of the knee jerk with both drugs. In two experiments on man, intravenous infusion over 15 min. of 1.0 g. methylpentynol was associated with a brief increase of respiratory rate and volume (Table II).

TABLE II

THE EFFECT ON RESPIRATION IN MAN OF INTRAVENOUS INFUSIONS OF SALINE OR METHYLPENTYNOL

		Before Infusion	During Infusion	10 min. after End of Infusion
Infusion of 20 ml. of saline during 15 min.	Respiratory rate/min.	16	12	16
	Vol. of expired air l./hr.	344·0	290·0	307·0
	O_2% in expired air	16·4	17·2	16·2
	CO_2 in expired air	3·9	3·4	3·0
Infusion of 1·0 g. of methylpentynol in 20 ml. during 15 min.	Respiratory rate/min.	16	24	17
	Vol. of expired air l./hr.	397·5	457·5	401·3
	O_2% in expired air	16·8	17·3	16·7
	CO_2% in expired air	4·4	3·9	4·4

Action on Smooth Muscle

Isolated Guinea-pig Ileum.—The changes in responses to acetylcholine and to coaxial electrical stimulation of the guinea-pig ileum with methylpentynol (M.W.98), methylpentynol carbamate (M.W.141), sodium pentobarbitone (M.W.248), and ethanol (M.W.46) was studied next. Fig. 6 shows the response of the electrically stimulated ileum to methylpentynol and its carbamate. Dose/response curves are given in Figs. 7 and 8. As the slopes differed to such an extent, no accurate relative potencies could be calculated. However, approximate relative potencies were determined by comparing doses required to reduce the maximal response to coaxial stimulation, or the response to acetylcholine by 50%, the dose of acetylcholine being adjusted to give a half of the maximal effect. In two experiments on the electrically stimulated guinea-pig ileum, the equipotent molar dose of sodium pentobarbitone was 1, and those for methylpentynol carbamate, 4.8; methylpentynol, 13.8; and ethanol, 1,071.5. In one experiment on the ileum stimulated by acetylcholine, the approximate equipotent molar ratios where sodium pentobarbitone was 1 were methylpentynol carbamate, 9.1; methylpentynol, 18.8; and ethanol, 1,084.6.

The effects of methylpentynol and its carbamate were also studied in 3 experiments on the guinea-pig ileum stimulated by $BaCl_2$ or nicotine, half maximal response to acetylcholine being matched by contractions of similar height produced by

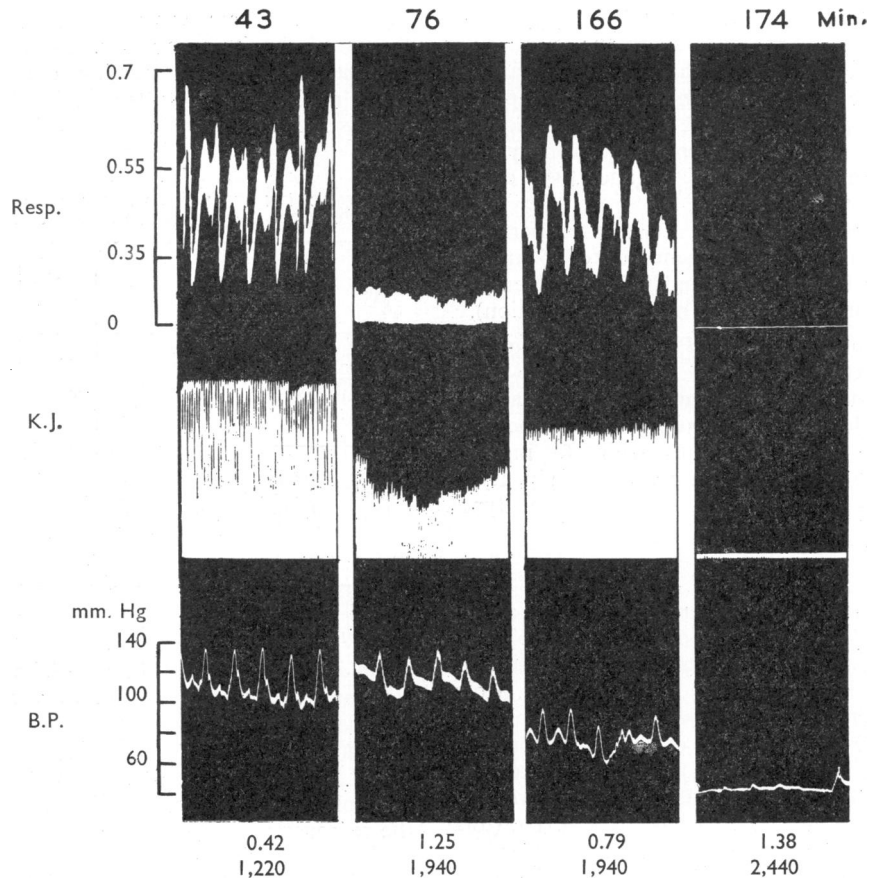

FIG. 4.—Records of respiration (**Resp.**), knee jerk (**K.J.**), and blood pressure (**B.P.**) in a cat (4.1 kg., chloralose anaesthesia). Records of **Resp.** and **B.P.** as in Fig. 3. The numerals in the upper row below the records indicate the whole blood concentration (in mg./ml.) and those in the lower row the total quantity of infused methylpentynol (in mg.).

the other two substances. The effect of methylpentynol or carbamate was tested only after the enhanced contraction to acetylcholine immediately succeeding the addition of $BaCl_2$ or nicotine had returned to normal. Methylpentynol carbamate was more potent on an equimolecular basis than methylpentynol (1 : 2.5) in reducing the acetylcholine response, which took longer to regain its full contraction height than after methylpentynol. In this dose ratio, the drugs produced approximately identical reductions (50 to 60%) of the acetylcholine and $BaCl_2$ contractions (Fig. 9). The nicotine response was reduced by 75 to 80%. In the presence of hyoscine (10^{-7}), the same doses of methylpentynol and the carbamate produced an 80 to 90% diminution of the acetylcholine and $BaCl_2$ contractions.

Contraction of the Stimulated Stomach in situ.—In 2 experiments, single intravenous doses of either drug up to 200 mg. (60 mg./kg.) or 800 mg. of ethanol (240 mg./kg.) had no effect on intestinal tone nor on the response of the saline-filled stomach to vagal stimulation.

