THE EFFECT OF INHALATION ANAESTHETICS ON BARORECEPTOR AND EFFERENT SYMPATHETIC ACTIVITY

by

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Thesis presented for the Degree of Doctor of Philosophy of the University of Edinburgh in the Faculty of Medicine, October, 1965.

ACKNOWLEDGEMENTS.

These studies were made possible through laboratory facilities kindly provided by the late Sir John Gaddum FRS at the Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge. Most of the experiments were carried out with the cooperation and assistance of Dr. T. J. Biscoe, while Professor D. Whitteridge and Dr. K. Krnjević have advised throughout. The author also appreciates the technical assistance, and help in the preparation of Figures, provided by Mr. J. B. Yates. Much of the electronic equipment used in these studies was obtained with the aid of a grant from the Board of Governors, United Cambridge Hospitals. Acid-base measurements were carried out with technical assistance and equipment supported by the Medical Research Council. Imperial Chemical Industries Ltd. provided funds for the purchase of several calibrated anaesthetic vaporizers.

CONTENTS

GENERAL INTRODUCTION

The experiments described here concern certain effects of three inhalation anaesthetics on the nervous regulation of the cardiovascular system. The anaesthetic agents studied - cyclopropane, halothane, and diethyl ether - were selected because each influences arterial pressure, and the circulation, in a characteristic and quite different manner when overdose is avoided. Thus, cyclopropane raises arterial pressure, halothane causes hypotension, and ether usually produces less deviation from control levels.

Figure 1 shows the systems examined in the present group of 5 interlinked investigations. The Figure is a diagrammatic representation of the circulatory reflex arc which was considered to be the simplest and most readily studied with present techniques. The experiments will be considered essentially in the order in which they were performed, as shown in the table of contents on p. ii.

In the first study in this series, cats were available; subsequently rabbits were used, with only a few experiments involving other species (in Study 1 and Study 4). The reasons for this were in part environmental and related to a recurrent and national uncertainty in obtaining a sufficient number of cats at the time these investigations were being planned; also, pilot studies and previous work suggested that the rabbit was especially suitable for the experiments in Study 2. Having then made successful use of rabbits in a large number of experiments, it was considered inadvisable to change to another species for Study 3 and Study 5.

BARORECEPTOR REFLEX ARC

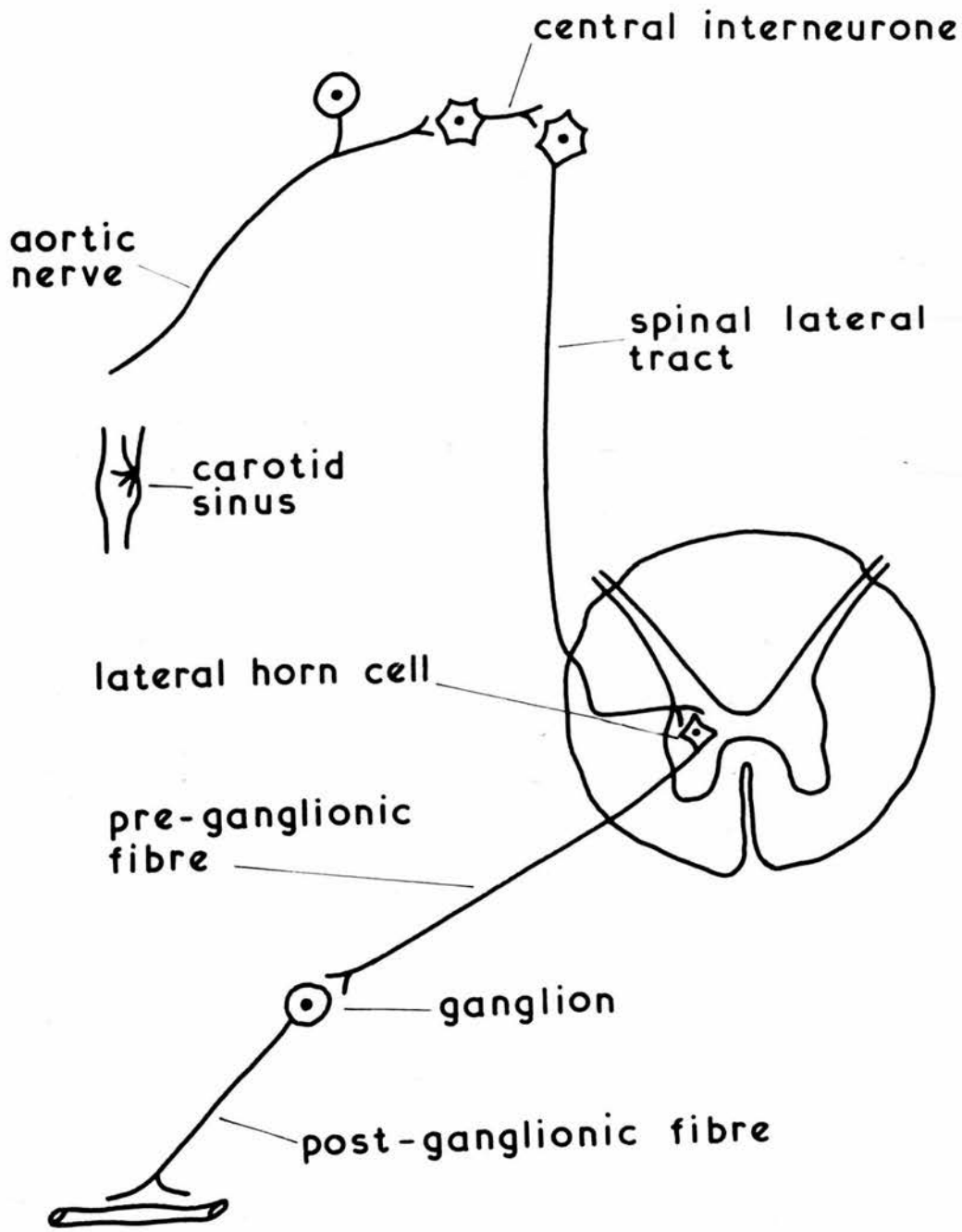


Fig. 1

It is possible, apart from technical considerations, to discern at least three factors which may have limited previous or more extended studies of this kind. Firstly, the complexity of the effects produced by general anaesthetics; secondly, and by definition, their widespread nature. Thirdly, and not unjustly, many physiologists may have considered anaesthetics largely as unfortunate necessities in laboratory investigations. But the fact that much physiological data acquired in the animal laboratory are strictly referable to the anaesthetized rather than to the conscious state, and the obvious dependence of anaesthetized animal preparations on adequate cardiovascular function, points out the need for more precise knowledge of the diverse ways in which anaesthetics may disrupt physiological systems. A more general purpose for the present studies, and sufficient in itself, is the limited current knowledge of the mode of action of general anaesthetics, in spite of 120 years of clinical use.

The rabbit is often regarded as a difficult or unsuitable animal for use in physiological studies extending over several hours. A brief account of experiences gained in the present investigations is therefore included. Finally, there is a general discussion of the possible role of the experimental findings in the cardiovascular actions of the three anaesthetics examined.

The findings of Study 1 have been published in the following paper (the manuscript was written by the author, from data obtained in collaboration with T. J. Biscoe).

"The effect of halothane on carotid sinus baroreceptor activity"
Biscoe, T. J., Millar, R. A., J. Physiol. 1964, 173, 24.

Preliminary communications referring to findings in Studies 2, 3, and 5 have been written and read by the author at scientific meetings, abstracts of which have been published:

Effect of anaesthetics on preganglionic sympathetic discharge
Millar, R. A., Biscoe, T. J. (1964).
3 Congressus Mundialis Anaesthesiologiae
Tomo 1, 120.

Effect of inhalation anaesthetics on postganglionic sympathetic discharge (Proceedings of Anaesthetic Research Group).
Millar, R.A., Biscoe, T. J. (1965)
Brit. J. Anaesth. 37, 291.

GENERAL METHODS

Apparatus employed

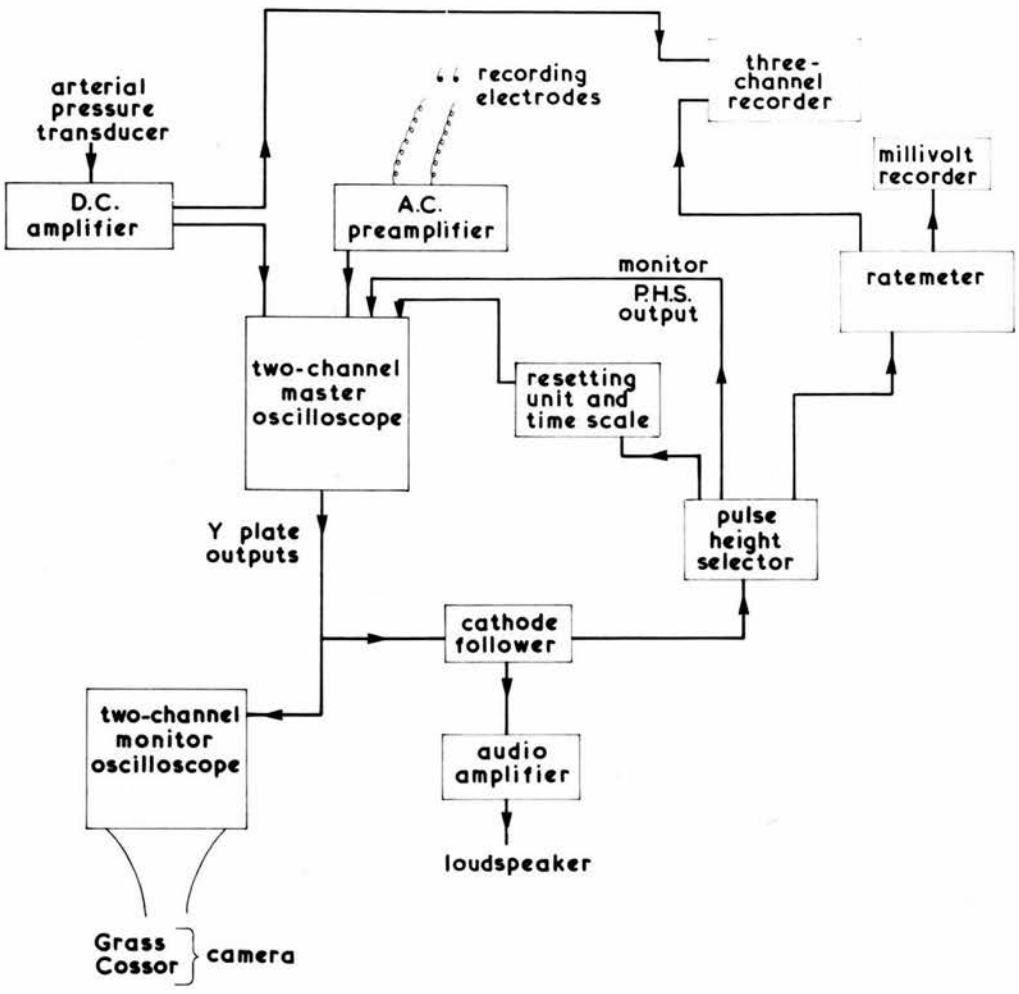
In Study 1, a standard animal operating table was used; subsequent experiments were carried out on a steel frame, freely adaptable in respect to size and attachments and mounted on a concrete table. The studies were performed within a grounded expanded-aluminium cage.

Fig. 2 shows a schematic diagram of the electronic equipment used for recording and counting of nerve impulses. Each item was faced into the screened cage, so that all electrical circuits carrying 220v. A.C. were outside the perimeter of the cage.

Recording electrodes: No. 36 Platinum wire; the attached screened leads passed through a 6 - 9" length of 5mm, outside diameter, glass tubing, to each end of which they were secured with Araldite. The glass tube was held in a micromanipulator (Prior and Company Ltd.), which was clamped to the steel table top on which the animal was placed.

A.C. preamplifier: Tektronix Type 122. The high frequency response was limited by a filter at 1 KC. The low frequency response was reduced below 80 cycles (coupling time constant 0.002 sec).

Two-channel master oscilloscope: Tektronix 502, dual beam. The Y-plate (vertical amplifier) outputs were taken to a similar monitor oscilloscope for photographing the traces displayed on the master oscilloscope. Two 6 v. miniature light bulbs were attached



SCHEMATIC DIAGRAM OF NERVE IMPULSE RECORDING AND COUNTING EQUIPMENT.

Fig. 2

above and at one side of the monitor oscilloscope tube face; one of these was used in conjunction with a standard Palmer timer for displaying time marks on moving film; the other light served as a signal marker, operated by a foot-operated relay switch.

Cossor (Study 1) and Grass cameras (Studies 2 - 5).

Pulse height selector: This was constructed by the electronics staff of the A.R.C. Institute of Animal Physiology. It was transistorised, and was designed to discriminate input pulses of up to 2 msec rise time; square pulses of 50 μsec duration, proportional in number to the discriminator output, were formed in the associated triggering and pulse-shaping circuit. The output from the pulse height selector was carried to a ratemeter and was also used to reset a time scale (see below).

The output from the upper Y-plate of the master oscilloscope was fed, through a cathode follower, to the input of the pulse height selector. Two potentiometers in the discriminator section of the pulse height selector were used to set upper and lower voltage limits to the signal delivered from the oscilloscope Y-plates. The upper voltage limit was 33 volts; since for whatever setting of the oscilloscope gain control the Y-plate voltage against earth was 6.5 v/cm, a maximum limit of 33 volts always permitted a 5 cm vertical deflection to be displayed on the oscilloscope trace. When this height was approached, the oscilloscope gain was reduced; otherwise, nerve impulse spikes which exceeded 5 cm (i.e. 33 volts) would not have been included in the total count.

In most experiments, the lower pulse height selector limit was adjusted to permit counting of all impulses remaining when noise was totally excluded with certainty. The upper voltage limit was left at maximum. Throughout every experiment, therefore, it was necessary to monitor the pulse height selector output, either directly, or by semi-continuous display of the resetting function (see below) on the lower trace of the master oscilloscope, in order to verify that changes in the signal-to-noise ratio were not influencing the individual spikes being counted. Where such a change occurred, the data were excluded from the results presented.

Resetting unit and time marker: Venner Reset Unit (Type TS 32) and Venner Frequency Source (Type TSA 602/A). The latter incorporated a 10 KC/sec crystal oscillator, and 4 decade units, providing outputs at 10 Kc/sec, 1 Kc/sec, 100 c/s, 10 c/sec, and 1 c/s. A time scale could therefore be presented according to the method described by Buller and Styles (1958), as illustrated in Fig. 6. Each dot represents 1 msec and the dots are arranged in columns of 10. Each column is displaced upwards and to the right in respect to its predecessor and after 10 columns, i.e. 100 msec, the scale resets to the base line. Alternatively, it is reset by an incoming pulse, as delivered from the output of the pulse height selector. By displaying the nerve impulse discharge on the upper oscilloscope trace, and the resetting function on the lower trace, it was possible at all times to identify the spikes being gated by the pulse height selector (and counted by the ratemeter).

Where used without the ratemeter, as in Study 1, this scale

allowed the measurement (on film) of intervals between nerve impulses to the nearest 1 msec.

With or without the resetting function, the time scale was not affected by changes in film speed.

Ratemeter: Nuclear Enterprises Ltd. High impedance input. Time constants could be selected between 0.0033 and 10 sec; the counting ranges were 0 - 10, 0 - 30, 0 - 100, 0 - 300, 0 - 1000, and 0 - 3000 per sec. In most studies, the ranges used were 0 - 100 or 0 - 300 per sec, with time constants of 0.33 or 1 sec.

The output of the ratemeter was carried, in many experiments, to one channel of a 4 channel recorder, and in all instances to a millivolt recorder.

Before each experiment the counting ranges of the ratemeter were checked; square waves at various frequencies were fed into the ratemeter from an electronic stimulator (see below) and were simultaneously displayed on the master oscilloscope for accurate determination of the impulse frequency.

Texas Instruments Servoriter: This millivolt recorder (high input impedance) was used to display continuously the ratemeter output, and to assess the changes measured throughout Studies 2, 3, and 5. The width of the scale (usually 0 - 100 or 0 - 300 impulses per sec) was $4\frac{1}{2}$ inches.

Sanborn strain gauge and D.C. amplifier: Arterial pressure was recorded by means of a Statham transducer Model P23A; this, and the connecting cannula, was filled and periodically flushed with heparinized saline, (5000 units heparin in 100 ml of 0.9% saline solution.

A Sanborn strain gauge amplifier and heated stylus recorder was used; mean arterial pressure was obtained by electronic damping of the pressure pulse. In most experiments, however, mean arterial pressure was calculated from the undamped pressure trace, in the conventional manner, as diastolic pressure plus 1/3 (pulse pressure).

In order to obtain a simultaneous display of mean integrated nerve impulse discharge (ratemeter output) and arterial pressure, the output from the Sanborn strain gauge amplifier was fed to a D. C. amplifier in one channel of a multi-channel recorder.

Sanborn 4-channel recorder: This was used for simultaneous recording of ratemeter output and arterial pressure; in a few experiments, respiration was also displayed as recorded by a Beckman infra-red carbon dioxide analyzer or by a thermistor bead placed in the tracheal cannula.

Electronic Stimulator and Stimulus Isolation Unit: Equipements Industriels, Paris. Stimulating voltages were applied to nerves through bipolar silver electrodes.

Thermosensitive Transistor Amplifier: A thermistor mounted in the tip of a probe inserted in the animal's rectum was used to regulate the current flowing through a heating pad (Krnjević and Mitchell, 1961). By this means, body temperature was maintained between 36 and 38° C.

The Beckman infra-red CO_2 analyzer incorporated a suction pump which sampled tidal air continuously from the tracheal cannula. The response time for display of tidal CO_2 was less than 100 msec for 90% deflection to full scale. In all the Figures the end tidal (alveolar) CO_2 corresponds to the upper, almost horizontal, part of the tidal CO_2 trace.

Nerve dissections

The nerves were freed from adjacent tissue by dissection under saline, using a Zeiss operating stereomicroscope; at this stage magnification was by times 6 or 10.

The nerves were laid on a stainless steel backplate, immersed in warmed liquid paraffin at 36 - 38° C, and dissected with the aid of magnification of times 16 or times 25.

During nerve dissections, use was made of fine needles, of razor blades with points sharpened on Arkansas stone and mounted in "Eclipse" pin-vice tongs, and of Salvo No.5 ultrafine forceps.

Earthing of the steel backplate to the steel frame on which the animal was placed, and from there to the A. C. preamplifier, minimised artefacts due to movement or to electrocardiographic potentials.

Cannulations

In all experiments, a metal tracheal cannula was inserted through an anterior neck incision, and a catheter was placed in a femoral vein. Intravenous and intra-arterial cannulae were of transparent vinyl tubing (Portex Ltd.).

Acid-base measurements

These were made at intervals during all the studies reported. Arterial pH was measured with a Radiometer glass microelectrode and pH Meter Model 27. Arterial P_{CO_2} was derived by the interpolation method of Astrup (1956) applied to whole blood. Standard bicarbonate i.e. the bicarbonate concentration in fully oxygenated whole blood

at Pco_2 40 mm Hg and at 38° C., was obtained from the nomogram of Siggaard Andersen et al. (1960).

Drugs

Sodium Pentobarbitone (Nembutal, veterinary solution, 60 mg/ml; Abbott Laboratories Ltd.).

Ethyl carbamate (Urethane, Hopkin and Williams Ltd.).

Chloralose (Hopkin and Williams Ltd.).

Heparin (5,000 International Units/ml., Evans Medical Ltd.).

Adrenaline Chloride (1 mg adrenaline base/ml., Evans Medical Ltd.).

Gallamine triethiodide (Flaxedil, 80 mg/ml., May and Baker Ltd.).

Hexamethonium Tartrate (Powder, May and Baker Ltd.).

Dextran, 6% in 0.9% saline (Intradex, Glaxo Laboratories Ltd.).

Halothane B.P. (Fluothane , I.C.I. Ltd.).

Diethyl ether (Anaesthetic Ether, May and Baker, Ltd.).

Cyclopropane, oxygen, carbon dioxide in oxygen, (British Oxygen Company Ltd.).

Statistical analysis of the data obtained in these studies was performed according to Snedecor (1959), and Fisher and Yates (1957); whenever possible, and most frequently, the paired t-test was used.

Administration of Inhalation Anaesthetics.

When the lungs were ventilated mechanically, as during the period of actual measurement in all the studies described, a Palmer pump was employed.

Toward the end of the preparatory period in all experiments, and earlier in many others, the lungs were inflated with 100% oxygen.

The inspiratory side of the Palmer pump was connected to a 2 l. rubber bag into which oxygen and the anaesthetics were passed.

The rate of ventilation was maintained at approximately 36 per minute, except when the effect of falls in ventilation rate was studied (see Fig. 22). The stroke volume was adjusted to maintain the end tidal CO_2 concentration in the range 3-5% (the stroke volume set on the Palmer pump was between 25 and 35 ml.).

through a Fluotec Mark II vaporizer; this was specially calibrated by Dr. H. G. Epstein (Physicist, Dept. of Anaesthetics, University of Oxford), and shown to be accurate to within 0.1 vol % at dial settings of 2 and 3% halothane and gas flow rates of 4 l./min.

Between the 2 l. bag and the halothane vaporizer a Heidbrink-type expiratory valve was placed; this was left in the open position to allow partial escape of the gas flows necessary for accurate vaporization of halothane, in order to avoid pressure effects which might have affected the concentrations of anaesthetic delivered (Hill and Lowe, 1962).

Selected concentrations of diethyl ether were obtained by dilution with oxygen of saturated ether vapour delivered from a Copper Kettle (Morris, 1952); the temperature within the vaporizer was measured with a mercury thermometer.

METHODS (contd.)

Study 1

Eight cats were used, of which six were anaesthetized with sodium pentobarbitone (40 mg/kg intraperitoneally) and two were given ethyl chloride and ether followed by chloralose (80 mg/kg intravenously); two rabbits were anaesthetized with intravenous urethane, 1.5g/kg; three goats and two dogs were given a mixture of chloralose (100 mg/kg) and urethane (1 g/kg) intravenously. The anaesthetics were supplemented by occasional doses of the same anaesthetic or, in one goat and one dog, by injections of sodium pentobarbitone.

The trachea was cannulated, and the carotid sinus nerve was approached from the medial side by reflection of the larynx and pharynx. The external carotid artery was ligated distal to the origin of the lingual artery, which was also tied. The occipital and internal carotid arteries were ligated when present, but other small arterial branches were left patent. Heparin 1 mg/kg was given intravenously. The apparatus used to apply static pressures to the carotid sinus (Fig.3) was similar to that described by Price & Widdicombe (1962). A T-cannula was inserted into the common carotid artery at the level of the superior thyroid artery, the vertical limb of the cannula being connected by a soft plastic tube provided with a clamp to a glass reservoir of 50 ml capacity. The upper end of the reservoir was attached to a rubber tube from a mercury manometer and a sphygmomanometer bulb. The flow rate out of the reservoir was tested by partly filling it with blood from the carotid artery.

Fig. 3

A diagram to show the experimental arrangement used for the application of pressure to the carotid sinus. The carotid artery clamp is normally open and the reservoir clamp is closed. The reservoir is filled by releasing its clamp. Both clamps are then closed and the response of the sinus to a step-wise rise in pressure is tested by raising the pressure in the reservoir with the sphygmomanometer bulb and releasing the reservoir clamp.

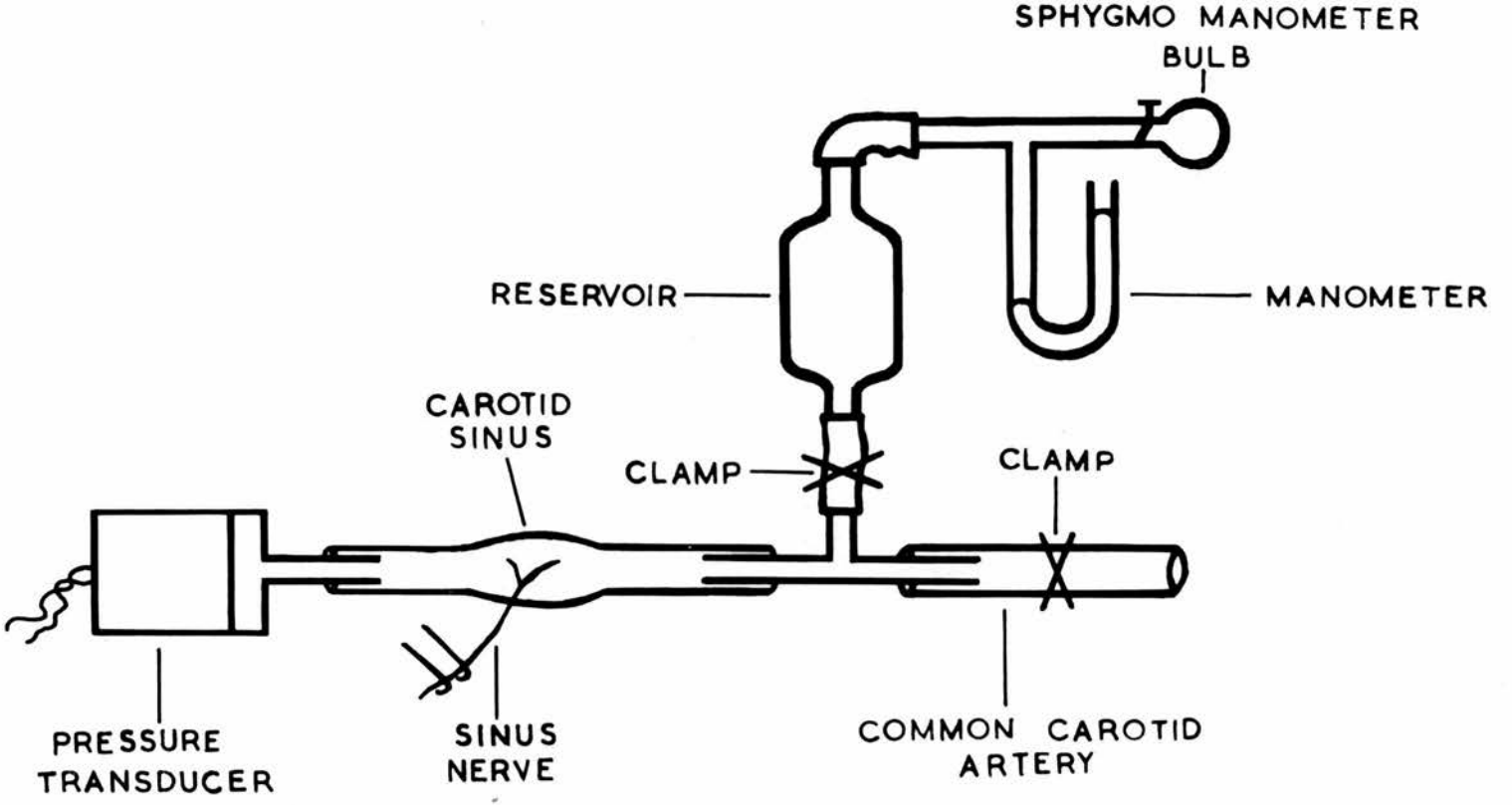

SPHYGMO MANOMETER
BULB
RESERVOIR
MANOMETER
CAROTID
SINUS
CLAMP
CLAMP
PRESSURE
TRANSDUCER
SINUS
NERVE
COMMON CAROTID
ARTERY

Fig. 3

The common carotid artery was clamped proximal to the cannula and the pressure within the reservoir was raised to 150 - 200 mm Hg. If the flow rate out of the reservoir was greater than about 5 ml./min, small arterial branches in the sinus region were tied off until a slower flow was obtained. The blood was then expelled from the reservoir by raising the pressure within it and removing the clip from the carotid artery; the soft plastic tube on the vertical limb of the cannula was clamped when it was almost empty.

When static pressures were applied to the reservoir the actual pressure in the sinus was higher than that shown by the mercury column by the height of the blood column within the reservoir. Sinus pressures (and the systemic arterial pressure when static pressures were not being applied) were recorded through a cannula inserted in the external carotid artery.

The sinus nerve was exposed and dissected in warm liquid paraffin until a single active baroreceptor fibre was obtained. Action potentials were recorded from strands of nerve and displayed on one beam of the oscilloscopes. On the other beam the time scale and resetting function was presented; this is illustrated in Fig.6.

Testing the receptor: About 10 ml. blood in cats and rabbits and about 20 ml. blood in dogs and goats was allowed to run into the reservoir, after which the common carotid artery was clamped on the cardiac side of the T-cannula. Transient small changes in systemic arterial pressure were sometimes associated with this manoeuvre before and during halothane administration. The threshold of the receptor for a continuous discharge of the

baroreceptor unit was measured by raising the air pressure in the reservoir. While the threshold pressure required to initiate firing could be estimated roughly for any particular fibre, accurate determination would have required a prolonged period to ensure consistent use of an identical pressure wave form; because of the pronounced systemic hypotension induced invariably by halothane, the more expeditiously determined threshold pressure for continuous firing was measured. The sinus was next exposed to a series of pressure steps each of approximately 20 mm Hg; in this manoeuvre the tube from the T-cannula to the reservoir was clamped and the pressure in the reservoir was raised; the clamp was then rapidly released and the sinus exposed to the pressure wave. After 3 - 4 sec the pressure was lowered to the base line, and the clamp was replaced. The procedure was then repeated at a higher pressure. A Spencer Wells artery forceps was used to clamp the connecting tube; this (with its spring loaded release) was simple to use and was easily capable of withstanding pressures up to 250 mm Hg without a slow leak. Fig. 5 shows the pressure step to be very nearly a square wave with some overshoot; the pressure waves as shown on the Sanborn recorder were not altered during halothane administration. The burst of action potentials associated with each of the pressure increments was photographed. The time taken to measure threshold and make a complete run of exposure to pressure was usually 3 - 4 min. Since the common carotid artery was clipped during this time, equilibration of the baroreceptors with halothane in this period depended on the flow of blood from the reservoir.

Measurements were made of: (a) the threshold of a receptor for continuous firing, (b) the shortest interval between nerve impulses on exposure to a pressure step, or in some cases the mean of the three shortest intervals (thus obtaining an index of the peak frequency of discharge), (c) the mean of three intervals between nerve impulses 1 sec after the shortest interval on exposure to a pressure step. The reservoir was too small in most of the experiments to measure the rate of adaptation beyond 2 - 3 sec, since the pressure in the reservoir sometimes fell a few mm Hg, especially at the higher pressures, as blood flowed through the sinus. Measurements were not made of adaptation, post-excitatory depression, the response to a pulsatile pressure, or the threshold pressure at which the receptor was first stimulated.

Cats and rabbits were allowed to breathe air spontaneously until shortly before starting the dissection of the sinus nerve; artificial ventilation with air was begun in dogs and goats soon after initial induction of anaesthesia. At least 30 min before the first pre-halothane control responses were measured, artificial ventilation with 100% oxygen was started in all experiments, and continued thereafter.

Acid-base measurements revealed that a progressive metabolic acidosis developed in all 4 species over the several hours of preparation required before single baroreceptor fibres could be studied. However, the effect of this on arterial pH was usually limited by inducing a respiratory alkalosis by pulmonary over-ventilation. The lowest pH measured, (in a dog), was 7.22, and

the highest, (in a cat), was 7.50. Arterial P_{CO_2} in the cat, goat, rabbit and dog averaged respectively 16, 20, 22 and 36 mm Hg. In the first studies by Bronk and Stella (1935), it was stated that baroreceptor discharge was insensitive to variations in the CO_2 and O_2 content of blood. In the experiments to be described oxygen lack can be discounted.

Study 2

Experiments were performed on 58 rabbits given sodium pentobarbitone intravenously as the basal anaesthetic. The dose initially required was assessed on the basis of respiratory rate, corneal reflex, pupil dilation, and response to a painful stimulus; it was usually 40 - 50 mg/kg. Subsequent injections were made through the femoral vein catheter. Mechanical ventilation with 100% oxygen was usually begun immediately. During the period of preparation the animals were given intravenous doses of 6 to 12 mg of pentobarbitone at intervals of approximately 45 minutes. The amounts required to maintain light and even anaesthesia were assessed prior to the injection of gallamine, and were given subsequently throughout the remainder of the experiment except during administration of the inhalation anaesthetics. These were given at least 30 min after any previous injection of pentobarbitone; further injections of pentobarbitone were administered after recovery from each inhalation anaesthetic.

Gallamine triethiodide was injected intravenously in doses of 4 mg at intervals of 45 - 60 minutes before and during studies of the inhalation anaesthetics. The first injection was given toward the end of the preparatory period. The muscle relaxant prevented spontaneous respiratory movements which could have interfered with nerve potential recording, and helped to ensure

steady mechanical ventilation of the lungs.

Nerve stimulation and recording. The aortic (depressor) and preganglionic cervical sympathetic nerves were exposed by reflecting the larynx and pharynx in the midline. In ten experiments the right aortic nerve, and in the remainder the left nerve was cut and dissected free for about 1 cm, for stimulation with constant voltage square wave shocks. In 35 rabbits both aortic nerves were cut; in 3 animals, both vagus nerves were cut in addition; and in another 3 rabbits the aortic, carotid sinus and vagus nerves were cut bilaterally.

The compound action potential in the aortic nerve was monitored in 9 experiments, at a point either proximal or distal to the stimulating electrodes, and the potential was photographed from an oscilloscope. The amplifier time constant was 1 sec. At the end of the experiment the aortic nerve was dissected out and removed; the length of nerve between the recording electrodes and the stimulating cathode was then measured with a horizontal micro-manipulator having a Vernier scale accurate to 0.1 mm.

In 11 rabbits, including the 3 in which the carotid sinus, aortic, and vagus nerves had been divided bilaterally, recordings were made from the cervical sympathetic nerve. The technique used was as described in Study 3 (p. 18 and Methods p.6).

Intravenous injections of adrenaline ~~hydr~~chloride (5 - 20 µg) were given in all studies involving sympathetic nerve recording, to obtain evidence that the impulse discharge was inhibited by a rise in arterial pressure, and to test the effectiveness of baroreceptor denervation.

Measurement of arterial pH, Pco_2, and standard bicarbonate were made at intervals in 12 experiments of Study 2. The means of the lowest (n = 12) and highest (n = 12) acid-base values from these experiments were respectively: for arterial pH, 7.35 (S.D. ± 0.10) and 7.46 (S.D. ± 0.08); for arterial Pco_2, 24 mm Hg (S.D. ± 6.1) and 33 mm Hg (S.D. ± 7.7); and for standard bicarbonate 17.4 mM/l (S.D. ± 2.8) and 21.9 mM/l (S.D. ± 2.6). This assessment is intended to show the variations in the limits within experiments. Several measurements were made in each of the 12 rabbits, and if a mean value for each experiment had been taken the common mean would have disregarded the variations within individual experiments.

Study 3

Twenty-three rabbits were anaesthetized intravenously with sodium pentobarbitone. The initial dose, maintenance of background anaesthesia, administration of gallamine triethiodide, and general methods were as described for sympathetic nerve recording in Study 2 (see Methods p. 6 and p. 15).

Maintenance of the mean arterial pressure at 80 - 100 mm Hg, as was usually possible, together with mechanical ventilation with 100% oxygen, allowed the experiments to be continued for long periods.

Exposure of the left or right cervical sympathetic nerve, by reflection of the larynx and pharynx in the midline, also gave access to the carotid sinus and aortic depressor nerves.

The splanchnic and adrenal nerves were approached from the lateral side retroperitoneally. In the rabbit there were frequently 2 splanchnic nerves, emerging from below the diaphragm and running towards the coeliac ganglion. Several branches usually passed to the adrenal gland; these were very small and could be identified only by using the operating microscope. Electrical stimulation of the splanchnic nerves, which produced the classical 2-phase rise in arterial pressure (Liddell & Sherrington, 1929) confirmed that they were efferent nerves to the adrenal gland; the second phase was abolished by section of the adrenal nerves. In one rabbit there was a well marked ganglion at the level of the adrenal gland, at a distance of 1-2 cm from the coeliac ganglion.

In order to ensure a sufficiently wide sampling of sympathetic fibres, recordings were made from slips of nerve containing several

or many active units. The sympathetic discharge was observed on the master oscilloscope for periods of 30 - 60 min, to establish the stability of the responses and of the signal-to-noise ratio. When these were shown to be satisfactory and constant, sympathetic nerve recordings were started, and could usually be maintained for several hours.

In all experiments, intravenous injections of adrenaline chloride were given to study the effect of increased arterial pressure on preganglionic sympathetic discharge. Sympathetic nerve strands were accepted for study on the basis of unequivocal inhibition of the discharge by a rise in arterial pressure. In every animal in which the carotid sinus and aortic nerves had been divided, absence of the baroreceptor-induced inhibition of sympathetic activity was confirmed by intravenous injections of adrenaline.

Respiration was occasionally monitored, qualitatively, by means of a thermistor probe in the tracheal cannula, the output from the associated bridge circuit being displayed on the multichannel recorder.

In 4 experiments, 0.5 ml. samples of arterial blood were withdrawn and the Po_2 was measured polarographically, using a Beckman Physiological Gas Analyzer Model 160. The arterial Po_2 was consistently above 250 mm Hg, the level being approximately halved when cyclopropane was given; halothane or ether anaesthesia was associated with insignificant changes in arterial oxygen tension.

In 10 animals the end-tidal CO_2 concentration was monitored

continuously with an infra-red analyzer (Beckman), and was maintained usually in the range 3 - 4%, by adjustment of the stroke volume of the respiration pump. The analyzer output was fed to the multi-channel recorder.

In two experiments the expired halothane concentration was measured with an ultraviolet halothane meter (Hook and Tucker, Ltd).

The three inhalation anaesthetics were usually studied in the order corresponding to their speeds of uptake and elimination: cyclopropane, halothane, ether. Sufficient time was allowed between each administration to permit maximum recovery of arterial pressure and sympathetic activity toward control levels. This occurred rapidly after cyclopropane, but in all cases the administration of another inhalation anaesthetic was delayed at least until the recovery period exceeded that of exposure to the preceding agent, and usually the delay was one and a half to two times the duration of the previous administration.

The times of administration presented here, and in all studies, include a lag of about 1 min due to the gas volume contained in the inspiratory delivery tube between the respiration pump and the animal.

Acid-base measurements were made in 11 experiments. The means of the lowest (n = 11) and highest (n = 11) values from each experiment were respectively: for arterial pH, 7.35 (S.D. $\pm$ 0.07)

and 7.44 (S.D. ± 0.06); for arterial Pco_2, 27 mm Hg (S.D. ± 4.6) and 32 mm Hg (S.D. ± 4.6); and for standard bicarbonate 18.0 mM/l. (S.D. ± 2.8) and 21.3 mM/l. (S.D. ± 2.8).

Study 4

Anaesthesia in rabbits was induced with intravenous sodium pentobarbitone, and in cats with intraperitoneal sodium pentobarbitone, 30 mg/kg; light anaesthesia was maintained during the period of preparation, with doses of 6 - 12mg given intravenously at intervals of 45 min or longer. Mechanical ventilation with 100% oxygen was started at least one hour before the administration of the inhalation anaesthetics; gallamine triethiodide was given, and the methods followed were as described for Studies 2 and 3.

Nerve action potentials were recorded, and a change in the amplitude of the postganglionic compound action potential was regarded as an indication of an effect on nerve impulse transmission through the ganglion. The amplifier time constant was 1 sec. The ganglia studied were the superior cervical ganglion in the rabbit and cat; the stellate ganglion in the cat, and the inferior mesenteric ganglion in the rabbit.

Superior cervical ganglion: The preganglionic cervical sympathetic nerve was stimulated cephalad to the middle cervical ganglion. The post-ganglionic compound action potential was recorded from one or more of the following branches: the external carotid nerve, the carotid body nerve, the internal carotid nerve, or between a postganglionic branch and the ganglion.

In one cat, studies were carried out following mid-collicular decerebration under halothane/oxygen anaesthesia, which was then discontinued; the animal was subsequently ventilated with oxygen, no pentobarbitone being given.

The stellate ganglion was studied in 3 cats and was approached by the procedure introduced by Anderson (1904) and elaborated by Liddell and Sherrington (1929). The cardiac nerves were identified anatomically (Holmes and Torrance, 1959; Sjöqvist, 1963) and also from the increase in heart rate and arterial pressure which occurred on electrical stimulation. There were usually two nerves, the larger of which was used for recording the postganglionic compound action potential. Various preganglionic nerves were stimulated in different experiments but usually the largest postganglionic potential was evoked from the 3rd and 4th thoracic branches.

Inferior mesenteric ganglion: A midline lower abdominal incision was made, and structures were retracted from the posterior abdominal wall with the aid of saline-soaked swabs. Several preganglionic branches of the inferior mesenteric ganglion were stimulated, and recordings of the postganglionic potential were made from the inferior mesenteric and hypogastric nerves.

Stimuli were delivered at 1/sec, 100 μsec duration, and variable intensity.

At the end of the experiment, hexamethonium (20 mg/kg) was usually administered to confirm that the potentials observed were postganglionic in origin.

Study 5

Eighteen rabbits were given sodium pentobarbitone intravenously as the basal anaesthetic. The methods employed, including those for sympathetic nerve recording, were as described in Studies 2 and 3. In some experiments the vagi, aortic, and carotid sinus nerves were divided. The sympathetic postganglionic nerves studied were the external carotid and carotid body branches of the superior cervical ganglion, and the cardiac and hypogastric nerves.

The external carotid nerve was approached by reflecting the pharynx and larynx in the midline to expose the superior cervical ganglion. In the rabbit there were several small postganglionic sympathetic branches coursing over the carotid sinus towards the external carotid artery, and also one branch to the carotid body. These nerves were bound in connective tissue around the artery; there was usually one postganglionic carotid nerve of sufficient length to dissect readily.

The cardiac nerve. The approach to the cardiac nerve in the rabbit was similar to that described for the cat by Liddell & Sherrington (1929). The scapula was subluxated and rotated ventrally and medially by traction on the forelimb. This manoeuvre exposed the dorsal surface of the thoracic cage. The first to the 4th ribs were removed from the angle to near the joint with the vertebrae. Preservation of an intact pleura was almost impossible, and was not attempted, because of its thinness and firm adherence to the ribs.

The phrenic nerve, the most ventral of the nerves in the region, was identified as it crossed the subclavian artery and coursed over the pericardium. The vagus nerve lay dorsal to the subclavian artery, running towards the root of the lung lateral to the trachea. The stellate ganglion in the rabbit was not a discrete pearl-like structure as in the cat but lay behind the brachial plexus, above the first rib, apparently fused with the middle cervical ganglion and receiving branches from the thoracic roots and sometimes from the vagus nerve. The cardiac nerve emerged from the caudal side of the ganglion plexus to pass dorsal to the subclavian artery. On the right side there were usually two tributaries of the innominate vein which passed dorsally towards the vertebral column at about the level of the second rib. The right cardiac nerve and the vagus lay deep to these veins, and were reached by dividing them. The cardiac nerve on both sides emerged dorsal to the subclavian artery and ventral to the vagus nerve and was buried deep in fat as it ran towards the heart. It lay ventro-medial to the vagus, was grey in colour, and was smaller than the phrenic or vagus nerves. The identification was confirmed by stimulating the cardiac nerve before it was divided; this produced a small rise in arterial pressure and heart rate (Liddell and Sherrington, 1929).

The hypogastric nerves. These were approached through a midline abdominal incision, the intestines being retracted with cotton wool swabs. The nerves were identified as they left the inferior mesenteric ganglion plexus around the origin of the inferior mesenteric artery, passing over the sacrum into the pelvis. There were usually several nerve strands of varying size.

Hexamethonium (20 mg/kg) was injected intravenously at the conclusion of some experiments, to confirm that the nerve potentials studied were postganglionic.

Measurements of arterial pH, Pco_2 and standard bicarbonate were made at intervals in 7 experiments, during assessment of the effects of the inhalation anaesthetics on postganglionic sympathetic discharge. The means of the lowest (n = 7) and highest (n = 7), acid-base values from each experiment were respectively: for arterial pH, 7.37 (S.D. ± 0.09) and 7.47 (S.D. ± 0.03); for arterial Pco_2 22 mm Hg (S.D. ± 6.2) and 29 mm Hg (S.D. ± 12); and for standard bicarbonate 18.6 m.M/l. (S.D. ± 2.6) and 20.1 m.M/l. (S.D. ± 2.3).