Action on Striated Muscle

Isolated Frog Rectus Abdominis Muscle.—In 5 experiments, methylpentynol and its carbamate in high concentrations (4×10^{-3}) elicited contracture of the frog rectus equivalent in height to that produced by 10^{-7} of acetylcholine (Fig. 10*a*). As neither drug dissociates, this was not a *p*H effect, nor was it an osmotic effect, as the addition to the bath of a solution of sucrose (42×10^{-3}) approximately three times the molar strength of a solution of methylpentynol (4×10^{-3})

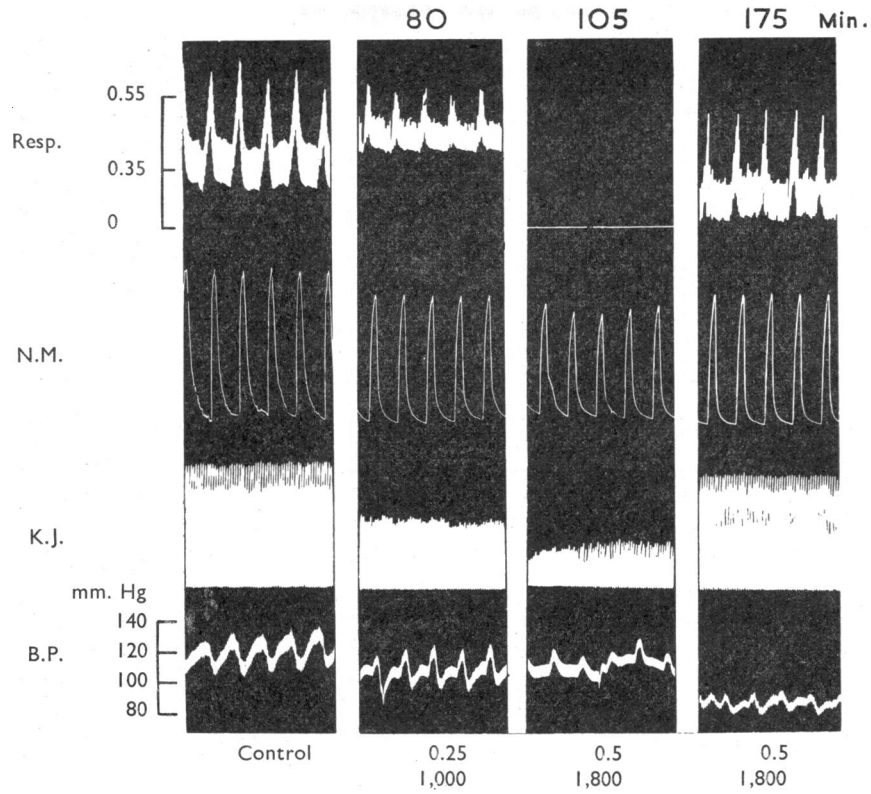

FIG. 5.—Records of respiration (Resp.), nictitating membrane stimulated preganglionically (N.M.), knee jerk (K.J.), and blood pressure (B.P.) in a cat (3.8 kg., chloralose anaesthesia). Records and numerals below as in Fig. 4. Responses before, during and after an infusion of 1,800 mg. of methylpentynol carbamate.

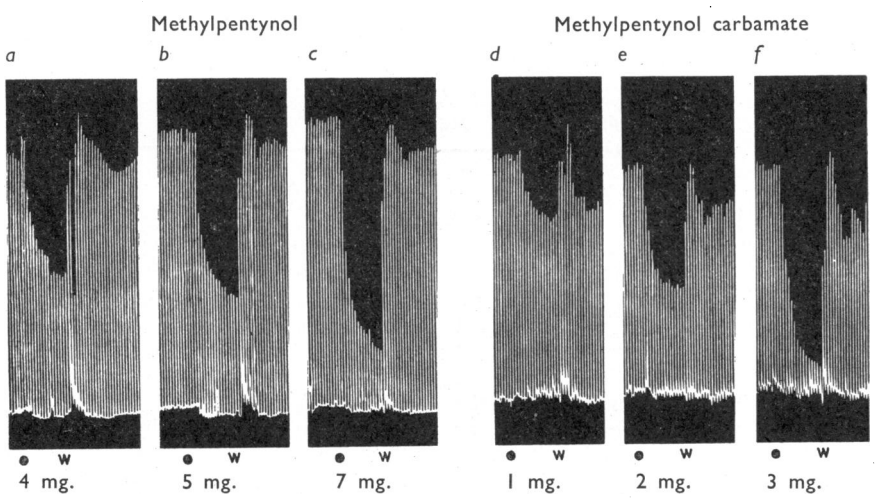

FIG. 6.—Effect of various doses of methylpentynol and methylpentynol carbamate on maximal twitches elicited by co-axial electrical stimulation of guinea-pig ileum (6/min.). Methylpentynol (*a*) 4 mg.; (*b*) 5 mg.; (*c*) 7 mg. Methylpentynol carbamate (*d*) 1 mg.; (*e*) 2 mg.; and (*f*) 3 mg. Bath vol. 10 ml. Contact time, 3 min. W indicates washing.

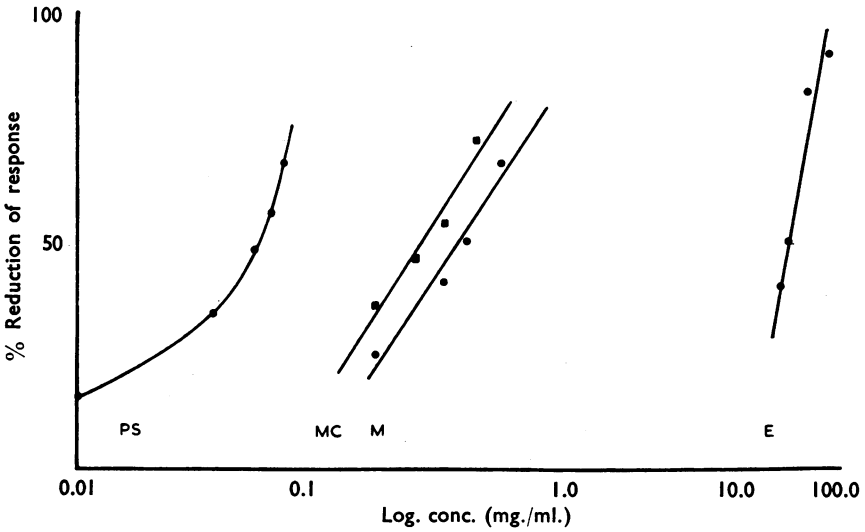

FIG. 7.—Dose/response relation for the reduction by pentobarbitone sodium (PS), methylpentynol carbamate (MC), methylpentynol (M), and ethanol (E) of the response of the guinea-pig ileum to acetylcholine.

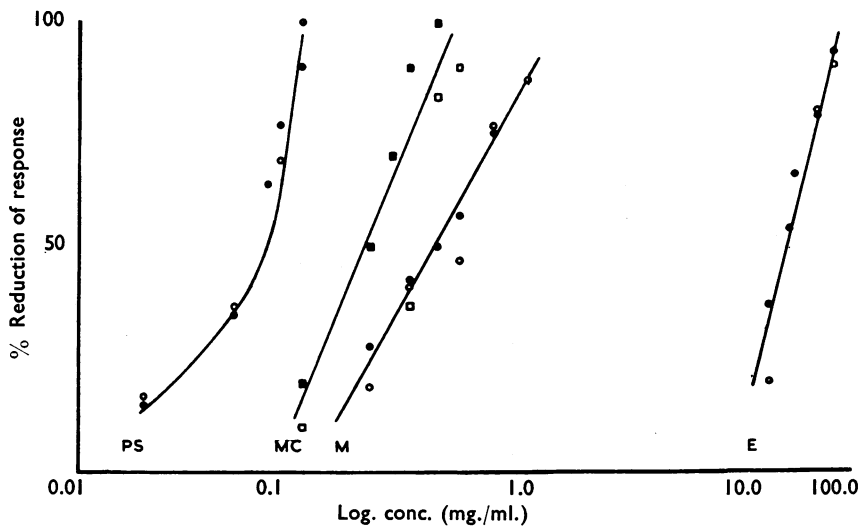

FIG. 8.—Dose/response relation for the reduction by pentobarbitone sodium (PS), methylpentynol carbamate (MC), methylpentynol (M), and ethanol (E) of the maximal twitch elicited by electrical stimulation of the guinea-pig ileum. Solid circles or squares indicate results from Expt. No. 1, open circles or squares those from Expt. No. 2.