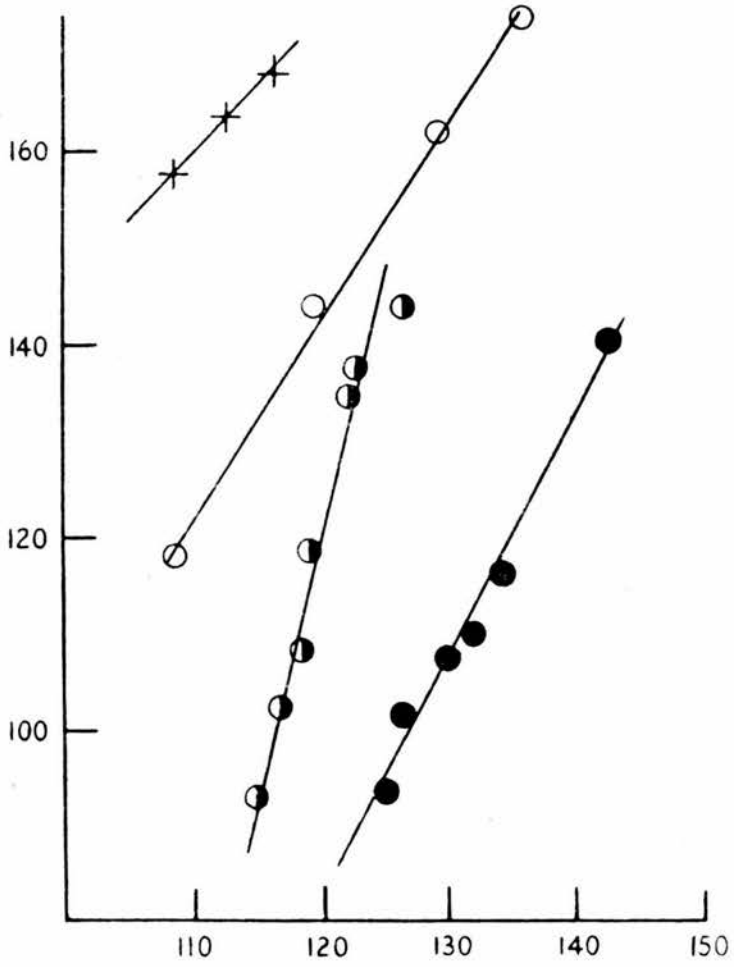
STUDY 1. THE EFFECT OF HALOTHANE ON CAROTID SINUS BARORECEPTOR ACTIVITY.

Introduction

Hëring (1927) stimulated the carotid sinus mechanically during chloroform anaesthesia, and suggested that in certain stages of anaesthesia the sensitivity of the afferent baroreceptor mechanism might be increased. This led to the study by Robertson, Swan and Whitteridge (1956), who showed for the first time that the inhalation anaesthetics diethyl ether, chloroform, and trichlorethylene exerted local effects on carotid sinus and aortic baroreceptors which might contribute to arterial hypotension and bradycardia during anaesthesia. These workers, in 1 experiment involving the aortic (depressor) nerve in a cat with normal circulation, and in 4 experiments involving perfusion of the carotid sinus region with the animal's own blood, showed that the number of impulses recorded from single baroreceptor units, over a range of pulsatile arterial pressures, was increased by 10 - 15% ether, and by 2 - 4% chloroform or trichlorethylene. This effect, which was termed sensitization, is illustrated in Fig.4 (from Whitteridge, 1958). In addition, the pressure threshold at which a baroreceptor fibre began to discharge was lowered by the anaesthetics.

In later experiments (Robertson and Swan, 1957) the addition of ether to Tyrode solution perfusing the carotid sinus at constant pressure caused a fall in systemic arterial pressure; this

SENSITIZATION OF A PRESSURE RECEPTOR FROM THE CAROTID SINUS, FOLLOWED BY DESENSITIZATION BY INHALATION OF 20% ETHER



Abscissae: pressure (mm. Hg)

Ordinates: impulses/sec.

● control observation

◑ after administration of 20% ether for 30 sec.

○ after administration of the same concentration of ether for 1.5 min.

\+ after administration of the same concentration of ether for 4.5 min.

At first the nerve-ending is sensitized, but although its frequency of discharge remains high, after 1 min. it becomes less sensitive to a change in carotid blood pressure.

(Whitteridge, 1958)

Fig. 4

suggested, in the absence of complicating actions of the anaesthetic on central baroreceptor pathways, that sensitization of the afferent mechanism was capable of exerting systemic effects. Subsequently, in the same experiments, arterial pressure increased and hypotension no longer occurred when the carotid sinus pressure was raised; this implied that depression of the baroreceptor nerve endings was eventually produced by the anaesthetic.

Additional findings of Robertson and Swan (1957) were that the reflex fall in arterial pressure, and bradycardia, induced by raising the carotid sinus pressure were initially increased by addition of ether or chloroform to the perfusing fluid. Also, when cats breathed high concentrations of ether, chloroform, or trichlorethylene, the fall in arterial pressure which occurred was lessened if the carotid sinus and aortic (depressor) nerves had been previously divided bilaterally.

The anaesthetic gases, nitrous oxide and cyclopropane, were tested by Robertson, Swan and Whitteridge (1956) and were found to be without effect on systemic baroreceptor discharge. However, baroreceptor sensitization was later reported to occur during cyclopropane anaesthesia in the cat and dog (Price and Widdicombe, 1962). The latter workers used static (non-pulsatile) pressures, with the methods employed for Study 1 in the experiments to be described here.

Halothane was not available at the time of the first studies of Robertson, Swan and Whitteridge (1956), but it was later suggested (Whitteridge, 1958) that this anaesthetic had no

definite effect on baroreceptor activity. Since halothane consistently causes arterial hypotension, further experiments were carried out to re-investigate the action of the anaesthetic on carotid sinus baroreceptor discharge in the cat, rabbit, goat and dog.

Results.

An increase in pressure in the carotid sinus, at levels above the threshold of the baroreceptor unit being studied, caused an immediate burst of impulses (Fig.5); while the pressure was held constant over the next 2 or 3 sec the response diminished as partial adaptation occurred (Figs. 5 and 6).

Figure 6 illustrates, for representative single baroreceptor fibres in the dog, cat, rabbit and goat, the usual discharge to pulsatile arterial pressure, together with the responses to various pressures applied artificially to the carotid sinus; the time-marking and resetting functions are also shown.

The means of the three shortest intervals measured, and the means of three intervals 1 sec later, are plotted separately against applied pressure in Fig.7, which illustrates the effects of various concentrations of halothane in the four species studied. These baroreceptor units exhibited an increased discharge over a wide range of applied pressures during halothane anaesthesia, shown by a shortening of the intervals between nerve impulses; subsequently this effect will be termed sensitization.

The shortest times of exposure for an effect to be apparent were of the order of: 2 - 3 min at a halothane concentration of 3%; 3 - 5 min at 2%; 6 - 7 min at 1 - 1.5%. Continued administration of the same anaesthetic concentration resulted in a progressive increase in sensitization to a maximum with no

Fig. 5

Two responses were recorded from a single baroreceptor fibre of the cat (upper trace in each record) on exposure of the carotid sinus to the pressure wave form in the lower trace of each record. a, shows the effect of an increase of intrasinusal pressure of 60 mm Hg; b, an increase in pressure of 105 mm Hg. The pressure was applied at the arrow. Time mark, 0.5 sec.

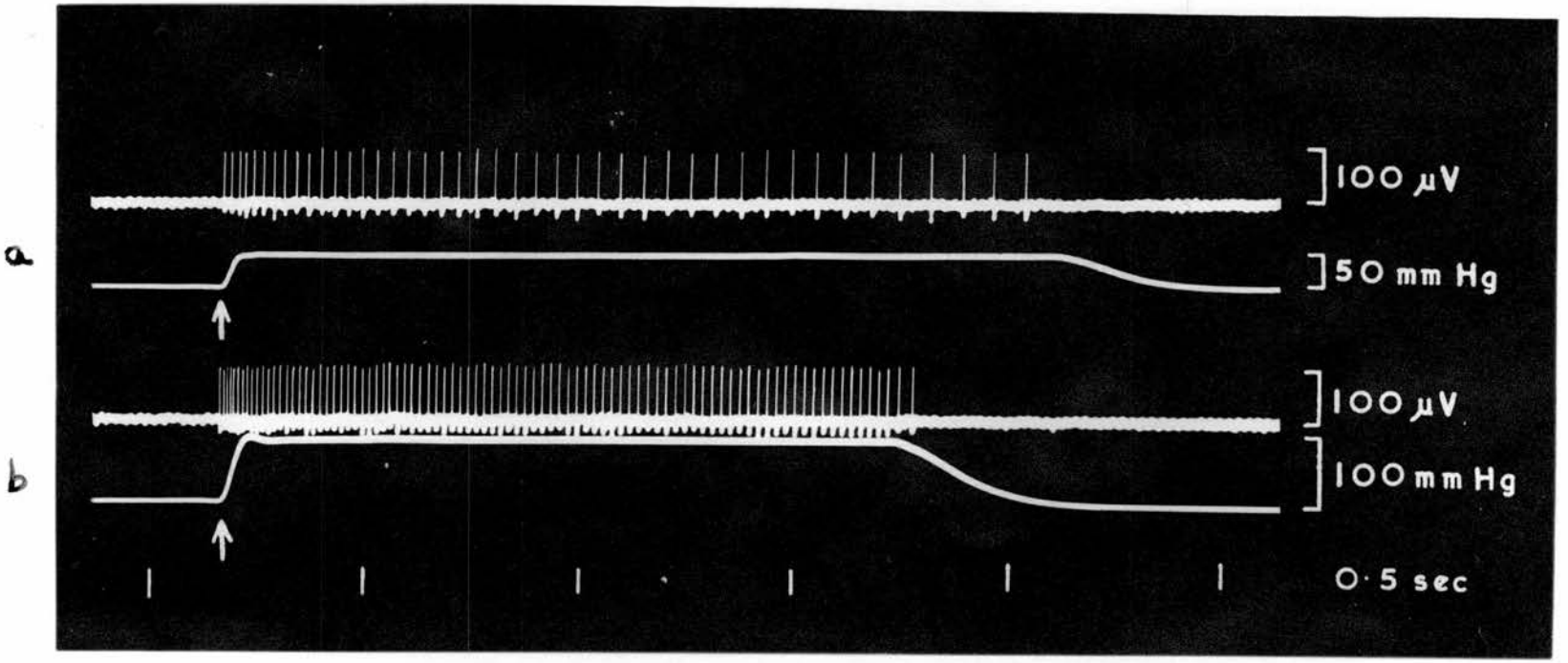


Fig. 5

Fig. 6

Single baroreceptor fibre responses, with resetting time scale, in the cat (A), rabbit (B), goat (C), and dog (D); the records on the left show the impulse discharge in response to the arterial pressure wave, and on the right the responses to pressure applied at the arrow; this was respectively 161, 91, 59 and 108 mm Hg from above downwards.

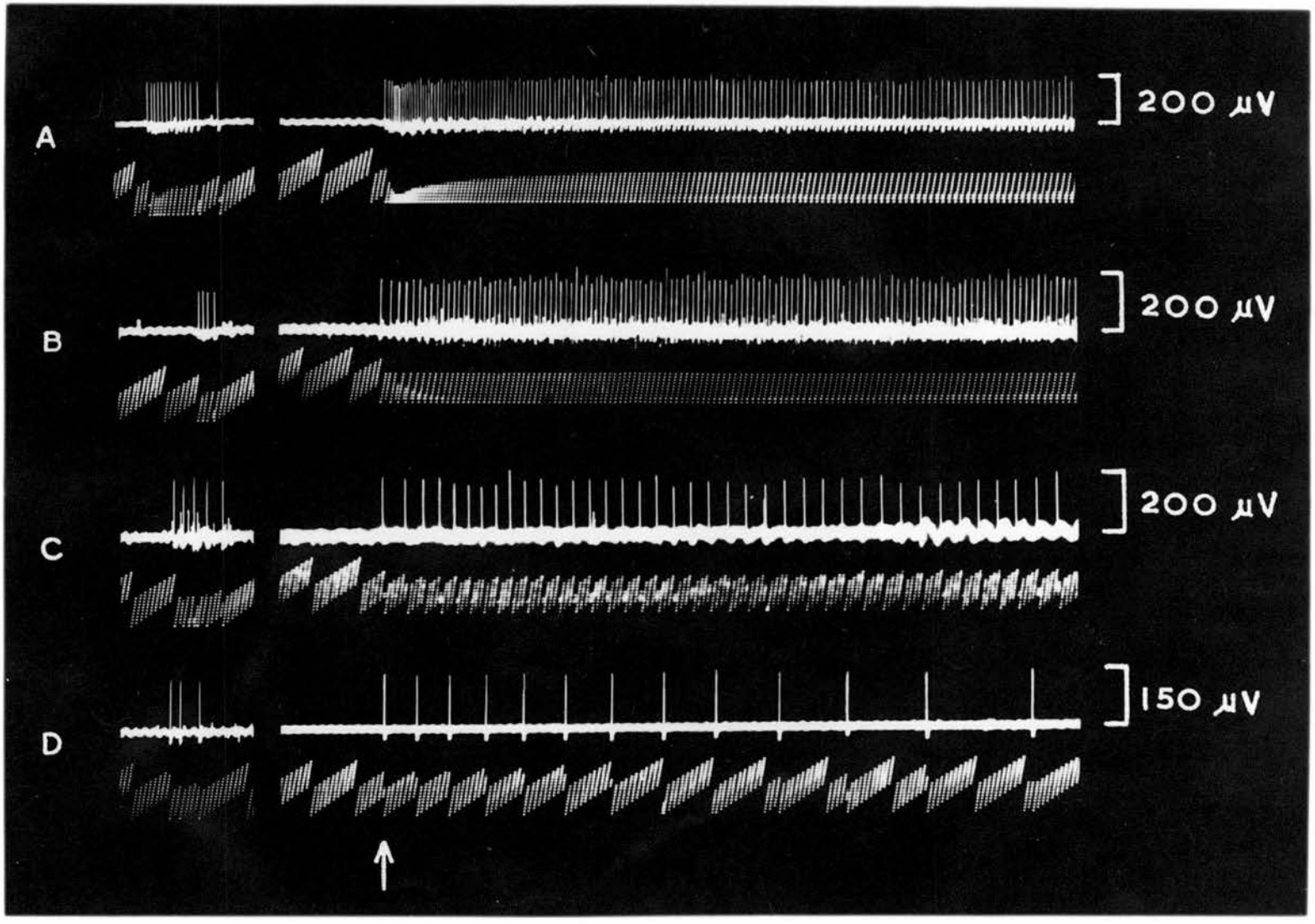


Fig. 6

Fig. 7

Graphs relating the mean of the three shortest intervals between impulses (left) and the mean of three intervals 1 sec later (right) to pressure applied to the carotid sinus, for single baroreceptor fibres in a cat (A), goat (B), dog (C), and rabbit (D). Control responses, O; those during halothane anaesthesia, ●. A, 13 min 2% halothane; B, 31 min 1% halothane; C, 5 min 2% halothane; D, 6 min 2% halothane.

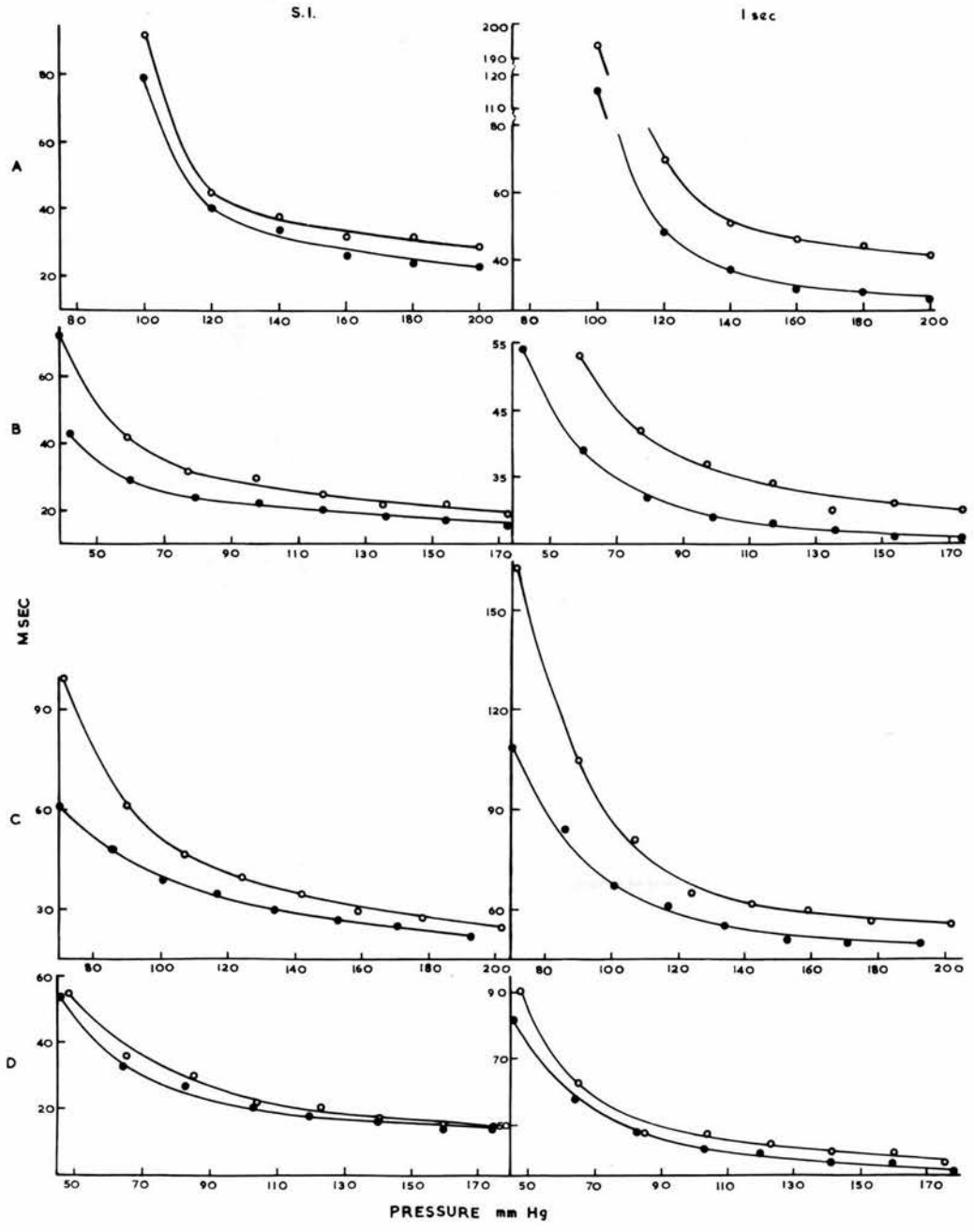


Fig. 7

evidence of recovery until the anaesthetic was discontinued (Figs. 8 and 9); if the concentration of halothane was reduced, for example from 2 to 1%, there was sometimes a small reverse trend toward control levels. The effects of increasing concentrations, or of those above 3%, were not studied because of the profound circulatory depression which resulted; also, concentrations above 3% are seldom required for anaesthesia.

Cats.

In the 6 cats given sodium pentobarbitone as basal anaesthetic there were 14 exposures of 12 baroreceptors to 1 - 3% halothane. Measurements were made of the effects of halothane administration at periods extending from 2 to 44 min. The reciprocal of the mean of the three shortest intervals was taken to indicate the peak frequency of discharge, and similar measurements were made 1 sec later.

Table 1 shows the mean maximum increase in frequencies during halothane anaesthesia expressed as a percentage of the averaged pre- and post-halothane control values, at two pressures from the range applied to the carotid sinus. p_1 was the lowest pressure at which baroreceptor discharge continued for longer than 1 sec, p_2 was the nearest recorded pressure equal to p_1 plus two-thirds of p_1. The increases differ significantly from zero.

Table 1. Data from 14 tests on 12 baroreceptor fibres from 6 cats given sodium pentobarbitone. The mean percentage increase in discharge frequency during halothane administration is indicated at two intrasinus pressures, p_1 and p_2.

	peak frequency		+ 1 sec frequency	
	p_1	p_2	p_1	p_2
Mean % increase with halothane	48	25	60	27
S.E. of mean	±10.5	±6.7	± 15.1	± 4.9
P	<0.005	<0.005	< 0.005	<0.001

P is the probability that the means differ significantly from zero

Further, the increase in discharge was significantly greater at the lower pressure than at the higher pressure for the 1 sec measurements; S.E. of the difference between the means ± 15.8, d.f. 24, $0.05 > P > 0.025$. The difference was not significant at the peak discharge frequency, S.E. ± 12.5, d.f. 25, $0.1 > P > 0.05$.

From the examples of sensitization shown in Figs.7A and 8, the mean percentage change in the rate of discharge was calculated by converting the interval measurements into frequencies and comparing them over the whole of each pressure range. The mean percentage increases in frequency were: in Fig.7A, 26% for the peak and 50% for the 1 sec rates of discharge; in Fig.8, the maximum frequency of discharge was increased by 19, 22 and 39% after 3, 14 and 44 min of halothane, respectively. Figure 8 also shows that continued administration was associated with a more marked effect at the lower pressures. Although an increased

Fig. 8

The relation of the mean of the three shortest intervals between impulses to the pressure applied to the carotid sinus, for a single baroreceptor unit in the cat; the curves represent control responses (○), and those after 3 (●), 14 (△), and 44 (□) min of halothane administration (concentrations of 3% for 3 min, followed by 1.5%). The curve is shifted downwards after 3 min; thereafter there is an increasing effect especially at the low pressures.

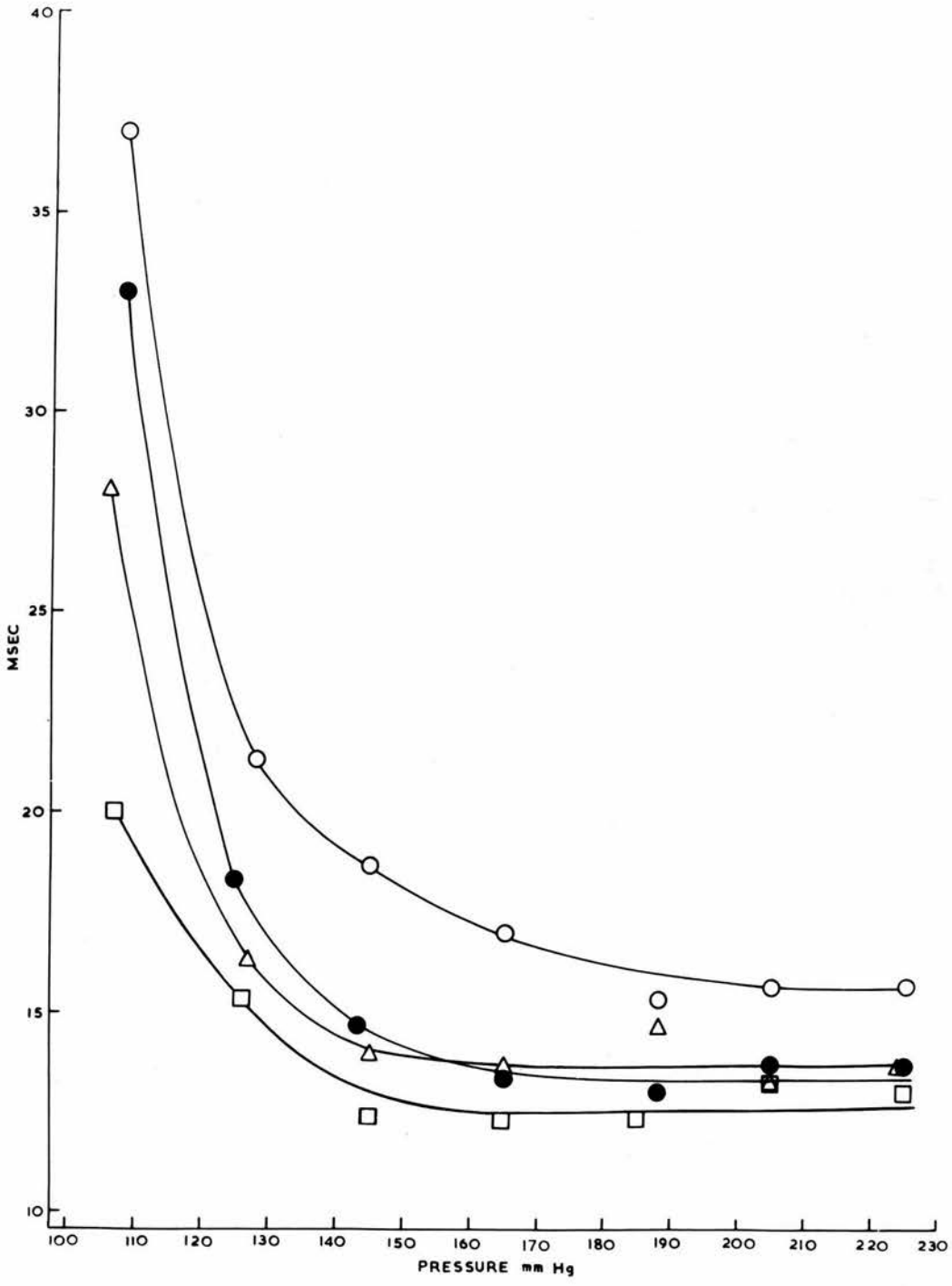

40
35
30
25
20
15
10
MSEC
100
110
120
130
140
150
160
170
180
190
200
210
220
230
PRESSURE mm Hg

Fig. 8

discharge frequency persisted at the high pressures there was a progressive flattening of the curve and the baroreceptor became less sensitive to a change in pressure (Whitteridge, 1958).

In one experiment the carotid sinus was exposed to pressure steps of 125 and 162 mm Hg, before and at various times during ventilation with 2% halothane for 30 min, followed by a further 30 min for recovery. Recordings were made from a single baroreceptor unit of the shortest interval between impulses and the mean of three intervals 1 sec later. Figure 9 illustrates the results obtained at 125 mm Hg pressure. A progressive decrease in the intervals accompanied halothane administration. When the halothane was discontinued progressive recovery occurred although this was still incomplete after 30 min. When expressed as frequencies the results in Fig. 9 show an increase in the peak and 1 sec firing rates of 167% and 133% after 27 min. The responses were of similar magnitude at 160 mm Hg pressure, the intervals between impulses being shorter throughout.

In the tests on the cats given sodium pentobarbitone as basal anaesthetic, the threshold for continuous firing of the baroreceptor during halothane administration was compared with the mean of the pre- and post-halothane measurements. There was a significant mean fall in threshold of 21%, S.E. ± 2.5, $0.001 > P$.

In 2 cats anaesthetized with chloralose the effect of 10 separate administrations on 7 single baroreceptor fibres was studied. A similar analysis to that presented for the cats given sodium

Fig. 9

Graph to show the effect of 2% halothane during a 30 min exposure, on the activity in a single baroreceptor fibre of the cat. The ordinate indicates in msec the shortest interval between impulses (●), and the mean of three intervals 1 sec later (○). The abscissa shows the time in min from the commencement of exposure to halothane, the limits of which are indicated by the arrows. The observations were made in response to pressure steps of 125 mm Hg. Lines drawn by eye.

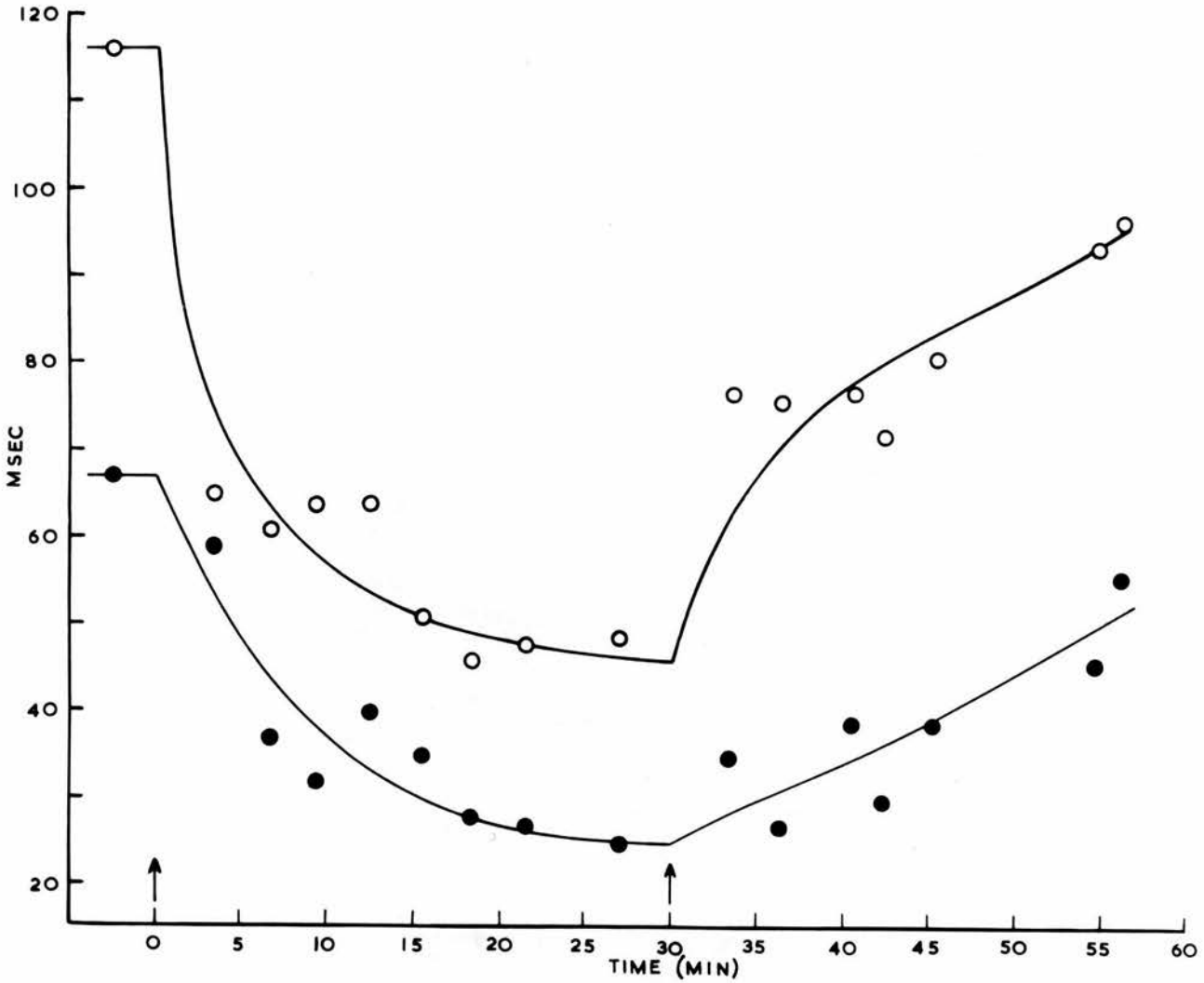


Fig. 9

pentobarbitone showed that the mean percentage increases in peak frequency at p_1 and p_2 were 33%, S.E. ± 4.6, and 21%, S.E. ± 6.8. The probability of these values differing significantly from zero, according to the t test, were $0.001 > P$ and $0.02 > P > 0.01$ respectively. The frequencies recorded 1 sec later showed at p_1 a mean decrease of 0.4%, S.E. ± 2.2, $0.99 > P > 0.98$ and at p_2 a mean increase of 11%, S.E. ± 3.6, $0.02 > P > 0.01$.

Comparison of the results obtained in cats given pentobarbitone with those given chloralose showed that the difference between the mean percentage increases at the peak frequency for the pressures p_1 and p_2 was not significant. The frequencies 1 sec later were significantly lower in the cats anaesthetized with chloralose. At p_1 the difference between the means was 61%, S.E. of the difference ± 17.4, d.f. 21, $0.005 > P > 0.001$. At p_2 the difference was 16%, S.E. ± 6.5, d.f. 21, $0.025 > P > 0.02$.

In one of the animals given chloralose the left vagus was divided above the ganglion nodosum and the left sympathetic trunk was cut low in the neck. Successive recordings were then made from 4 baroreceptors in the sinus on the same side. There was no evidence of any change in the sensitization response to halothane.

Table 2 shows sensitization of a baroreceptor unit in this cat, during two successive halothane administrations separated by an interval for recovery. The responses of peak frequency to the complete range of pressures are indicated.

Table 2.

Cat, chloralose. Responses of a single baroreceptor fibre during two administrations of halothane, separated and followed by an interval for recovery. The measurements in columns represent the peak discharge frequency in impulses/sec (reciprocal of mean of 3 shortest intervals) at each pressure level. The times in min from the first control response are indicated at the top of each column; the pressures are shown in the left-hand column.

Pressure (mm Hg)	Control	2%		OFF		3% → 1.5%		OFF
	0	+3min	+8min	+20min	+30min	+33min	+40min	+52min
50	35	63	70	56	46	137	-	45
68	98	121	121	108	89	130	130	91
88	137	149	159	137	130	167	175	137
106	137	200	200	167	167	200	213	175
124	167	200	213	175	175	233	233	200
141	189	233	250	213	189	250	250	233
159	213	270	250	200	200	270	250	233
178	213	250	250	233	233	270	303	250

Goats.

In the 3 goats studied there were 5 tests of 1 - 2% halothane on 4 baroreceptor units. The data were analysed as in the preceding section.

The mean percentage increases in the peak frequency of

discharge at the lower and higher pressures were respectively: at p_1, 34%, S.E. $\pm$ 13.2, $0.1 > p > 0.05$; p_2, 40%, S.E. $\pm$ 2.3, $0.001 > p$.

The mean percentage increases in the frequency of discharge after 1 sec at the two pressures were: at p_1, 22%, S.E. $\pm$ 6.0, $0.025 > p > 0.02$ and at p_2, 23%, S.E. $\pm$ 7.1, $0.05 > p > 0.025$.

Figure 7B shows an example of sensitization in the goat at the shortest interval and 1 sec later. Conversion of the interval measurements to discharge rates shows that the mean percentage increase in peak frequency was 36% and after 1 sec, 33%, over the whole range of pressures studied.

Table 3 shows that with continued administration in the goat, as in the cat, the sensitizing effect of halothane became more pronounced especially at the lower pressures.

Table 3.

Goat, background anaesthesia, chloralose and urethane. 1% halothane in oxygen was given throughout.

The columns show the peak frequency of discharge from a single baroreceptor unit, impulses per sec, in response to the pressure steps shown in the left hand column at the indicated times before (control) and during halothane administration. The percentage increases in the discharge frequencies after 31 min, compared to the controls, are shown in the right-hand column. The threshold levels are in the lowest row.

Pressure mm Hg	Control	+ 7 min	+ 15 min	+31 min	% change at 31 min
40	14	18	22	23	64
59	24	29	33	35	45
78	31	36	42	42	33
98	35	42	48	46	32
117	40	46	53	50	25
154	48	53	56	56	17
172	53	59	63	63	19
Threshold mm Hg	62	59	51	48	Mean 32

Dogs.

In the 2 dogs studied there were 9 tests of 1 - 2% halothane on 5 baroreceptor units. The mean percentage increases in the peak frequency of discharge at the lower and higher pressures were: p_1, 26%, S.E. $\pm$ 7.2, $0.01 > p > 0.005$; p_2, 20%, S.E. $\pm$ 7.5, $0.05 > p > 0.025$.

Similarly the mean percentage increases in frequency 1 sec later were: p_1, 21%, S.E. $\pm$ 6.9, $0.02 > p > 0.01$; p_2, 9%, S.E. $\pm$ 3.8, $0.1 > p > 0.05$.

The results presented in Fig.7C, were again converted to frequencies and the percentage increase in discharge was calculated. For the peak frequency this was 28%, and after 1 sec 22% for the whole range of pressures.

Rabbits.

In the 2 rabbits studied there were 5 tests of 1 - 2% halothane on 3 baroreceptor units. The mean percentage increases in the peak frequency of discharge at the two pressures were: p_1, 9%, S.E. $\pm$ 2.8, $0.057 > P > 0.025$; p_2, 21%, S.E. $\pm$ 2.3, $0.001 > P$.

The mean percentage increases in the frequency of discharge after 1 sec at the lower and higher pressures were: p_1, 7%, S.E. $\pm$ 2.5, $0.1 > P > 0.05$; p_2, 9%, S.E. $\pm$ 2.7, $0.05 > P > 0.025$.

In Fig.7D, the mean percentage increase in peak discharge was 8% and after 1 sec 9%, for the whole range of pressures shown.

Discussion.

Selection of the carotid sinus pressure range over which recordings of the effects of halothane were made was determined by assessment of the normal working range of the receptor under study. This was to some extent arbitrary. Calculation of a mean change in frequency for the whole range of pressures conceals variations in baroreceptor sensitization at different pressures. Two pressure levels were chosen for presentation of the results in order that comparisons might be made at points having a reasonably consistent relation within the interval-pressure curve.

The shortest interval between nerve impulses occurring after exposure to the pressure wave probably represents the response of the baroreceptor to change in pressure: this, the dynamic component, is comparable to the n_{max} of Landgren (1952), the value for which was given as 250 - 350 impulses/sec. In the present experiments intervals as short as 2 msec (a discharge frequency of 500 impulses/sec) were occasionally observed immediately after exposure to the pressure wave. In Fig. 6A a succession of 3 msec intervals may be seen. The interval between nerve impulses 1 sec after the shortest interval represents the response to steady pressure, the static component, at a time when adaptation may be about 80% complete (Landgren, 1952).

There are two distinct baroreceptor thresholds: the pressure at which a response first occurs but does not persist, and the pressure at which activity in the afferent nerve continues indefinitely. The former is in part dependent on the wave-form

of the rising pressure pulse, and the pressure level at which this response is first evoked is difficult and time-consuming to measure with accuracy. The threshold for steady discharge is more easily determined, since it is dependent only on maintaining a constant pressure, the form of the wave-front being unimportant; since about 90% of adaptation is probably complete in 5 sec this measurement can be made quite rapidly (Landgren, 1952).

Reference is frequently made to "small" and "large" baroreceptor fibres, but only on the basis of action potential size (Landgren, 1952). In the present studies it was not possible to distinguish two fibre groups, and a small action potential was often converted into a large one by thinning the nerve strand containing the active unit, or by adjusting the position of the strand on the recording electrodes.

It has been shown that variations in the tension of the wall of the carotid sinus may alter baroreceptor activity (Landgren, Neil and Zotterman, 1952), and it might be considered that an effect of this kind could underlie the sensitizing action of general anaesthetics on baroreceptor discharge. The available evidence, although conflicting (Heymans & Neil, 1958), suggests that the required effect should be constriction; adrenaline and noradrenaline, for example, increase baroreceptor discharge when injected around the sinus of wall, while sodium nitrite reduces it (Landgren, Neil and Zotterman, 1952). It is clear that of several anaesthetic agents which sensitize baroreceptors, diethyl

ether (Millar & Morris, 1961) and cyclopropane (Deutsch, Linde & Price, 1962) are associated in the dog with increased plasma catecholamine concentrations, indicative essentially of adrenal medullary release with both agents, and of extra-adrenal sympathetic excitation with ether. There are, nevertheless, reasons against supposing that an effect of halothane on baroreceptors is mediated through sympathetic influence on vascular tone. First, the sensitizing effect was observed in the present studies in the cat after vago-sympathetic section on the same side, and in the rabbit in which the sympathetic branches to the carotid sinus had been cut. Secondly, it was observed previously that halothane anaesthesia in the dog is not associated with sympatho-adrenal excitation (Millar & Morris, 1960). Also, it was noted by Price & Widdicombe (1962) that baroreceptor sensitization by cyclopropane was not prevented by cold block of the vago-sympathetic trunk in the dog.

The possibility that halothane may directly affect the tension of the carotid sinus wall cannot be excluded, although there is evidence in animals (Burn & Epstein, 1959) and in man (Black & Mc.Ardle, 1962) that halothane is a vascular dilator; an indirect action on baroreceptor discharge secondary to relaxation of the blood vessel wall adjacent to the carotid sinus seems unlikely.

While some uncertainty exists about the possible role of circulating adrenaline and noradrenaline, the evidence points to an action of halothane at the baroreceptor nerve ending. Sensitization, defined by Whitteridge (1958) and by Paintal (1956) as

an increased frequency of discharge in response to a physiological stimulus, is produced by other anaesthetics, not only on systemic baroreceptors but also on pulmonary stretch afferents (Whitteridge and Bulbring, 1944) and muscle spindles (Matthews, 1933). Stimulation by certain anaesthetics of the sciatic nerve of the bull-frog (Lorente de Nó, 1947), of nerve elements in the guinea-pig intestine (quoted by Paton and Speden, 1965), of gamma efferent nerve fibres - possibly reflexly (Andrew, 1961) - and of smooth muscle (Rang, 1964), are other findings of possible relevance. Also, Terda (1943) found that the contractions of the frog rectus abdominis muscle induced by acetylcholine were enhanced by ether and chloroform. Baroreceptor sensitization by halothane is therefore probably a non-specific effect which is shared by many or all anaesthetic molecules and exerted on other similar structures. Paintal (1956), from the work of Katz (1950), described two possible mechanisms of sensitizing a receptor: (a) by increasing the amount of depolarization for a given physiological stimulus and (b) by increasing the repetition frequency (set up in the nerve fibre) for a given depolarization. Paintal (1956) and Whitteridge (1958) discuss these possibilities in greater detail; an extension of knowledge of baroreceptor sensitization by inhalation anaesthetics awaits a detailed analysis of the properties of the isolated carotid sinus.

The difference in the degree of baroreceptor sensitization between the cats anaesthetized with chloralose and those anaesthetized

with pentobarbitone, shown by the discharge rate 1 sec after the peak frequency, suggests that the initial anaesthetic may have affected the response of the receptor. These results support the observation of Neil, Redwood & Schweitzer (1949a+b), that chloralose depresses baroreceptor nerve endings. Morse, Price & Price (1963) who used cats anaesthetized with chloralose and urethane, have recently reported that halothane (0.5 - 2%) caused an initial baroreceptor sensitization averaging 15% followed by a return to normal or below normal discharge frequencies as the inhalation was continued. Their briefly-described findings are at variance with the results obtained here; a full description of the study of Morse, Price and Price (1963) has not yet been published.

Summary of Study 1.

1. The nerve impulse discharges from single baroreceptor units in the carotid sinus nerve were studied before, during and after pulmonary ventilation with halothane in concentrations of 1 - 3% in oxygen.

2. Measurement of the shortest interval between nerve impulses and the average of three intervals recorded 1 sec later, during application of static pressures to the carotid sinus, showed that the impulse discharge was increased and maintained during halothane anaesthesia, throughout a wide range of applied pressures.

3. Cats whose initial anaesthetic was pentobarbitone were studied most frequently, but this effect of halothane was also seen in cats anaesthetized with chloralose, in rabbits given urethane, and in dogs and goats anaesthetized with chloralose and urethane.

STUDY 2. THE EFFECT OF CYCLOPROPANE, HALOTHANE, AND ETHER ON CENTRAL BARORECEPTOR PATHWAYS.

Introduction

Study 1 showed that the anaesthetic halothane caused baroreceptor sensitization, an effect which also occurs during anaesthesia with diethyl ether (Robertson, Swan & Whitteridge, 1956), and cyclopropane (Price & Widdicombe, 1962). Baroreceptor sensitization could cause hypotension and bradycardia during anaesthesia, but the typical circulatory response to different anaesthetics varies; for example cyclopropane is usually associated with a normal or raised arterial pressure, halothane invariably causes hypotension, while ether is intermediate in its effects. The importance of baroreceptor sensitization, and the cardiovascular effects of each anaesthetic, must depend also on simultaneous actions on central baroreceptor pathways.

The experiments to be described were undertaken to analyze the effects of the anaesthetics on the reduction in arterial pressure and preganglionic sympathetic activity which occurs when the central end of the aortic nerve is stimulated. The rabbit was selected for experiment because the available evidence suggests that the aortic (depressor) nerve in this species contains many baroreceptor afferents but few or no chemoreceptor fibres (Douglas, Ritchie & Schaumann, 1956).

RESULTS

Physiological responses to aortic nerve stimulation

Douglas, Ritchie & Schaumann (1956) showed in the rabbit that electrical stimulation of the aortic nerve produced progressively greater reductions in arterial pressure as the applied voltage was increased. The series showed two phases, attributable to stimulation of low threshold A fibres, and of C fibres the threshold of which was higher than the maximal A fibre stimulus. Their observations were confirmed in the present experiments, and it was shown further that the inhibition of preganglionic cervical sympathetic activity which is associated with aortic nerve stimulation also has two phases. Fig.10, from one experiment, shows the responses of arterial pressure and sympathetic discharge to two stimulation frequencies; the second rise in the magnitude of the effect begins at the threshold for C fibre excitation, and is much more marked at the lower frequency of stimulation (Douglas, Ritchie & Schaumann, 1956).

Compound action potentials recorded from an aortic nerve are shown in Fig.11 . Fig.11a shows a large A fibre spike followed by smaller potentials continuing for about 4 msec after termination of the A fibre spike. The compound action potential in Fig.11b was evoked by a higher voltage and shows a large A fibre spike, a small potential following the A fibre spike, and about 10msec later the C fibre potential. Three groups of fibres in the aortic

Fig. 10

Simultaneous % fall in preganglionic cervical sympathetic discharge rate, left, closed symbols; and % fall in mean arterial pressure, right, open symbols; against stimulus voltage. ●, O, stimulus frequency 10/sec. ▲, △, stimulus frequency 100/sec. Stimulus duration 100 μsec and period of stimulation in each case was 20 sec. The C fibre threshold was estimated by monitoring the compound action potential.

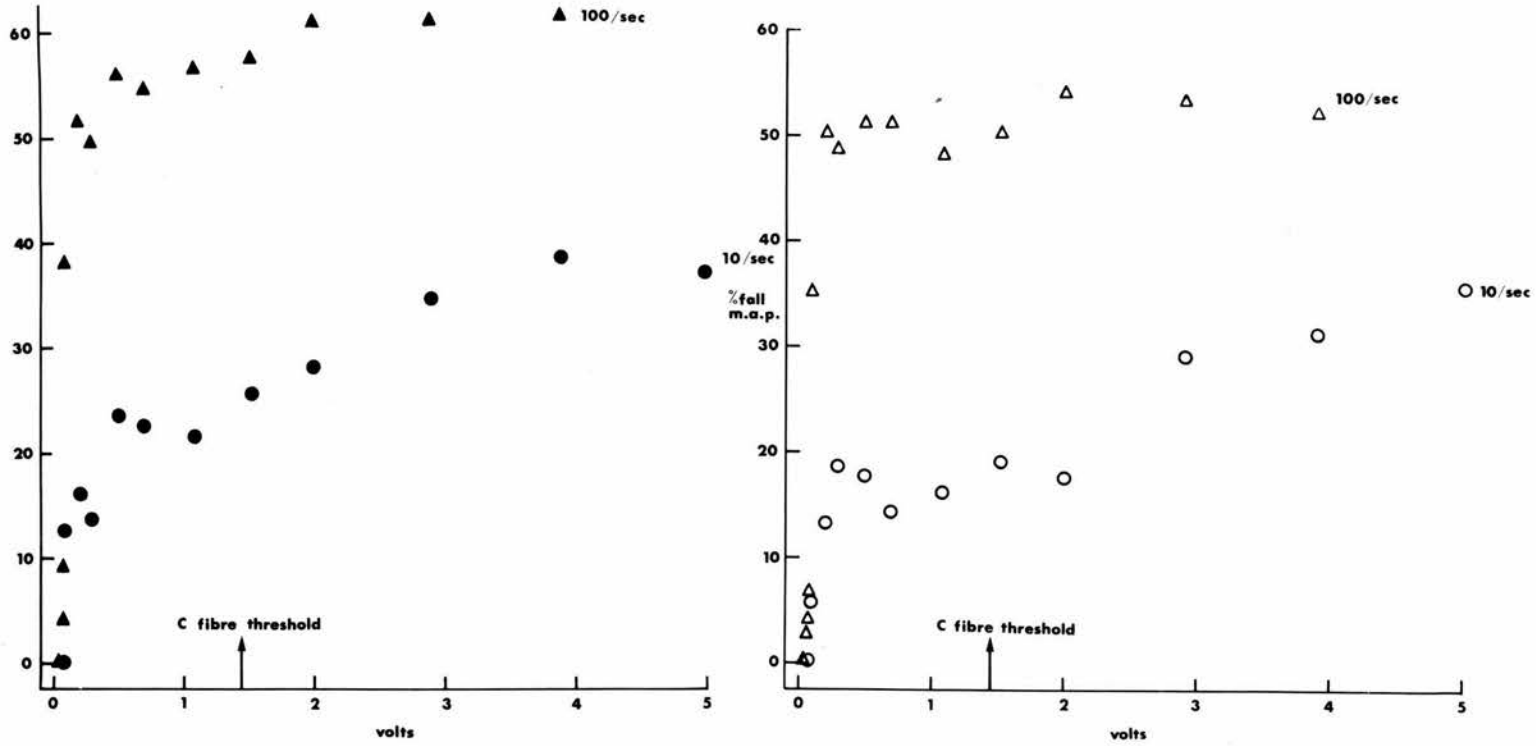

100/sec
10/sec
% fall m.a.p.
C fibre threshold
volts
0
10
20
30
40
50
60
1
2
3
4
5

Fig. 10

Fig. 11

Compound action potential recordings from the rabbit aortic nerve.

a. in response to a stimulus of 1.4 volts. t = 1 msec;

b. in response to a stimulus of 8 volts. t = 10 msec.

The amplifier time constant was 1 sec.

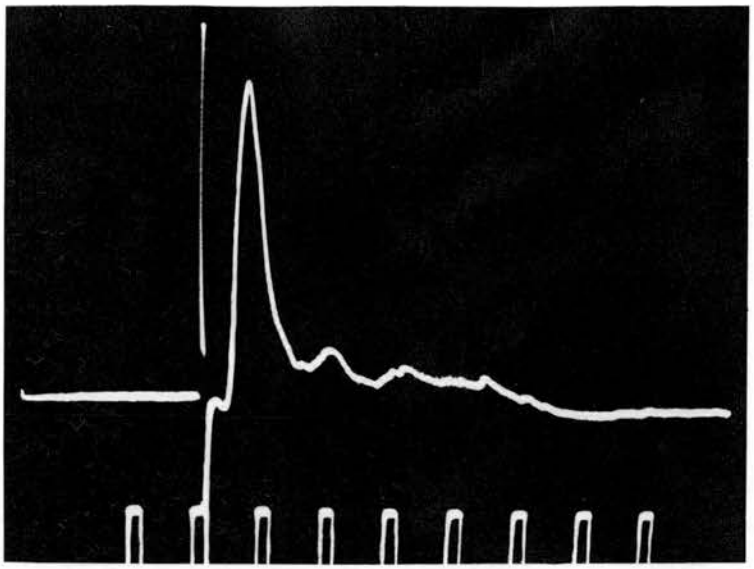


Fig. 11

nerve were described previously by O'Leary, Heinbecker & Bishop (1934); conduction velocity measurements in one aortic nerve from each of 5 rabbits agree with their findings. The velocities of the fastest conducting fibres were 20, 23, 23, 26, and 39 m/ sec, and those of the slowest conducting group were in the range 0.9 - 1.5 m/ sec. These are compatible with A and C fibre groups respectively. The conduction velocity of the third group of action potentials was in the range 4 - 12 m/ sec. All three groups of fibres showed clear-cut thresholds.

The effects of maximal stimulation of A fibres in the aortic nerve of the rabbit, in the presence of gallamine, are shown in Fig.12A. The response to combined A and C fibre excitation is illustrated in Fig. 12B where the reductions in arterial pressure and sympathetic discharge were much greater, and prolonged beyond the period of stimulation, especially in the case of the arterial pressure. Sympathetic activity began to increase before aortic nerve stimulation was discontinued; this was more pronounced with the A type response. In the example shown in Fib. 12B, excitation of the A fibres reduced the heart rate from 50 in 10 sec, to 48 in the first and second 10 sec periods of stimulation. Recovery of heart rate occurred within 4 sec of discontinuing aortic nerve stimulation. When both A and C fibre groups were excited maximally the heart rate was reduced from 48 in 10 sec, to 43 in the first 10 sec of stimulation and to 39 in the second 10 sec period. Recovery was

Fig. 12

The records from above down in both A and B are: femoral artery pressure, mm Hg; integrated preganglionic cervical sympathetic discharge rate in impulses/sec, time constant 3.3 sec; film strip taken simultaneously, calibration 200 μv. The time marks are at 10 sec intervals. In each case the aortic nerve was stimulated at a rate of 50/sec for 20 sec with pulses of duration 100 μsec. The stimulus intensities were 2v (A) and 10v (B). The vagi, aortic and sinus nerves were cut.

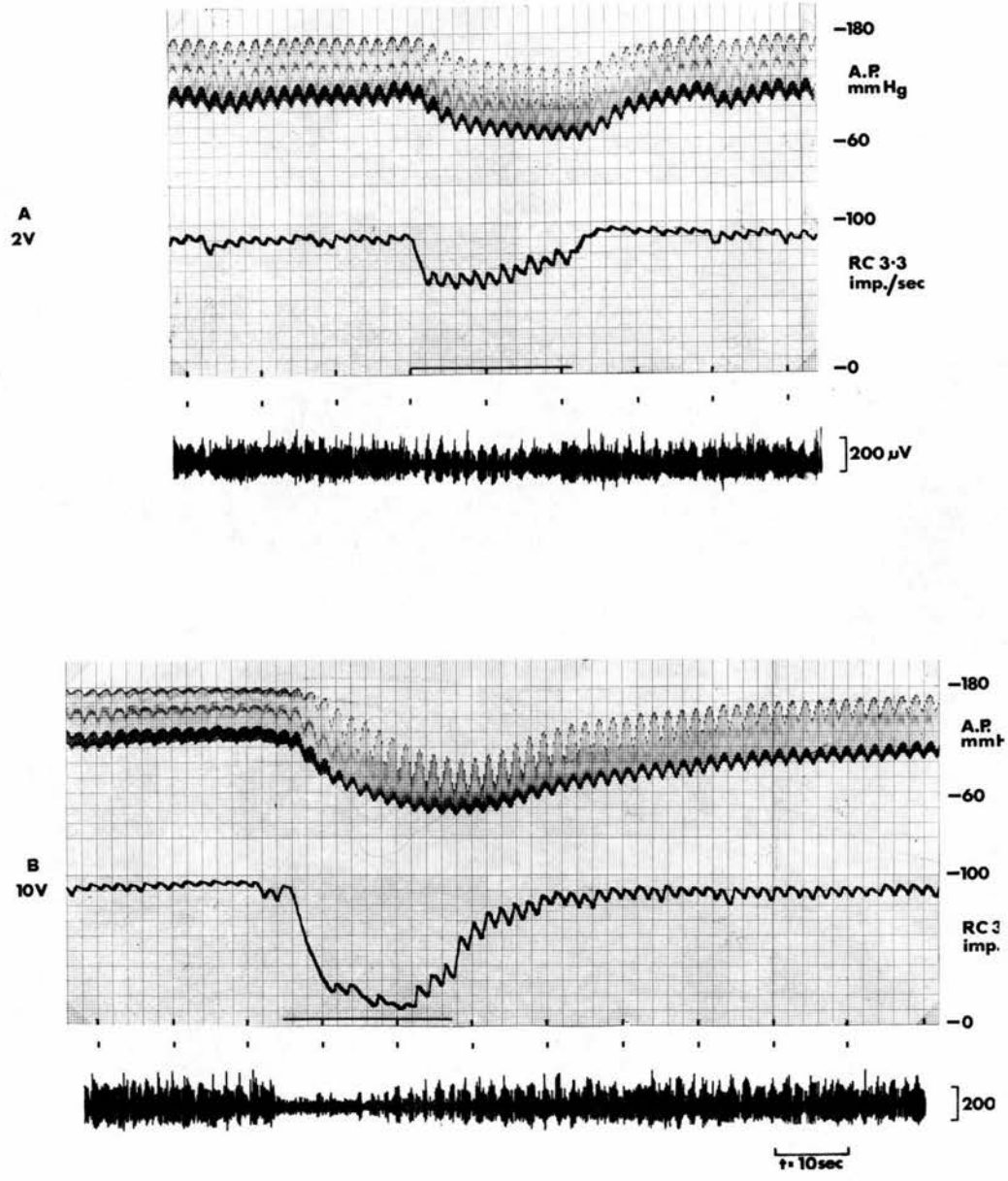

A
2V
-180
A.P.
mm Hg
-60
-100
RC 3·3
imp./sec
-0
200 μV
B
10V
-180
A.P.
mm
-60
-100
RC 3
imp.
-0
200
t = 10sec

Fig. 12

not complete until 20 sec later. Similar results were obtained in 3 rabbits to which, as in all experiments, gallamine had been given and heart rate changes during aortic nerve stimulation were analyzed before and after vagotomy. For example in one experiment, stimulation at 2V. and 15V. reduced heart rate within the first 10 sec of stimulation by 3 and by 8 beats respectively, and the same responses were obtained in this animal after cutting the vagi. No consistent alteration in the magnitude of the maximum fall in arterial pressure evoked by aortic nerve stimulation resulted from vagotomy under these conditions. The responses to both A and C fibre excitation appeared to be reduced in two animals and increased in the other, but the changes were small.

In 19 rabbits, before administration of the inhalation anaesthetics, an assessment was made of the lowest levels of systolic and diastolic pressure reached during aortic nerve A fibre excitation. In each animal, the mean of 2 - 4 responses was determined. The prestimulation systolic pressure was on average 39 mm Hg higher than the diastolic pressure, and the reductions in systolic and diastolic pressures induced by aortic nerve stimulation averaged 41 mm Hg and 32 mm Hg respectively. The maximum percentage falls in systolic and diastolic pressures were compared in individual animals, and the significance of the mean difference between the reductions was determined by Student's t-test. The percentage reduction in diastolic pressure exceeded that in systolic pressure by 5% (S.E. $\pm$ 0.81, $0.001 > P$).

A possible influence of the prestimulation arterial pressure

level on the magnitude of the reduction in pressure produced by aortic nerve stimulation was sought in 20 rabbits during control periods prior to administration of any inhalation anaesthetics. In each rabbit the mean of two consecutive depressor responses, and corresponding arterial pressure levels, was used. The mean arterial pressures ranged from 70 to 110 mm Hg, and the reductions in pressure produced by maximal aortic A fibre excitation were in the range 25 to 45%, with a single measurement of 65%. No correlation could be established between the mean arterial pressure level and the magnitude of the depressor response. Further data were obtained in four experiments by withdrawing blood in order to lower arterial pressure to within the range 20 to 60 mm Hg, several measurements being made in each rabbit. Again, it was not possible to establish a correlation between the prevailing arterial pressure level and the percentage reduction in pressure caused by aortic nerve stimulation.

The experiment of Fig.10 showed that a similar quantitative response of arterial pressure and preganglionic discharge occurred during depressor nerve stimulation, and this was substantiated in several other experiments. However, in an overall direct comparison involving a total of 91 measurements on 7 sympathetic nerve strands in 6 rabbits (sinus nerves intact), the maximum reduction in mean arterial pressure exceeded that in preganglionic discharge by a mean of 7.8% (S.E. $\pm$ 1.6, $0.001 > P$). In these experiments action potentials were not always recorded from the

aortic nerve, although the voltages were adjusted to produce maximal A fibre responses. Similar results were also obtained in a small number of experiments involving combined A and C fibre excitation; in 6 measurements on 3 rabbits the mean maximum reduction in arterial pressure exceeded that in sympathetic activity by 11%. Following baroreceptor denervation in 3 rabbits, however, no significant differences could be established between the maximum arterial pressure and sympathetic responses either to A type or to A and C type excitation of the aortic nerve, involving 28 and 15 measurements respectively.

Effects of gallamine triethiodide.

1 - 2 mg/kg doses of gallamine had negligible effects on preganglionic sympathetic activity, heart rate, or arterial pressure in the rabbit (see Study 3). In confirmation of the earlier work of Van Den Ostende (1951), in 5 experiments studied specifically there was no modification in the arterial pressure or sympathetic responses to aortic nerve stimulation following intravenous injection of gallamine 1 - 2 mg/kg.

Effects of sodium pentobarbitone

In the doses used (6 - 12 mg), supplementary intravenous injections of pentobarbitone caused variable and transient effects on sympathetic discharge, heart rate, and arterial pressure (see Study 3). The effects on the depressor responses were also small, and occurred only within 2 to 3 min after injection. At least 5 minutes were always allowed to elapse after injection of pentobarbitone before control responses were obtained for assessing

the effects of the inhalation anaesthetics.

Effects of inhalation anaesthetics on conduction in the aortic nerve.

In agreement with previous findings on other nerves (Forbes, McIntosh & Sefton, 1916; Larrabee & Posternak, 1952; Austin & Pask, 1952), the inhalation anaesthetics (in the clinical doses used) did not affect the conduction velocity or stimulation threshold of fibres in the aortic nerve.

Fig. 13 shows a sequence of compound action potentials, recorded at voltages maximal for both A and C aortic fibres. The potentials in Fig. 13A were unaffected by 50% cyclopropane (B) although Fig. 13C, which was taken 15 min after discontinuing the inhalation anaesthetic, shows that some decrement occurred with time.

Fig. 14 illustrates aortic nerve action potentials from another experiment. Records a to c show that halothane had no effect on the amplitudes. Row c was recorded 24 min after discontinuing halothane; at this time the C fibre potential was smaller, probably due to a change in stimulation threshold, since an increase in voltage (d) brought the potential to above the previous control level (note here the change in calibration). Between records c and e there was also a change in the recording conditions, shown by a fall in the maximal A fibre potential height (middle column). Sequence d and e in Fig. 14 demonstrate that ether did not reduce the height of the aortic nerve action potentials.

Effects of the inhalation anaesthetics on the baroreceptor reflex.

In the present experiments, the effects of the 3 inhalation

Fig. 13

Aortic nerve compound action potential showing maximal A and C fibre excitation in response to 1.4v. Stimulus duration, 100 μsec. A is the control, and B was taken 11½ min after exposure to 50% cyclopropane. C, 15 min after discontinuing cyclopropane. The amplifier time constant was 1 sec.

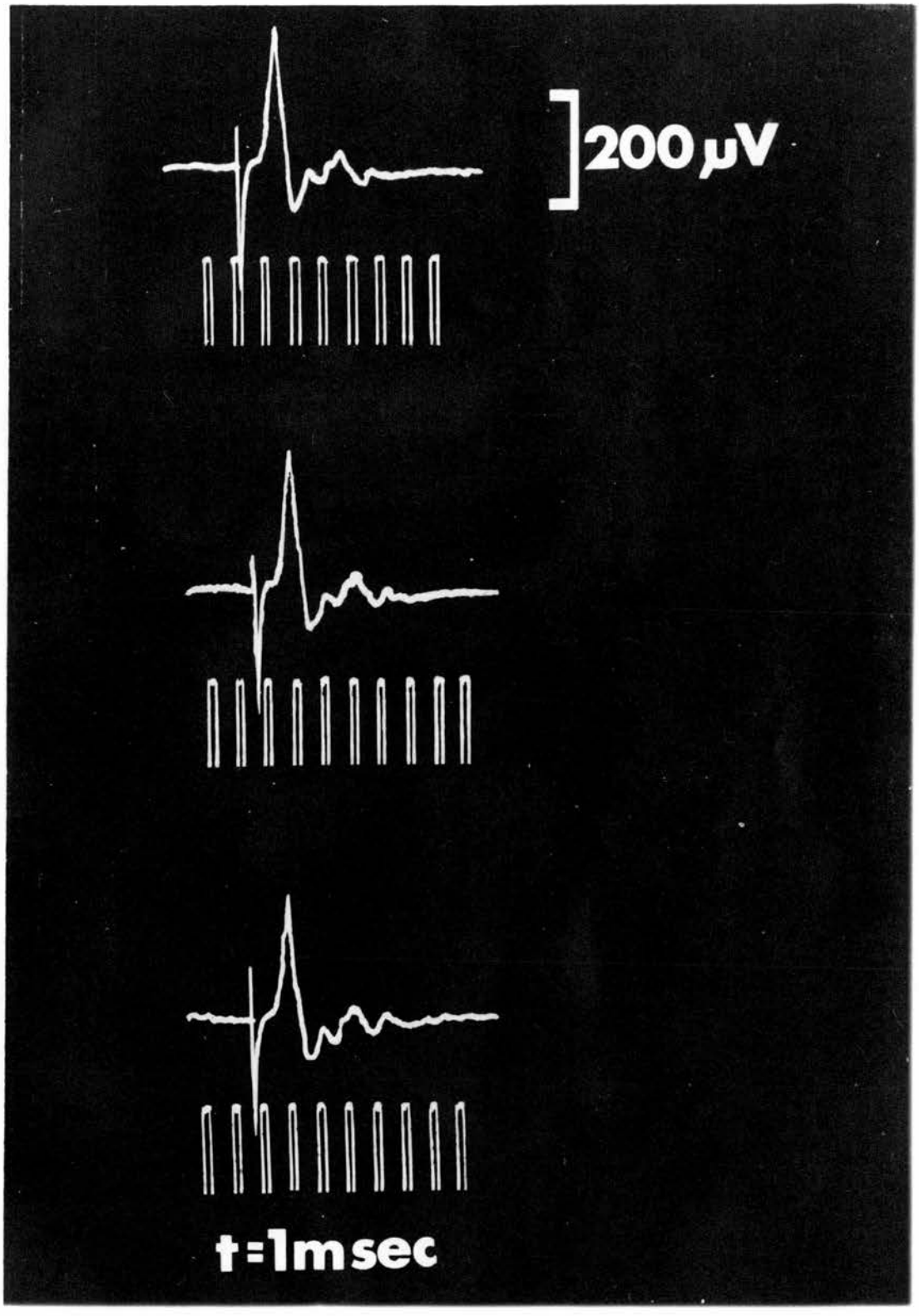

A
B
C
200 µV
t=1msec

Fig. 14.

Aortic nerve compound action potential, showing responses to threshold stimulus, 0.9 volts; to maximal A fibre stimulus, 5v; and to maximal C fibre stimulus 6 volts (a-c) and 60 volts (d and e). Stimulus duration 100 usec. a, before halothane. b, after 23 min 3% halothane. c, 24 min after halothane was discontinued. d, after 12 min of 10% ether. e, responses 15 min after stopping ether. The calibration for 0.9 and 5 volts was 800 μv; for 6 volts it was 200 μv, and for 60 volts it was 400 μv. The amplifier time constant was 1 sec.

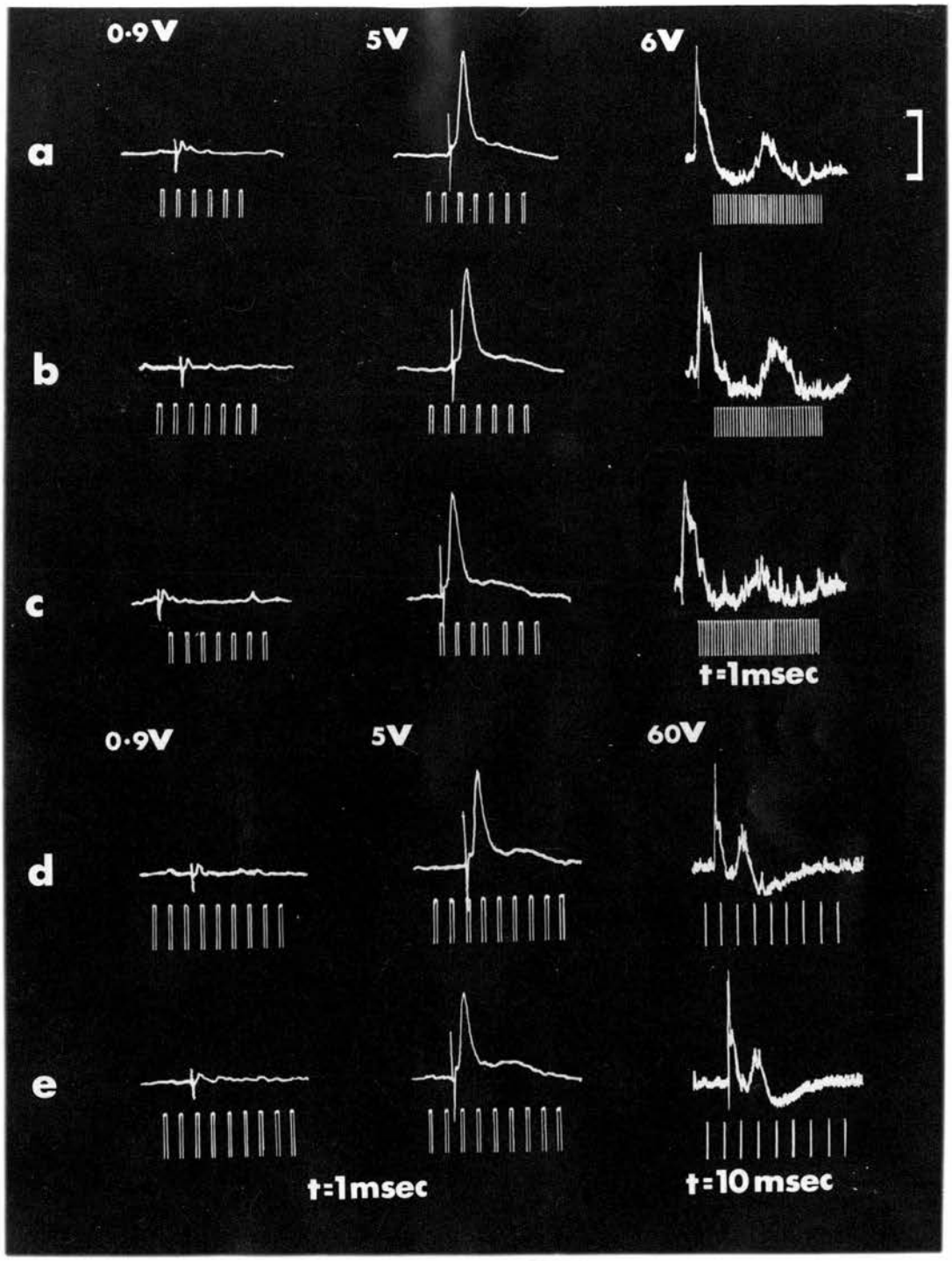


Fig. 14

anaesthetics on central baroreceptor pathways was assessed by comparison of the percentage reductions in arterial pressure (and sympathetic discharge) evoked by aortic nerve stimulation before, in contrast to during, administration of the inhalation anaesthetics. The mean of 2 to 4 control responses was used, and to determine whether changes with time alone were likely to have introduced errors into assessment of the anaesthetic effects, a comparison was made between the percentage reductions in arterial pressure evoked by aortic nerve stimulation before, and after, administration of each inhalation anaesthetic. Thus, comparison of the arterial pressure responses before administration of cyclopropane, and after recovery from this anaesthetic, showed a mean difference of 2% (S.E. ± 1.4) for 18 measurements in 15 rabbits. For halothane, the mean difference was less than 1% (S.E. ± 1.6) for 26 administrations in 16 animals. For ether, the difference was 3% (S.E. ± 1.6) for 23 administrations in 18 rabbits. In each case, therefore, the mean difference between the depressor responses before and after administration of the inhalation agent was insignificantly different from zero.

In presenting the reductions in the depressor responses caused by the three inhalation anaesthetics, it is necessary to avoid weighting of the data attributable to the magnitude of individual control responses. The differences between the control responses and those during inhalation anaesthesia have been expressed, therefore, as a percentage of the control responses. This gives a figure which indicates the percentage inhibition of the depressor

response caused by the anaesthetics. Thus, if aortic stimulation caused a fall in arterial pressure of 40% before administration of an inhalation anaesthetic, and of 20% during anaesthesia, then the reduction in the depressor response was by 20%, but the percentage inhibition of the response (as used subsequently throughout this study) was 20/40 x 100 = 50%.

Cyclopropane. 50% cyclopropane in oxygen caused rapid and progressive inhibition of the depressor reflex; the averaged results obtained from measurements of arterial pressure responses to aortic nerve stimulation are shown in Table 4. In these experiments the voltages used produced maximal A fibre excitation. After 2 - 3 min the depressor response was inhibited by 62%, and by 8 - 12 min there was 93% inhibition. Table 4 also indicates the average mean arterial pressure during administration of 50% cyclopropane, the preanaesthetic control level being 100 mm Hg. There was a fall in mean arterial pressure averaging 16% in 9 of the 14 tests after 2 - 3 min, with an associated reduction in the depressor response of 55%; the inhibitory effect of cyclopropane on the depressor response was therefore not dependent on the increased arterial pressure which usually followed. After 4 - 6 min, mean pressure was increased by an average of 22% in 11 of the 14 tests; the average levels shown in Table 4 are weighted by large falls in arterial pressure which occurred in 3 rabbits in which the depressor response was completely abolished. Mean arterial pressure was above the control level in 3 of the 8 tests after 8 - 12 min of 50% cyclopropane; in 6 of the 8 administrations continued for this time, there was 100% inhibition of the depressor response.

Table 4

Mean percentage inhibition of the A fibre depressor response by cyclopropane at the indicated times after commencing administration. P is the probability that the percentage inhibition departs from zero by chance (t test). The lower line shows the mean arterial pressure just preceding aortic nerve stimulation. The mean arterial pressures before 50% cyclopropane and 25% cyclopropane were 100 mm Hg and 95 mm Hg respectively.

	50% Cyclopropane			25% Cyclopropane			
Time min	2 - 3	4 - 6	8 - 12	2 - 3	4 - 6	8 - 12	14 - 18
n	14	14	8	16	15	6	6
Mean % inhibition of depressor response	62	86	93	35	53	64	72
S.E.	± 6.8	±3.4	±4.7	±5.7	±5.9	±3.7	±2.5
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean arterial pressure, mm Hg	98	105	93	95	97	97	87

Similar, although less pronounced, effects occurred with 25% cyclopropane (Table 4), arterial pressure being maintained close to the pre-anaesthetic control level. Inhibition of the depressor response was highly significant after only 2 - 3 min of administering this concentration and there was a 72% reduction after 14 - 18 min.

Cyclopropane increased the heart rate, and after 4 - 6 min abolished or reversed the change in heart rate produced by maximal excitation of the aortic nerve A fibres; Fig.15a shows the measurements from one experiment.

50% cyclopropane was given to one rabbit subsequent to mid-collicular decerebration. Arterial pressure was reduced by the anaesthetic, from a control level of 71 mm Hg, to 31 and 25 mm Hg after 3 min and 8 min respectively; at these times the arterial pressure response to maximal aortic A fibre stimulation was inhibited by 76% and 81%. The effect of combined A and C fibre excitation was reduced by 78% from control after 5 min of 50% cyclopropane. The arterial pressure did not recover when cyclopropane was discontinued at 8 min.

Halothane

The effects of 3% halothane on the A type arterial pressure response to aortic nerve stimulation are shown in Table 5. In contrast to that of 25% or 50% cyclopropane, the inhibitory effect of halothane was less pronounced and slower in onset. After 2 - 3 min there was an apparent increase in the depressor response, probably due to the hypotensive action of halothane, which progressively lowered arterial pressure during the period of

Fig. 15.

The effects on heart rate (O) of a) 50% cyclopropane, b) 3% halothane, and c) 12.5% ether (administered between arrows), in 3 different experiments. The change in heart rate in response to aortic nerve stimulation is also shown (●). Ordinate: heart rate, beats per 5 sec. The time scale on the 2 lower graphs is twice that on the upper graph. The values before anaesthesia are the mean of three measurements.

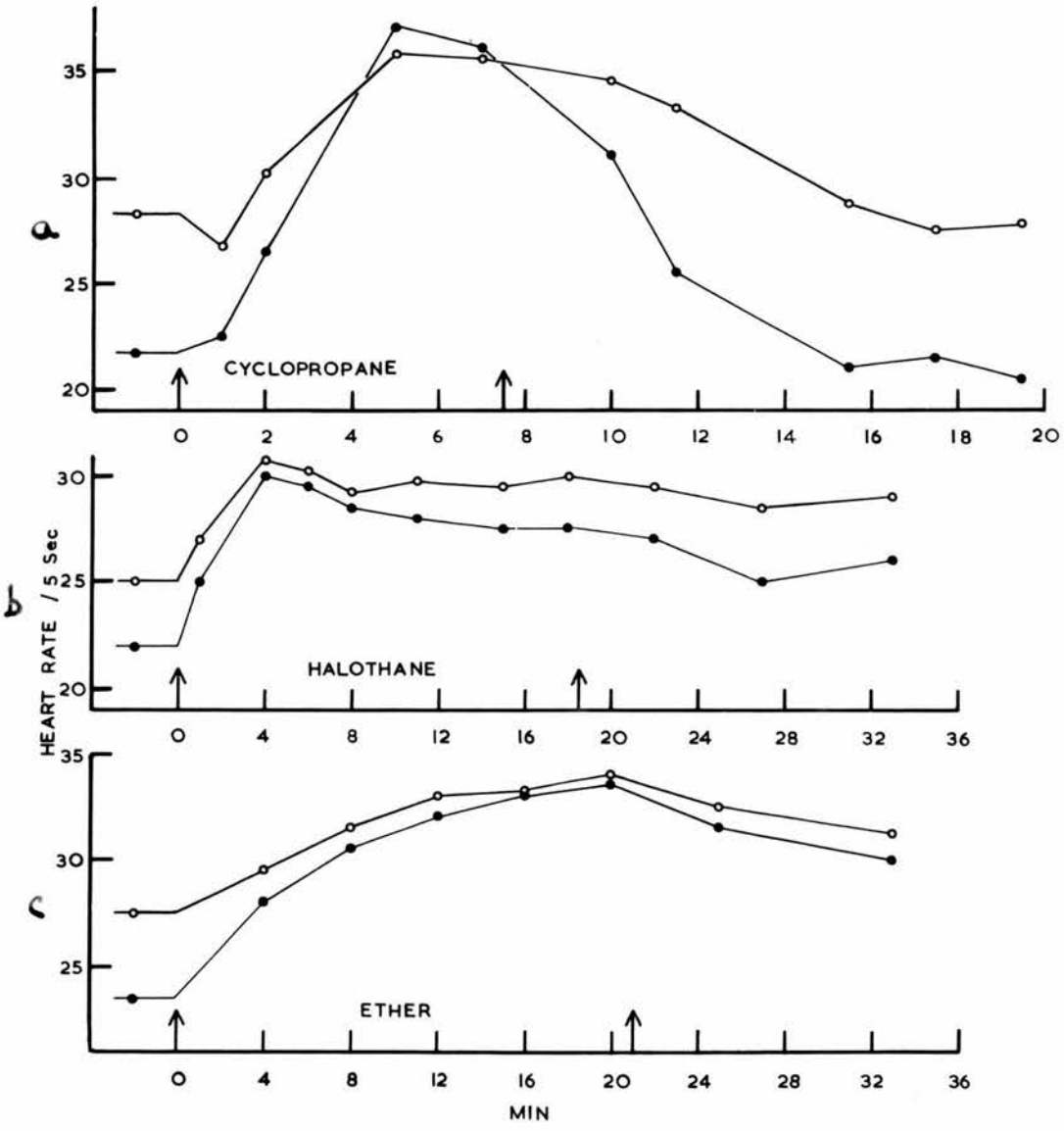

a
35
30
25
20
CYCLOPROPANE
0 2 4 6 8 10 12 14 16 18 20
b
HEART RATE / 5 Sec
30
25
20
HALOTHANE
0 4 8 12 16 20 24 28 32 36
c
35
30
25
ETHER
0 4 8 12 16 20 24 28 32 36
MIN

Fig. 15

stimulation. Highly significant reductions in the depressor response were evident after 4 - 6 min of 3% halothane, and this effect subsequently became more pronounced (Table 5). However, block of the response never became complete although arterial pressure was often reduced by this anaesthetic to levels of 30 mm Hg or lower. Comparison of the average percentage inhibition after 14 - 18 min of 3% halothane (by 46%, Table 5), with that after the same period of 25% cyclopropane (by 72%, Table 5) showed a highly significant difference between the effects of these anaesthetics (S.E. ± 8.8; ϕ = 20; $0.01 > P > 0.001$).

After 20 - 24 min of 3% halothane, at an average mean arterial pressure of 35 mm Hg, the depressor response was inhibited by 57%; this was also a significantly smaller effect than that caused by 14 - 18 min of 25% cyclopropane (S.E. ± 6.3; ϕ = 11; $0.05 > P > 0.025$). Thus even in the presence of extreme hypotension during halothane anaesthesia it was possible to reduce arterial pressure to a relatively greater extent than at the near normal pressure levels accompanying anaesthesia with cyclopropane.

The depressor response was reduced significantly, by 17%, after 20 - 24 min of 2% halothane (Table 5). The effects of a 1.5% concentration were variable and insignificant over periods up to 30 min.

Table 5

Mean percentage inhibition of the A fibre depressor response by halothane in the concentrations shown, at the indicated times after commencing administration. P is the probability that the percentage inhibition departs from zero by chance (t test). The lower line shows the mean arterial pressure just preceding aortic nerve stimulation. The mean arterial pressures before administration of 3% halothane, 2% halothane, and 1.5% halothane, were 96 mm Hg, 91 mm Hg, and 89 mm Hg respectively.

	3%					2%		1.5%
Time min	2 - 3	4 - 6	8 - 12	14 - 18	20 - 24	8 - 12	20 - 24	20 - 24
n	12	23	24	16	7	14	11	8
Mean % change* of depressor response	Increased by 9.6%	- 24	-38	-46	-57	-1.7	-17	-13
S.E.	±4.9	±4.8	±3.3	±5.2	±5.4	±7.1	±5.0	±11.2
P	<.1	<0.001	<0.001	<0.001	<0.001	<.9	<0.01	<.3
Mean arterial pressure, mm Hg	61	48	37	31	35	55	45	61

* Decrease indicated by 'minus' sign

Heart rate was usually increased by halothane (this was also observed in the absence of gallamine administration), and there was partial inhibition of the fall in heart rate produced by A fibre excitation of the aortic nerve. In the example shown in Fig. 15b the fall in heart rate caused by aortic nerve stimulation was minimal after 4 min of halothane, but subsequently there was some recovery of the response before the anaesthetic was discontinued at 18 min.

Ether.

In high concentrations (10 - 15%) ether caused significant blockade of the depressor response after 4 - 6 min (Table 6). There was 75% inhibition after 14 - 18 min, when arterial pressure was 53 mmHg compared to a control level of 93 mm Hg. Thus, while lowering arterial pressure moderately, high concentrations of ether produced a roughly similar degree of inhibition of the depressor response after 14 - 18 min as did 25% cyclopropane (Table 4). At this time, also, 10 - 15% ether inhibited the depressor response to a significantly greater extent than did 3% halothane (S.E. $\pm$ 9.8; ϕ = 23; $0.01 > P > 0.001$). However, although in the case of ether these effects were exerted at a higher arterial pressure level than with halothane, such high ether concentrations were always liable to cause circulatory collapse, sometimes abruptly.

Table 6

Mean percentage inhibition of the A fibre depressor response by ether in the concentrations shown, at the indicated times after commencing administration. P is the probability that the percentage inhibition departs from zero by chance (t test). The lower line shows the mean arterial pressure just preceding aortic nerve stimulation. The mean arterial pressures before 10 - 15% ether, 5 - 8% ether, and 2 - 3% ether were 93 mm Hg, 85 mm Hg, and 89 mm Hg respectively.

	10 - 15%			5 - 8%			2 - 3%
Time min	4 - 6	8 - 12	14 - 18	4 - 6	8 - 12	20 - 25	30 - 40
n	16	14	7	9	10	9	6
Mean % change of depressor response	-31	-53	-75	-20	-33	-45	Increased by 6.8%
S.E.	± 5.1	±5.9	±8.9	±5.3	±5.8	±5.2	±8.4
P	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001	<.5
Mean arterial pressure, mm Hg	89	71	53	80	75	53	77

5 - 8% ether, which produced a gradual moderate lowering of arterial pressure, significantly reduced the depressor response after 4 - 6 min, the effect increasing to reach 45% inhibition after 20 - 25 min; thus, although at a higher arterial pressure level, the effects of these ether concentrations approached those of 3% halothane at this time. However, the inhibitory action of 5 - 8% ether after 20 - 25 min was significantly less than that of 25% cyclopropane after 14 - 18 min (S.E. $\pm$ 3.8; $\emptyset$ = 13; $0.01 > P > 0.001$).

There was no inhibitory effect on the arterial depressor response when 2 - 3% ether concentrations were administered over periods up to one hour (Table 6).

Heart rate was increased during ether anaesthesia, and there was progressive inhibition of the heart rate response to aortic nerve stimulation (Fig.15c).

The effects of anaesthetics on preganglionic sympathetic responses to aortic nerve stimulation.

The data presented, while demonstrating highly significant depressant inhibitory effects of the inhalation anaesthetics on the circulatory responses to aortic nerve stimulation, do not establish conclusively the role of central baroreceptor blockade in this effect. A central action of the anaesthetics was demonstrated, however, by simultaneous measurement of the percentage fall in arterial pressure and in preganglionic cervical sympathetic discharge evoked by aortic nerve stimulation before and during administration of the inhalation anaesthetics. The results are shown in

Table 7, which includes the mean value of 10 measurements in the case of cyclopropane and halothane, and 6 measurements in the case of ether. For each anaesthetic there were equal numbers of A and C type responses to aortic nerve stimulation.

Table 7 shows that the relative effects of the three anaesthetics, already described in relation to the arterial pressure response to aortic nerve stimulation, are quite closely paralleled in their inhibitory action on the associated preganglionic sympathetic responses. The inhibition of both responses was most pronounced and rapid with 50% cyclopropane, and least marked with 3% halothane after a much longer time and at a low arterial pressure; the effects of ether were inter-immediate.

The pronounced block of the depressor response which could be produced by cyclopropane is illustrated in Fig.16 for both A and combined A and C fibre effects on arterial pressure and cervical sympathetic discharge. Fig.16A shows well marked depressor responses before cyclopropane, which were completely blocked after 3 - 4 min of the anaesthetic (B). The changes in arterial pressure and preganglionic sympathetic discharge produced by cyclopropane are more fully considered in Study 3. The increased sympathetic discharge rate illustrated in Fig.16B is a typical response to cyclopropane, occurring throughout administration. The loss of the respiratory oscillation in arterial pressure is also characteristic, but in this experiment the pressure was not elevated above the control level, as usually occurs (Study 3).

Fig. 16.

The effect of aortic nerve stimulation at 50/sec for 20 sec, stimulus duration 100 usec, on femoral artery pressure and cervical sympathetic discharge rate. Below each set of records are the simultaneous filmed traces of the action potentials; the period of stimulation is indicated by the line under the records. A, response 1, stimulus intensity 1 volt, maximal for A fibres; response 2, stimulus intensity 6 volts, supramaximal for A and C fibres. B, response 3, 1 volt, after 3 min 50% cyclopropane; response 4, 6 volts, after 4 min 50% cyclopropane. Time calibration = 10 sec for the ratemeter and pressure records, 5 sec for the film records. Action potential amplitude calibration = 200 uv. The ranges and time constants of ratemeter records A and B respectively are 0 to 100, 1 sec, and 0 to 300, 3.3 sec.