produced only a small contracture. Ethanol in a solution approximately three times the molar strength of methylpentynol (4×10^{-3}) also had no effect. Both drugs in doses without apparent action on the rectus (Fig. 10*b*) potentiated the contractions due to submaximal doses of acetylcholine, an effect that persisted in the presence of either physostigmine (10^{-6}) or gallamine (5×10^{-6}) (Fig. 10*c*). The contraction elicited by decamethonium (5×10^{-6}) was also augmented.

Cat Sciatic Nerve Tibialis Anterior Muscle Preparation. — In 5 experiments, retrograde injections of up to 200 mg. (50 mg./kg.) of either methylpentynol or its carbamate into the contralateral common iliac artery had no effect on twitches elicited by single stimuli applied to the sciatic nerve tibialis anterior preparation. Similarly, no effect on this preparation was found with infusions of 2,884 mg. of methylpentynol or 1,627 mg. of methylpentynol carbamate, the respective drug blood concentrations immediately before death being 0.64 mg./ml. and 0.45 mg./ml. In the tetanized preparation, however, single intravenous injections of 50 mg./kg. (125 mg.) of methylpentynol carbamate or 100 mg./kg. (250

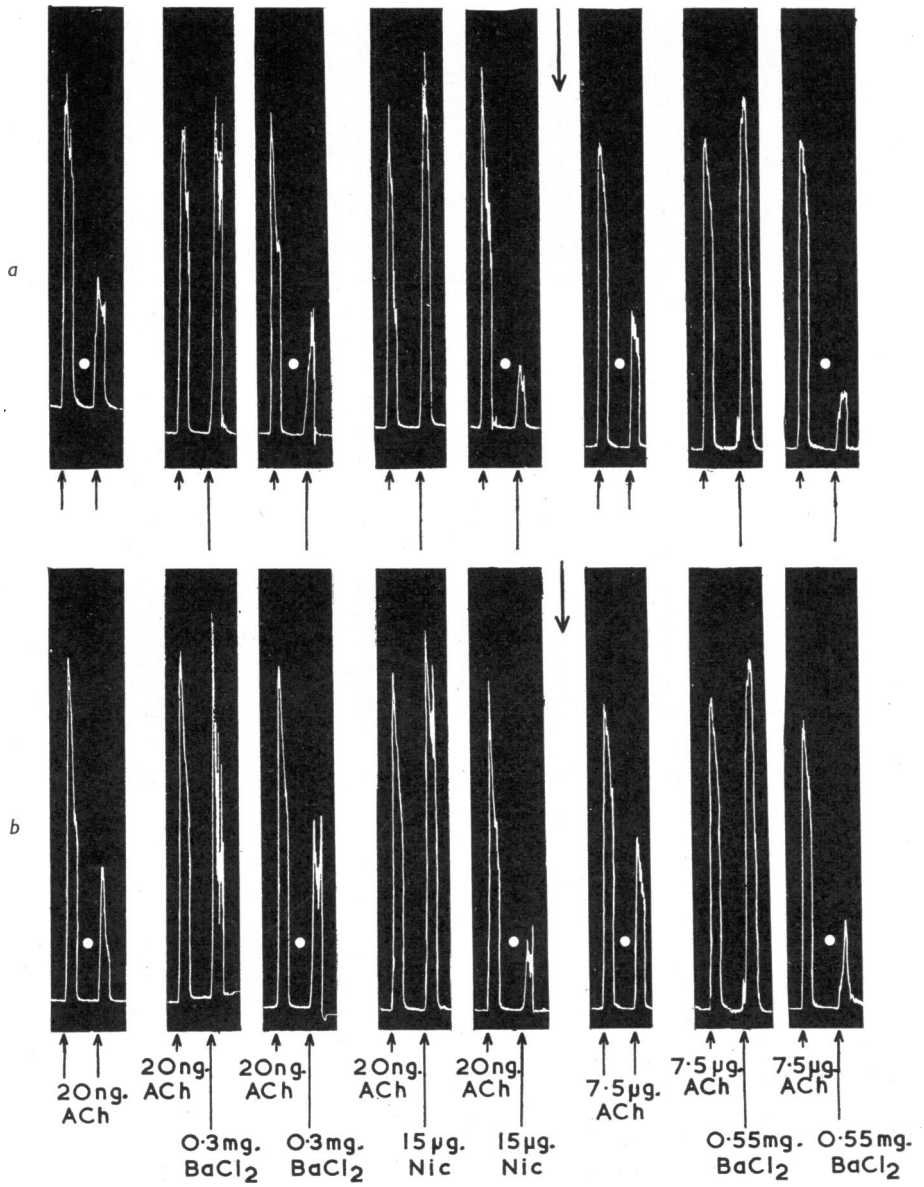

FIG. 9.—Isolated guinea-pig ileum preparation. Effect of 3.0 mg. of methylpentynol (at white dots in *a*) and of 1.75 mg. of methylpentynol carbamate (at white dots in *b*) on the half-maximal acetylcholine (ACh) contractions and matched $BaCl_2$ responses (before and after hyoscine 10^{-7} at downward pointing arrow) and matched nicotine (Nic) contractions. Note enhanced acetylcholine response after $BaCl_2$ and nicotine was allowed to return to normal before addition of methylpentynol or carbamate to bath.

mg.) of methylpentynol led to a 20% reduction of peak tension height followed by full recovery within 10 to 15 min. (Fig. 11). In the combined tibialis-soleus preparation, doses up to 100 mg./kg. (350 mg.) of methylpentynol carbamate or 250 mg./kg. (875 mg.) of methylpentynol had no effect on the single twitch response of these indirectly stimulated muscles, but with these doses artificial respiration was required.

Isolated Phrenic Nerve Rat Diaphragm Preparation. — In 2 experiments, diminution, preceded by brief augmentation of twitch, followed

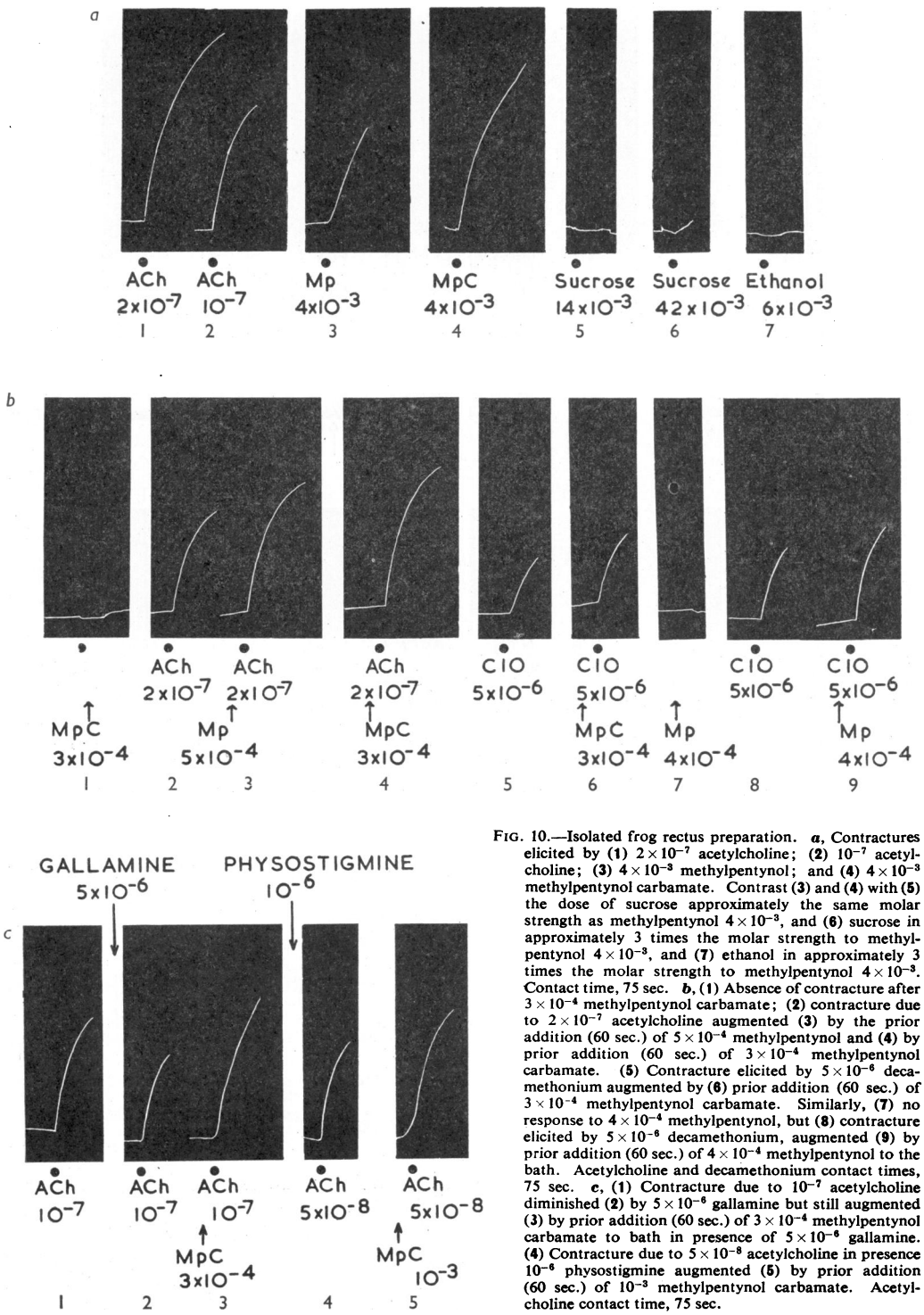

FIG. 10.—Isolated frog rectus preparation. *a*, Contractures elicited by (1) 2×10^{-7} acetylcholine; (2) 10^{-7} acetylcholine; (3) 4×10^{-3} methylpentynol; and (4) 4×10^{-3} methylpentynol carbamate. Contrast (3) and (4) with (5) the dose of sucrose approximately the same molar strength as methylpentynol 4×10^{-3}, and (6) sucrose in approximately 3 times the molar strength to methylpentynol 4×10^{-3}, and (7) ethanol in approximately 3 times the molar strength to methylpentynol 4×10^{-3}. Contact time, 75 sec. *b*, (1) Absence of contracture after 3×10^{-4} methylpentynol carbamate; (2) contracture due to 2×10^{-7} acetylcholine augmented (3) by the prior addition (60 sec.) of 5×10^{-4} methylpentynol and (4) by prior addition (60 sec.) of 3×10^{-4} methylpentynol carbamate. (5) Contracture elicited by 5×10^{-6} decamethonium augmented by (6) prior addition (60 sec.) of 3×10^{-4} methylpentynol carbamate. Similarly, (7) no response to 4×10^{-4} methylpentynol, but (8) contracture elicited by 5×10^{-6} decamethonium, augmented (9) by prior addition (60 sec.) of 4×10^{-4} methylpentynol to the bath. Acetylcholine and decamethonium contact times, 75 sec. *c*, (1) Contracture due to 10^{-7} acetylcholine diminished (2) by 5×10^{-6} gallamine but still augmented (3) by prior addition (60 sec.) of 3×10^{-4} methylpentynol carbamate to bath in presence of 5×10^{-6} gallamine. (4) Contracture due to 5×10^{-8} acetylcholine in presence 10^{-6} physostigmine augmented (5) by prior addition (60 sec.) of 10^{-3} methylpentynol carbamate. Acetylcholine contact time, 75 sec.

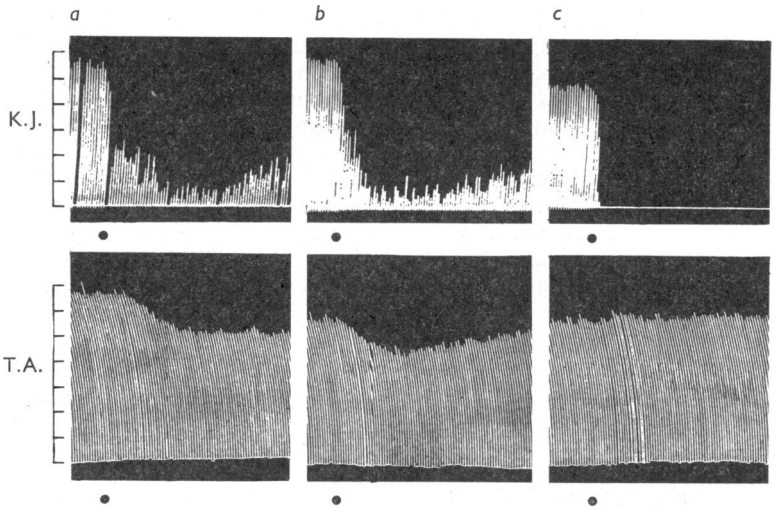

FIG. 11.—Records of knee jerk (K.J.) elicited at 12/min. and twitch of tibialis anterior muscle (T.A.) tetanized for 1 sec. in every 5 sec. in a cat (2.5 kg., anaesthetized with chloralose). Effect of single intravenous injections at black dots of (*a*) methylpentynol (100 mg.); (*b*) methylpentynol carbamate (50 mg.); and (*c*) sodium pentobarbitone (25 mg.). Scale, height of twitch in cm.

the addition to the bath of methylpentynol carbamate, methylpentynol and paraldehyde (M.W.132). After washing in Tyrode solution, the amplitude of the muscle twitch was restored to that seen in fresh muscle. Dose/response curves were plotted for the % reduction of maximum response 5 min. after the addition of the test substance to the bath (Fig. 12) and the approximate equipotent molar ratios were methylpentynol carbamate 1, methylpentynol 4.4, and paraldehyde 5.3.