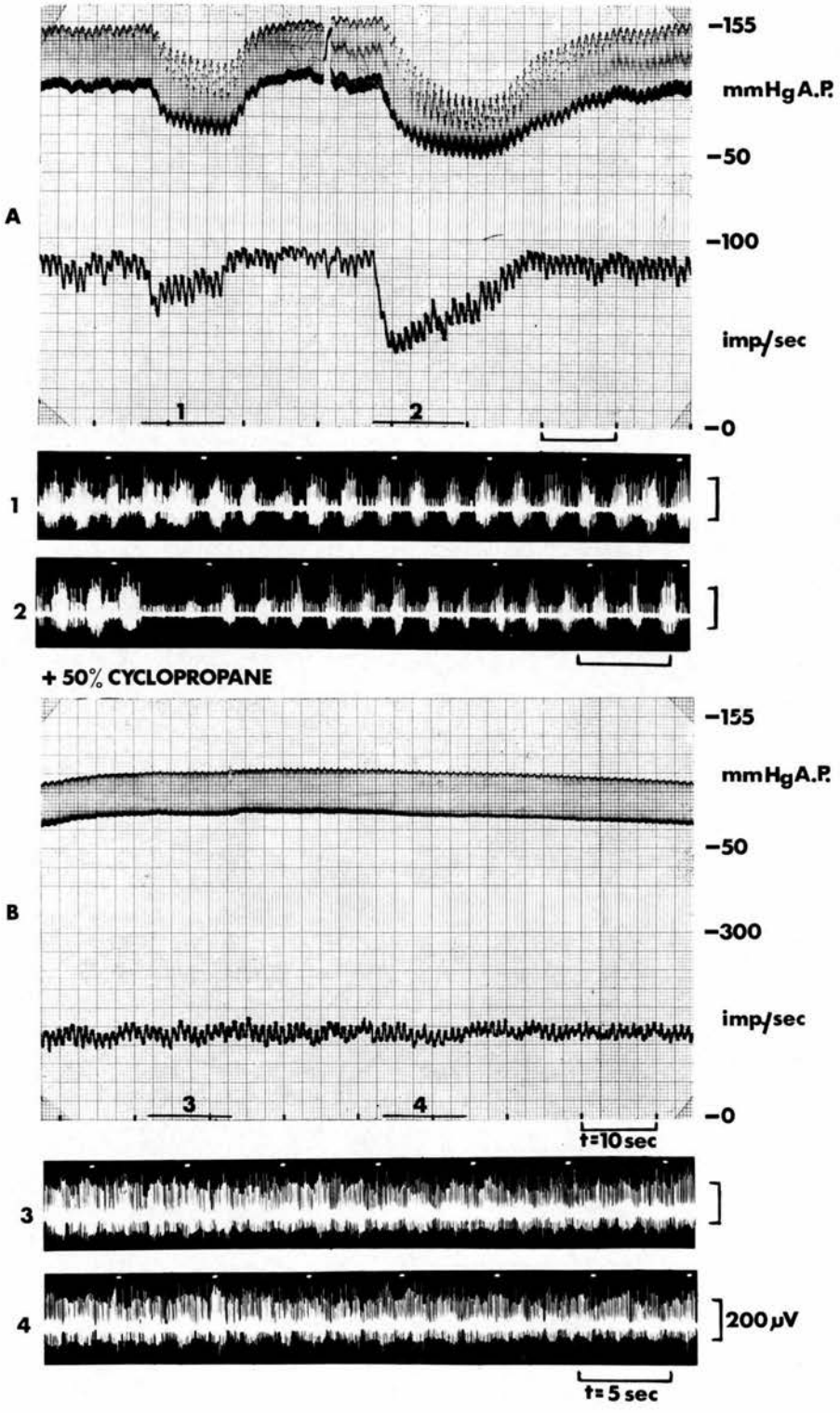

A
−155
mmHgA.P.
−50
−100
imp/sec
−0
1
2
1
2
+ 50% CYCLOPROPANE
B
−155
mmHgA.P.
−50
−300
imp/sec
−0
3
4
t=10sec
3
4
200μV
t=5 sec

Fig. 16

Table 7

Mean percentage inhibition by cyclopropane, halothane and ether, of the reductions in mean arterial pressure and preganglionic sympathetic discharge evoked by A or combined A and C fibre aortic nerve stimulation. The mean arterial pressures are those at the time of eliciting the baroreceptor reflex, the figures in brackets being the level before administration of the inhalation anaesthetic.

	Time (average in min)	Mean Arterial Pressure	% Inhibition of arterial pressure response (mean ± S.E.)	% Inhibition of preganglionic sympathetic response (mean ± S.E.)
50% Cyclopropane	5	101 (96)	93 ± 3.3	94 ± 4.4
3% Halothane	19	37 (93)	52 ± 7.0	62 ± 8.2
10 -15% Ether	12	53 (96)	75 ± 7.6	87 ± 4.7

Fig.17A shows recovery from cyclopropane, later in the same experiment. The partial block produced by halothane is illustrated in Fig.17B, 3 and 4. The final trace, Fig.17B,5, was taken after subsequent recovery from halothane and during exposure to ether. This shows a response to stimulation at higher voltage, but inhibition of the depressor responses was marked. Changes in preganglionic sympathetic activity during halothane and ether anaesthesia are considered in Study 3.

In another experiment, recordings were made from the post-ganglionic nerve from the superior cervical ganglion to the carotid body. Stimulation of the aortic nerve reduced the discharge rate in this nerve, an effect which was blocked by the three anaesthetics. Abolition of the depressor response after 4 min of cyclopropane is shown in Fig.18B; complete recovery occurred when the anaesthetic had been discontinued for 27 min, Fig.18D.

The actions of 50% cyclopropane and 3% halothane were compared, in respect to both arterial pressure and sympathetic responses to aortic nerve stimulation, using the data summarised in Table 7. The mean reduction in the cervical sympathetic response to aortic nerve stimulation was by 62% for 3% halothane, and by 94% for 50% cyclopropane; the average durations of administration were respectively 19 min and 5 min. These reductions differed significantly (S.E. $\pm$ 9.3; $\emptyset$ = 18; $0.01 > P > 0.001$). Similarly, arterial pressure responses to aortic nerve stimulation were reduced by 52% with 3% halothane, and by 93% with 50%

Fig. 17.

The effect of aortic nerve stimulation at 50/sec for 20 sec, stimulus duration 100 μsec, on femoral artery pressure and cervical sympathetic discharge rate. Below each set of records are film strips of the simultaneous action potentials; the period of stimulation is indicated by the line under the potentials. A, response 1, stimulus intensity 2 volts, maximal for A fibres; response 2, stimulus intensity 8 volts, maximal for A and C fibres. B, response 3, 2 volts, after 13 min of 3% halothane; response 4, 8 volts, after 15 min of 3% halothane. Subsequent recovery of the potential occurred to the control, A, magnitude. 15% ether was then given. B, response 5, 8 volts, after 7½ min ether. The different blood pressure calibrations should be noted. Time calibration 10 sec for the pressure and ratemeter records, 5 sec for the film records. Action potential amplitude calibration = 200 μv. The ranges and time constants of ratemeter records A and B (left) are 0 to 100, 1 sec, and of B (right) 0 to 300, 3.3 sec.

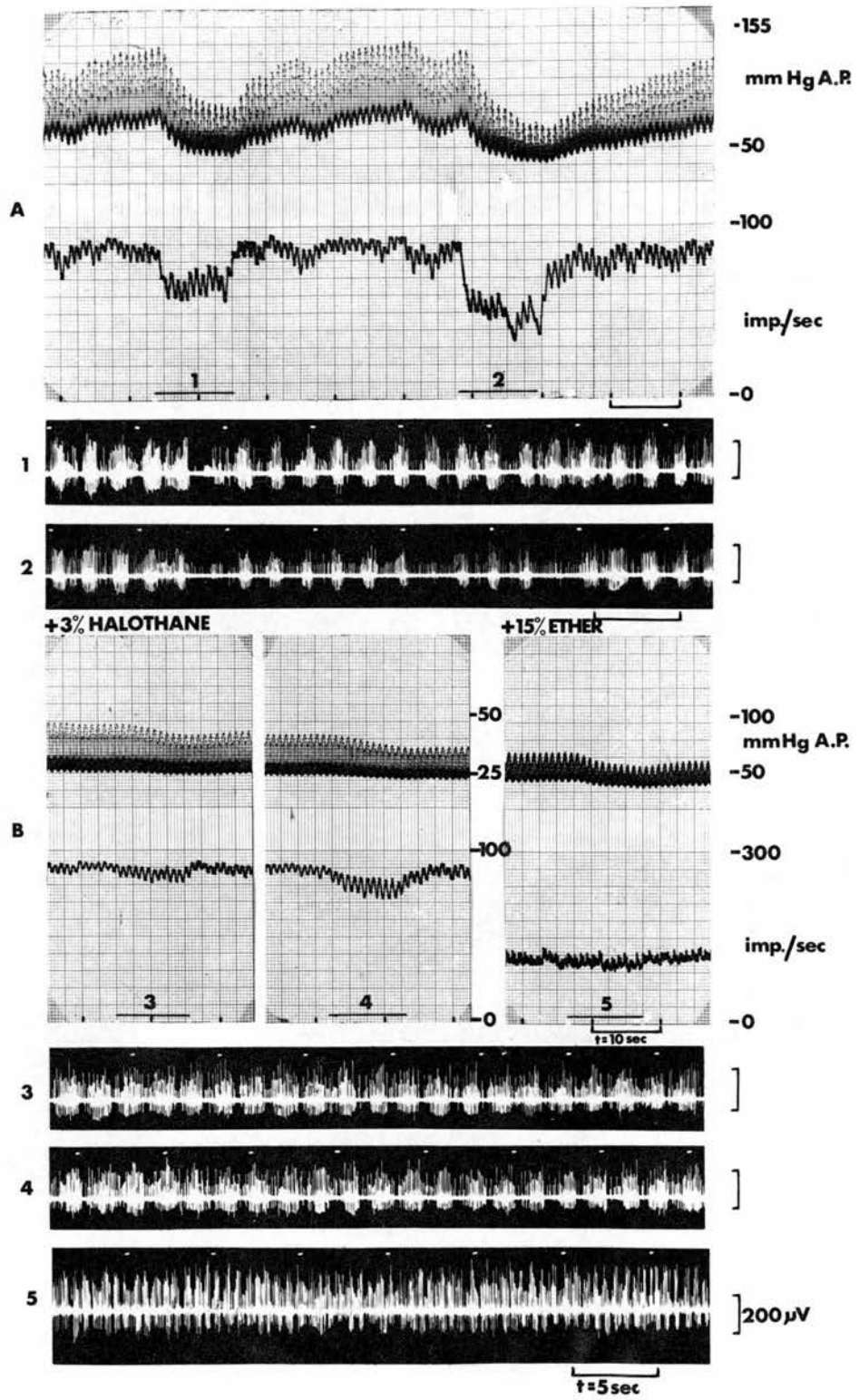

A
-155
mm Hg A.P.
-50
-100
imp./sec
-0
1
2
1
2
+3% HALOTHANE
+15% ETHER
B
-50
-25
-100
-100
mmHg A.P.
-50
-300
imp./sec
-0
3
4
5
t=10 sec
3
4
5
200 μV
t=5 sec

Fig. 17

Fig. 18.

Recording from the branch of the superior cervical ganglion to the carotid body, with stimulation of the aortic nerve at the horizontal line in each case. A, before cyclopropane. B, after 4 min of 50% cyclopropane. C, after 10 min 50% cyclopropane. D, 27 min off cyclopropane.

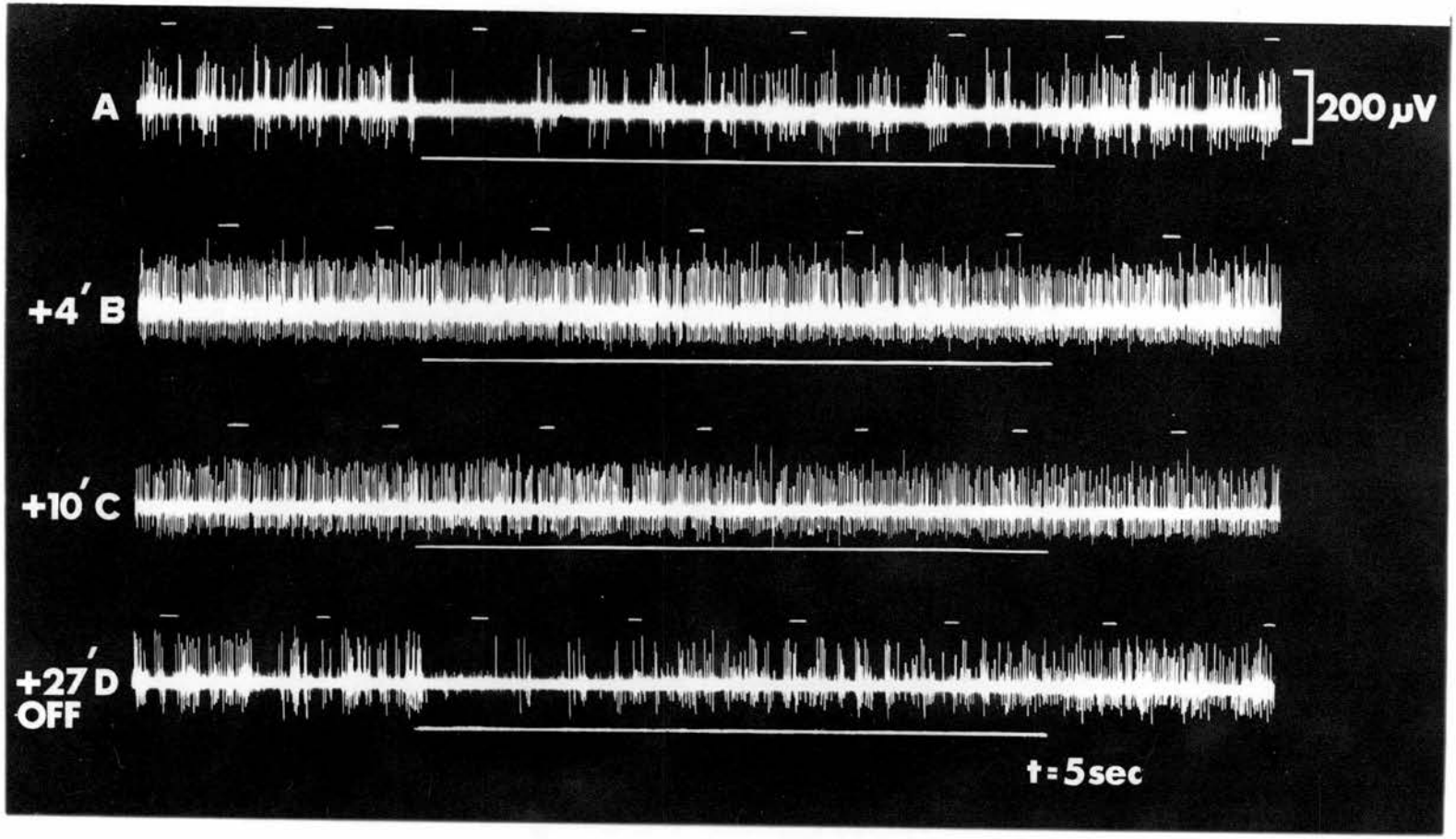


Fig. 18

cyclopropane. This difference was again highly significant (S.E. ± 7.8; ϕ = 18; 0.001> P).

Comparison between the inhibitory actions of the anaesthetics on the responses of arterial pressure and of preganglionic sympathetic discharge to combined A and C fibre stimulation of the aortic nerve, and applied to coincident measurements using Student's t-test, showed a significantly smaller inhibition of the arterial pressure responses (mean difference between percentage inhibitions of sympathetic and arterial pressure responses 12%, S.E. ± 4.1; ϕ = 12; 0.02>P7 0.01). A similar comparison in regard to the A type changes showed no significant difference (2.5% greater inhibition of arterial pressure responses, S.E. ± 5.2).

Possible differences in the relative effects of the inhalation anaesthetics on A and C type arterial pressure responses were sought in 6 animals, in 3 of which the carotid sinus and aortic depressor nerves had been cut previously. Individual measurements inevitably had to be made after different times of anaesthetic administration in each experiment, and the data are insufficiently homogeneous for precise comparison or for statistical analysis. In 19 measurements of each type of response, and including all three inhalation anaesthetics, the mean percentage inhibition of A and combined A and C responses was 74% and 62% respectively, at equivalent average times of administration of each anaesthetic. This suggests that the depressor effects of C fibre stimulation may be more resistant to blockade by the inhalation anaesthetics than are the A fibre responses. Different effects could not be established

in vagotomized animals, 12 measurements from which are included in the above comparison.

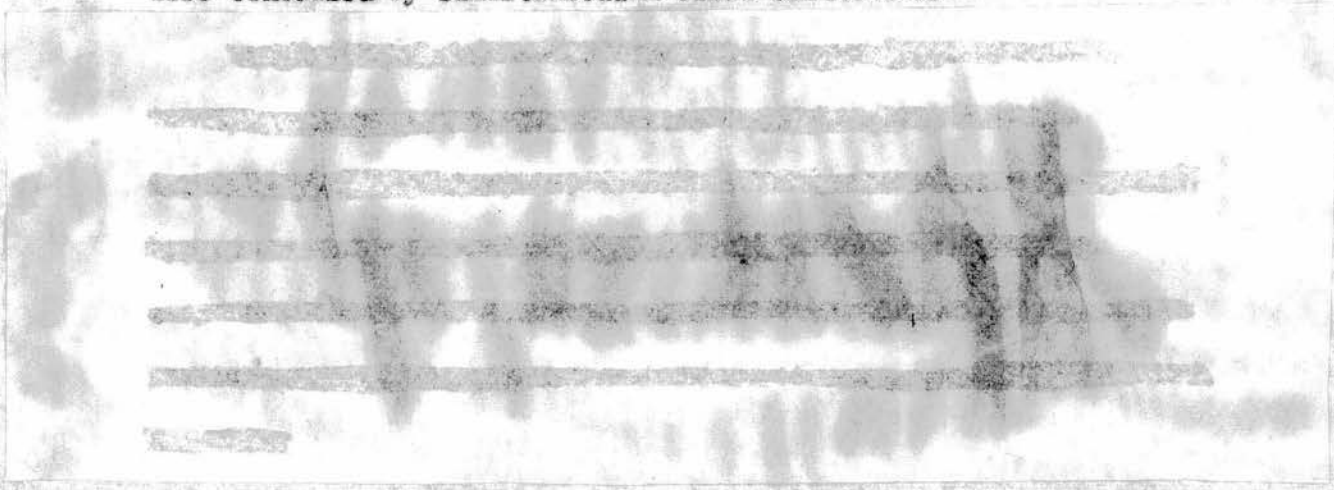
The inhibitory effects of the inhalation anaesthetics on the heart rate responses to combined A and C fibre excitation in the depressor nerve were similar to those already described in the case of maximal A fibre stimulation, and were observed in vagotomized animals.

Discussion

Douglas, Ritchie and Schaumann (1956) found no evidence of chemosensory afferents in the aortic nerve of the rabbit; this view was also held by earlier workers (Schmidt, 1932; Gernandt, 1946; Neil, Redwood and Schweitzer, 1949b). However, Mott (1963) attributed increases in rate and depth of respiration to aortic nerve stimulation with 2 msec pulses; this result could not be confirmed here with pulses of 100 - 500 μsec, and it was found that above a duration of 500 μsec double stimulation of the A fibres occurs. In a total of some 80 experiments, there was never any increase in arterial pressure on aortic nerve stimulation, which agrees with the observations of Mott (1963) and Douglas, Ritchie, and Schaumann (1956), and contrasts with the effects of carotid sinus nerve stimulation which in the rabbit excites respiration and often increases arterial pressure. Electrical stimulation of the aortic nerve in the rabbit appears to be a convenient method of eliciting pure baroreceptor reflexes.

The nature of the third aortic nerve action potential, with a conduction velocity of 4 - 12 m/sec, is uncertain because the diffuseness of the action potential makes it difficult to measure changes in amplitude with accuracy. The conduction velocity of the fibres is in the range of aortic chemoreceptor afferents found by Paintal (1953), but there was no evidence that spontaneous respiration was stimulated when this group was maximally excited in addition to maximal excitation of the A fibres, nor when the pulse width was increased from 100 μsec to 2 msec (Mott, 1963).

In such an experiment, it is possible that respiratory effects were concealed by simultaneous A fibre excitation.



While the responses to aortic nerve stimulation of arterial pressure and cervical sympathetic activity were quantitatively similar in many rabbits, an overall comparison on the basis of maximum percentage reductions in these responses showed a significantly smaller inhibition of sympathetic discharge. Although gallamine triethiodide was given in all experiments, this suggested the presence of an important vagal component in the rabbit's depressor response. This could not be confirmed, however, since the results were similar in vagotomized animals. It is possible that gallamine, which has an atropine-like action, may have obscured differences in the responses of intact and vagotomized rabbits to aortic nerve stimulation, and a vagal component in the depressor responses of the normal animal is of course not excluded by the present experiments. The fact that a significant difference between the depressor arterial and sympathetic responses was not detectable following baroreceptor denervation suggests that the intact baroreceptor nerves may have affected the sympathetic

depressor response more than that of arterial pressure. It is possible that this could depend on differing time-relations of the two responses; thus, the reflex may operate fast enough to influence the fall in sympathetic rate although it cannot limit the slower changes in the effectors which have already commenced.

Bronk, Pitts, and Larrabee (1940) found that inhibition of efferent sympathetic discharge by afferent baroreceptor impulses was influenced by variations in hypothalamic activity. It might be expected, therefore, that in the present experiments the magnitude of the depressor responses would be related to the background level of sympathetic activity, during control periods before administration of the inhalation anaesthetics. The total sympathetic activity could not be assessed under the experimental conditions used since recordings were made only from one or two active cervical sympathetic strands. In addition, the magnitude of the arterial depressor response could not be significantly related to the level of arterial pressure, neither in a group of rabbits, nor in single experiments when arterial pressure was altered by haemorrhage; nor was it possible to demonstrate conclusively any change in the arterial or sympathetic depressor responses subsequent to division of the carotid sinus and aortic nerves, although there were less consistent differences between the relative magnitudes of the two responses under those conditions. Since baroreceptor and chemoreceptor denervation, and haemorrhagic hypotension, have widespread effects and do not only alter sympathetic activity and arterial pressure, it is likely that

failure to demonstrate a correlation between the magnitude of the depressor response and the background level of arterial pressure and sympathetic discharge does not necessarily exclude such a relationship, particularly in individual animals under normal conditions.

These experiments have demonstrated inhibitory actions of inhalation anaesthetics on the central pathways linking systemic baroreceptors and preganglionic sympathetic neurones. Many previous investigations have referred to the efficacy of baroreceptor reflexes during anaesthesia with various agents, but precise interpretation of the data is difficult. In dogs (Brown & Hilton, 1956) and rabbits (Gordh, 1945), diethyl ether abolished the arterial pressure response to carotid occlusion; similar changes occurred during halothane anaesthesia (Raventos, 1956). Differential effects of anaesthetics on central chemoreceptor and baroreceptor pathways have also been suggested (Dripps & Dumke, 1943; Douglas, Innes & Kosterlitz, 1950). Further consideration of the actions of cyclopropane, halothane and ether on central baroreceptor pathways, will be included in the General Discussion.

Summary of Study 2

1. The reductions in arterial pressure and preganglionic sympathetic activity evoked by aortic nerve stimulation in the rabbit were studied before and during administration of constant inspired concentrations of the inhalation anaesthetics cyclopropane, halothane, and ether. The background anaesthetic was pentobarbitone, gallamine triethiodide was given, and pulmonary ventilation was with 100% oxygen.

2. During light pentobarbitone anaesthesia, aortic nerve stimulation usually induced similar reductions in arterial pressure and preganglionic discharge, expressed as the maximum percentage reduction from prestimulation levels. There were two components in the sympathetic responses, attributable to A and C fibre excitation in the aortic nerve, which was also shown to contain a third fibre group with properties similar to those of B fibres.

3. The arterial pressure, heart rate, and preganglionic sympathetic responses to aortic nerve stimulation were rapidly and profoundly inhibited by 50% cyclopropane, which also produced arterial hypertension.

4. 3% halothane significantly inhibited the depressor responses, but even in the presence of severe hypotension the arterial pressure could usually be reduced further by aortic nerve stimulation. The inhibitory effects of 2% halothane were slow in onset and not pronounced. In the concentrations used, these actions of halothane were significantly less than those of cyclopropane.

5. The inhibitory effects of ether on the depressor responses

were roughly intermediate between those of cyclopropane and halothane; complete suppression of the responses occurred with high ether concentrations, which were also liable to cause circulatory collapse.

STUDY 3. PREGANGLIONIC SYMPATHETIC ACTIVITY AND THE EFFECTS OF INHALATION ANAESTHETICS.

Introduction

Changes in preganglionic sympathetic activity produced by inhalation anaesthetics have not been studied directly apart from a brief communication by Martin & Marrazzi (1942), stating that cyclopropane and chloroform do not affect cervical sympathetic discharge in cats. However, Deutsch, Linde & Price (1962) measured an increased plasma adrenaline level during cyclopropane anaesthesia in the dog, while in the same species Millar & Morris (1960) found no increase in circulating catecholamines when halothane was given. The former result suggests that excitation of the sympathetic nervous system by cyclopropane may account for the arterial hypertension which usually occurs. This view is supported by head perfusion experiments (Price et al.,1963), also in the dog, while similar studies suggest that there is depression of central sympathetic discharge during halothane anaesthesia (Price, Linde & Morse, 1963), which accords with the reduced arterial pressure and the catecholamine measurements.

In an attempt to confirm and extend these findings, recordings have been made directly from preganglionic sympathetic nerves during the administration of cyclopropane, halothane and diethyl ether.

Results

During control periods, when the level of basal anaesthesia with pentobarbitone was evenly maintained, the integrated preganglionic sympathetic discharge from multifibre strands usually remained constant for 30 min or longer, and activity could be monitored for several hours.

The effects of sodium pentobarbitone, when given in doses of 6 - 12 mg intravenously, were inconsistent but produced only small alterations in arterial pressure and preganglionic sympathetic activity. Eight experiments were examined in detail. In four of these arterial pressure was unchanged after injection of 6 mg doses of pentobarbitone; in 3 of the 4 rabbits showing transient hypotension in response to 6 or 12 mg, recovery was complete within 3 min. Sympathetic discharge rate was unaltered in 2, increased in 2, and reduced in 4 of these 8 experiments; on 5 of the 6 occasions in which sympathetic activity was modified there was a return to the pre-injection level within 90 sec. Changes in arterial pressure, in one experiment, and in preganglionic discharge rate, in another, had not recovered until four min after the injection of sodium pentobarbitone.

The effects of gallamine triethiodide on sympathetic activity appeared to be negligible. In 8 of the 15 injections in 12 animals there was a mean fall in the discharge frequency of 3%, with complete recovery in 1 min; in the other 7 examples there was no change. A small fall in arterial pressure, lasting for

less than 30 sec, occurred in only two animals. In the only other rabbit to show any response, there was a brief rise in arterial pressure lasting for 90 sec. The injection of gallamine was associated with a fall in heart rate of 10 - 20/min, lasting less than 30 sec; this represented a small change, since the control heart rates were usually about 300 per min.

Fig.19 illustrates a typically transient reduction in mean arterial pressure and heart rate, following injection of a mixture of 12 mg sodium pentobarbitone and 4 mg gallamine. This also caused a brief increase in the mean cervical sympathetic discharge rate and a temporary loss of the respiratory modulations. Cervical sympathetic fibres showed a respiratory rhythm during positive pressure ventilation of the lungs; towards the end of expiration and at the start of inspiration there was a burst of activity; an example is shown in Fig. 20. This rhythm was disrupted briefly by administration of pentobarbitone (Fig.19).

Further records are shown in Fig. 21, where positive pressure inflation of the lungs is indicated by changes in end-tidal P_{CO_2} (expiration upwards). In the example A, the rate of impulse discharge reached a peak during both inspiration and expiration. Fig. 21B shows the effect on the discharge of stopping mechanical ventilation; the peaks of activity continued with the same period but were no longer coupled as in Fig. 21A. The coupling persisted after the vagi had been cut (Fig. 22A) but was less constant when the rate of respiration was slowed (Fig. 22B). Inspection of

Fig. 19.

Records from above down; heart rate counted for 5 sec periods (■); mean arterial pressure, mm Hg; preganglionic cervical sympathetic nerve, integrated discharge rate in impulses/sec (time constant, 1 sec). At the arrow 12 mg sodium pentobarbitone and 4 mg gallamine triethiodide were injected intravenously.

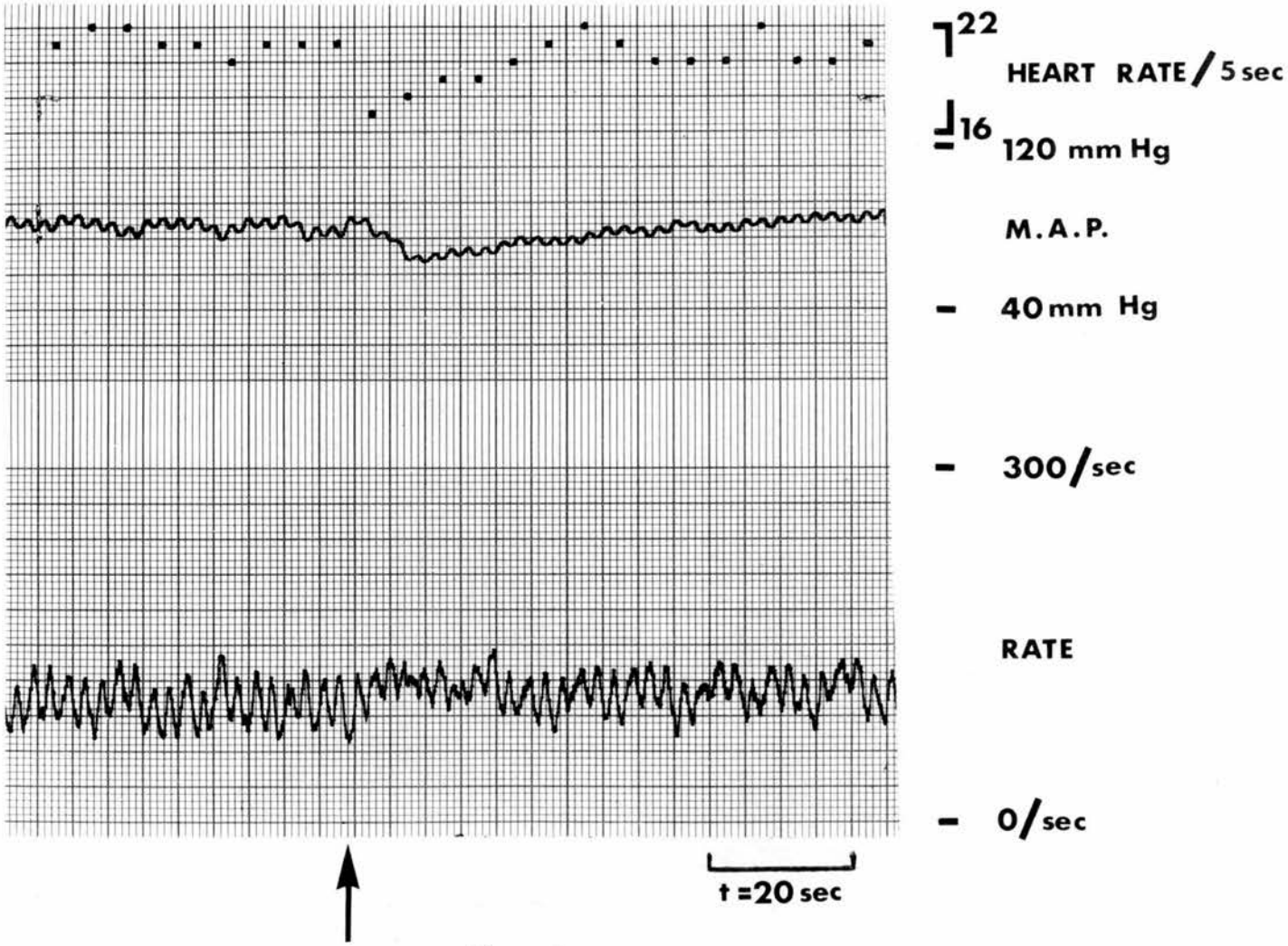

22
HEART RATE / 5 sec
16
120 mm Hg
M.A.P.
40 mm Hg
300/sec
RATE
0/sec
t = 20 sec

Fig. 19

Fig. 20.

Film record. Upper trace: action potentials recorded from the preganglionic cervical sympathetic nerve; impulse discharge is mainly during expiration. Lower trace: arterial pressure, mm Hg.

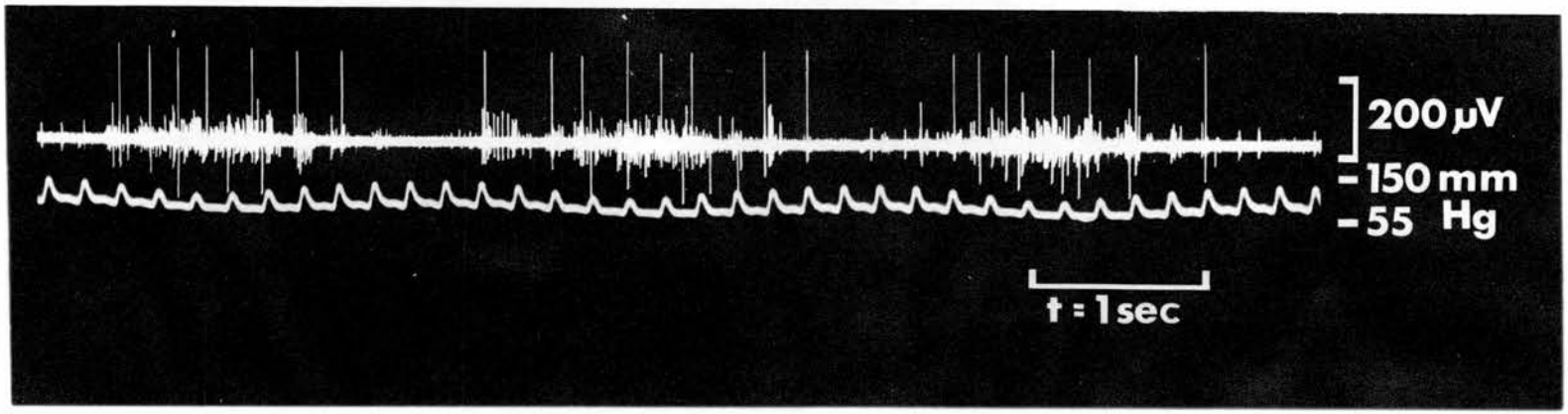


Fig. 20

Fig. 21

From above down: end-tidal P_{CO_2}, mm Hg; arterial pressure, mm Hg; preganglionic cervical sympathetic nerve, integrated discharge rate in impulses/sec (time constant, 0.33 sec); film record of the action potentials taken simultaneously. A: the sympathetic discharge shows synchronized bursts which are coupled, during both inspiration and expiration. B: the effect on this rhythm of stopping mechanical ventilation.

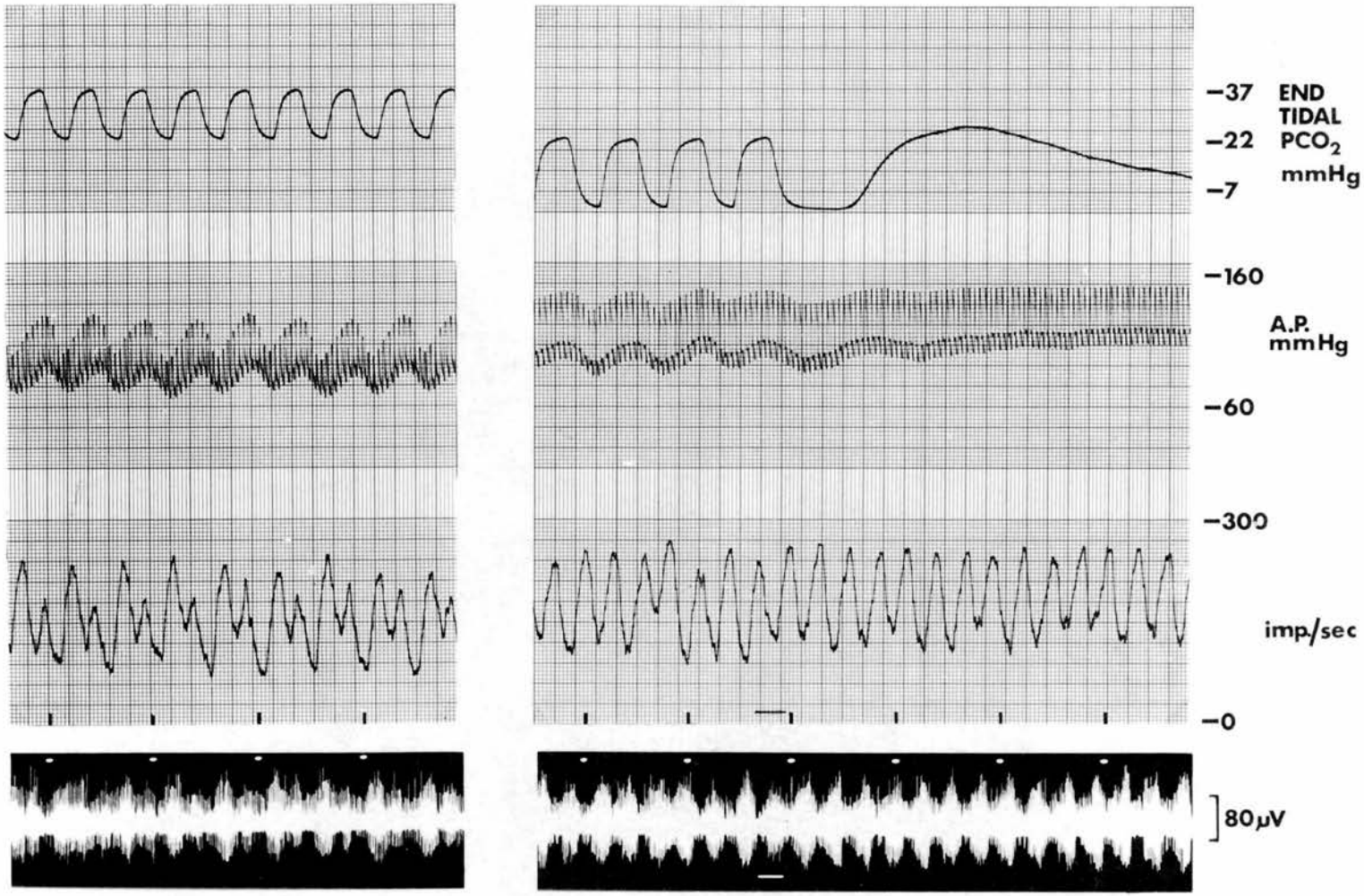


Fig. 21

Fig. 22.

The records show from above down: end-tidal P_{CO_2}, mm Hg; arterial pressure, mm Hg; preganglionic cervical sympathetic nerve, integrated discharge rate in impulses/sec (time constant, 0.33 sec); these records are from the experiment illustrated in Fig. 21, but after the vagi had been cut. A shows persistence of the coupled rhythm. B shows the effect of stopping mechanical ventilation.

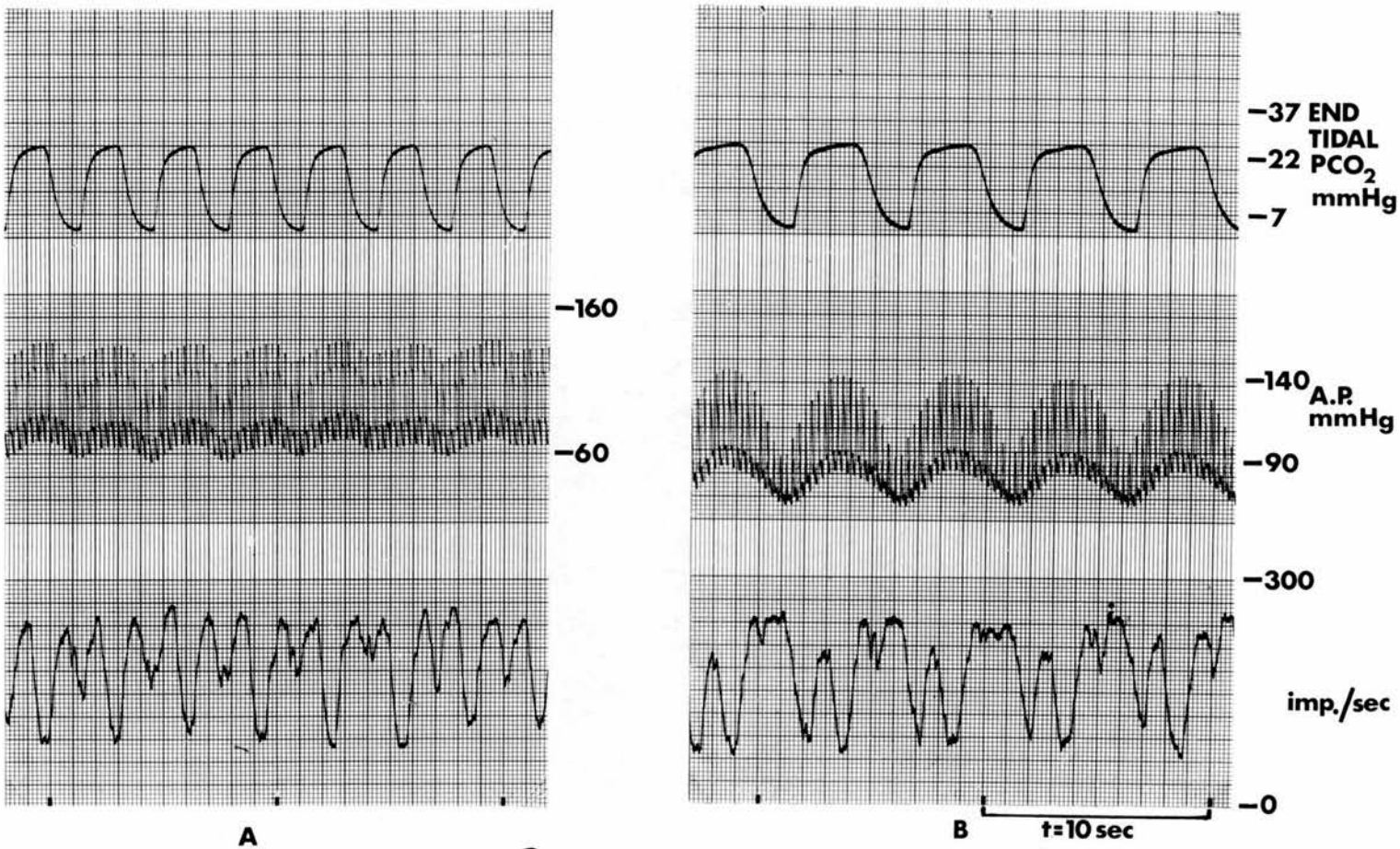

−160
−60
A
−37 END
TIDAL
−22 PCO2
mmHg
−7
−140 A.P.
mmHg
−90
−300
imp./sec
−0
B
t=10 sec

Fig. 22

these records shows that the coupling did not have a constant relation either to the end-tidal P_{CO_2} or to the arterial pressure wave.

The nature of the rhythmic activity shown in Figs. 21 and 22 is further clarified by reference to the findings in another rabbit in which the vagi, carotid sinus, and aortic nerves had been cut. Fig. 23a shows above, the end-tidal P_{CO_2} during positive pressure ventilation (expiration upwards) and below, the integrated sympathetic discharge with a rhythm which is faster than the ventilation rate. Fig. 23b is a film record taken later in the same experiment and shows sympathetic action potentials occurring rhythmically in bursts. The end-tidal P_{CO_2} trace is irregular because the animal was breathing against the pump as the effect of gallamine wore off. When the pump was stopped the animal breathed spontaneously, shown in the P_{CO_2} trace, and the bursts of action potentials were in time with this spontaneous respiration. This clearly suggests a central origin for certain types of sympathetic respiratory rhythm (Adrian, Bronk & Phillips, 1932) which can occur even when the end-tidal P_{CO_2} is so low as about 20 mm Hg (Fig. 23). A further example of this rhythm is shown in Fig. 34, from another experiment wherein the vagi and baroreceptor nerves had been cut.