Action on Gastric Secretion

In doses between 10 mg./kg. and 100 mg./kg. neither methylpentynol (5 experiments) nor its carbamate (2 experiments) had any constant action on histamine induced gastric secretion.

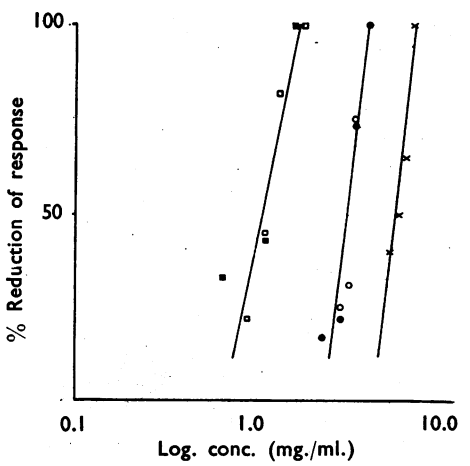

FIG. 12.—Dose/response relation for the reduction by methylpentynol carbamate (solid and open squares); methylpentynol (solid and open circles), and paraldehyde (crosses) of the maximal twitch of the indirectly stimulated rat phrenic nerve diaphragm preparation. Solid circles or squares are results from Expt. No. 1 and open circles or squares results from Expt. No. 2.

Action on the Nervous System

Anaesthesia. — The brain concentrations in guinea-pigs after intraperitoneal injections of methylpentynol during deep anaesthesia varied between 0.34 and 0.46 mg./g. and for the carbamate between 0.25 and 0.35 mg./g. (Table III). The righting reflex returned when brain concentrations of the drugs were still fairly high

TABLE III

BLOOD AND BRAIN CONCENTRATIONS OF METHYLPENTYNOL AND ITS CARBAMATE IN GUINEA-PIGS

Results from 12 male guinea-pigs following intraperitoneal injection of either methylpentynol or methylpentynol carbamate dissolved in 65% aqueous propylene glycol. The asterisk denotes result obtained from a total exsanguination sample. Brain concentrations of drugs are those for wet weight of organs.

Expt. No.	Weight (kg.)	Dose (mg./kg.)	Min. after Intraperitoneal Injection	State of Animal	Blood Conc. (mg./ml.)	Brain Conc. (mg./g.)
Methylpentynol						
1	0·552	400	15	Unconscious	0·15	0·34
2	0·510	400	20	,,	0·10	0·46
3	0·533	400	15	,,	0·06	0·37
4	0·446	300	270	Able to roll on side	0·03	0·21
5	0·565	300	100	,, ,,	0·06	0·17
6	0·546	400	125	,, ,,	0·21*	0·22
7	0·547	200	75	Righting reflex present	0·03	0·19
8	0·469	200	120	,, ,,	0·03	0·16
Methylpentynol carbamate						
9	0·469	200	15	Unconscious	0·15	0·35
10	0·525	200	15	,,	0·25	0·25
11	0·526	100	315	Righting reflex present	0·05	0·15
12	0·659	150	375	,, ,,	0·05	0·15

(0.16 to 0.19 mg./g. for methylpentynol and 0.15 mg./g. for methylpentynol carbamate). During anaesthesia, blood concentrations ranged between 0.06 mg./ml. and 0.15 mg./ml. with methylpentynol and 0.15 to 0.25 mg./ml. with its carbamate.

Similar results were obtained with cats anaesthetized first with ethyl chloride and ether, allowed to recover partially and then given intravenous injections or infusions of methylpentynol or the carbamate (3 experiments). A cat given a single intravenous injection of 250 mg./kg. of methylpentynol was still anaesthetized 20 min. later when the blood concentration of the drug was 0.33 mg./ml. Another animal infused with 20 mg. of methylpentynol/min. for 40 min. began to recover 15 min. after cessation of the infusion, by which time the blood concentration had fallen to 0.15 mg./ml. A cat given a single intravenous injection of 200 mg./kg. of methylpentynol carbamate was still anaesthetized 60 min. later with a blood concentration of 0.25 mg./ml.

Blood concentrations of methylpentynol in guinea-pigs after return of the righting reflex varied between 0.03 and 0.06 mg./ml., the one exception being Expt. No. 6 in which a high blood level was found, the specimen being obtained by total exsanguination. There was good accord between these values and results from unanaesthetized rabbits (2 experiments) which were given 100 mg./kg. daily of either methylpentynol or the carbamate by stomach tube, blood samples being removed from the ear vein before each dose of the drug. On the fourth day of this regime, the blood concentration of methylpentynol had risen to 0.03 mg./ml. and that of the carbamate to 0.035 mg./ml. and there were no signs referable to the central nervous system.

No free methylpentynol was found either in the blood or brain after the administration of methylpentynol carbamate.

Reflexes

Knee Jerk.—In 5 experiments, doses up to 200 mg. (100 mg./kg.) of ethanol were without effect on the knee jerk, but a 90% reduction in amplitude with full recovery in 50 min. followed the injection of single intravenous doses of 100 mg./kg. (250 mg.) of methylpentynol and 50 mg./kg. (125 mg.) of methylpentynol carbamate (Fig. 11). There was no augmentation before diminution of the knee jerk, maximum reduction occurring within 1 to 2 minutes of drug administration. More persistent diminution of the knee jerk was produced by intravenous infusion of the substances. Associated blood concentrations are shown in Figs. 4 and 5. Respiration tended to fail before disappearance of the knee jerk.

Reflex Alteration of Respiration.—The increase of respiratory minute volume in response to stimulation of the central end of the cut femoral nerve was reduced in 5 experiments for about 20 min. after a single intravenous injection of 100 mg. (30 mg./kg.) of methylpentynol and for 85 min. after the same dose of its carbamate (Fig. 13). The inhibition of respiration produced by stimulating the central end of the cut vagus remained unmodified in cats and rabbits after single intravenous injections of either 100 mg. (40 mg./kg.) of methylpentynol or of its carbamate.

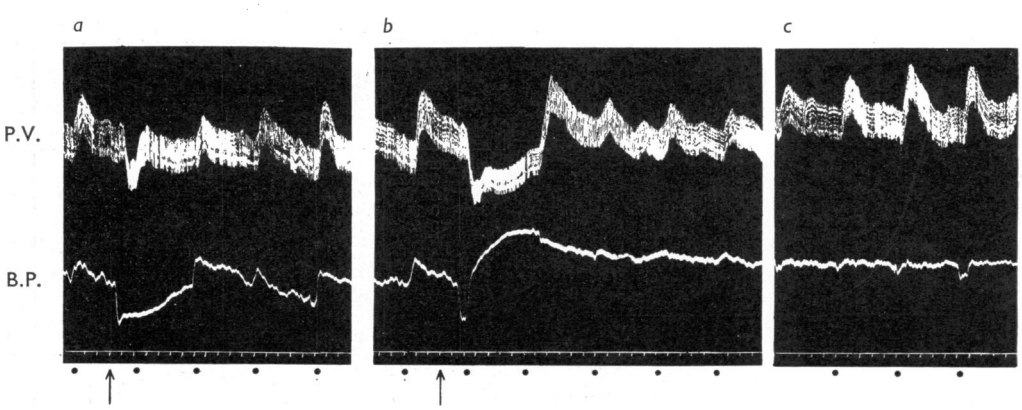

FIG. 13.—Record of pulmonary ventilation (P.V.) and blood pressure (B.P.) in a cat (3.3 kg., chloralose anaesthesia). Effect of intravenous injection at arrow in (*a*) of 100 mg. of methylpentynol; in (*b*) of 100 mg. of methylpentynol carbamate. In (*c*) recovery of response 85 min. after (*b*). Each black dot indicates stimulation of the femoral nerve at 10/sec. Time, min.

Ganglionic Transmission

Superior Cervical Ganglion (7 experiments).—The effect of intra-arterial injections of methylpentynol, methylpentynol carbamate and pentobarbitone sodium (their potencies in the reverse order) on the response of the nictitating membrane to preganglionic excitation is depicted in Fig. 14. A similar reduction of response occurred during the intravenous infusion of methylpentynol carbamate (Fig. 5). It transpired, during infusions of large quantities of methylpentynol or its carbamate, that the response of the nictitating membrane to direct stimulation by intravenous injections of 10 μg. of adrenaline was reduced *pari passu* with the decline in response to both pre- and post-ganglionic stimulation of the cervical sympathetic nerve. Once the contraction disappeared as a consequence of such infusions, it was impossible to elicit any response of the nictitating membrane either by adrenaline or pre- or post-ganglionic nerve stimulation for at least the next 6 hr. It was inferred that this was an effect of methylpentynol or carbamate on the muscle of the nictitating membrane, and not necessarily indicative of any action at the superior cervical ganglion.

To ascertain whether these drugs acted on the superior cervical ganglion, advantage was taken of the fact that both carotid arteries (from which the nictitating membrane and the superior cervical ganglion derive their blood supply) arise together from the innominate artery. Each drug was injected into the right internal mammary artery with the distal aorta occluded. That the injected substances reached both nictitating membranes in equivalent concentrations was indicated by identical responses to 10 μg. of adrenaline (Fig. 15). Injections of 25 mg. of methylpentynol carbamate and 50 mg. of methylpentynol led to similar evanescent relaxations of the nictitating membrane when stimulated preganglionically but not postganglionically, suggesting that the substances possessed weak ganglion-blocking properties, the carbamate being about twice as potent as methylpentynol.

Vasomotor Ganglia.—Pressor responses in 3 spinal cats which had received 1 mg./kg. atropine sulphate were induced by intravenous injections at

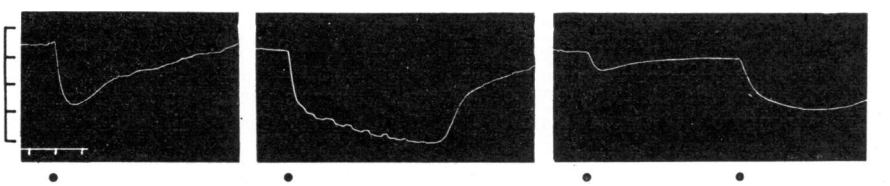

FIG. 14.—Record of contracture of the nictitating membrane in a cat (2.75 kg., chloralose anaesthesia) excited by continuous stimulation of cervical sympathetic at 10/sec. Single retrograde injections were made at black dots into the stump of the ligatured lingual artery, in (*a*) methylpentynol (12 mg.); in (*b*) methylpentynol carbamate (12 mg.); and in (*c*) sodium pentobarbitone, first 0.25 mg. and then 1 mg. Time, min. Scale, cm.

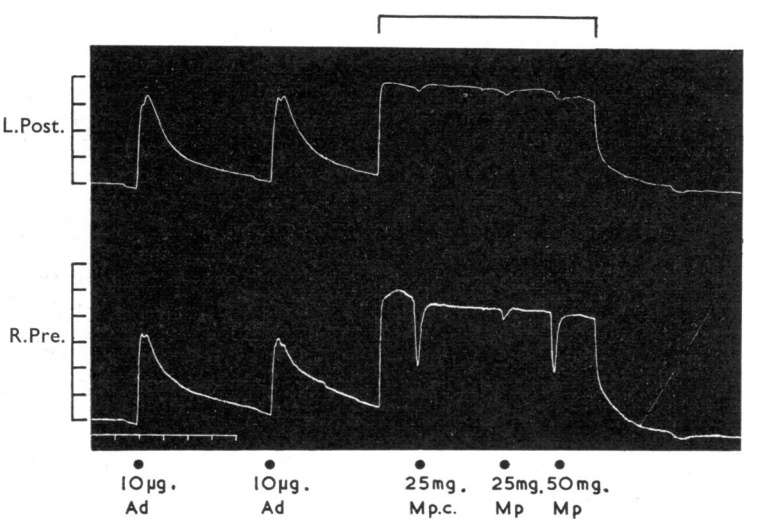

FIG. 15.—Record of contracture of both nictitating membranes in a cat (2.1 kg., anaesthetized with chloralose) excited by continuous preganglionic (**R.Pre.**) and postganglionic (**L.Post**) stimulation of cervical sympathetic at 10/sec. for period indicated. Single injections into right internal mammary artery of methylpentynol (**Mp**), of methylpentynol carbamate (**Mp.c.**) and of adrenaline (**Ad**). Time, min. Scale, cm.

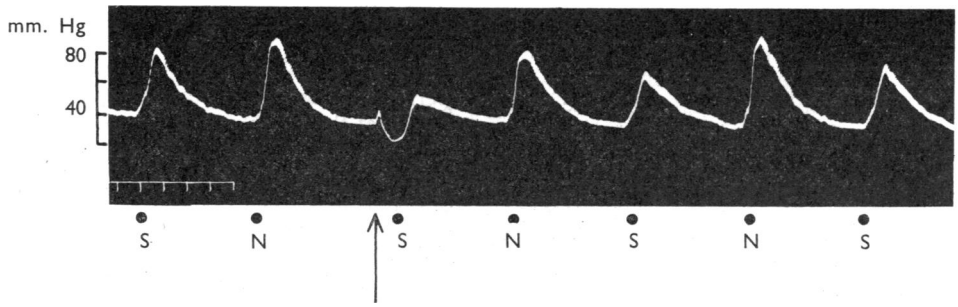

FIG. 16.—Effect on the blood pressure in a pithed and eviscerated cat (3.0 kg.) of intravenous injection of 150 mg. of methylpentynol (at arrow) 45 sec. before stimulation (10/sec.) of the peripheral end of the sectioned nerve to the left suprarenal gland (S) alternating every 5 min. with the intravenous injection of 3 μg. of noradrenaline (N). Time, min.

3 min. intervals of 0.4 mg. of nicotine alternating with 5 μg. of noradrenaline. Following the injection of 100 mg. of methylpentynol (50 mg./kg.) or of 50 mg. of methylpentynol carbamate (25 mg./kg.), the nicotine pressor response was reduced for 30 min. but that for noradrenaline remained unaltered.