A cardiac rhythm, (grouped impulses in time with the arterial pulse wave), was seen occasionally in the cervical sympathetic nerve, 3 examples being obtained. In one rabbit in which the

Fig. 23

a shows above, end-tidal P_{CO_2}, mm Hg; below, integrated preganglionic cervical sympathetic discharge rate in impulses/sec, time constant 3.3 sec.

b is a film record showing, above, action potentials recorded in the same experiment as in a, and below, the end-tidal P_{CO_2} in mm Hg. During the period marked 'pump off', mechanical ventilation of the lungs was stopped.

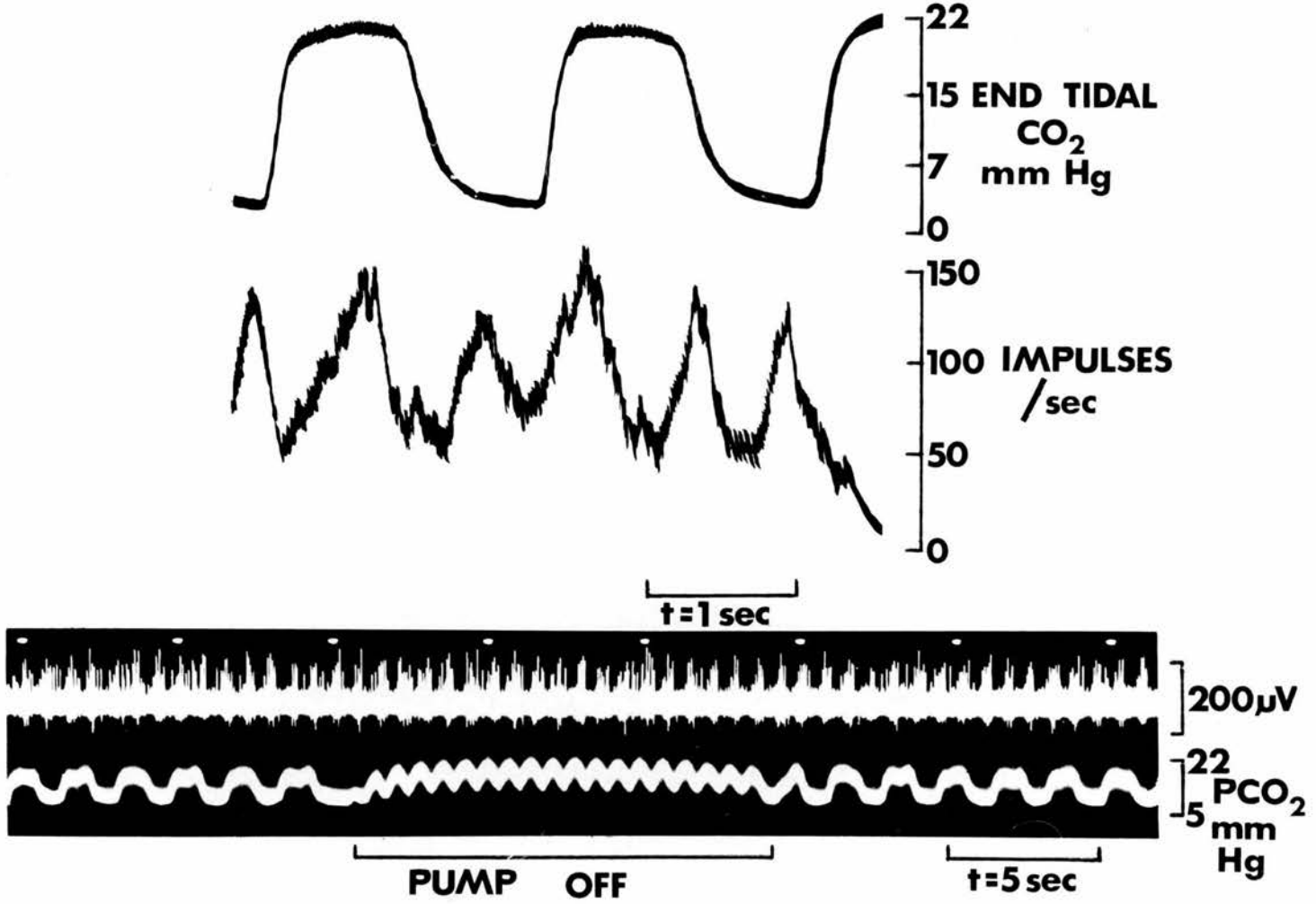

22
15 END TIDAL
CO_2
7 mm Hg
0
150
100 IMPULSES
/sec
50
0
t=1 sec
200μV
22
PCO_2
5 mm
Hg
PUMP OFF
t=5 sec

Fig. 23

carotid and aortic sinus nerves were divided in stages the rhythm persisted until the last (aortic) baroreceptor nerve was cut.

Sympathetic responses to an increase in inspired P_{CO_2}

Records were obtained from the cervical sympathetic nerve in 3, and from the adrenal nerve in 2, rabbits. In every experiment an exaggeration of the respiratory modulation of sympathetic activity was produced by carbon dioxide; when the inspired carbon dioxide concentration was increased by 5 - 10%, the amplitude of the sympathetic rhythm was approximately doubled. Fig. 24 shows a series of action potential records from the preganglionic cervical nerve. In sequence a, the animal was breathing 100% oxygen; mean arterial pressure was 66 mm Hg. Measurements of the amplitude of the variation in sympathetic discharge, from the ratemeter record, showed a fluctuation of 26 per sec about a mean rate of 90 per sec. After 6 min of 3% carbon dioxide the variation was 35 per sec and the mean rate 87 per sec (Fig. 24b). Following administration of 5% carbon dioxide for 6 min, the sympathetic rate was 84 and the variation 38 per sec (Fig. 24c). Sequence d, taken during ventilation with 8% carbon dioxide, shows more marked synchronization of the action potential bursts; the variation was now 40 per sec and the mean rate had returned to the control level, 90 per sec. When the inspired carbon dioxide was raised to 10% for 6 min, there was no further change in mean sympathetic discharge rate or rhythm,

Fig. 24.

Action potentials recorded from the cervical sympathetic preganglionic nerve, illustrating the effect on the discharge rate of increasing the inspired P_{CO_2}. The inspired CO_2 concentration in oxygen is indicated to the left of the Figure. In a, the rabbit breathed 100% oxygen; the time during which the indicated CO_2 concentrations were administered was 6 min in each case.

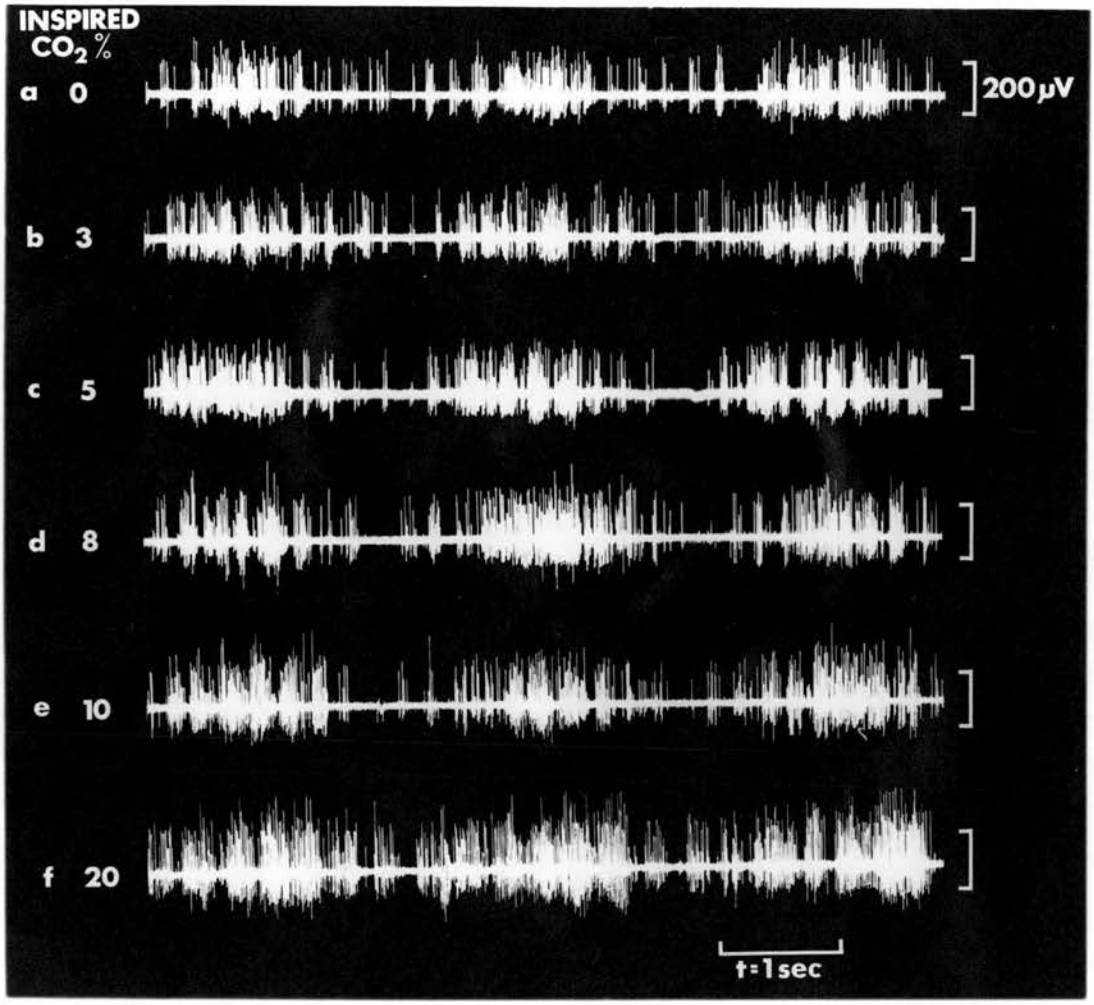


Fig. 24

although there was greater synchronization of the bursts (Fig. 24e). Until this point, mean arterial pressure during administration of carbon dioxide had remained at 77 mm Hg, but the level increased to 90 mm Hg when 20% carbon dioxide was given (Fig. 24f). At this concentration, cervical sympathetic discharge showed a marked increase, to 127 per sec, the amplitude of the rhythm remaining at about 38 per sec, but becoming more regular.

The experiment just described illustrates that at carbon dioxide concentrations below about 10%, the effect on the mean preganglionic sympathetic discharge rate may be relatively small although there is a pronounced increase in the amplitude of the rhythmic oscillation associated with pulmonary ventilation.

In contrast, Fig. 25 illustrates another experiment wherein the mean rate of discharge did increase in the cervical sympathetic nerve when carbon dioxide was administered. The films of action potentials were taken simultaneously with the corresponding ratemeter records. Sequences a and b show, respectively, the control responses and those after 5 min of 5% carbon dioxide. The amplitude of the rhythm had slightly increased in b, but there was also a rise in the mean discharge rate. After 5 min of 8% carbon dioxide, the rhythm was greatly increased, with a further small rise in mean rate (Fig. 25c). Sequences d and e show later stages of the same process, at carbon dioxide concentrations of 10% and 20%; the most striking effect was again the increase in amplitude of the respiratory rhythm.

Fig. 25.

Action potential recordings from the cervical sympathetic preganglionic nerve to show the effect on the activity of increasing the inspired CO_2 concentration. To the left are ratemeter recordings calibrated in impulses/sec (time constant, 1 sec). To the right are film records taken during the corresponding ratemeter records. a: the inspired gas was 100% oxygen. In each case the gas mixtures were given for 5 min before the records were taken. b, 5% CO_2 in oxygen; c, 8% CO_2 in oxygen; d, 10% CO_2 in oxygen; e, 20% CO_2 in oxygen. e shows the changes in sympathetic discharge on returning to 100% oxygen. Note the different time scales of the film strips and the ratemeter.

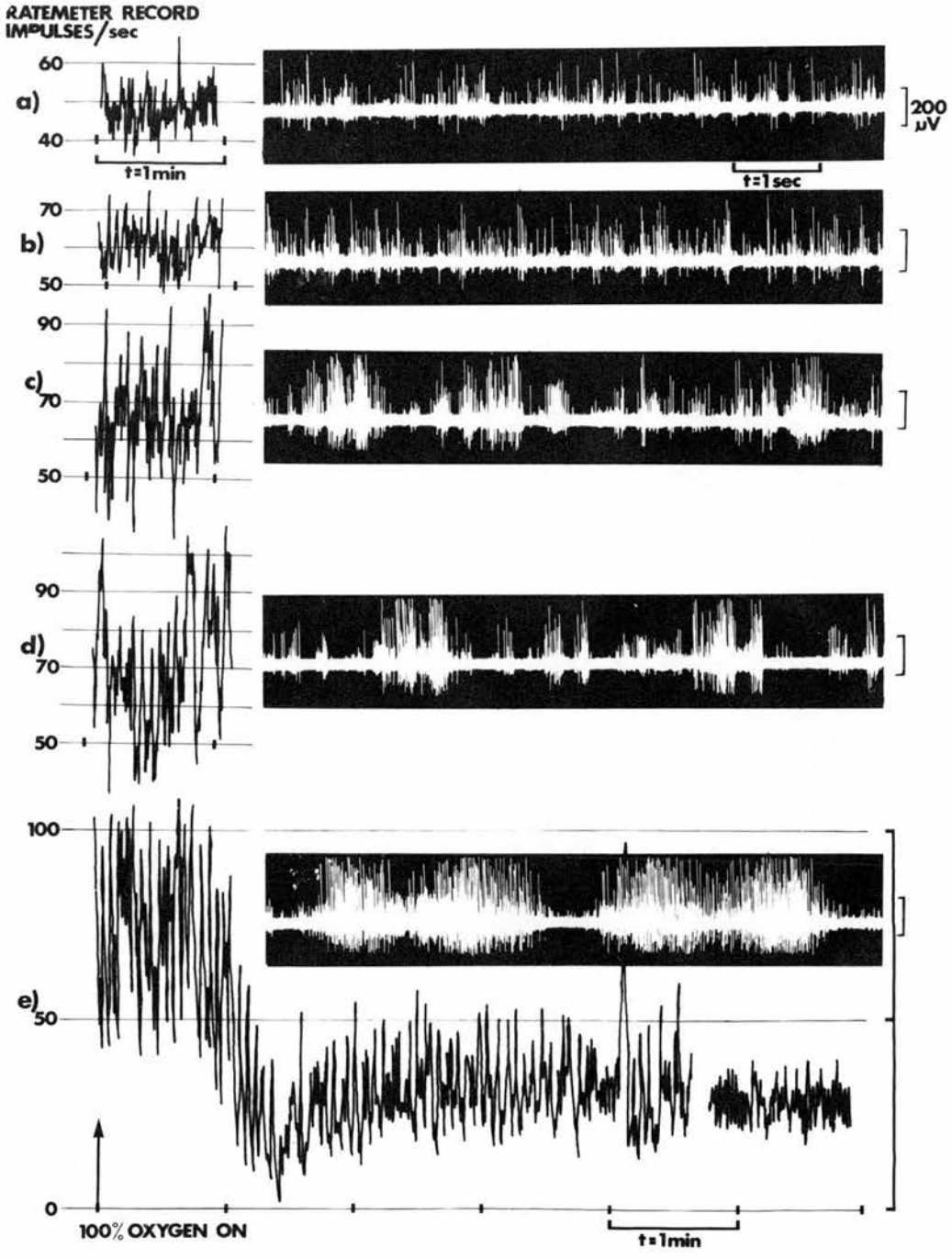

RATEMETER RECORD
IMPULSES/sec
60
a)
40
t=1min
200 µV
t=1sec
70
b)
50
90
c)
70
50
90
d)
70
50
100
e)
50
0
100% OXYGEN ON
t=1min

Fig. 25

The final sequence, illustrated in Fig. 25e, shows the ratemeter record on returning to administration of 100% oxygen. A fall in the mean sympathetic discharge rate occurred to below the control level, with a reduction in the amplitude of the rhythmic oscillations, both effects being observed within 1 minute. After a further 4 min the respiratory fluctuations were still more marked than before carbon dioxide administration, and did not return to the previous level until another 2 min had passed, indicated by the gap in the trace. The mean impulse discharge rate remained lowered, however.

A change from ventilation with 100% oxygen to room air, or vice versa, caused no detectable alteration in the mean level of sympathetic activity in several experiments.

Haemorrhage.

During splanchnic nerve recording, in two experiments, arterial hypotension was induced by haemorrhage, after allowing time for elimination of previously administered inhalation anaesthetics. Activity in the sympathetic strands under study was shown to be inhibited by intravenous adrenaline. Pre-ganglionic sympathetic discharge was increased as arterial pressure was reduced but this was not associated with effects on the amplitude of the respiratory oscillations in sympathetic discharge. Changes in the mean splanchnic discharge rate in one experiment are plotted against mean arterial pressure in Fig. 26. The numbers adjacent to the points refer to the order in which the measurements were made as blood was removed or replaced. The points are grouped

Fig. 26.

The frequency of firing of action potentials in a strand from the splanchnic nerve (impulses/sec) is plotted against the mean arterial pressure (mm Hg.) The changes in pressure were induced by removing and replacing blood from the femoral artery. The numerals adjacent to the points indicate the order in which the measurements were obtained. The line was drawn by eye.

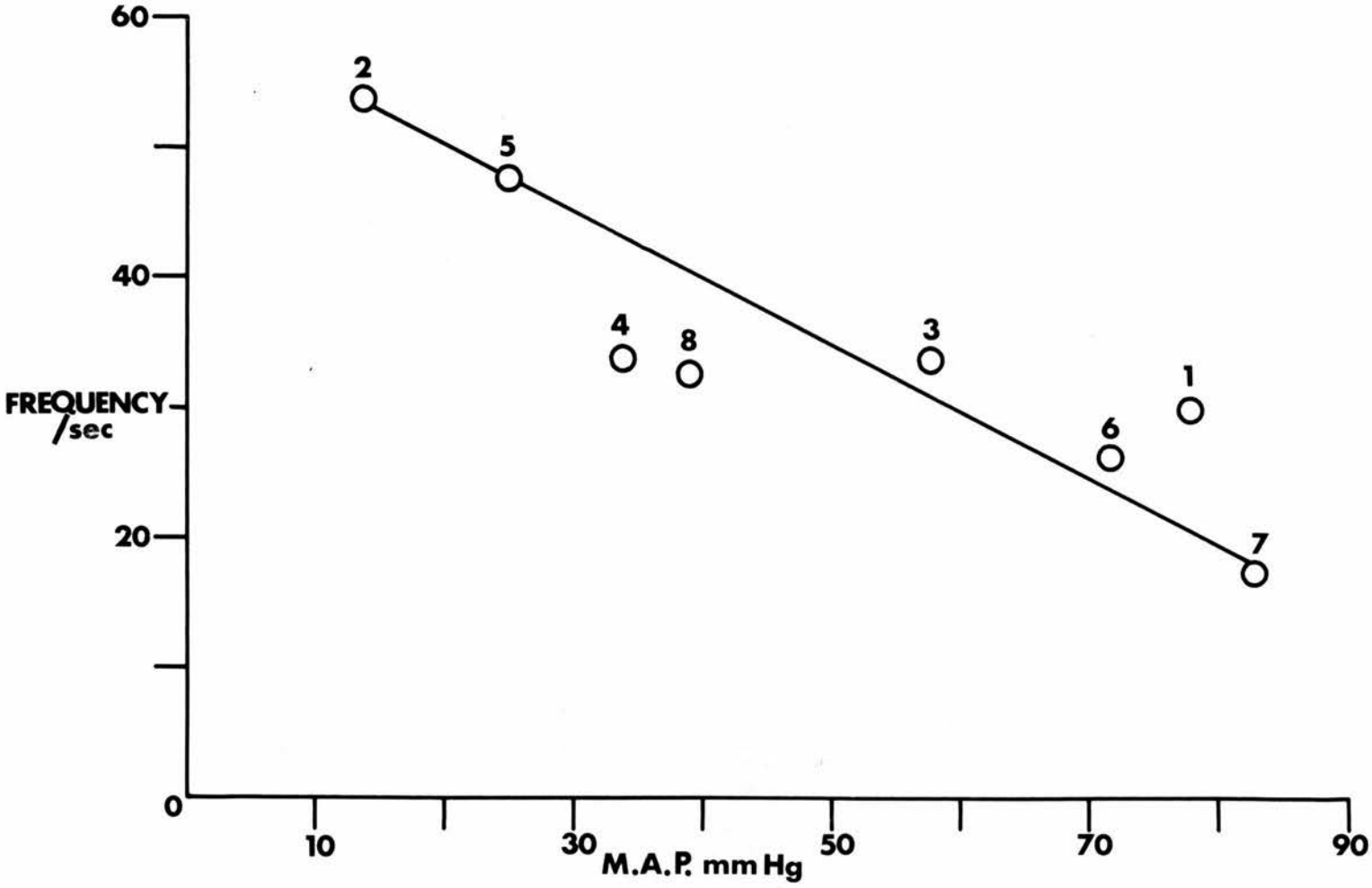


Fig. 26

around the line drawn by eye and suggest a positive inverse correlation.

Vasomotor fibres

Since recordings were made from the cut end of cervical and splanchnic sympathetic nerves, it was not possible to be certain of the destination of fibres whose discharge rates were being measured, or of their relation to the peripheral vascular control. The following criteria suggested, however, that their responses were similar to those of vasomotor fibres. Firstly, there was a reflex reponse to arterial pressure changes. This was shown by partial or complete inhibition of preganglionic discharge when a rise in arterial pressure was produced by intravenous adrenaline (5 - 10 μg), this test being applied one or more times during every experiment (Fig. 27a); again, by fleeting sympathetic inhibition when a small volume of saline or dextran in saline was injected rapidly intravenously; also, by the increase in sympathetic activity which occasionally accompanied the brief hypotension caused by intravenous pentobarbitone; and by the inverse linear relation between discharge frequency and arterial pressure demonstrated above for haemorrhage.

Secondly, electrical stimulation of the depressor (aortic baroreceptor) nerve in the rabbit evoked simultaneous reductions in arterial pressure and preganglionic sympathetic discharge, the two effects being well correlated quantitatively in several experiments (see Study 2).

Thirdly, stimulation of the rabbit during light anaesthesia,

Fig. 27.

Action potentials from the splanchnic nerve (a, b, and c) and adrenal nerve (d), showing the types of activity which may be found in different strands. a: Upper trace shows grouped discharge in time with respiration. Lower trace, the mean arterial pressure in mm Hg. At the first arrow 5 µg adrenaline ~~hydro~~chloride were injected intravenously, at the second arrow the drug was washed in with 0.9% NaCl solution. b: Upper trace, action potentials. Lower trace, arterial pressure (mm Hg). At the first arrow 7.5 µg adrenaline hydrochloride were injected intravenously, and washed in at the second arrow. c: Upper trace, action potentials; lower trace, resetting time scale described under Methods. d: Upper trace, action potentials recorded from the adrenal branch of the splanchnic nerve and having the same characteristics as those in c; lower trace, resetting time scale. These spontaneous high-frequency discharges in the splanchnic (c) and adrenal (d) nerves were unaffected by rises in arterial pressure.

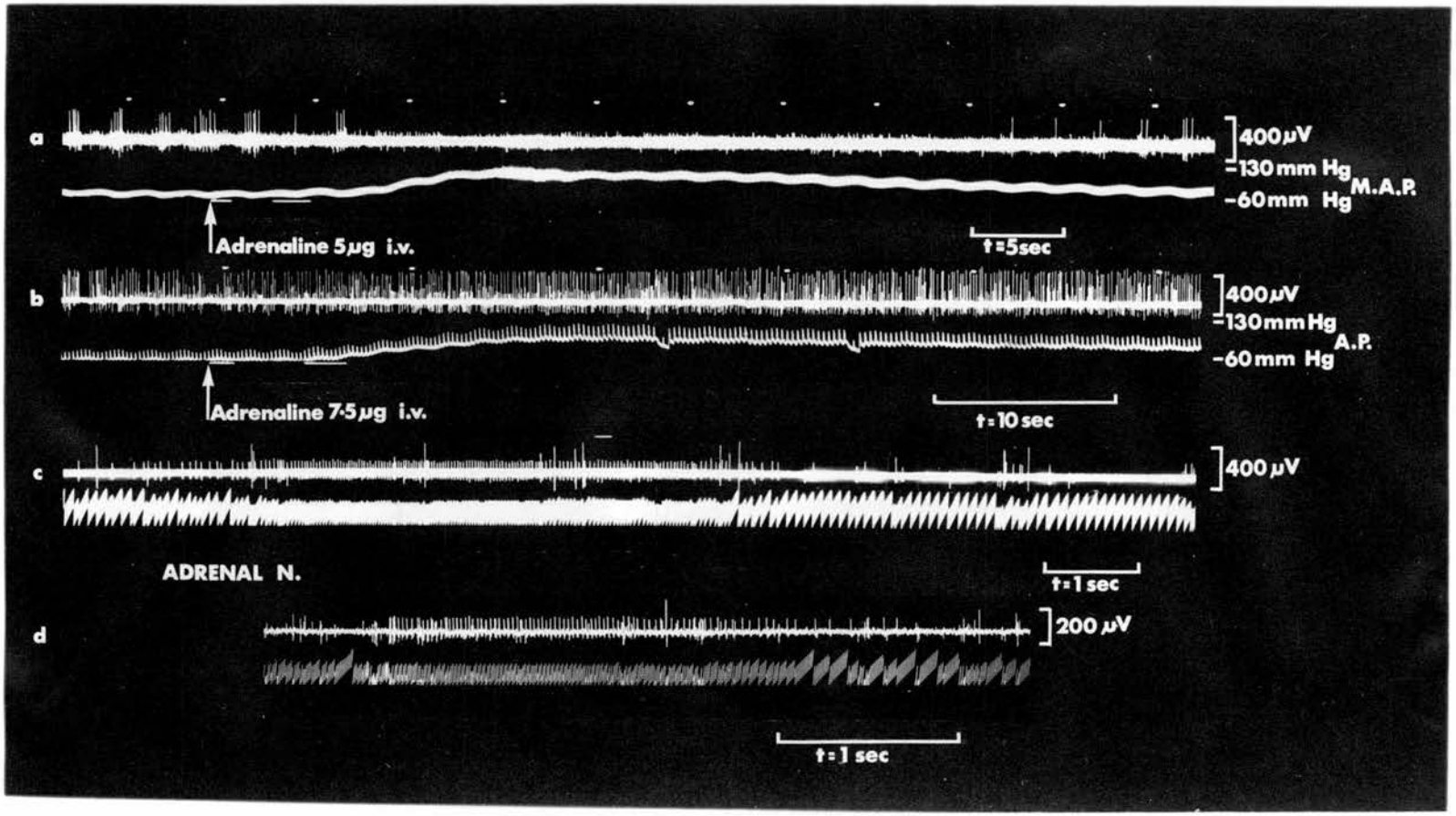

a
400 μV
130 mm Hg
60 mm Hg
M.A.P.
Adrenaline 5 μg i.v.
t = 5 sec
b
400 μV
130 mm Hg
60 mm Hg
A.P.
Adrenaline 7·5 μg i.v.
t = 10 sec
c
400 μV
ADRENAL N.
t = 1 sec
d
200 μV
t = 1 sec

Fig. 27

for example by touching the wound edges, commonly produced an abrupt and parallel fall in both sympathetic discharge and arterial pressure.

Lastly, the characteristics of the sympathetic discharge observed during the control periods in the present experiments are similar to those observed by previous workers (Adrian, Bronk & Phillips, 1932; Iggo and Vogt, 1960) who have assumed a close interrelation between cervical sympathetic responses and those of arterial pressure.

The effectiveness of baroreceptor denervation, when undertaken, was confirmed by showing a negligible, or no, reduction in preganglionic discharge in response to intravenous adrenaline 5 - 10 µg.

Patterns of activity observed in the splanchnic and adrenal nerves

In the adrenal and other branches of the splanchnic nerve, four types of impulse discharge could be distinguished;-

1. Spontaneous activity which showed a respiratory rhythm and which could be partially or completely inhibited by the rise in arterial pressure produced by intravenous adrenaline. This response was similar to that of cervical sympathetic strands (Fig. 27a). Sixteen groups of fibres showing these characteristics were identified in 16 nerve strands.

2. An irregular spontaneous discharge apparently without relation to respiration or arterial pulse. The fibres exhibiting this activity were excited by the rise in arterial pressure induced by

adrenaline, and were present in five of the sixteen strands (Fig. 27b).

3. Spontaneous activity showing a fairly regular discharge which could be increased by a rise in arterial pressure, and which was inhibited during inspiration. This was observed in two groups of fibres in 16 strands.

4. Brief high-frequency bursts of action potentials, unaffected by a rise in arterial pressure, were seen in 3 of the 16 strands (Fig. 27c and d).

Acid-base changes

Measurements of the effects of the inhalation anaesthetics on preganglionic sympathetic discharge were made only during pulmonary ventilation with high oxygen concentrations. In addition to maintaining a viable preparation for many hours, it was considered that good oxygenation would limit the degree of metabolic acidosis which develops during long experiments on the rabbit. Nevertheless, a degree of pulmonary over-ventilation was usually required in order to maintain arterial pH at near normal levels. This was preferred to under-ventilation, since in previous studies progressive increases in plasma catecholamine concentrations were measured as pH was reduced by CO_2 ventilation or acid infusions (Morris and Millar, 1962a,b).

Effects of inhalation anaesthetics

In assessing the actions of the inhalation anaesthetics, control levels based on the mean preganglionic sympathetic discharge

rate and arterial pressure both before and after anaesthetic administration would have been influenced by the frequent failure of arterial pressure to return to exactly the same level after discontinuing each anaesthetic; sometimes, also, 5 to 20 ml dextran in saline was required to restore the pressure to near the initial level. The effects of the anaesthetics were assessed, therefore, by comparison only with the impulse discharge rate and arterial pressure level which preceded administration.

It is possible that gradual deterioration of the animals during the progress of an experiment may have influenced measurements made during the latter part; this could have affected certain responses, though no difference in the qualitative effects observed could be detected when the order of administration of agents was altered. Nevertheless, in apparently healthy rabbits the responses observed in consecutive administrations of one anaesthetic were seldom identical quantitatively. In order to minimise effects attributable to repeated administrations, mean values and statistical inferences usually refer only to one (almost invariably the first) administration of each of the three anaesthetics in any animal.

Preganglionic cervical sympathetic nerve

Cyclopropane

Nine rabbits were ventilated with 50% cyclopropane in oxygen. In 8 of these animals, arterial pressure increased progressively after 2 to 3 min, to a maximum level averaging 21% above control after 4 to 8 minutes (S.E. ± 4.1, $0.01 > P > 0.001$. In each

case there was an associated rise in preganglionic cervical sympathetic discharge rate, to a mean of 80% above the pre-anaesthetic level at the times corresponding to the peak rise in arterial pressure. This increase was highly significant (S.E. $\pm$ 18, $0.01 > P > 0.001$). In the single rabbit which did not show an increase in arterial pressure above control, the sympathetic discharge rate was increased by 50% after 4 min of cyclopropane.

The maximum increase in sympathetic activity evoked by cyclopropane, which was by a mean of 93% above the control level (S.E. $\pm$ 5.3, $P < 0.001$), coincided with the peak rise in arterial pressure in 3 of the 8 tests; in 4 instances the effects were separated by 2 min, and in one case by 4 min. At the time of peak sympathetic discharge rate, the average increase in arterial pressure in all 9 tests was by 10% above control, which was insignificant (S.E. $\pm$ 4.7, $0.1 > P > 0.05$).

Arterial pressure showed variable effects within the first 2 - 3 min of administration of 50% cyclopropane. In one of the 9 rabbits studied, there was no change from the control level. In another three animals, arterial pressure had already started to rise. A brief period of hypotension, most pronounced 2 min after induction, occurred in 4 other experiments, in 3 of which cervical sympathetic discharge had already increased above the control level. One of these 3 is illustrated in Fig. 23 (left), where the mean arterial pressure fell as preganglionic sympathetic activity increased. After 2 min the arterial pressure also

Fig. 28.

The upper graphs, ●, are plots of the impulse discharge rate in the cervical sympathetic preganglionic nerve (impulses/sec) against time (min). The lower graphs, O, represent mean arterial pressure, mm Hg, taken at the same time as the upper graphs and on the same time scale in min. 50% cyclopropane was given between the arrows. Left, the response with all other nerves intact. Right, the response with the vagus, sinus, and aortic nerves cut bilaterally.

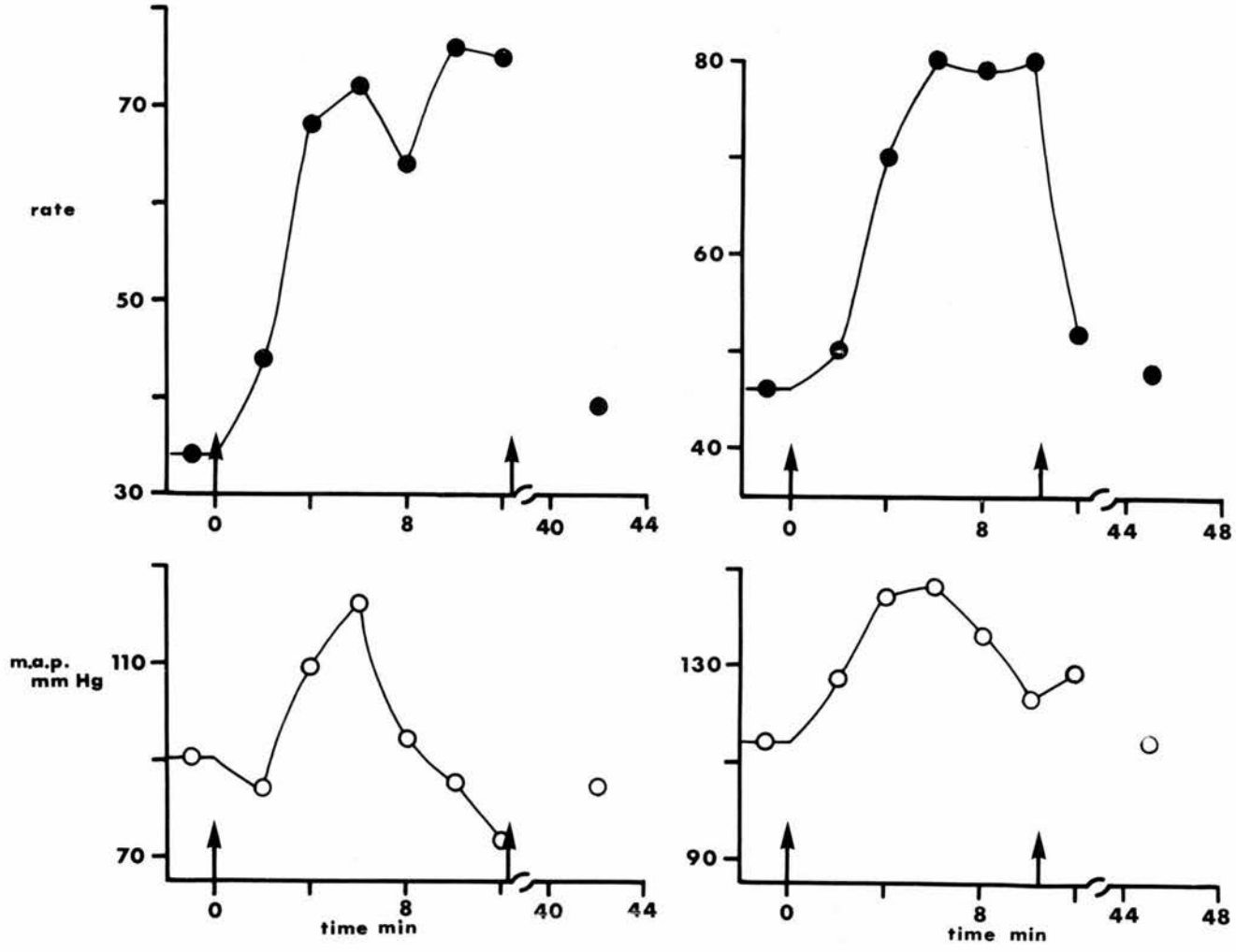

rate
70
50
30
0
8
40
44
80
60
40
0
8
44
48
m.a.p.
mm Hg
110
70
0
8
40
44
time min
130
90
0
8
44
48
time min

Fig. 28

started to rise. The one experiment in which there was an initial fall both in sympathetic rate and arterial pressure is illustrated in Fig. 29a. In this case the pressure reached its lowest point about 30 sec before the sympathetic discharge rate, and then began to rise slowly. By contrast, cervical sympathetic activity showed a slower fall but recovered more rapidly. Both arterial pressure and sympathetic rate eventually exceeded their control levels.

Fig. 28 (left) also shows the characteristic, and associated, increase in preganglionic discharge and arterial pressure within the first 8 min of cyclopropane administration. After reaching a peak the pressure usually declined towards control levels as the 50% concentration was maintained. In Fig. 28 (left) this effect was very marked; after 10 min the pressure was below control while the sympathetic rate, after showing a transient fall, remained elevated. This maintained increase in sympathetic discharge was the usual response, and in only one experiment did the rate fall transiently below the control level during continuous administration of 50% cyclopropane. This is shown in Fig. 30. Arterial pressure and sympathetic rate were both at a maximum at 4 min; subsequently the pressure fell and remained at a level more than 50% below control, until the anaesthetic was discontinued at 30 min. In contrast, the sympathetic activity, though also showing a fall in rate below control at 10 min, later recovered to a new level maintained 11% above control throughout the remainder of the administration. Both pressure and sympathetic rate

Fig. 29.

a: Preganglionic cervical sympathetic discharge frequency, ●, in impulses/sec; O, systolic arterial pressure in mm Hg; □, diastolic arterial pressure in mm Hg; abscissa, time in min. At the arrow the administration of 50% cyclopropane was started.

b: Recording from the splanchnic nerve. The upper record is traced from the ratemeter output (impulses/sec). The lower records as in a. Time is in min. At the arrow 50% cyclopropane was given.

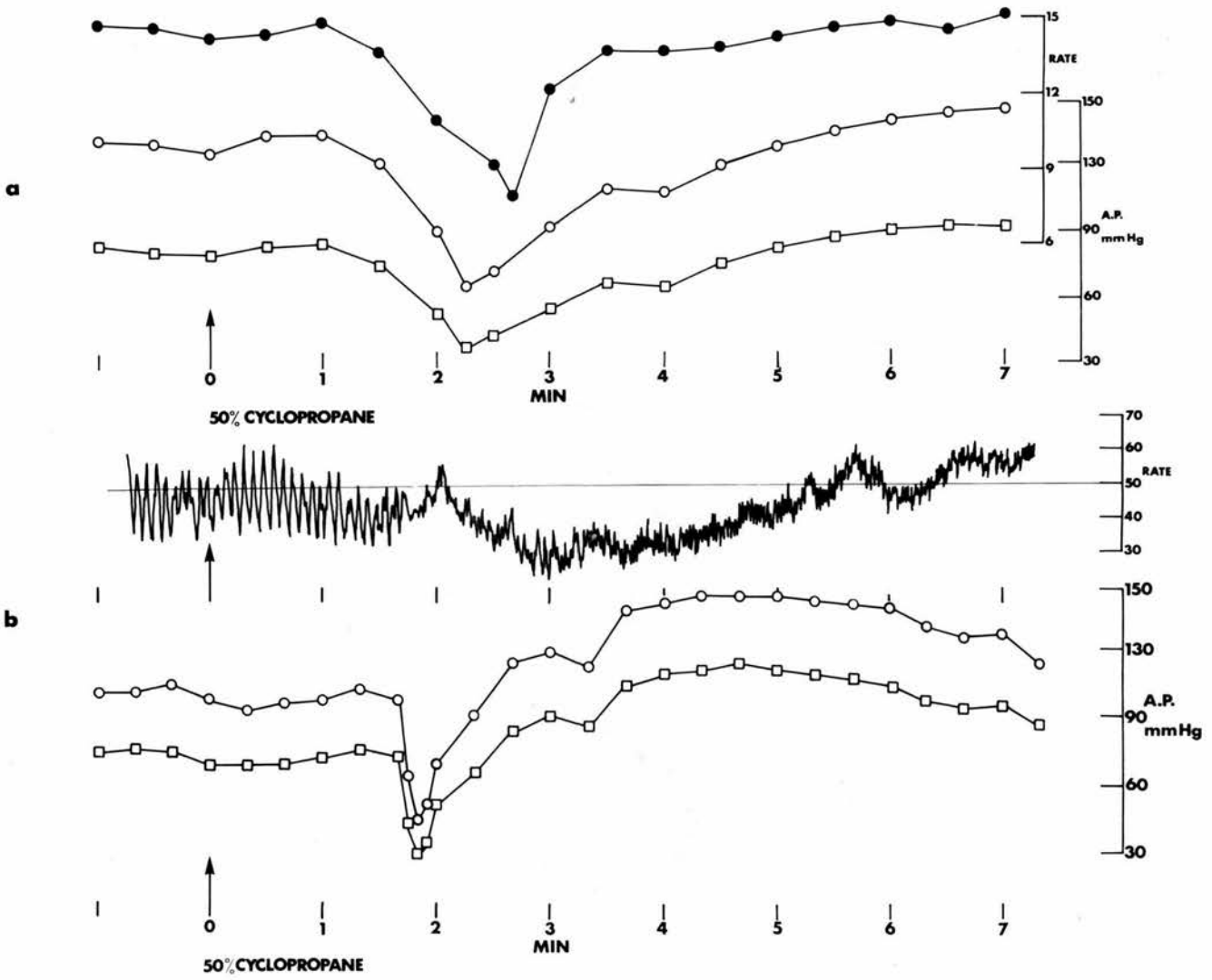

a
15
RATE
12
9
6
150
130
90
A.P.
mm Hg
60
30
0
1
2
3
4
5
6
7
MIN
50% CYCLOPROPANE
b
70
60
50
RATE
40
30
150
130
90
A.P.
mm Hg
60
30
0
1
2
3
4
5
6
7
MIN
50% CYCLOPROPANE

Fig. 29

Fig. 30.

Preganglionic cervical sympathetic nerve responses. Upper graph, ●, impulses/sec; lower graph, O, mean arterial pressure, mm Hg; both are plotted against the same time scale in min. 50% cyclopropane was administered between the arrows.

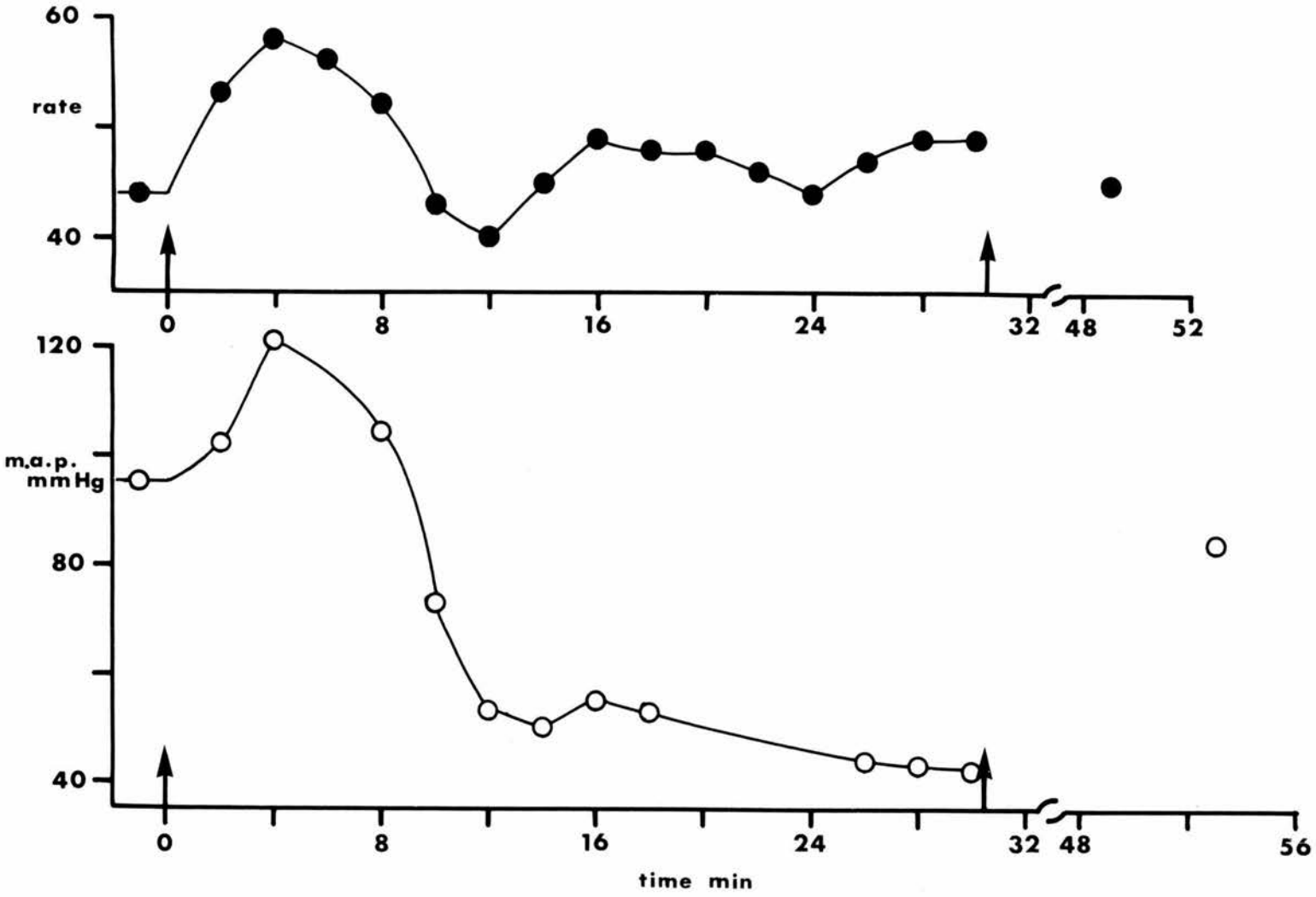

60
rate
40
0
8
16
24
32
48
52
120
m.a.p.
mm Hg
80
40
0
8
16
24
32
48
56
time min

Fig. 30

recovered to near control levels when cyclopropane was discontinued.

Filmed records of action potentials illustrating the effects of cyclopropane are shown in Fig. 31 a-d. The first trace shows the discharge before administration, and Fig. 31 b,c that after 6 min and 14½ min of 50% cyclopropane. There was a progressive increase in activity and a loss of the synchronized bursts shown in the first trace, a; these returned after recovery from cyclopropane, d.

Following induction with 50% cyclopropane, this concentration was continued beyond the time of maximum increase in arterial pressure in 7 of the 9 rabbits studied; in the other 2 animals the anaesthetic concentration was reduced to 25%. The sympathetic discharge rate continued to increase in 7 animals, while the rate declined in 2 to levels below those corresponding to the maximum rise in arterial pressure. After administration of 50% cyclopropane throughout, or of this concentration followed by 25% cyclopropane, for periods of 14 - 30 min in 4 animals, arterial pressure was finally reduced on average by 25% whereas the sympathetic rate was still 46% above the control level.

In 2 experiments, following a first administration of the higher concentration, 25% cyclopropane was given subsequently for periods of 28 and 30 min respectively. Sustained increases in systolic and diastolic pressures and cervical sympathetic discharge were then measured throughout the entire period, as shown for a 30 min exposure in Fig. 32.

An early but brief rise in arterial pressure occurred within

Fig. 31.

Action potential records from preganglionic cervical sympathetic strands. a, 100% oxygen; b, after 6 min 50% cyclopropane in oxygen; c, after 14½ min 50% cyclopropane in oxygen; d, 15 min off cyclopropane.

Records e - i from a second experiment: e, 100% oxygen; f, after 4 min of 3% halothane in oxygen; g, after 13½ min 3% halothane in oxygen; h, after 14 min off halothane; i, 14½ min off halothane.

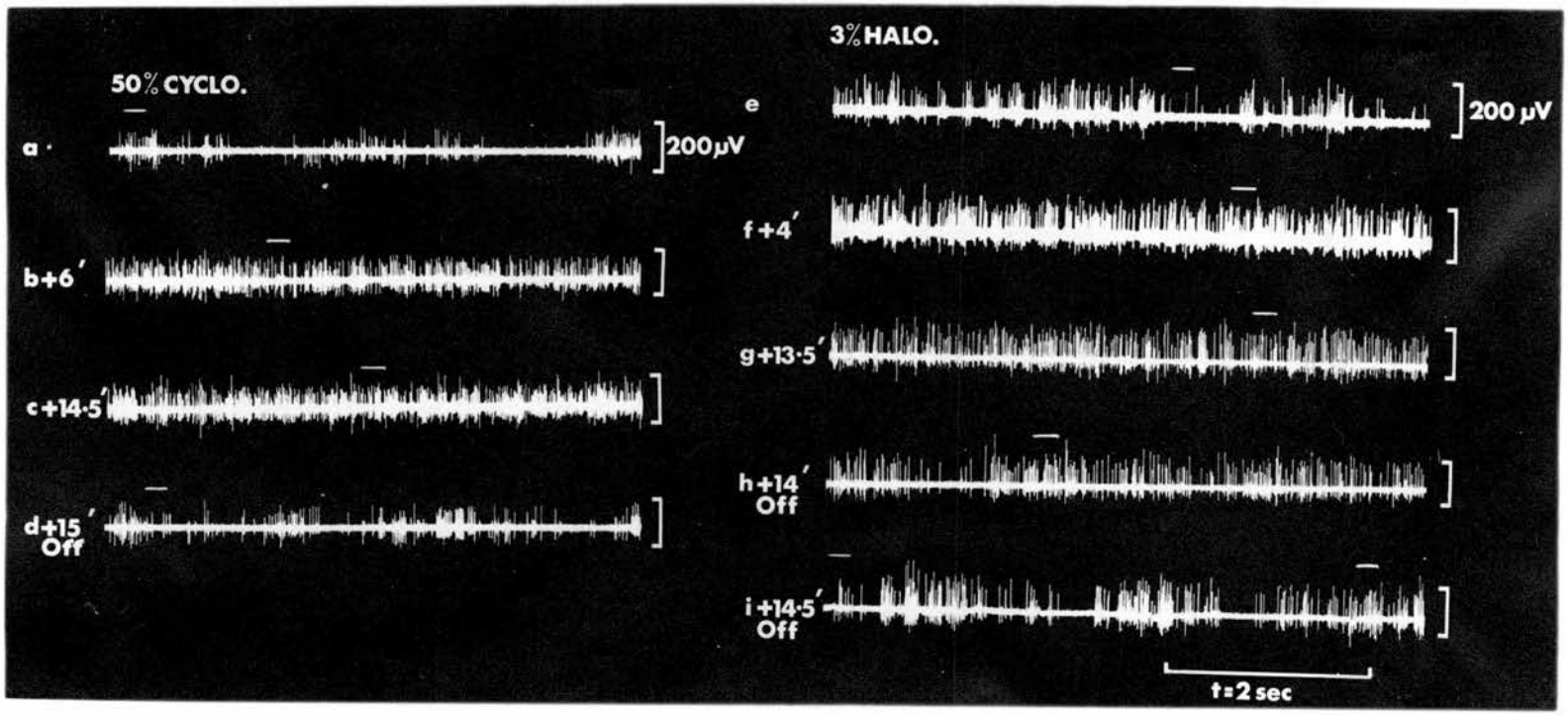

50% CYCLO.
a
200 µV
b +6′
c +14·5′
d +15′ Off
3% HALO.
e
200 µV
f +4′
g +13·5′
h +14′ Off
i +14·5′ Off
t = 2 sec

Fig. 31

Fig. 32.

Upper graph, ●, preganglionic cervical sympathetic discharge rate (impulses/sec); lower graph, O, systolic and □, diastolic arterial pressure (A.P.). Same time scale. 25% cyclopropane was administered between the arrows.

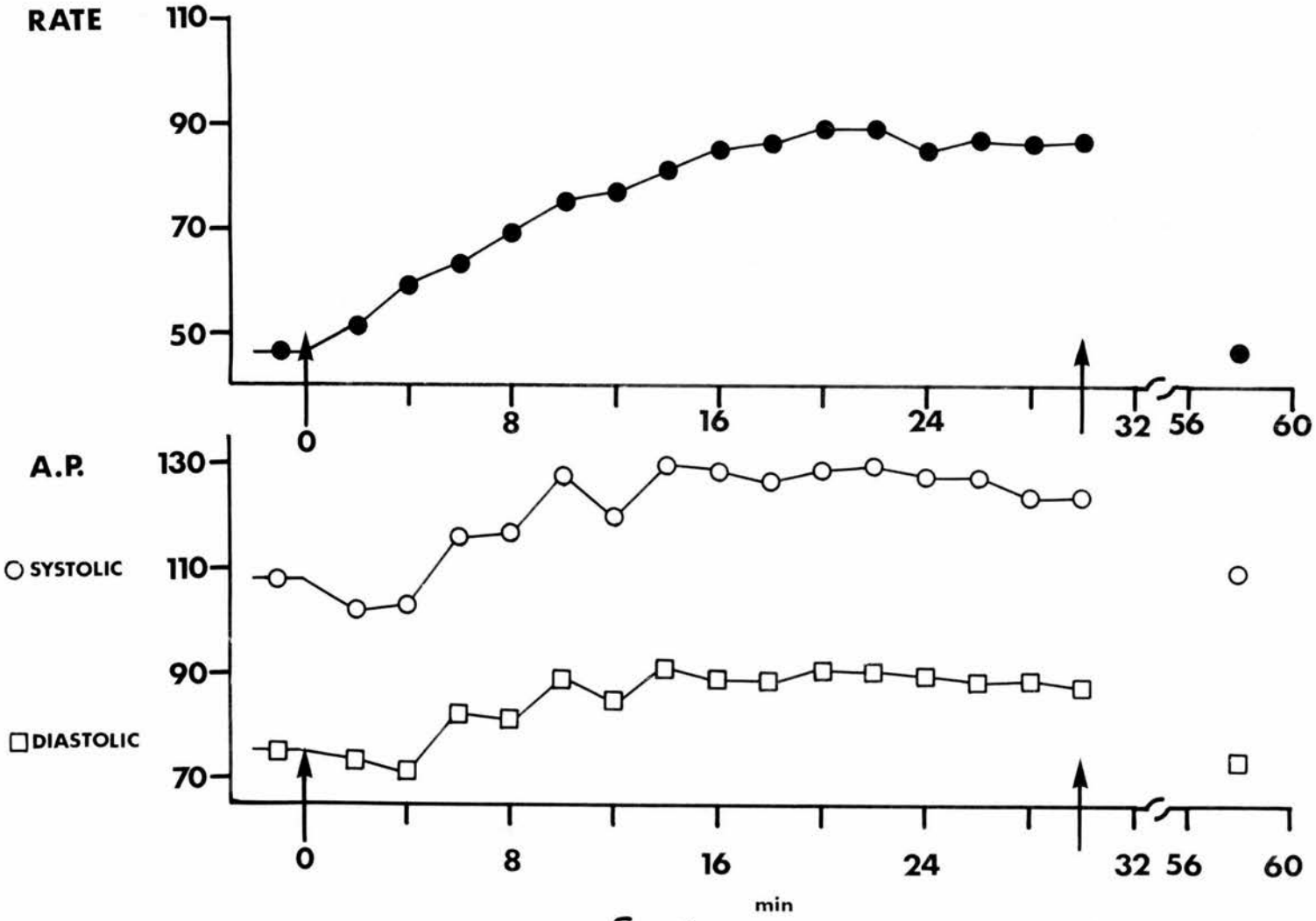

RATE
110
90
70
50
0
8
16
24
32
56
60
A.P.
130
110
90
70
SYSTOLIC
DIASTOLIC
0
8
16
24
32
56
60
min

Fig. 32

1 to 3 min of discontinuing cyclopropane. At this time sympathetic discharge was unchanged or already beginning to decline. This effect was noted in 7 of the 8 rabbits anaesthetized with 50% cyclopropane for periods of 8 to 12 min during cervical sympathetic recording; in the other animal, studied for 30 min, arterial pressure responses were obscured by cardiac arrhythmias (which ceased within 30 sec of stopping cyclopropane). The changes in one experiment are shown in Fig. 33; in this case sympathetic discharge fell as cyclopropane was discontinued, an effect perhaps attributable, reflexly, to the rise in arterial pressure. The maximum effect noted, and occurring as in all the other experiments without an associated increase in preganglionic discharge, was a rise in mean arterial pressure from 59 mm Hg after 8 min of 50% cyclopropane, to 118 mm Hg 3 min later. After the early rise in arterial pressure the level fell and later increased gradually, with a reduction in preganglionic discharge, as the anaesthetic was eliminated.

Effects of cyclopropane after division of carotid sinus, aortic, and vagus nerves in another group of animals.

In the 8 denervated rabbits studied, the average initial arterial pressure level, 114 mm Hg, was higher than that in the animals with intact nerves. In one animal, the pressure increased to reach a maximum 23% above the control level after 6 min of 50% cyclopropane (Fig. 28 right), while another rabbit showed a small transient rise in arterial pressure only on a second administration (excluded from the statistical analysis below).

Fig. 33.

Recordings above of mean arterial pressure (mm Hg); below, integrated impulse discharge rate in the preganglionic cervical sympathetic nerve (impulses/sec, time constant 3.3 sec). At the arrow, when 50% cyclopropane was discontinued, 100% oxygen was given.

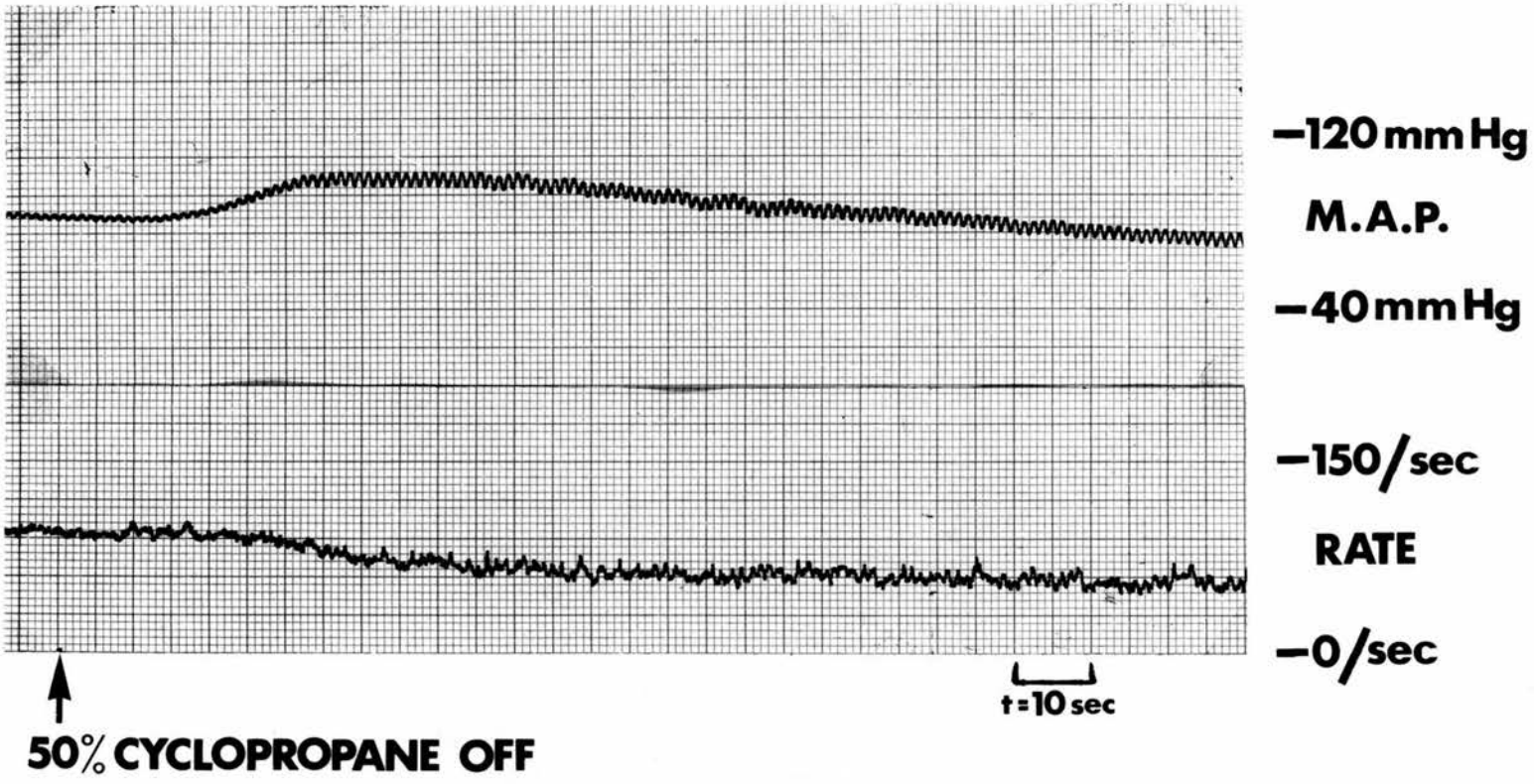

—120 mm Hg
M.A.P.
—40 mm Hg
—150/sec
RATE
—0/sec
t = 10 sec
50% CYCLOPROPANE OFF

Fig. 33

Otherwise, although cervical sympathetic discharge was increased by cyclopropane in all the denervated animals, arterial pressure was reduced by an average of 20% (S.E. ± 8.4, $0.05 > P > 0.02$) at the time of the maximum rises in sympathetic activity; these occurred 4 to 8 min after induction, and were significant (mean increase 55%, S.E. ± 22, $0.05 > P > 0.02$). The response to 50% cyclopropane in a denervated animal is shown in the filmed records of Fig. 34 a-c. In b after 10 min the rate of the counted impulses was increased from 48/sec to 57/sec; there was also fragmentation of the sympathetic rhythm of central origin.

Halothane

3% halothane was administered to 7 rabbits, the other 3 animals studied being given a concentration of 1.5% or 2.0%. Since arterial pressure was consistently lowered by concentrations above 1.5%, the effects in all 10 animals have been considered together. Changes in cervical sympathetic activity have been related arbitrarily, to two levels of arterial pressure during halothane anaesthesia, corresponding as nearly as possible to 30% and 60% reductions from the control value. For each pressure level, 8 measurements were available from the 10 rabbits. Cervical sympathetic activity was increased by a mean of 43% (S.E. ± 13, $0.02 > P > 0.01$) above control at an average arterial pressure of 64 mm Hg reached after 2 to 12 min of halothane anaesthetic. At a mean pressure of 37 mm Hg, attained after 6 to 24 min, the impulse discharge rate was 45% above control (S.E. ± 16, $0.05 > P > 0.02$).

Fig. 34.

Vagi, sinus and aortic nerves cut. Film records of action potentials from the preganglionic cervical sympathetic nerve. a, 100% oxygen; b, after 10 min 50% cyclopropane in oxygen; c, 14 min off cyclopropane; d, after 10 min of 10% ether.

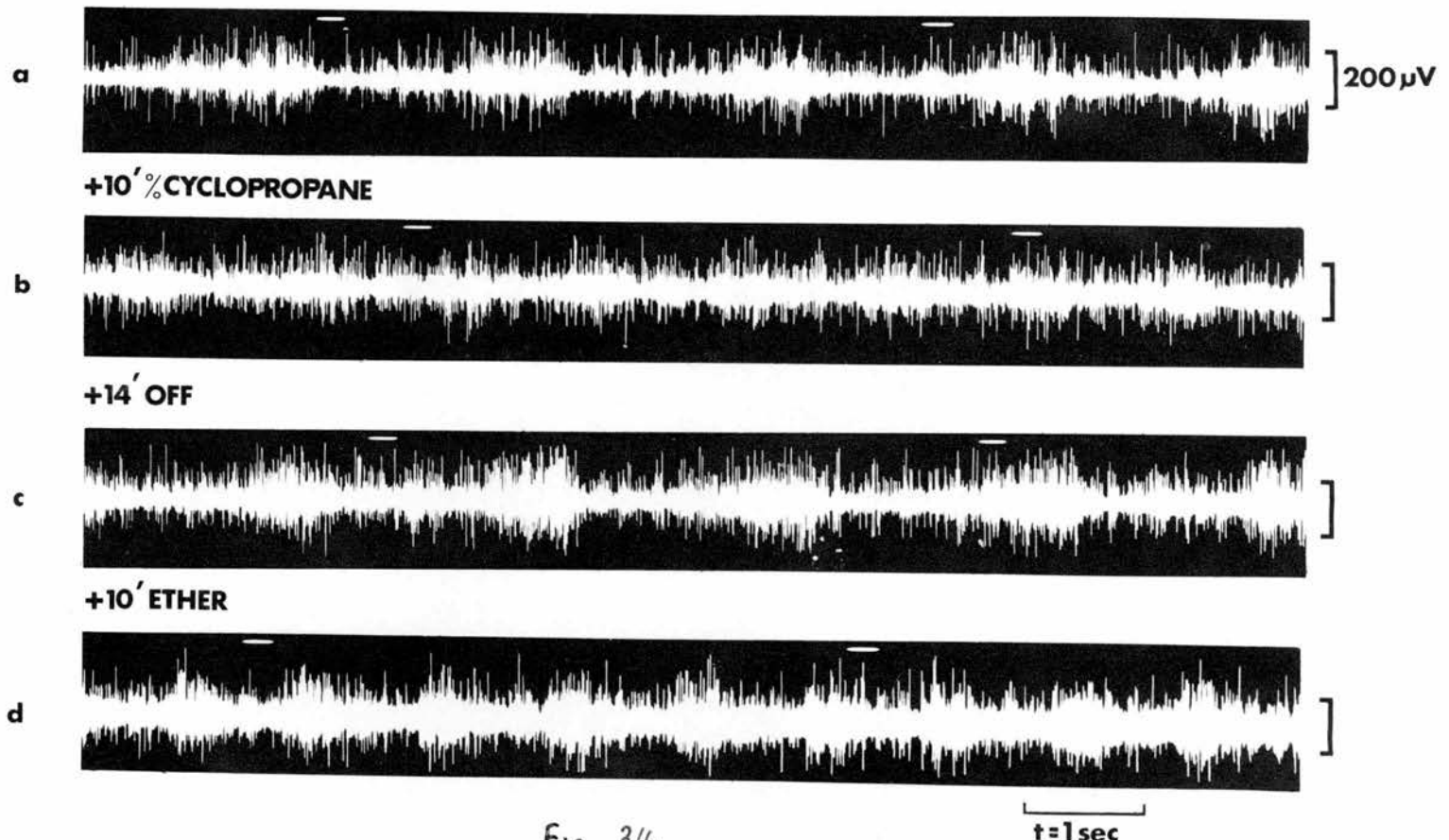


Fig. 34

The results in one experiment are shown in Fig. 35, where the time course of a 26 min exposure to 3% halothane is plotted for sympathetic rate and mean arterial pressure. The pressure fell progressively for 16 min and eventually approached a steady low level. By contrast, sympathetic activity increased to reach a peak at 9 min; at 16 - 20 min there was a decline, followed by subsequent recovery. When halothane was discontinued, a precipitous fall in sympathetic rate occurred, and there was a rise in arterial pressure followed by a more gradual recovery to control levels. The photographic records of Fig. 31 e - i, show the increase in sympathetic activity during halothane anaesthesia in another experiment. The control rate, e, was 70/sec and there was a synchronized respiratory rhythm. After 4 min, f, the discharge rate reached a maximum of 120/sec, which subsequently fell slightly to 111/sec after 13½ min. In addition to this considerable increase, the rhythmical characteristics of the sympathetic discharge were partly abolished, but returned, quite suddenly, between 14 and 14½ min after discontinuing halothane (compare Fig. 31 h and i).

While arterial pressure became progressively lower as anaesthesia with halothane was continued, sometimes reaching 20 mm Hg with the 3% inspired concentration, the result shown in Fig. 35 illustrates the typical finding that in the rabbit these low arterial pressure levels were not associated with reductions in the cervical sympathetic discharge rate.

Similarly, although administration of 1.5 and 2.0% halothane

Fig. 35.

Preganglionic cervical sympathetic nerve responses. Upper graph, ●, discharge rate in impulses/sec; lower graph, O, mean arterial pressure, mm Hg. The time scale in min is the same for each graph. Between the arrows 3% halothane was given.

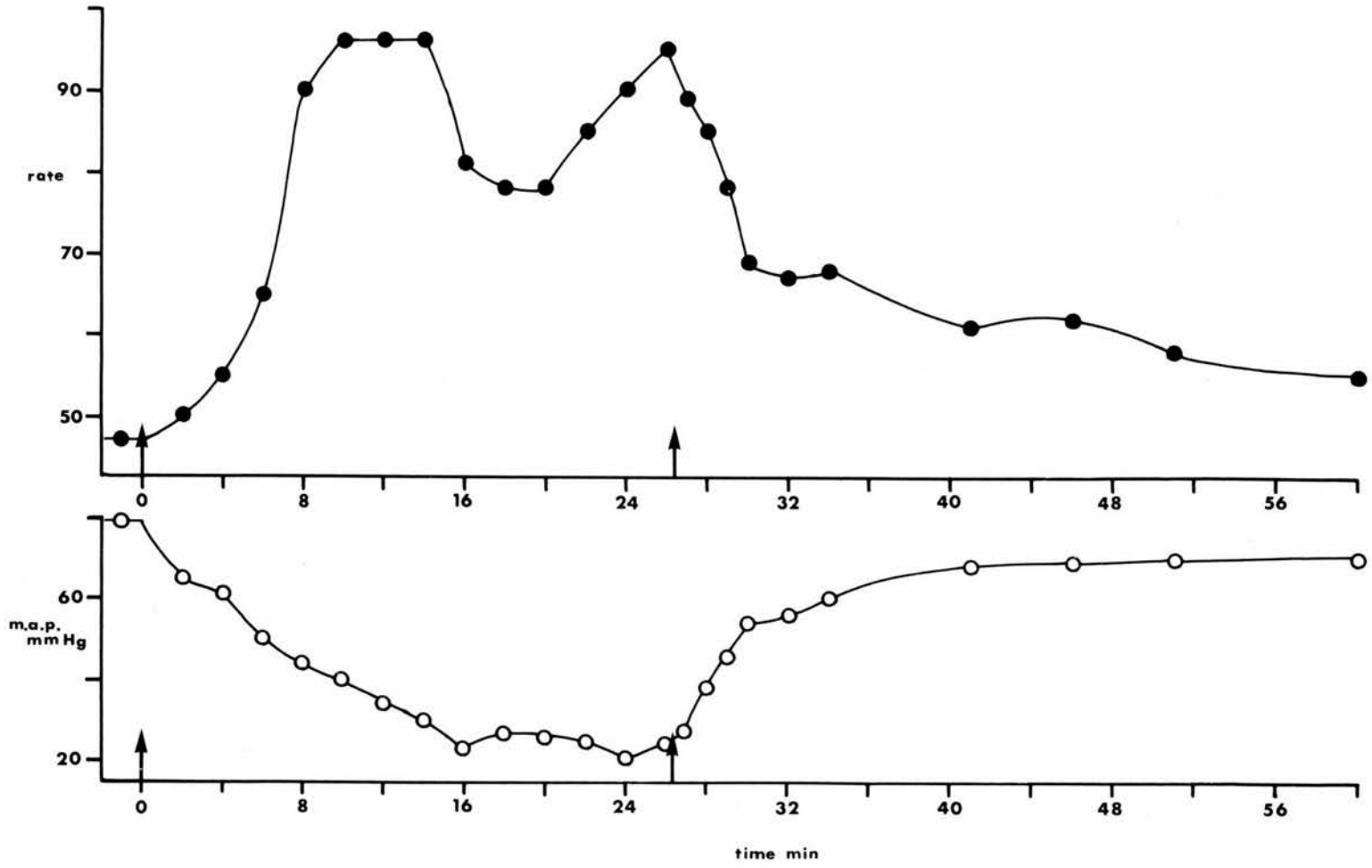

90
rate
70
50
0
8
16
24
32
40
48
56
60
m.a.p.
mm Hg
20
0
8
16
24
32
40
48
56
time min

Fig. 35

was associated with greater variability of sympathetic activity, the mean impulse discharge rate generally remained slightly or moderately above control levels.

In 2 rabbits, the arterial pressure and sympathetic responses to halothane were studied over 30 min periods during which the expired halothane concentration was held constant at approximately 1 vol%. This required adjustment of the inspired concentration to match the uptake of halothane, which became progressively less as the inhalation anaesthetic was continued. In one animal there were 2 4-minute periods, 9 - 13 min and again 20 - 24 min after starting administration, when the inspired concentration was at 2.0% and the mixed expired concentration remained steady between 0.95 and 1.14 vol %. Since pulmonary ventilation was unaltered, it may be assumed that the uptake of halothane by the animal stayed almost constant during these periods. In this experiment, arterial pressure was lowered from a control level of 107 mm Hg, to 43 mm Hg after 12 min and to 41 mm Hg after 22 min of halothane; the associated increases in preganglionic sympathetic discharge were by 12% and by 16% respectively. The results in the other experiment were similar.

Thus, while most of the measurements reported here were associated with a fixed inspired concentration of halothane, there was no evidence that preganglionic sympathetic discharge was reduced by halothane when the uptake of the anaesthetic was maintained at a more constant level.

Effects of halothane after division of Carotid sinus, Aortic, and Vagus nerves in another group of rabbits.

Before halothane administration, the average control arterial pressure in 6 denervated animals was 118 mm Hg. 6 measurements of sympathetic discharge were available during halothane anaesthesia at the selected arterial pressures of approximately 30% and 60% below the control level. At a 30% reduction in arterial pressure, sympathetic activity showed variable increases above control in every animal, although the mean rise, by 20%, was insignificantly different from zero (S.E. $\pm$ 9.6, $0.1 > P > 0.05$). At an arterial pressure level 60% below control, sympathetic discharge was increased by 22%, this being a significant change (S.E. $\pm$ 8.2, $0.05 > P > 0.02$). In 3 of the 6 halothane administrations, arterial pressure and sympathetic discharge showed a parallel decline within the first 2 - 3 min; sympathetic activity increased subsequently. This early response was not observed in the rabbits with intact baroreceptor connections.

Diethyl ether.

9 to 14% ether in oxygen was given to 7 rabbits. After 4 min, cervical sympathetic discharge was increased by an average of 29% above control; this was a highly significant change (S.E. $\pm$ 7.4, $0.01 > P > 0.001$). At this time, mean arterial pressure was reduced by 11% (S.E. $\pm$ 3.1, $0.05 > P > 0.02$). After 10 min of ether, the rises in sympathetic discharge rate were

greater, reaching a mean of 71% above control, but due to the wide range of increase (by 7 to 224%) this effect was not statistically significant (S.E. ± 30, 0.1> P >0.05); at this time, arterial pressure was reduced on average by 28%, a highly significant change from the control level (S.E. ± 6.9, 0.01> P > 0.001). Fig. 36 (left) illustrates the time course of the changes in sympathetic rate and mean arterial pressure in response to 12.5% ether. There was a progressive increase in the discharge rate, until after 10 min a new level was maintained. The arterial pressure showed initial variation, followed by progressive decline reversed only by discontinuing the administration.

Effects of ether after division of carotid sinus, aortic and vagus nerves in another group of animals.

Seven to fifteen per cent ether was administered to 6 denervated rabbits. After 8 min, cervical sympathetic activity was increased by 56%, which was a significant change from control (S.E. ± 12, 0.05> P >0.02). At this time, arterial pressure was reduced by a mean of 22%, which was also significant (S.E. ± 7.7, 0.05> P > 0.02). The records in Fig. 34c and d show some effects of ether administration after the baroreceptor nerves and vagi had been cut. The sympathetic rhythm seen in Fig. 34c which was presumably of central origin, increased in frequency after 10 min of 12% ether, while the mean discharge rate rose from 57/sec to 62/sec (d). A similar increase in frequency of the rhythm was seen in other experiments during ether administration. Fig. 36 (right) also shows a response to ether in a denervated

Fig. 36.

Preganglionic cervical sympathetic nerve responses. Upper graph, ●, impulses/sec; lower graph, O, mean arterial pressure, mm Hg. Same time scale in min for each vertically aligned pair. Left, 12.5% ether was given between the arrows. Right, from another experiment, the vagi, aortic and sinus nerves had been cut, and 14% ether was given between the arrows.

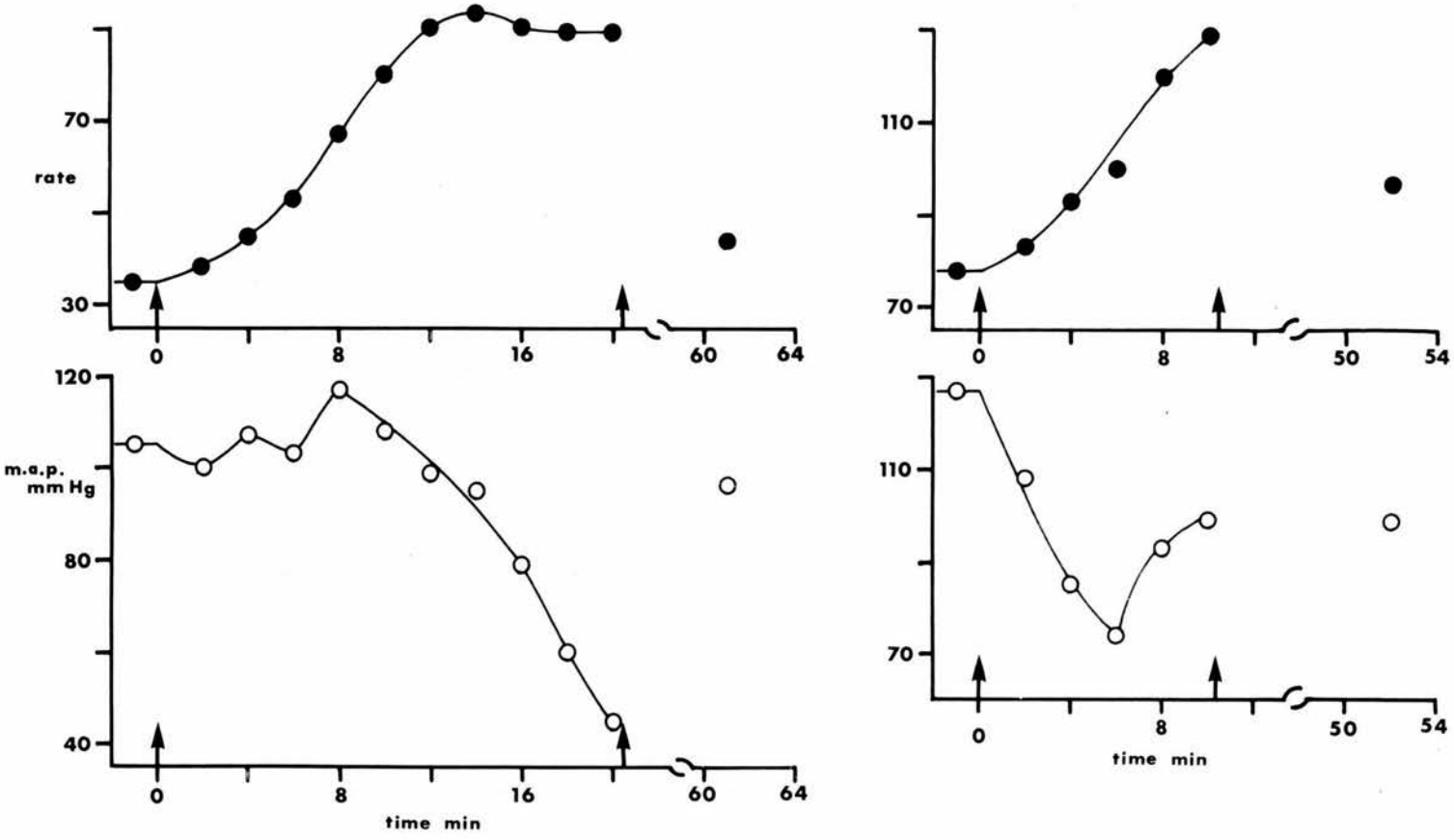

70
rate
30
0
8
16
60
64
120
m.a.p.
mm Hg
80
40
0
8
16
60
64
time min
110
70
0
8
50
54
110
70
0
8
50
54
time min

Fig. 36

rabbit anaesthetized for 11 min. There was a steady rise in sympathetic rate throughout, while the arterial pressure, after a rapid fall, recovered to a higher level which was still below control. This pattern of partial recovery of arterial pressure was seen on 2 other occasions when the carotid sinus, aortic, and vagus nerves had been divided.

Splanchnic Nerve

Nine strands were dissected from the splanchnic nerve in 6 rabbits. Variable responses to the anaesthetics of the atypical fibre groups mentioned previously, were usually concealed in the total integrated discharge rates, but were identified on film.

Changes in the activity of rhythmically discharging fibres which were unaffected by adrenaline were not studied during administration of the inhalation anaesthetics, although their activity was seen to persist.

Those units whose discharge frequency was reduced by intravenous adrenaline showed similar responses to cyclopropane, halothane, and ether as those previously described for cervical sympathetic nerve strands. The results presented below refer to one administration of each anaesthetic in individual animals.

Cyclopropane.

In 4 rabbits, 4 splanchnic sympathetic strands showing uniform inhibition by intravenous adrenaline were studied during ventilation with 50% cyclopropane for periods of 8 to 14 min. Arterial pressure increased to reach a maximum averaging 44%

above control levels after 6 to 10 min, this being associated with a mean increase in the sympathetic discharge rate of 124% (S.E. ± 34, 0.05> P>0.02). The results in one of these experiments are illustrated in Fig. 37 (right). In this case the major rise in sympathetic activity was delayed, uncharacteristically, for 8 min. The arterial pressure had already risen, and increased more steeply as the sympathetic rate increased. The photographic records of Fig. 38 illustrate several features of cyclopropane excitation. In a, there was synchronization of the activity of a single unit, which became more marked, b, after 2 min of 50% cyclopropane, when the rate of firing was increased from 35 to 48 per 20 sec period. After 6 min, c, the rhythm began to fragment, and the discharge rate increased further, to a maximum of 55 per 20 sec period. At d, 15 min after the start of anaesthesia, the rate was reduced to 41 in a 20 sec period, and the activity within bursts was irregular. In addition a second downward-going spike was recruited. Record e shows the discharge 12 min after discontinuing cyclopropane, when the frequency was 19 per 20 sec period.

Fig. 38 f - h shows the effect of 50% cyclopropane on a splanchnic nerve strand in another experiment. The rate of firing of all the spikes was increased after 8 min, and there was recruitment of a small upward going potential towards the centre of the record. Fig. 39 a - c is unusual, and shows depression by cyclopropane of an upward going spike (compare b, after 7 min

Fig. 37.

Graphs above, ●, nerve impulses/sec and below, O, mean arterial pressure, both plotted against the same time in min. Between the arrows 50% cyclopropane was given. Left, from the adrenal nerve; Right, from the splanchnic nerve in the same experiment.

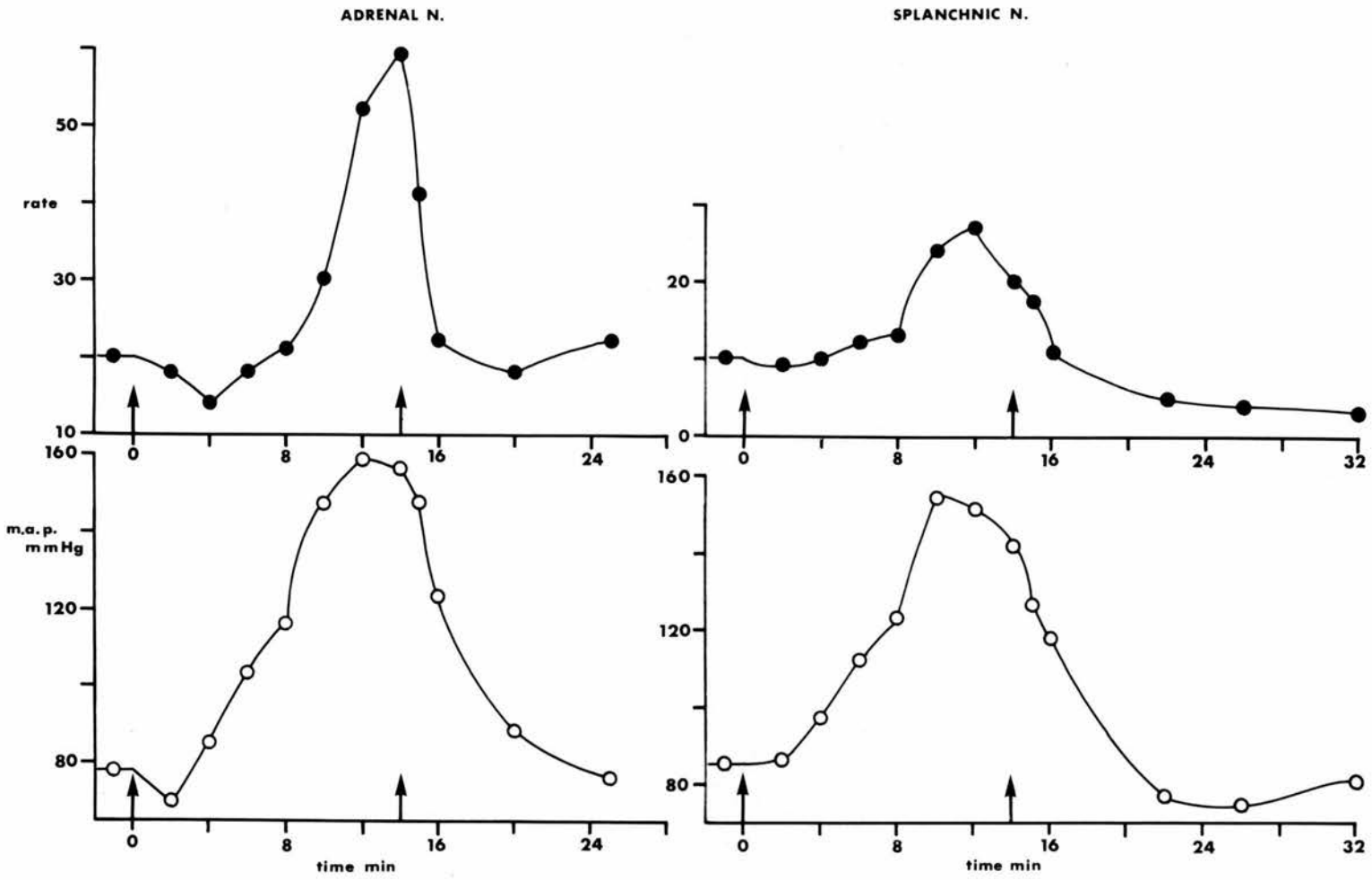

ADRENAL N.
SPLANCHNIC N.
rate
50
30
10
20
0
m.a.p.
mmHg
160
120
80
0
8
16
24
32
time min

Fig. 37

Fig. 38.

Action potential records from the splanchnic nerve.

a, - 100% oxygen; b - after 2 min, c - after 6 min, and d - after 15 min 50% cyclopropane in oxygen. e, 12 min off cyclopropane.

f, from another rabbit given 100% oxygen; g, after 8 min 50% cyclopropane in oxygen; h, 15 min off cyclopropane.