Suprarenal Gland

Three pithed eviscerated cats were given injections of 3 μg. of noradrenaline alternating at 5 min. intervals with stimulation of the peripheral end of the sectioned nerve to the left suprarenal gland. Intravenous injections of 20 mg./kg. of methylpentynol (60 mg.) had no effect on the blood pressure response to suprarenal nerve stimulation, but a larger dose of 150 mg. of methylpentynol (50 mg./kg.) reduced the response (Fig. 16), full recovery occurring in about 20 min. The reaction to noradrenaline was little affected. The blood pressure response to stimulation of the sectioned nerve to the suprarenal gland 45 sec. after the injection of 60 mg. of methylpentynol carbamate (20 mg./kg.) was usually greater than the control; then, as with methylpentynol, the response to stimulation fell. Recovery was complete in 20 min.

DISCUSSION

It was intended to compare, as far as possible, the actions of methylpentynol and methylpentynol carbamate with those of other central nervous system depressants, particularly ethanol, and to correlate blood levels of the drugs with their activity. Marley and Vane (1958) likened the tissue and fluid distribution of both drugs following injection to that of ethanol, and suggested that the relation between methylpentynol and the carbamate resembles that between ethanol and urethane. But methylpentynol is a tertiary unsaturated alcohol, and as the activity of an alcohol increases with the size of its molecule (Gaddum, 1956) it was anticipated that methylpentynol would be more potent than ethanol.

Whereas ethanol in concentrations of 0.05 to 0.2% produces slowing of the heart with dysrhythmia and diminished systolic amplitude without effect on coronary flow in the perfused mammalian heart (Tunicliffe and Rosenheim, 1903; Backman, 1906), methylpentynol in concentrations of 0.1% is said not to affect rate of systolic contraction of either the isolated frog or rabbit hearts although a 50% increase of coronary flow ensued (Gialdroni and Grassi, 1952). In the present experiments with isolated kitten hearts, marked reduction of systolic amplitude and dysrhythmia together with a 15 to 30% increase of coronary flow occurred with the perfusion of solutions of 1:1,160 of methylpentynol or 1:750 of methylpentynol carbamate respectively.

Increases of arterial blood flow resulted from intra-arterial injections of either drug; and Hemmeter (1891) found augmented arterial blood flow after the intravenous injection of alcohol. The effect of alcohol on the blood pressure is a composite of its various actions on the heart, blood vessels and central nervous system. Both methylpentynol and the carbamate produced a fall of blood pressure in the intact animal, the carbamate being slightly more potent than methylpentynol. Smaller falls of blood pressure occurred in spinal and pithed cats.

There has been controversy as to whether alcohol stimulates respiration at low blood concentrations or not, although the stimulating action seems to have been demonstrated fairly conclusively (Wilmanns, 1897; Hitchcock, 1942), and seems to be due to a direct and not a reflex action. Certainly methylpentynol or its

carbamate, in single intravenous doses up to 10 mg./kg. in cats or as an infusion of 1.0 g. of methylpentynol in man, led to a small increase of respiratory rate and minute volume. Single intravenous doses greater than 20 mg./kg. resulted in short-lived respiratory depression in cats, both drugs being much less potent than pentobarbitone sodium. Margolin *et al.* (1951) stated that methylpentynol even in large doses did not depress respiration, although Roberts, Kane, Percival, Snow, and Please (1957) found that methylpentynol given to the pregnant mother depressed the respiratory minute volume of the newborn child. Both methylpentynol and the carbamate are more potent respiratory depressants than ethanol. According to Haggard, Greenberg, and Rakieten (1940) a blood concentration of 9.3 mg./ml. ethanol in fasting rats was associated with respiratory failure; this occurred in cats at a blood concentration of 1.2 mg./ml. with methylpentynol and 0.5 mg./ml. for the carbamate.

Both drugs reduced the response of the guinea-pig ileum to acetylcholine, $BaCl_2$, and nicotine. The contraction of the guinea-pig ileum to acetylcholine is mainly a direct effect on muscle, that produced by barium being mediated primarily through ganglia, whereas nicotine acts wholly through ganglia (Feldberg, 1951). Since both methylpentynol and the carbamate diminished the response of the guinea-pig ileum to acetylcholine and $BaCl_2$ in the presence of hyoscine 10^{-7}, their action is most likely to be on the smooth muscle. Histamine also contracts the guinea-pig ileum by a direct action on muscle, the response being attenuated by many central depressants including alcohols and urethanes (Farmer, 1938). That methylpentynol and the carbamate may also act on ganglia is shown by the fact that they produced greater diminution of the nicotine than of the acetylcholine and barium induced contractions of the isolated guinea-pig ileum. But the ganglionic action on gut is not great, since, in the cat, intravenous doses up to 60 mg./kg. of either drug or 240 mg./kg. ethanol in no way altered the contraction of the stomach *in situ* during vagal nerve stimulation. The results do not agree with those of Gialdroni and Grassi (1952), who found that, with the rabbit isolated intestine, methylpentynol had no "antispastic action with regard to the common convulsants (acetylcholine, histamine, barium)." The approximate equipotent molar ratios of methylpentynol and methylpentynol carbamate in reducing the response of the guinea-pig ileum stimulated electrically was 2.9:1, which agrees well with the ratio of 2.5:1 between LD50 values for intraperitoneal injection of the drugs into mice.

Methylpentynol and the carbamate in high doses elicited contractions of and augmented the submaximal acetylcholine contracture of the frog isolated rectus muscle, even in the presence of gallamine or physostigmine. Similarly, the decamethonium induced contracture of the rectus was increased. These phenomena could not be ascribed to changes in *p*H or osmotic effects of the drugs, and as neither substance dissociates into ions, an interaction with acetylcholine or similar receptors can hardly be postulated. Meng (1941) demonstrated that the sensitizing effect of alcohols and allied substances on the acetylcholine and nicotine contractions of the toad isolated rectus could not be related to inhibition of the cholinesterases but was non-specific and presumably attributable to their direct action on the muscle.

Both drugs have feeble neuromuscular blocking properties. They reduced the response of the indirectly stimulated phrenic nerve rat diaphragm preparation, the half-maximal response with methylpentynol occurring at a concentration of 2.7 mg./ml., well above that required for anaesthesia in cats. The twitch responses of the cat tibialis anterior or soleus muscle preparations in response to single stimuli applied to the sciatic nerve were unaffected by single intravenous injections of the drugs, and those of the tibialis anterior were unaltered even by infusions giving final blood concentrations of 0.64 mg./ml. of methylpentynol or of 0.45 mg./ml. of its carbamate. However, in the tetanized tibialis muscle preparation, small reductions of peak tension height followed the intravenous injections of 50 mg./kg. of the carbamate and 100 mg./kg. of methylpentynol. Quilliam (1955) noted that methylpentynol and paraldehyde produced neuromuscular block of the rat diaphragm preparation with unaltered response of the muscle to direct stimulation. Nicholls and Quilliam (1956) later concluded that the neuromuscular blocking activity of paraldehyde and methylpentynol could be accounted for only if they reduced the amount of acetylcholine released by nerve impulses.