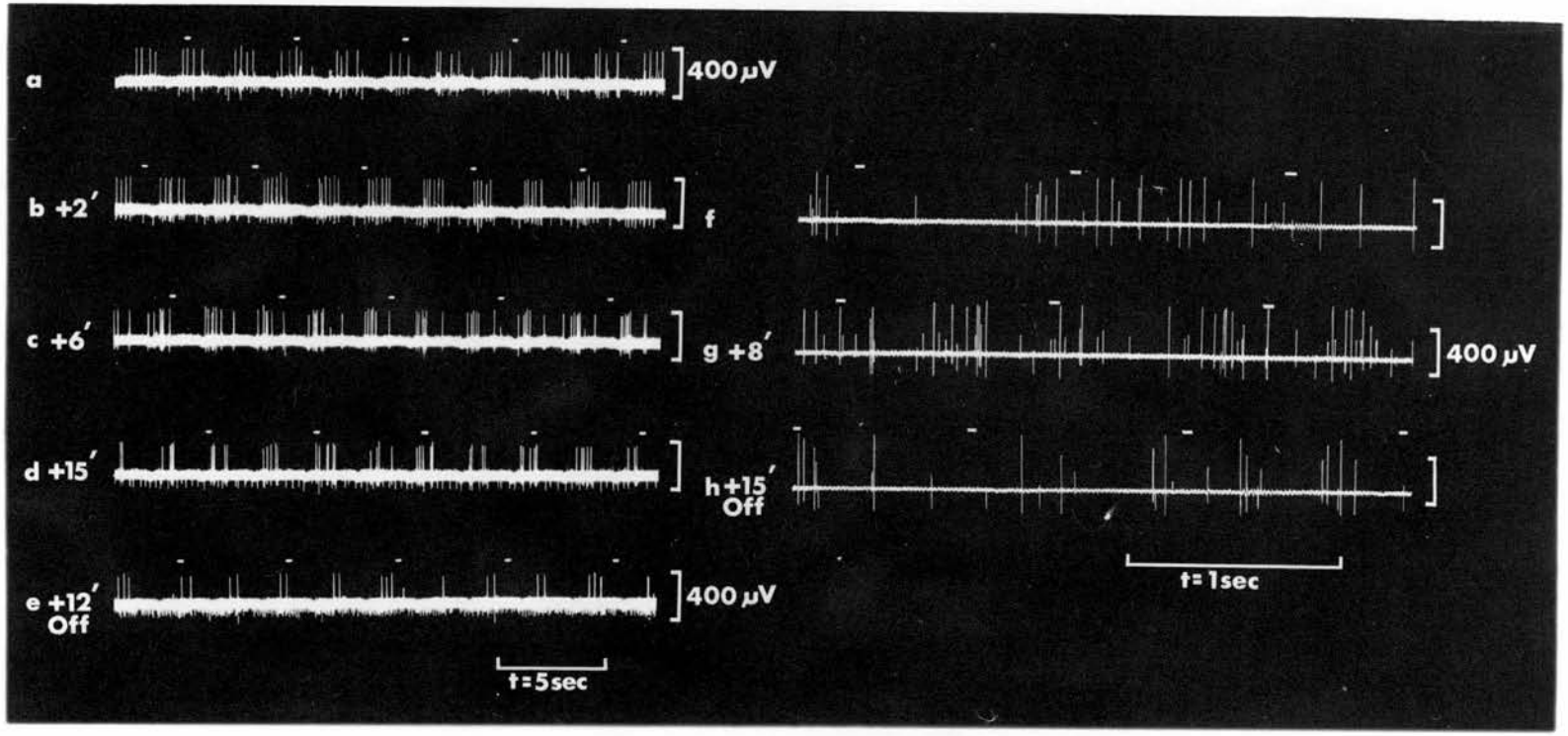


Fig. 38

Fig. 39.

Action potential records from the splanchnic nerve.

a, 100% oxygen; b, after 7 min 50% cyclopropane in oxygen; c, 6 min off cyclopropane. d to g, a second strand from the same nerve. d, 100% oxygen; e, after 6½ min and f, after 12½ min 3% halothane; g, 20 min off halothane.

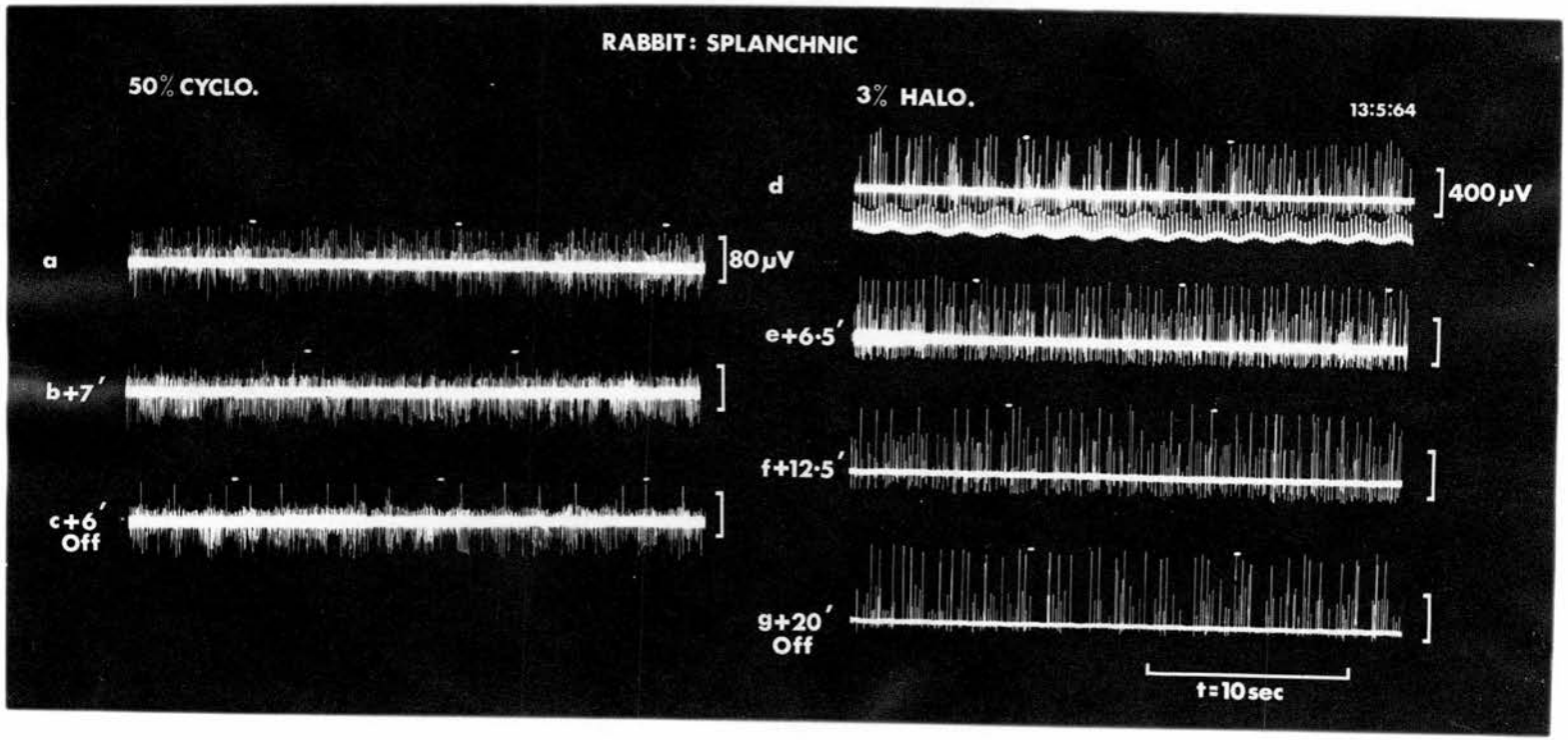

RABBIT: SPLANCHNIC
50% CYCLO.
3% HALO.
13:5:64
a
80 µV
b+7′
c+6′
Off
d
400 µV
e+6·5′
f+12·5′
g+20′
Off
t=10 sec

Fig. 39

50% cyclopropane, with a and c). The other potentials show marked excitation. In one animal a splanchnic cardiac rhythm became audible during cyclopropane administration.

Halothane.

Five splanchnic sympathetic strands were studied in 5 rabbits anaesthetized with 3% halothane. At arterial pressure levels 30% below control (reached after 2 to 14 min of anaesthesia) changes in sympathetic discharge were variable; the average increase, by 20%, was insignificantly different from zero (S.E. $\pm$ 17, $0.4 > P > 0.3$). A 60% reduction in arterial pressure was reached after 6 to 24 min, when the discharge frequency was 76% above control. This increase was significant (S.E. $\pm$ 26, $0.05 > P > 0.02$). A representative experiment is illustrated in Fig. 40 (right); the sympathetic rate was at first reduced with the arterial pressure, but at 4 min the activity recovered and remained above control, with some variation until the halothane was discontinued. Fig. 39 d - g are film records taken during this experiment. Fig. 39e shows a marked increase in sympathetic discharge corresponding to the first peak on the graph in Fig. 40 (right); after 12 - 13 min of halothane (Fig. 39f) there was a fall towards control levels, and the last sequence, g, shows the subsequent fall in activity below control when the halothane was stopped.

In one animal from this group the arterial pressure responses to 3% halothane were unusual; after an early small reduction in pressure (associated with a rise in sympathetic discharge), the

Fig. 40.

Graphs above, ●, nerve impulses/sec and below, O, mean arterial pressure, mm Hg. Same time scale for each vertically aligned pair. 3% halothane was given between the arrows. Left, from the adrenal nerve; Right, from the splanchnic nerve, in another experiment.

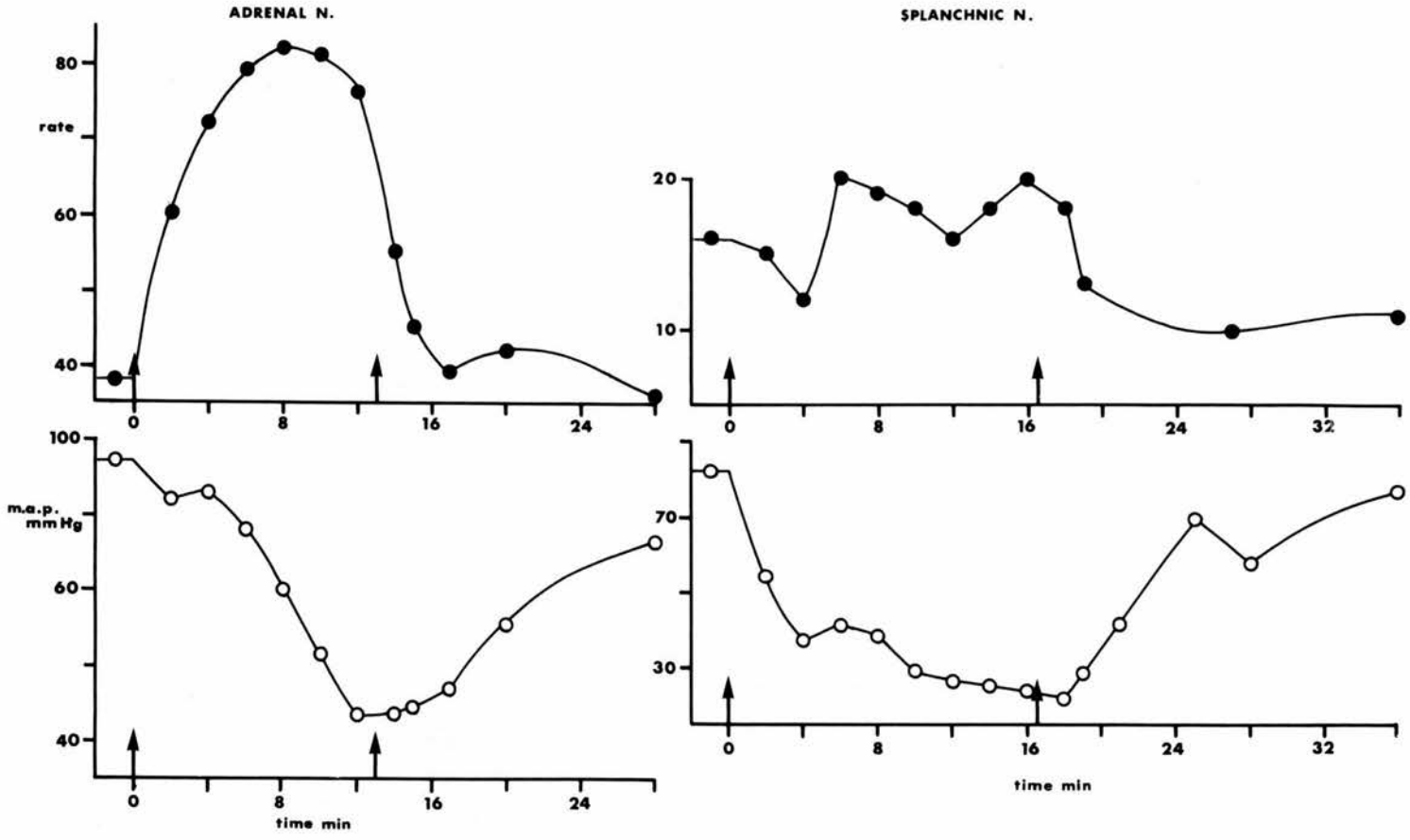

ADRENAL N.
SPLANCHNIC N.
80
rate
60
40
20
10
0
8
16
24
32
100
m.a.p.
mm Hg
60
40
70
30
time min

Fig. 40

pressure increased to above control levels between 6 and 12 minutes; at the latter time splanchnic sympathetic discharge had increased by 91%. Thereafter arterial pressure fell to reach a level 66% below control after 28 minutes of 3% halothane; at this time sympathetic activity was increased by 100%. Subsequently, recovery of both arterial pressure and sympathetic discharge occurred to control levels.

Diethyl ether.

Four splanchnic sympathetic strands were studied in four rabbits during administration of diethyl ether in concentrations of 8 to 10%. The impulse discharge rate was increased, after periods of 16 to 20 min, to an average of 77% above control, this being significant (S.E. $\pm$ 24, $0.05 > P > 0.02$). Arterial pressure was progressively reduced to a level 22% below control, at these times. In Fig. 41 (right), ether is shown to cause a progressive rise in sympathetic rate and an associated fall in arterial pressure.

Adrenal nerve

In three experiments the response of the adrenal branch of the splanchnic nerve was studied during anaesthesia with cyclopropane. In two of these experiments, one of which is shown in Fig. 37 (left), increases in sympathetic activity (mean, 110%) occurred over approximately the same periods as the rises in arterial pressure (mean, 72%) produced by 50% cyclopropane. In the third study the responses were unlike those of other sympathetic nerves; the rise in arterial pressure induced by cyclopropane reached a maximum 50% above control after 4 min, but at this time adrenal

Fig. 41.

Graphs above, ●, nerve impulses/sec and below, O, mean arterial pressure, mm Hg. Same time scale for each vertically aligned pair. 8% ether was given between the arrows. Left, from the adrenal nerve; Right, from the splanchnic nerve, in the same experiment.

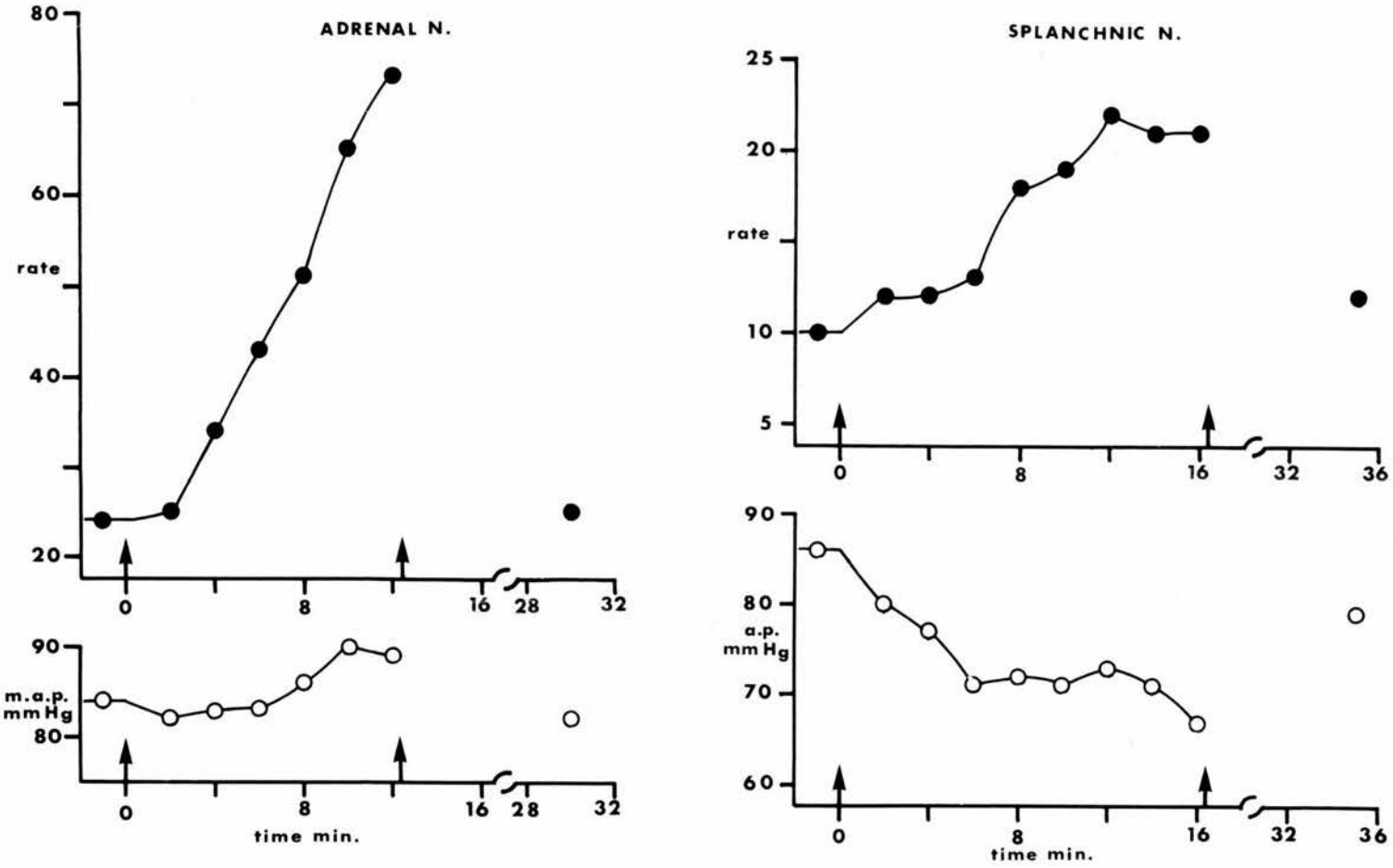

ADRENAL N.
SPLANCHNIC N.
rate
m.a.p. mm Hg
a.p. mm Hg
time min.
0
8
16
28
32
36

Fig. 41

nervous activity was reduced by 33%; subsequently arterial pressure fell to 80% of control after 10 min, when the impulse discharge rate was 27% above control level. These unusual effects may have resulted from persisting activity of central baroreceptor pathways during cyclopropane anaesthesia.

Adrenal nervous activity was studied in two rabbits during ventilation with 3% halothane. 30% and 50% reductions in arterial pressure were associated with mean increases in the discharge rate of 69% and 77% respectively. In the example illustrated in Fig. 40 (left) there was a rise in sympathetic activity of over 100% at 8 min; recovery from halothane was very rapid.

Ether, administered to 2 rabbits for periods of 12 and 14 min, raised arterial pressure at these times by 6% and 4% respectively, while the corresponding increases in adrenal impulse discharge rate were by 204% and 14%. The former dramatic increase in sympathetic rate is plotted in Fig. 41 (left), which shows the associated small change in mean arterial pressure.

Changes in heart rate. These were assessed by counting the number of beats in five second periods. In the rabbit, all three inhalation anaesthetics usually produced increases in heart rate of about 10 - 20% (shown in Fig. 15 of Study 2); in only one of the 9 animals given halothane there was a fall in heart rate which persisted throughout a 12 min administration.

DISCUSSION

Many original observations of Adrian, Bronk, and Phillips (1932) on the activity recorded from the cervical sympathetic nerve of the rabbit were confirmed in these experiments, and the usefulness of a pulse-height selector and rate meter was established for assessing changes in the activity of multifibre sympathetic strands.

The identification of the destination of the sympathetic fibres under study was, and to some extent remains, an obvious problem but data relevant to the effects of the inhalation anaesthetics was restricted to those units whose activity was closely related to alterations in arterial pressure. All nerve strands dissected from the cervical sympathetic of the rabbit appeared to reflect the inter-relation of arterial pressure and sympathetic discharge, in a reproducible and consistent manner.

Eccles (1935a), confirming the earlier work of Bishop and Heinbecker (1932) described 4 components in the main spike potential wave set up in the superior cervical ganglion by preganglionic stimulation. These corresponded to 4 groups of preganglionic sympathetic fibres, and there was no evidence for functional overlap within the ganglion i.e. each fibre group was in functional relationship with its own ganglion cells. The fastest conducting fibres - the S_1 group described by Eccles (1935a), corresponding to the M_1 group of Bishop and Heinbecker (1932) - were in functional relationship with postganglionic nerves to the orbit (pupillodilator and nictitating membrane); their

conduction velocity was about 20 metres/sec. The M_2 group of preganglionic fibres described by Bishop and Heinbecker (1932) (S_2 of Eccles, 1935a) conducted at about 12 metres/sec, and was functionally related to postganglionic vasoconstrictor nerves. Presumably, this slower conduction rate implies that the M_2 fibres are smaller than those responsible for pupillomotor responses. However, the amplitude of the S_2 ganglionic spike potential exceeds that of the S_1 wave (Eccles, 1935a), indicating that there are greater numbers of preganglionic fibres with a vasoconstrictor than with a pupillomotor distribution. Eccles (1935a) suggested that the M_2 preganglionic fibres synapse in the ganglion cell group of intermediate size; this was shown histologically by de Castro (1932) to include 50% of the total number of ganglion cells, compared with 27% of the total occupied by ganglion cells with pupillomotor connections.

From the above evidence it seems likely that when dissecting multifibre sympathetic strands there is a greater likelihood of recording from fibres which are ultimately pupillomotor rather than vasoconstrictor, on the basis of fibre size, and a greater likelihood of recording from vasoconstrictor fibres on the basis of relative numbers.

On the facts of the present studies, it is not considered reliable evidence to draw conclusions about fibre size from the action potentials as recorded, since the spike amplitude of single sympathetic units depended closely on the technique of nerve dissection. Provided that the fibres were not killed as a result

of the manipulations required, it was usually possible to alter the signal-to-noise ratio of individual sympathetic fibres either by further division of the nerve strand under study, or sometimes merely, by adjusting its position on the recording electrodes. On the other hand, the larger fibres may have been more likely to survive nerve dissection.

There is also no evidence to suggest that the preganglionic component of the pupillomotor sympathetic outflow shows physiological responses which are different to those of the vasoconstrictor outflow. For example, sympathetic discharge in the long ciliary nerve is inhibited by afferent baroreceptor stimulation, when the carotid sinus pressure is raised by perfusion (Okada, Kado, and Nisida, 1961) or by intravenous injection of adrenaline (Nisida, Okada, and Nakano, 1960). A systematic study of the pupillary responses to the three anaesthetics tested was not undertaken in the present studies; while ether is well known to cause pupillary dilatation in animals and man, this is not a constant feature of cyclopropane or halothane anaesthesia.

While many splanchnic nerve fibres responded similarly to the preganglionic cervical sympathetic, there was less uniformity; no information was obtained regarding the functions of the atypical splanchnic and adrenal units.

These experiments confirm the previous observation of Iggo and Vogt (1960), that rhythms in preganglionic sympathetic

activity may have several origins, involving both central and peripheral mechanisms. Single baroreceptor units show a rhythm in time with the respiratory variations in arterial pressure in artificially ventilated rabbits (unpublished observations), while chemoreceptor fibres in the cat also show a respiratory rhythm (Biscoe & Purves, 1965). Systemic baroreceptor and chemoreceptor stimuli, separately or together, appear to be mainly responsible for sympathetic rhythms of peripheral origin. Bursts of sympathetic activity, synchronized with inspiration, were occasionally observed in the present experiments in rabbits; but an expiratory rhythm was more usual, as described for this species by Adrian, Bronk, and Phillips (1932). The cat is said to show a predominant inspiratory synchronization (Iggo & Vogt, 1960), but some of these apparent species differences may depend on whether respiration is spontaneous or mechanical.

Continuous monitoring of the rhythmical sympathetic discharge clarified the effects of increasing the inspired carbon dioxide concentration. Thus, while there was always a striking increase in the amplitude of the sympathetic rhythm, the mean rate of discharge either remained unchanged or increased. It may therefore be questioned whether an increase in the rate of change of sympathetic efferent discharge could be a more effective stimulus to liberation of sympathetic transmitter at effector organs than is a rise in the mean frequency of firing. It is at any rate curious that increases in the mean sympathetic discharge rate did

not invariably accompany administration of carbon dioxide concentrations up to 10%, since these have been shown to increase plasma noradrenaline levels in the dog (Morris & Millar, 1962a).

It was found that 6 - 12 mg sodium pentobarbitone, given at intervals of about 45 min, suffices to maintain light but adequate anaesthesia in the rabbit, without influencing preganglionic sympathetic discharge other than temporarily. This was fortunate, and unexpected in view of known depressant actions of pentobarbitone on nervous transmission (Brooks & Eccles, 1947; Eccles, 1946; Eccles, Schmidt & Willis, 1963; Pradham & Galambos, 1963; Schmidt, 1963; Thesleff, 1956). However, Elmes & Jefferson (1942) measured a fall in the adrenaline content of the innervated, compared to the denervated, adrenal gland when pentobarbitone preceded by morphine was given to cats. While this result is difficult to interpret, it does show, in accord with the present experiments, that excitation of the sympathetic nervous system can occur in the presence of pentobarbitone.

Discussion of the preganglionic effects of cyclopropane, halothane, and ether is deferred until the General Discussion.

Summary of Study 3

1. Preganglionic cervical and splanchnic sympathetic discharge was recorded before and during administration of inhalation anaesthetics in rabbits ventilated with oxygen and given gallamine. The background anaesthetic was pentobarbitone.

2. Cyclopropane increased arterial pressure and preganglionic activity, which reached a maximum after 4 to 8 min with the 50% concentration. Subsequent effects on arterial pressure depended on the inspired concentration, sympathetic discharge remaining above control levels. Similar sympathetic responses occurred in rabbits in which the vagus, carotid, and aortic nerves had been divided.

3. Halothane reduced arterial pressure and increased preganglionic discharge; the effect on sympathetic activity was usually maintained, and occurred after baroreceptor denervation. The evidence indicates that in the rabbit halothane hypotension is not attributable to central sympathetic depression.

4. Preganglionic sympathetic discharge was increased during ether anaesthesia.

5. Increased arterial P_{CO_2} exaggerated the amplitude of the respiratory sympathetic rhythm, and had more variable effects on the mean preganglionic discharge rate.

6. In rabbits, central sympathetic activity is increased by cyclopropane, diethyl ether, and halothane, in descending order of effect; the actions of cyclopropane and halothane appear to

be partly influenced, respectively, by blockade of central baroreceptor pathways and by reflex effects secondary to arterial hypotension.

7. Since a raised level of preganglionic sympathetic discharge was consistently associated with the arterial hypotension produced by sufficiently high concentrations of these agents, the present experiments question the concept of "central vasomotor depression" during inhalation anaesthesia in the rabbit.

STUDY 4. THE EFFECT OF CYCLOPROPANE, HALOTHANE, AND ETHER ON TRANSMISSION THROUGH SYMPATHETIC GANGLIA

Introduction

Depression of transmission through the superior cervical ganglion was demonstrated in cats by Larrabee and Holaday (1952) during administration of ether, chloroform, and thiopentone. Similar effects were shown on the isolated perfused stellate ganglion of the cat, in anaesthetic concentrations lower than those required to depress conduction along nerve fibres (Larrabee and Posternak, 1952). These results were confirmed in experiments on the rabbit's superior cervical ganglion (Larrabee, Ramos, and Bülbring, 1952). According to Norman and Löfström (1955), cyclopropane also caused weak depression of transmission in the stellate ganglion of the cat, while Raventos (1956, 1961) emphasised ganglion blockade as a cause of arterial hypotension during anaesthesia with halothane.

Study 3 showed that there was an increase in the impulse discharge rate in preganglionic sympathetic nerves during anaesthesia with cyclopropane, halothane, and diethyl ether. The effects of these anaesthetics on impulse transmission through sympathetic ganglia, under identical conditions of anaesthetic administration, will now be described.

Results

Superior cervical ganglion of the rabbit

Cyclopropane. In five rabbits, the effect of 50% cyclopropane was tested on the compound action potential evoked in post-ganglionic branches of the superior cervical ganglion by stimulation of the preganglionic cervical sympathetic nerve. The height of the maximal potential was reduced by a mean of 40%, the range being from 15% to 60%. The stimulation threshold was raised in 4 of the 5 experiments; in the other rabbit there was no change. In one test, administration of 50% cyclopropane for 7½min raised the threshold voltage from 0.7 volt to 6 volts, although the maximum action potential height was reduced by only 10%.

The time course of these changes was variable. In 3 experiments, depression of the maximal potential approached 50% within 3 min of starting administration of cyclopropane. In the other two experiments the effect was less marked and slower in onset, but progressed to reach a maximum after about 10 min.

Fig. 42 illustrates the ganglionic action of cyclopropane in the rabbit. There was a change in the stimulation threshold during the experiment, shown by the failure of the potential to return to the control level at the lowest voltage; recovery over the remaining voltage range was good, however.

Halothane. In five experiments, 3% halothane reduced the height of the maximal compound action potential by an average of 28%,

Fig. 42.

Graph of compound action potential amplitude (μv) from the internal carotid postganglionic branch of the superior cervical ganglion of the rabbit, plotted against the stimulating voltage applied to the preganglionic cervical sympathetic. ● , before cyclopropane; Δ , after 4½ min 50% cyclopropane; O, 18½ min off cyclopropane.

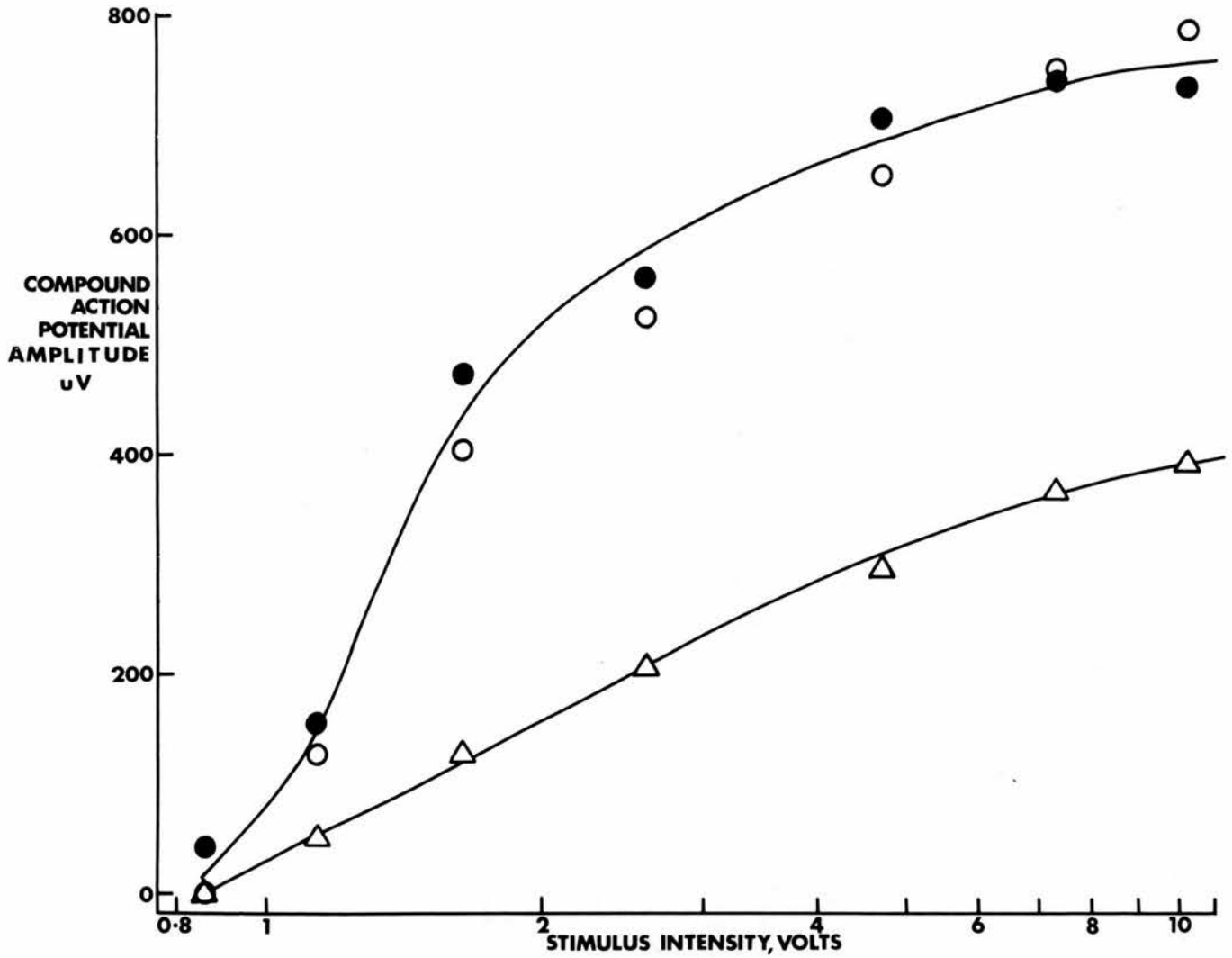

800
600
400
200
0
COMPOUND ACTION POTENTIAL AMPLITUDE uV
0·8
1
2
4
6
8
10
STIMULUS INTENSITY, VOLTS

Fig. 42

with a range of 14% to 50% depression. The effects were apparent within 4 min, progressing to a maximum in 10 to 15 min. The threshold voltage was increased in 4 of the 5 tests.

The time course of the ganglionic actions of 3% halothane in one experiment is shown in Fig. 43, where the amplitudes of the postganglionic compound action potential are plotted against the stimulation voltages. Depression of the action potential appeared quickly, then progressed more slowly; there was eventually a rise in the threshold voltage. Virtually complete recovery occurred after halothane was discontinued.

In a single administration of 1% halothane, the height of the maximal compound action potential was reduced by 26% after 10½ min, and there was a rise in the threshold voltage.

Ether. In two rabbits, 5% and 10% concentration of ether reduced the maximal height of the compound action potential by 25% and 24% respectively after 10 min; there was little change when ether administration was continued for a further 10 min. The effects of ether, as with the other inhalation agents, were relatively greater at lower stimulus voltages, when reductions in the action potential height of up to 50% were recorded.

Superior cervical ganglion of the cat

In one decerebrate cat, the compound action potentials evoked in the internal carotid and carotid body postganglionic nerves by preganglionic cervical stimulation, were monitored alternately before and during administration of the 3 inhalation anaesthetics.

Fig. 43.

Graph of compound action potential amplitude (μv) from the internal carotid postganglionic branch of the superior cervical ganglion of the rabbit, plotted against the stimulating voltage applied to the preganglionic cervical sympathetic. Same experiment as Fig. 42 ● , before halothane; △, after 3 min 3% halothane; □ , after 8 min and ▲ , after 22 min 3% halothane; 0, 25 min off halothane.

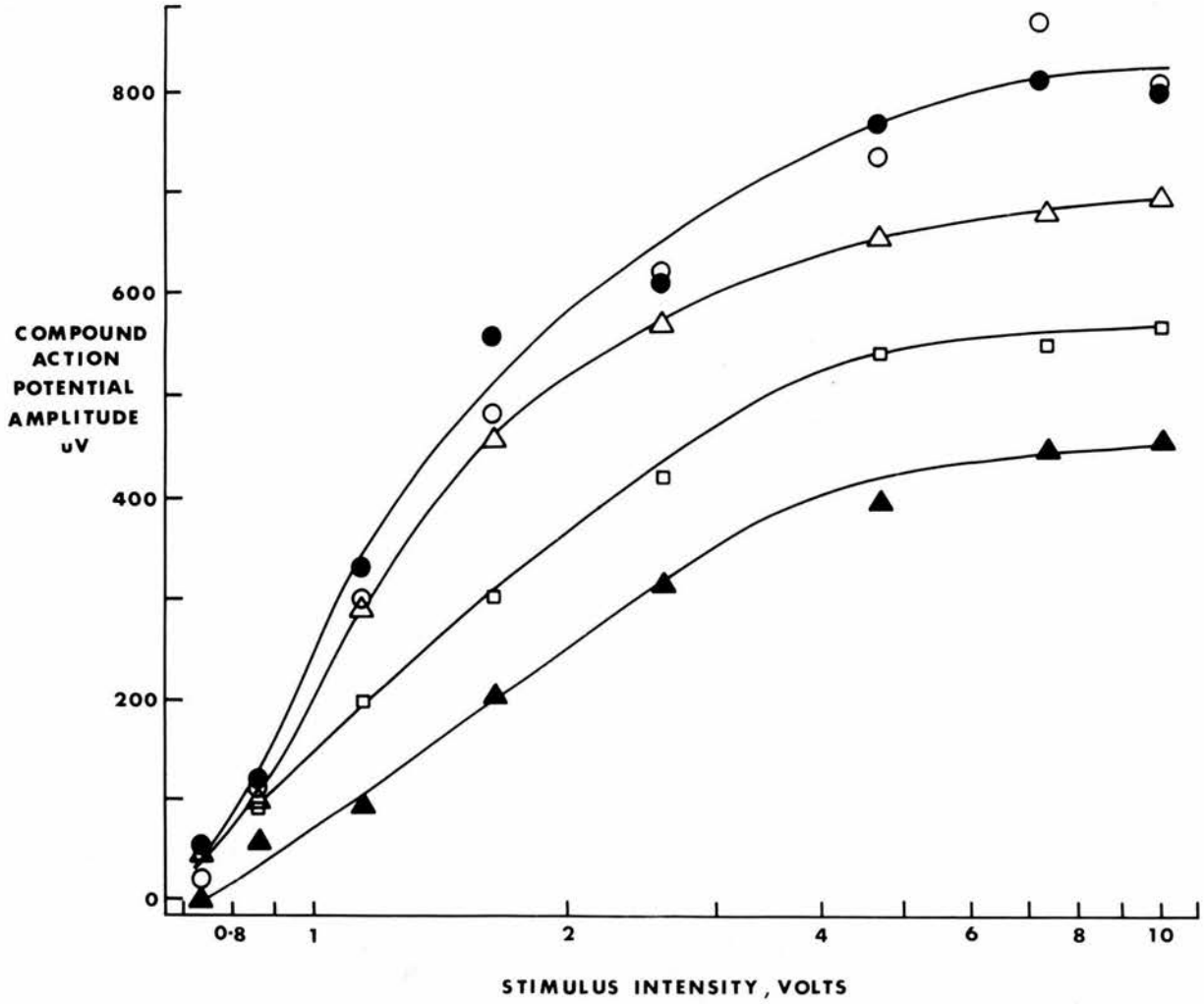

800
600
400
200
0
COMPOUND ACTION POTENTIAL AMPLITUDE uV
0·8
1
2
4
6
8
10
STIMULUS INTENSITY, VOLTS

Fig. 43

The effects of 25% cyclopropane, followed after an interval for recovery by those of 50% cyclopropane, were tested over periods of 12 min. The lower cyclopropane concentration had little effect on the responses to near-threshold voltages, but depressed the maximal action potential height in the internal carotid and carotid body branches by 20% and 15% respectively. The 50% concentration of cyclopropane reduced the height of the internal carotid and carotid body action potentials, at all stimulus voltages, by 50% and 30% respectively; the stimulation thresholds were raised, and the effects were apparent after 3 min of administration, remaining unchanged at 10 min. Recovery occurred 10 min after discontinuing cyclopropane.

The responses in these nerves were studied during administration of 2% halothane. The internal carotid branch showed 65% and 70% depression of the maximal action potential after 4 and 10 min respectively. The carotid body nerve action potential was reduced by 30% at maximum voltage, and by 50% at just-above threshold voltage after 4 min of 2% halothane. After 11 min, the responses were reduced to only 5% of the control height, with an associated rise in the threshold voltage.

For both nerves, recovery was complete within 11 min of discontinuing halothane.

Stellate ganglion of the cat

Cyclopropane. In 4 experiments, 50% cyclopropane consistently reduced the height of the compound action potential evoked in the

cardiac nerve by preganglionic stimulation, although the time course and magnitude of the responses varied. Fig. 44A, B, and C illustrate the most rapid and pronounced effects observed; after 3 min of 50% cyclopropane, B, the maximal potential was depressed by 80%, and the threshold voltage was increased. Rapid recovery occurred within 7 min of discontinuing cyclopropane, C.

Halothane. In the 3 experiments undertaken, 3% halothane depressed the postganglionic action potentials in the cardiac nerve. The most profound effect was a 60% reduction in the maximal response after 3 min of halothane. In the experiment illustrated in Fig. 45, there was 40% depression of the maximal response after 3 min of halothane, without a threshold change, B; there was a greater effect after 5 min, C. The partial recovery noted after 11 min of halothane, D, may have been associated with a change in the recording conditions since the stimulus artefact is increased in size. Recovery is shown in Fig. 45E.

Ether. Effects of ether on impulse transmission through the stellate ganglia, which were studied in two experiments, are illustrated in Fig. 44 C, D, and E. After 9½ min of 9% ether in this cat, the maximal responses were depressed by 20%; the effect increased to 80% depression after 13½ min of ether, D. Recovery followed when the anaesthetic was stopped, E.

Inferior mesenteric ganglion of the rabbit

In two of the three experiments in which transmission through the inferior mesenteric ganglion complex was investigated, recordings

Fig. 44.

The postganglionic potential evoked in the left cardiac nerve by stimulation of the thoracic preganglionic trunks 3, 4 and 5. The stimulation voltage for each column is indicated at the top. A, before administration of inhalation anaesthetic; B, after 3 min of 50% cyclopropane, C, 7 min off cyclopropane; D, after 13½ min of 8% ether; E, 11 min off ether. The amplifier time constant was 1 sec.

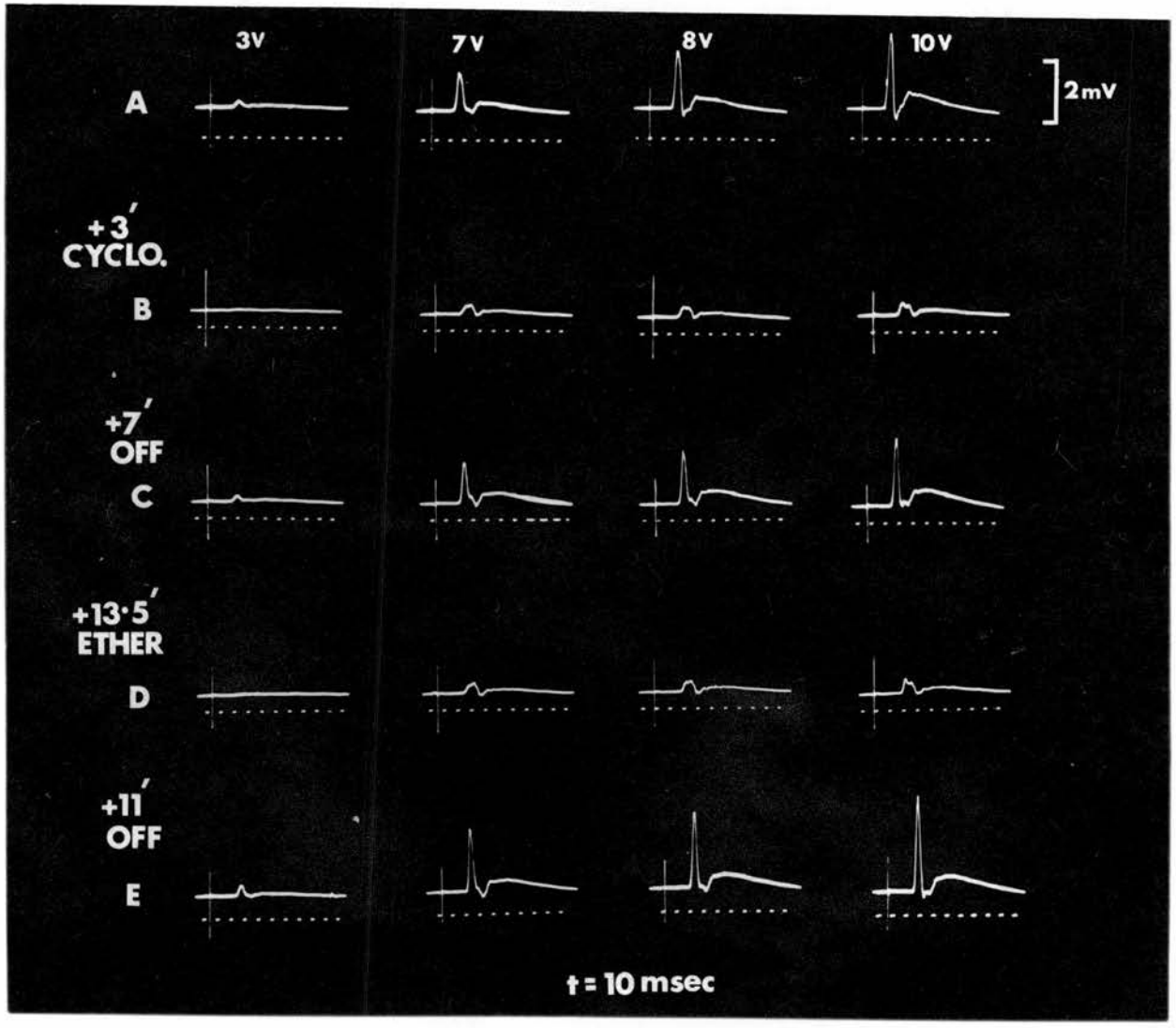


Fig. 44

Fig. 45.