The most striking effect of the drugs is on the central nervous system. Although anaesthesia has been said not to occur with "methylpentynol administered to dogs in sublethal amounts" (Margolin *et al.*, 1951), the experiments reported above show that unconsciousness could be produced by the intravenous injection of both drugs, persisting for at least 60 min. in one cat

given 200 mg./kg. of the carbamate. In guinea-pigs, intraperitoneal doses of 300 to 400 mg./kg. methylpentynol were followed by unconsciousness persisting for 1 to 4 hr., a similar result occurring with 100 to 150 mg./kg. of the carbamate. Brain concentrations of methylpentynol during deep anaesthesia varied between 0.34 and 0.45 mg./g. and between 0.25 and 0.35 mg./g. for the carbamate. As the wet weight of the brain is composed of about one tenth fat (McIlwain, 1955) and assuming this to behave like oleyl alcohol, then with a partition coefficient of 2.6 and a brain concentration of 0.35 mg./g. for methylpentynol, the molar concentration for anaesthesia would be 0.008 moles/l. Similarly for the carbamate, with a partition coefficient of 3.8 and a brain concentration of 0.25 mg./g., then the molar concentration for anaesthesia would be 0.005 moles/l.

The righting reflex of the guinea-pigs returned when brain concentrations of the drugs were still fairly high (0.16 to 0.19 mg./g. for methylpentynol and 0.15 mg./g. for the carbamate). This contrasts with the finding of Perlman and Johnson (1952) for rats given 800 mg./kg. of methylpentynol by gavage that no drug was found in any organ once the hypnotic effect had disappeared. The blood concentration on return of the righting reflex (some 75 to 375 min. after injection of the drugs) was 0.03 to 0.06 mg./ml. for methylpentynol or 0.05 mg./ml. for its carbamate. These blood and tissue results are consistent with the conclusion of Marley and Vane (1958) that the excretion and inactivation of either drug is slow. Their results were obtained from cats the majority of which were anaesthetized with chloralose. However, the cat has a much higher level of glucuronide excretion than other animals (Pryde and Williams, 1934), and as methylpentynol is eliminated as a conjugate of glucuronic acid (Perlman *et al.*, 1953) it could be argued that the persistence of methylpentynol or the carbamate for long periods in the cat was a consequence of their metabolic sparing, the available glucuronides having combined competitively with the chloralose. But the results from the guinea-pigs which received these drugs alone, from mice which often remained asleep 24 hr. after injection, and those from unanaesthetized rabbits in which blood concentrations of 0.030 to 0.035 mg./ml. were demonstrated for both drugs 24 hr. after their administration had ceased, show that prolonged action was not restricted to the cat under chloralose. Methylpentynol and its carbamate were shown also to persist in human beings for 48 hr. after withdrawal of these drugs (Bartholomew, Bourne, and Marley, 1958) in spite of the fact that in man (Perlman *et al.*, 1953) only minute amounts of methylpentynol are excreted as a glucuronic acid conjugate.

The failure to find any free methylpentynol in blood or brain after administration of the carbamate implies that these tissues cannot break down the carbamate, but the possibility still remains that after oral administration of the drug, acid hydrolysis occurs with release of small quantities of methylpentynol which is then absorbed from the stomach into the blood stream.

Jacobsen (1958) regarded methylpentynol as having no effect on polysynaptic reflexes. However, 30 mg./kg. doses of either drug produced quite long-lasting inhibition of the reflex increase of pulmonary ventilation following stimulation of the femoral nerve, although 40 mg./kg. doses of either drug failed to modify reflex inhibition of respiration produced by stimulating the central end of the cut vagus nerve. Single intravenous doses of 50 mg./kg. of the carbamate and 100 mg./kg. of methylpentynol significantly reduced the knee jerk which is mediated through a monosynaptic reflex and therefore should be fairly resistant to central nervous system depressants. During infusions with methylpentynol or the carbamate, reduction of the knee jerk only occurred with blood concentrations of the drugs known to be associated in cats and guinea-pigs with anaesthesia, respiration tending to fail before the knee jerk.

Quilliam (1957, 1959) obtained evidence that methylpentynol blocks transmission in the superior cervical ganglion of the cat and this was confirmed with both that substance and methylpentynol carbamate, the effect being transitory. During infusion experiments, a reduced response of the nictitating membrane to preganglionic excitation occurred only with blood concentrations of the drugs above those required for anaesthesia, but this is almost certainly due to an effect of the drug both on the membrane and on the ganglion. Suitable doses of methylpentynol or the carbamate also reduced the blood pressure response to stimulation of the peripheral end of the sectioned nerve to the left suprarenal gland, whereas the blood pressure response to injections of noradrenaline which acts directly on the blood vessels was little affected. Dicker and Steinberg (1957) found in man that 0.5 g. of methylpentynol by mouth diminished autonomic responses (increase in pulse rate or blood flow) provoked by anticipation of, or performance of, difficult tasks.

It is illuminating to contrast the almost identical results for equimolar potency ratios for the two drugs derived from a variety of whole animal and isolated tissue experiments (Table IV). The potency ratios of the drugs could well have been predicted for brain concentrations during anaesthesia (where the drug may well be distributed through a fat phase) from their equimolar potencies on the electrically stimulated guinea-pig ileum (where the drug is rapidly distributed through the Tyrode phase surrounding the tissue). That such a logical extension is possible furnishes more evidence for the consideration (Paton, 1957b) that the enteric autonomic network might be a valuable simple paradigm of the far more complicated networks of the brain itself.

TABLE IV

EQUIPOTENT MOLAR RATIOS OF METHYLPENTYNOL AND METHYLPENTYNOL CARBAMATE

The values are those obtained from experiments on whole animals or isolated organs.

	Methylpentynol	Methylpentynol Carbamate
LD50 (mice)	2·5	1
Guinea-pig brain conc. for anaesthesia (mole l.)	2·3	1
Reduction of response of nictitating membrane in the cat to preganglion stimulation	2·9	1
Reduction of knee jerk (cat)	2·9	1
ED50 (acetylcholine stimulated guinea-pig ileum)	2·1	1
ED50 (electrically stimulated guinea-pig ileum)	2·9	1
ED50 (rat diaphragm phrenic nerve prep.)	4·4	1

Thus while the distribution of methylpentynol and its carbamate in the tissues is more reminiscent of that for ethanol than that of the barbiturates, their activity resembles both types of drug but with a different order of potency. On the electrically stimulated guinea-pig ileum, methylpentynol is 77 times more potent than ethanol but approximately 14 times less so than pentobarbitone sodium, the blood concentrations associated with unconsciousness being 10 to 20 smaller than those for ethanol. Even the features of intoxication in man produced by methylpentynol or methylpentynol carbamate closely resemble that seen with alcohol or barbiturates (Marley and Bartholomew, 1958). It would be unwise therefore to stigmatize methylpentynol as only another alcohol (or the carbamate as merely its ester). Both substances exhibit a number of distinctive properties in animals and humans.

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