The postganglionic potential evoked in the left cardiac nerve by stimulation of the thoracic preganglionic trunks T 3,4 and 5. The stimulation voltage for each column is indicated at the top. A, before administration of halothane; B, C, and D after 3, 5 and 11 min of 3% halothane; E, 18 min off halothane. The amplifier time constant was 1 sec.

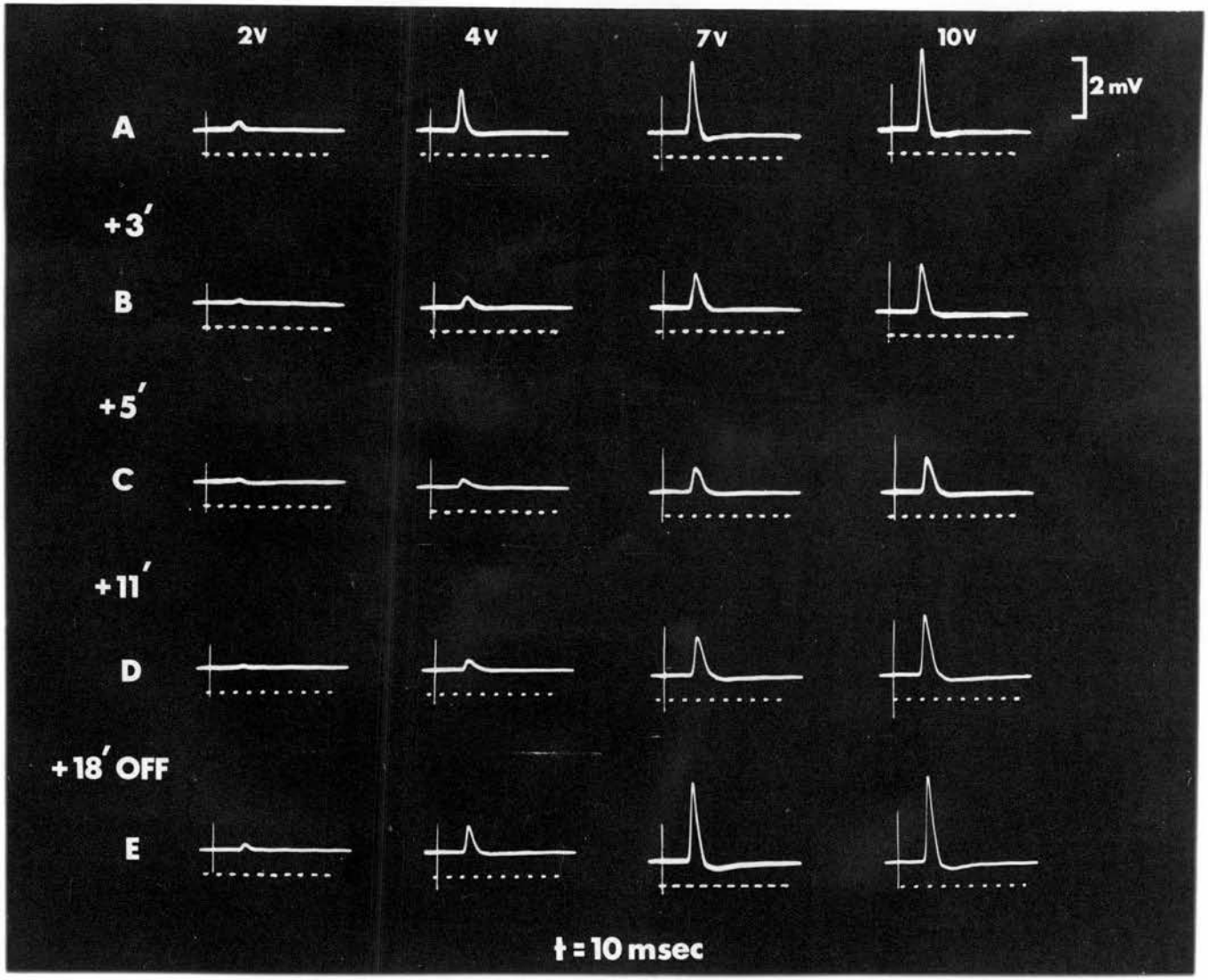


Fig. 45

were made from the inferior mesenteric nerve; in the other experiment, the hypogastric branch was used. The postganglionic action potentials were usually dispersed in time, and there was no discrete action potential. In one experiment, short-latency compound action potentials were observed while recording responses from the inferior mesenteric nerve; these were probably preganglionic in origin.

Cyclopropane. The two tests undertaken involved the inferior mesenteric nerves. In one rabbit, there was almost complete disappearance of the postganglionic action potentials after only 2 min of 50% cyclopropane, with little further change over the ensuing 8 min of administration. The responses in the other experiment, for 2 of the range of stimulus voltages, are shown in Fig. 46. Depression of the temporally dispersed postganglionic potentials appeared after 3 min, and was more pronounced after 10 min of cyclopropane, B. Those potentials which appeared to be preganglionic in origin persisted throughout the administration of cyclopropane. Recovery of the postganglionic potentials was complete 11 min after discontinuing cyclopropane, C.

Halothane. The effects of this anaesthetic were tested on inferior mesenteric and hypogastric pathways. The potentials evoked from the hypogastric nerve in response to preganglionic stimulation showed a progressive reduction, at all voltages, after 10 min of 3% halothane. The reduction in the maximal potential was by about 25%, and there was a rise in the threshold voltage. The effect was similar after 15 min of halothane, and there was recovery when

Fig. 46.

Recordings of potentials evoked in the inferior mesenteric nerve of the rabbit by preganglionic stimulation at 2 voltages; A, before cyclopropane; B, after 10 min of 50% cyclopropane; C, 11 min off cyclopropane; D, after 8½ min 3% halothane; E, 23 min off halothane; F, after 17 min 9% ether; G, 22 min off ether. The amplifier time constant was 1 sec.

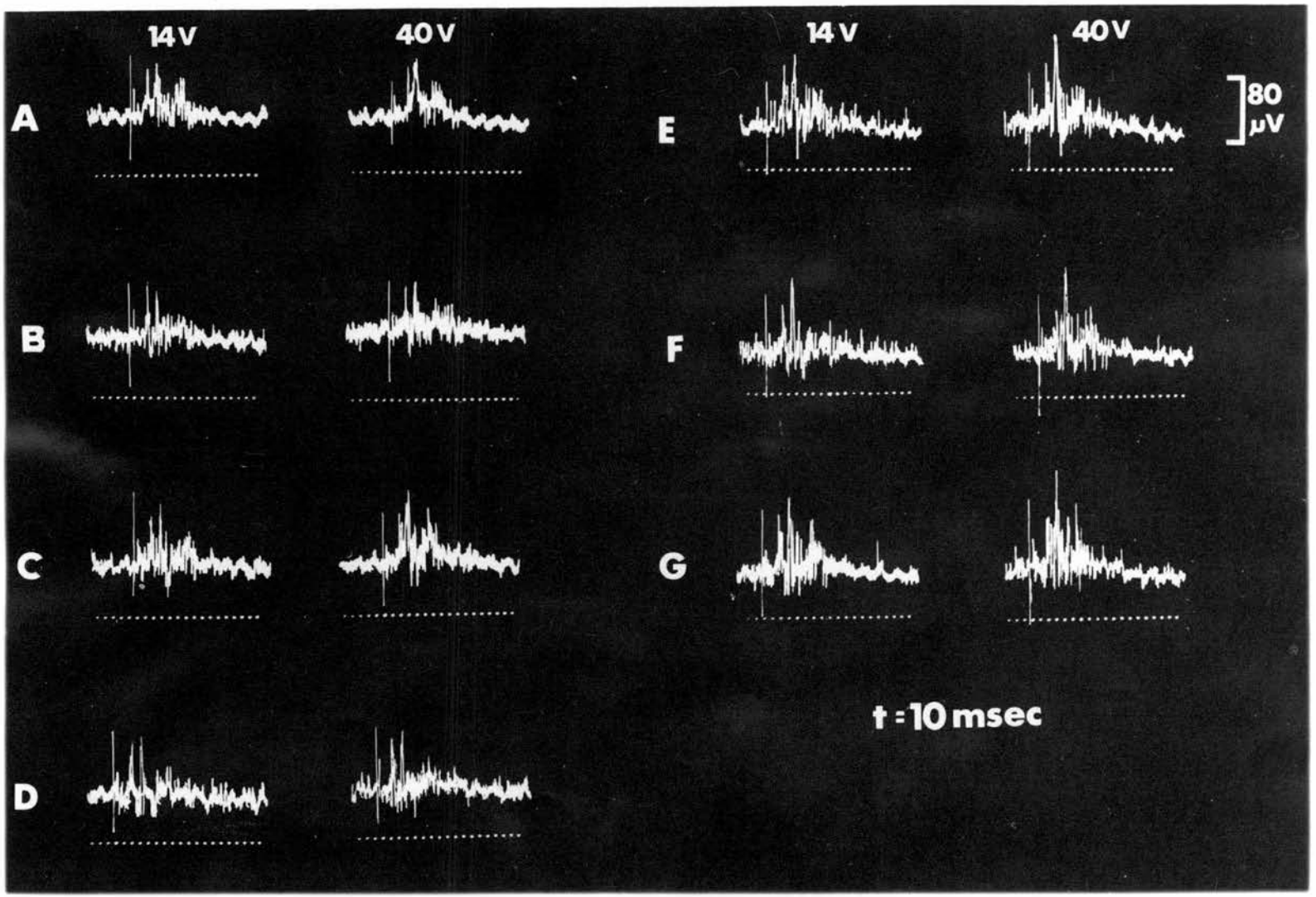


Fig. 46

the anaesthetic was discontinued.

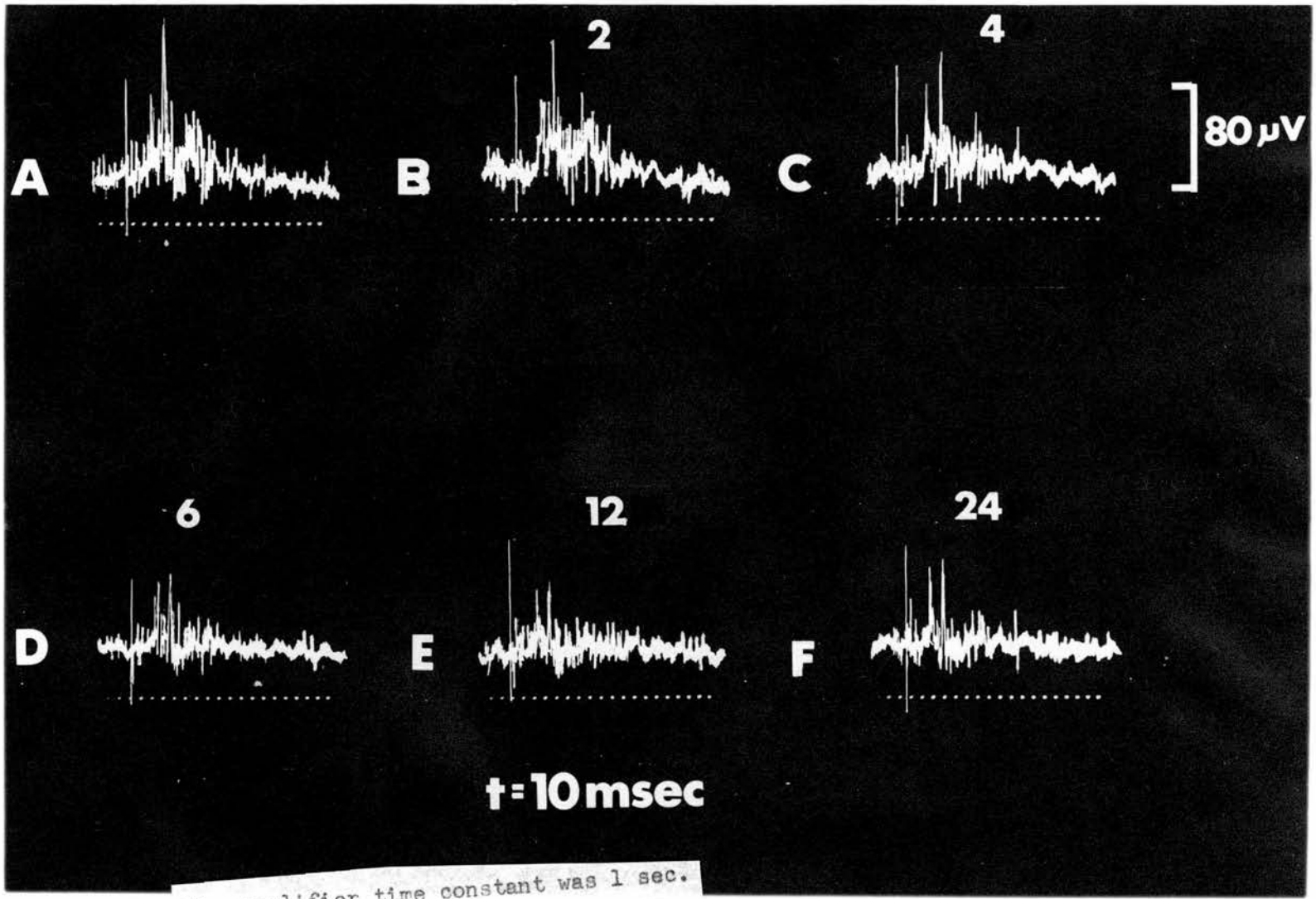
In one of the two studies involving the inferior mesenteric nerves, depression of the evoked postganglionic potentials was complete within 2 min of starting administration of 3% halothane; this effect persisted until the anaesthetic was discontinued after 13 min. Recovery then followed. In the other experiment, illustrated in Fig. 46 C,D,E the effect was less pronounced; thus, there was little change from the control response, C, after 3 min of halothane, but depression of the dispersed postganglionic spikes was evident after 8½ min, D. Recovery followed when halothane was discontinued, E. Halothane caused little or no change in the amplitude of the short-latency potentials.

Ether. A concentration of 9% ether was used to test the effects on the inferior mesenteric pathways, in two experiments. In one rabbit, depression of the maximal action potential height was almost complete after only 3 min of ether administration. In the other experiment, the results from which are illustrated in Fig. 46 E, F, G, there was little change from control, E, after 6 min of ether, but depression was evident after 17 min, F, with subsequent recovery, G; the short-latency potentials were unaffected by ether.

Fig. 47 illustrates the action of hexamethonium tartrate on the action potentials shown in Fig. 46. Ganglion block appeared rapidly, leaving the two large, short-latency potentials unaltered (see especially Fig. 47F); as stated above, these potentials were also unchanged by the inhalation anaesthetics.

Fig. 47.

The same postganglionic potentials as in Fig. 46 showing the effect of the injection of hexamethonium tartrate 20 mgm/Kgm. A is the control response while B, C, D, E and F are 2, 4, 6, 12 and 24 sec later. Note the persistence of the 2 large potentials which are probably preganglionic. The amplifier time constant was 1 sec.



The amplifier time constant was 1 sec.

Fig. 47

Discussion

The use of hexamethonium at the end of these experiments established that the compound action potentials studied were arising post-synaptically and were not preganglionic potentials to ganglion cells outside the well-defined sympathetic ganglia. This was an important consideration, since myelinated fibres have been identified in the external carotid nerve (Kuntz, Hoffman, and Napolitano, 1957), and in the postganglionic nerve to the carotid body (Eyzaguirre and Uchizono, 1961). Foley and Dubois (1940) found many, probably postganglionic, nerve fibres surviving degeneration in the cervical sympathetic trunk, while Pokrovskya (1959) described nerve cells in the internal carotid branch of the superior cervical ganglion. In spite of these findings, evoked potentials with a short enough latency to be preganglionic in origin were not observed in any postganglionic branches of the superior cervical ganglion in the present experiments. The compound action potential usually had a smooth outline, presumably because any preganglionic potentials formed only a small part of the total.

In the inferior mesenteric region ganglion cells have been identified over a wide area (Kuntz and Jacobs, 1955; Kuntz, 1956); in accord with this, the postganglionic action potentials were often temporally dispersed, as in the experiments of Brown and Pascoe (1952). In addition, in one experiment potentials were recorded which were not affected by the anaesthetics. Although definite evidence for their origin was not obtained,

the fact that they were not depressed by hexamethonium while the longer latency potentials were suppressed, suggests that they were from preganglionic fibres.

The observation that stimulation of the thoracic roots, T 3 - 4, evoked the largest stellate postganglionic action potential supports earlier work (Langley, 1900; Bronk et al., 1936).

Confirmation of the ganglionic effects of anaesthetics described by earlier workers has therefore been obtained, although the action of cyclopropane on the cat stellate ganglion was considerably more potent than that suggested by Norman and Löfström (1955). Raventos (1956, 1961) emphasised the role of ganglion block, particularly in the splanchnic area, in the hypotension caused by halothane, but the results obtained do not show that halothane exerts a more profound depressant action on transmission through the inferior mesenteric ganglion than do ether and cyclopropane.

Summary of Study 4

1. The effects of cyclopropane, halothane, and ether on sympathetic ganglionic transmission were investigated by recording the compound action potential evoked in postganglionic nerves by single shock stimulation of the preganglionic pathways. The ganglia studied were the superior cervical and inferior mesenteric in the rabbit, and the superior cervical and stellate ganglia in the cat. Except in one decerebrate cat, the background anaesthetic was pentobarbitone, and gallamine was given.

2. All three anaesthetics reduced the height of the post-ganglionic compound action potential. The time course of the effects was variable, and quantitative differences in the magnitude of the changes produced by each anaesthetic could not be demonstrated.

3. It is concluded that cyclopropane, halothane, and ether depress impulse transmission through sympathetic ganglia.

STUDY 5. POSTGANGLIONIC SYMPATHETIC DISCHARGE AND THE EFFECT OF INHALATION ANAESTHETICS

Introduction

In the preceding Study 3 it was shown that preganglionic activity was increased by cyclopropane, which raised arterial pressure. A similar although less pronounced sympathetic response also occurred in the rabbit during anaesthesia with halothane, which lowered arterial pressure. Diethyl ether increased preganglionic discharge, but short of overdose this change was accompanied by less distinctive alterations in arterial pressure.

The responses of effector organs (heart and blood vessels) to the increased sympathetic excitation induced by these anaesthetics is complicated by the occurrence of partial ganglion blockade, as demonstrated in the previous Study 4. In the present experiments, therefore, postganglionic sympathetic activity has been recorded in rabbits before and during anaesthesia with cyclopropane, halothane, or ether.

Results

Physiological Responses. The patterns of activity recorded in postganglionic sympathetic nerves were very similar to those observed in preganglionic fibres (Study 3). A respiratory rhythm, with an increased sympathetic discharge during expiration, was usually present. Fig. 48 illustrates an example from the external carotid nerve: the pronounced rhythmical variation showed a constant relation to the respiratory modulation of arterial pressure. Similar examples, from the cardiac and hypogastric nerves, are shown in several later figures. This respiratory rhythm was at least temporarily disrupted by baroreceptor denervation, as occurred in the case of preganglionic fibres (Study 3). In one rabbit in which the vagus, carotid sinus, and aortic nerves had been cut, rhythmical variations in cardiac sympathetic discharge became more pronounced throughout the experiment (Fig. 49A, E, G). Fig. 50A & B, from later in the same experiment, shows that there was a constant relation of the sympathetic rhythm to the preceding phrenic discharge (down-going spikes), but not to the pulmonary stretch afferent (up-going spikes) whose discharge was determined by the mechanical ventilation. Since the major chemoreceptor and baroreceptor afferents had been cut, it can be presumed that the postganglionic sympathetic rhythm was probably of central origin.

In the cardiac nerve, a rhythm in time with the heart beat was always present; an example is shown in Fig. 50F, from another

Fig. 48.

From above down; arterial pressure, mm Hg; mean integrated discharge rate in postganglionic sympathetic external carotid nerve (time constant 0.1 sec); film strip showing, above, external carotid nerve action potentials, and the arterial pressure below. The impulse discharge is modulated by rhythms in time with both respiration and heart rate.

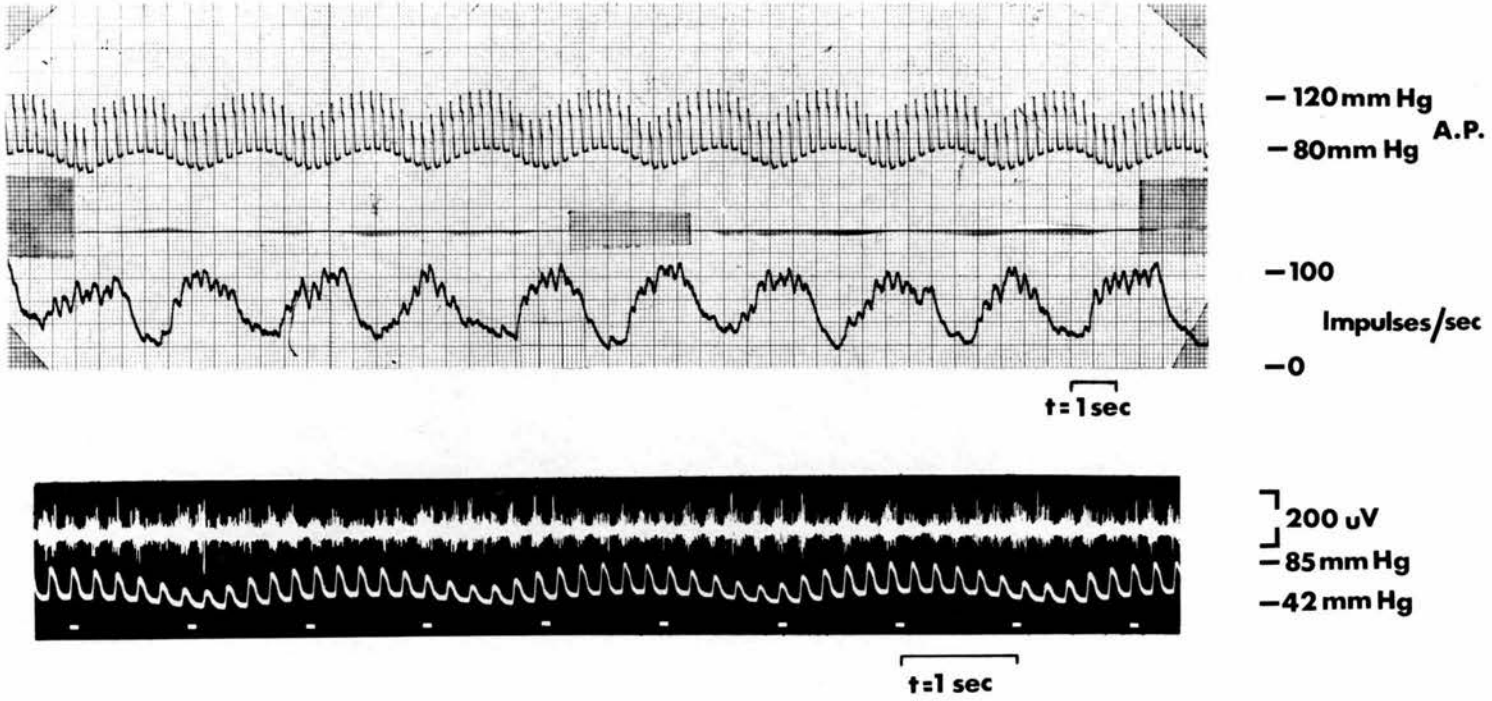

— 120 mm Hg
— 80 mm Hg
A.P.
— 100
Impulses/sec
— 0
t = 1 sec
200 uV
— 85 mm Hg
— 42 mm Hg
t=1 sec

Fig. 48

Fig. 49.

Cardiac sympathetic nerve action potentials in a rabbit in which the vagus, carotid sinus and aortic nerves had been divided bilaterally.

A: ventilated with 100% oxygen, and showing the arterial pressure. B, C, and D: during anaesthesia with 3% halothane. E, F, and G: before, during and after cyclopropane anaesthesia. H and I: during anaesthesia with 11.5% ether.

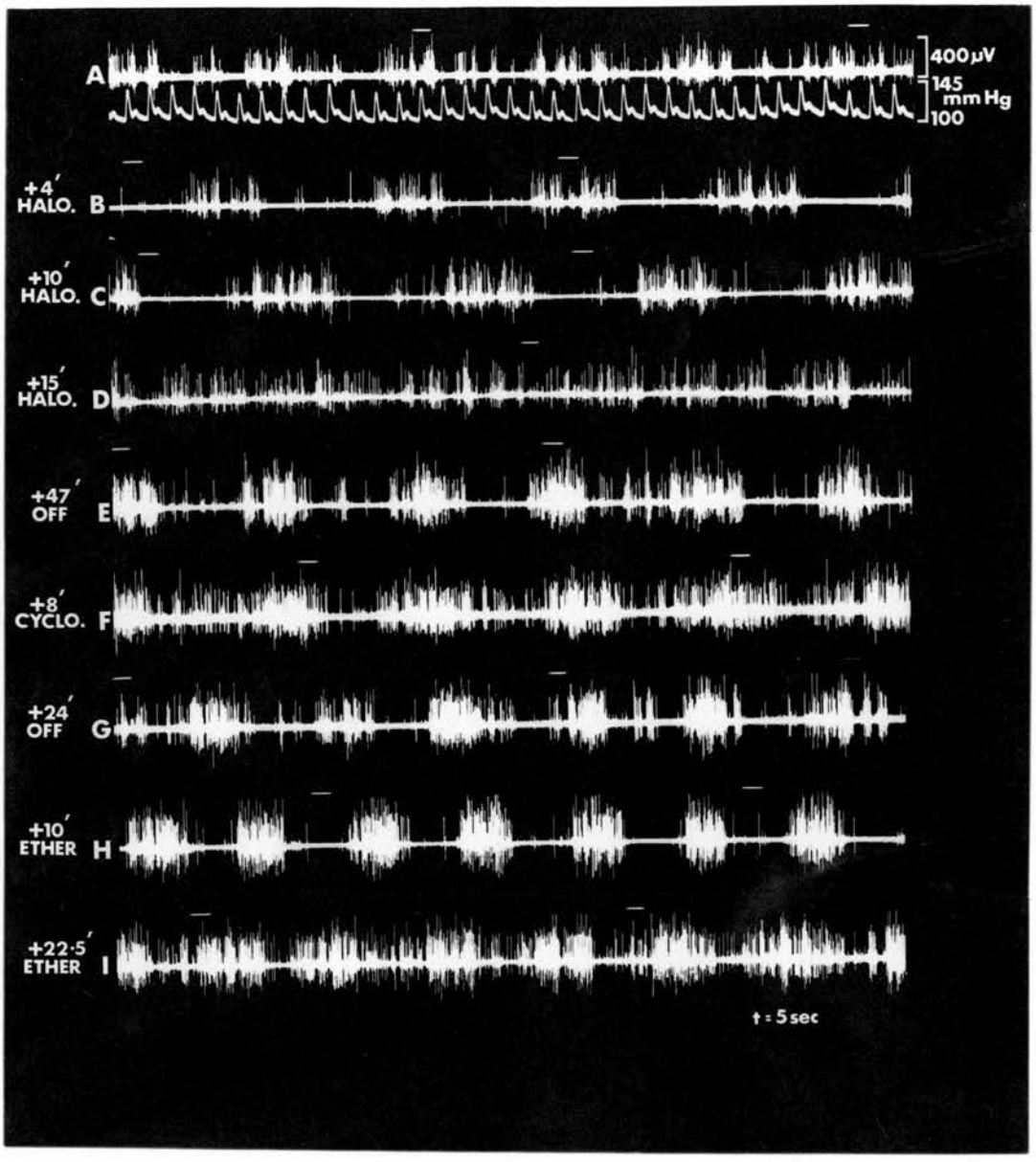

A
400 μV
145
mm Hg
100
+4′
HALO. B
+10′
HALO. C
+15′
HALO. D
+47′
OFF E
+8′
CYCLO. F
+24′
OFF G
+10′
ETHER H
+22·5′
ETHER I
t = 5 sec

Fig. 49

Fig. 50.

From later in the experiment illustrated in Fig. 49. Records A and B: from above down, cardiac sympathetic nerve action potentials, vagal afferent action potentials (upgoing spikes), and phrenic nerve action potentials (downgoing spikes). C - E: above, cardiac nerve action potentials; below, phrenic nerve potentials. Record F: cardiac nerve action potentials and arterial pressure trace.

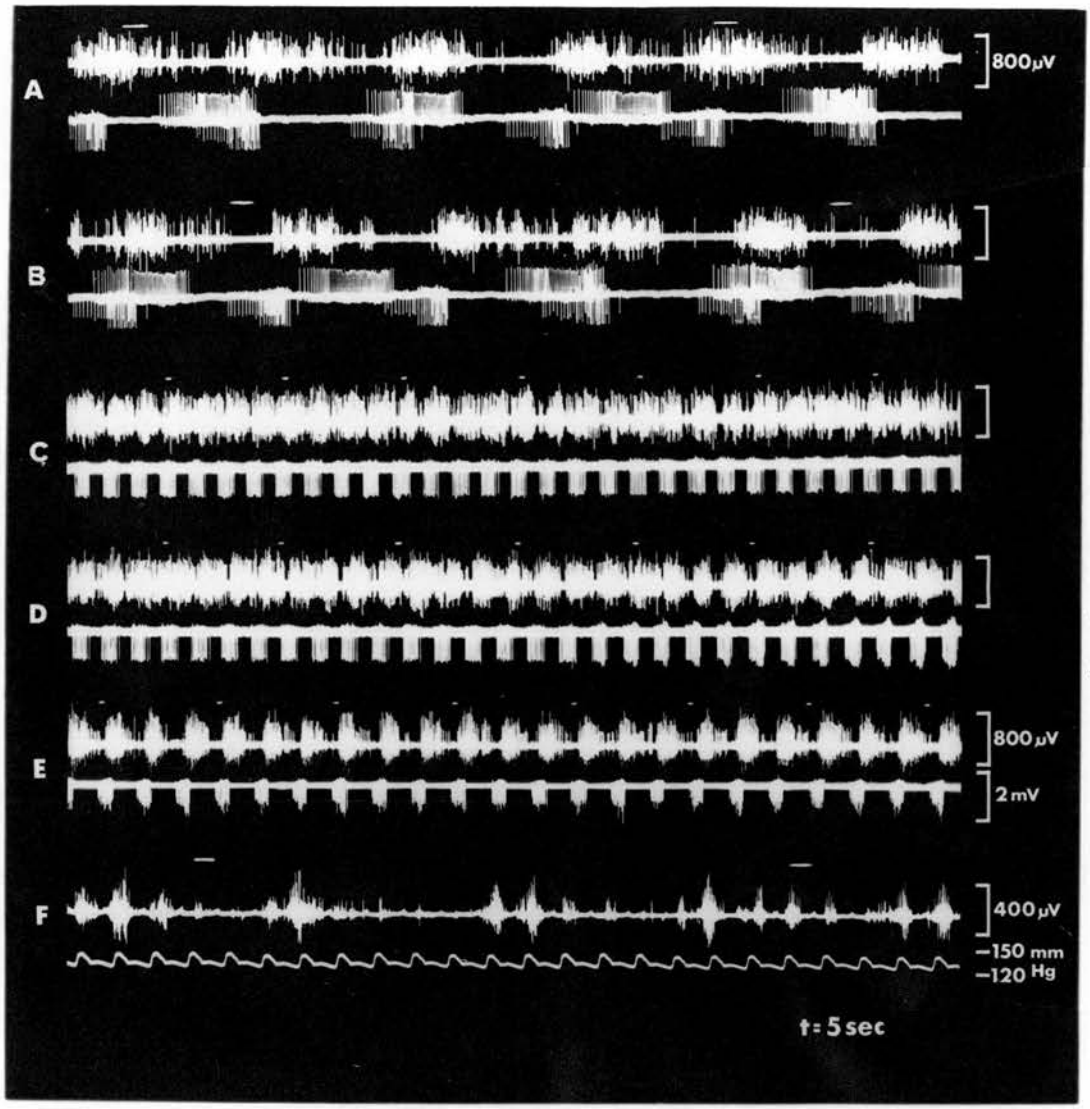


Fig. 50.

experiment, where a secondary modulation in time with respiration led to periodic complete quiescence of sympathetic activity when only a small E.C.G. artefact was visible (noted especially towards the right of the film strip). Fig. 49A suggests that the cardiac modulation of the discharge largely disappeared when the vagi, aortic, and carotid sinus nerves had been divided. The close relation between bursts of activity in the cardiac nerve and arterial pressure changes is clearly demonstrated in Fig. 51, where the spasmodic variations in impulse discharge precede the changes in pressure.

A cardiac rhythm was also sometimes seen in records from the external carotid nerve, as shown in Fig. 48. Smaller peaks with the same period as the pulse wave are superimposed on the respiratory rhythm; these are also seen in the film strip.

Increases in arterial pressure produced by intravenous injection of small doses of adrenaline [redacted]chloride inhibited postganglionic sympathetic discharge, as with preganglionic fibres (Adrian, Bronk, and Phillips, 1932, Study 3). Partial inhibition of external carotid sympathetic discharge is shown in Fig. 52, and of hypogastric nerve discharge in Fig. 66, both in response to 5 µg adrenaline. More complete and prolonged depression of hypogastric activity in response to 10 µg adrenaline is illustrated in Fig. 53. Such delays in recovery were frequent in postganglionic nerves, but rare in preganglionic strands.

Aortic nerve stimulation produced similar effects on post-ganglionic sympathetic discharge to those described for preganglionic

Fig. 51.

Showing a close direct relation between changes in cardiac sympathetic discharge and arterial pressure. From above down: end-tidal P_{CO_2}, mm Hg; arterial pressure, mm Hg; mean integrated cardiac sympathetic discharge, impulses/sec, time constant 0.33 sec; film strip of cardiac nerve action potentials.

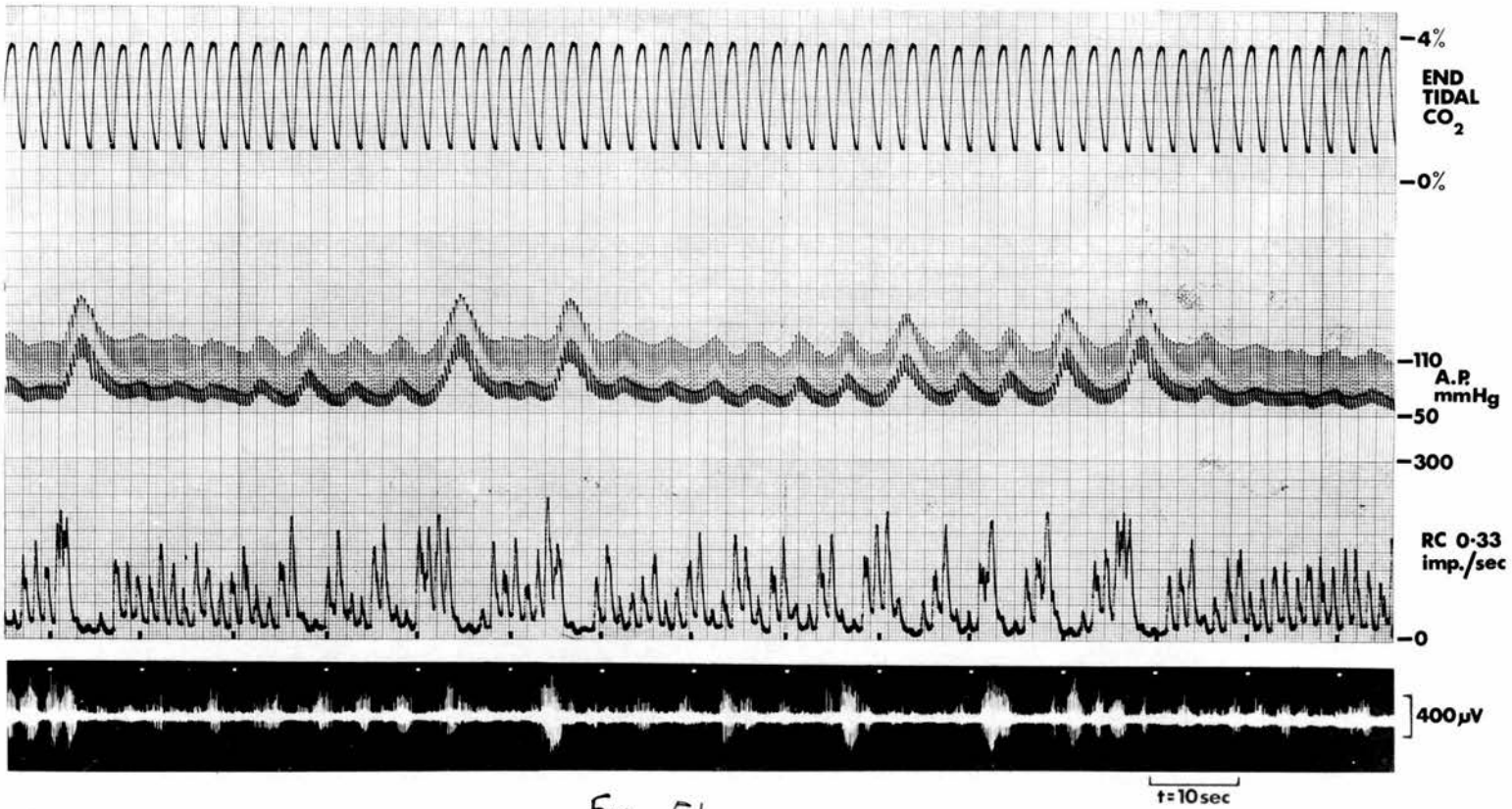

4%
END TIDAL CO_2
0%
110
A.P. mmHg
50
300
RC 0·33 imp./sec
0
400μV
t=10sec

Fig. 51

Fig. 52.

Postganglionic external carotid action potentials.

A: partial inhibition of the discharge produced by 5 µg adrenaline ~~hydro~~chloride injected intravenously at the arrow and washed in with saline at second horizontal mark. B and C: after 6 and 13½ min of anaesthesia with 3% halothane. D - F: before and after 8½ and 17 min of anaesthesia with 11% ether. G: inhibition of postganglionic discharge by 25 mg/kg hexamethonium injected intravenously at the arrow.

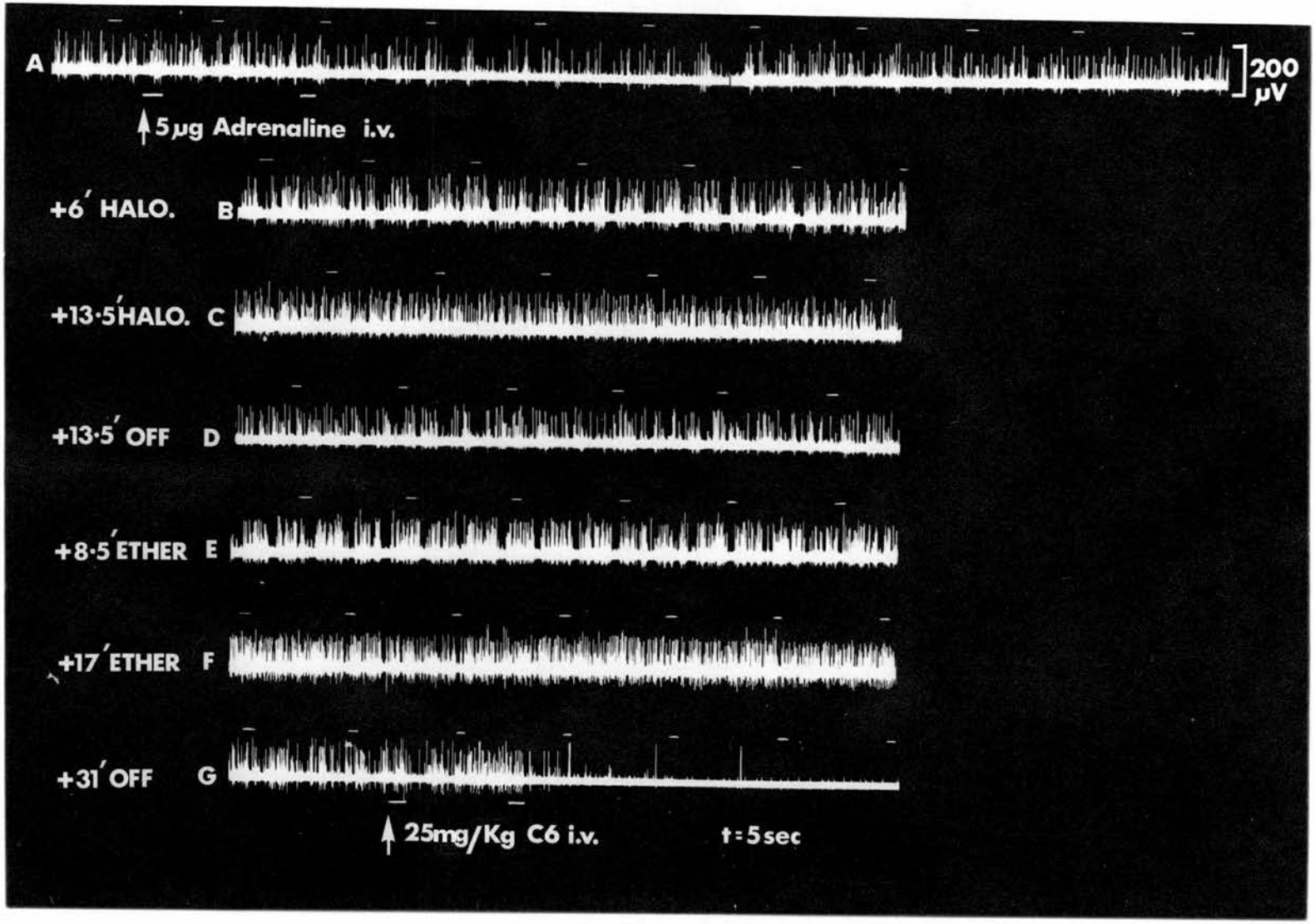

A
200 µV
5µg Adrenaline i.v.
+6′ HALO. B
+13·5′HALO. C
+13·5′ OFF D
+8·5′ ETHER E
+17′ ETHER F
+31′ OFF G
25mg/Kg C6 i.v.
t=5sec

Fig. 52

Fig. 53.

Effect of adrenaline-induced arterial hypertension on postganglionic hypogastric sympathetic activity. Above: mean arterial pressure, mm Hg; below: mean integrated sympathetic discharge (impulses/sec). There is a postganglionic sympathetic respiratory rhythm.

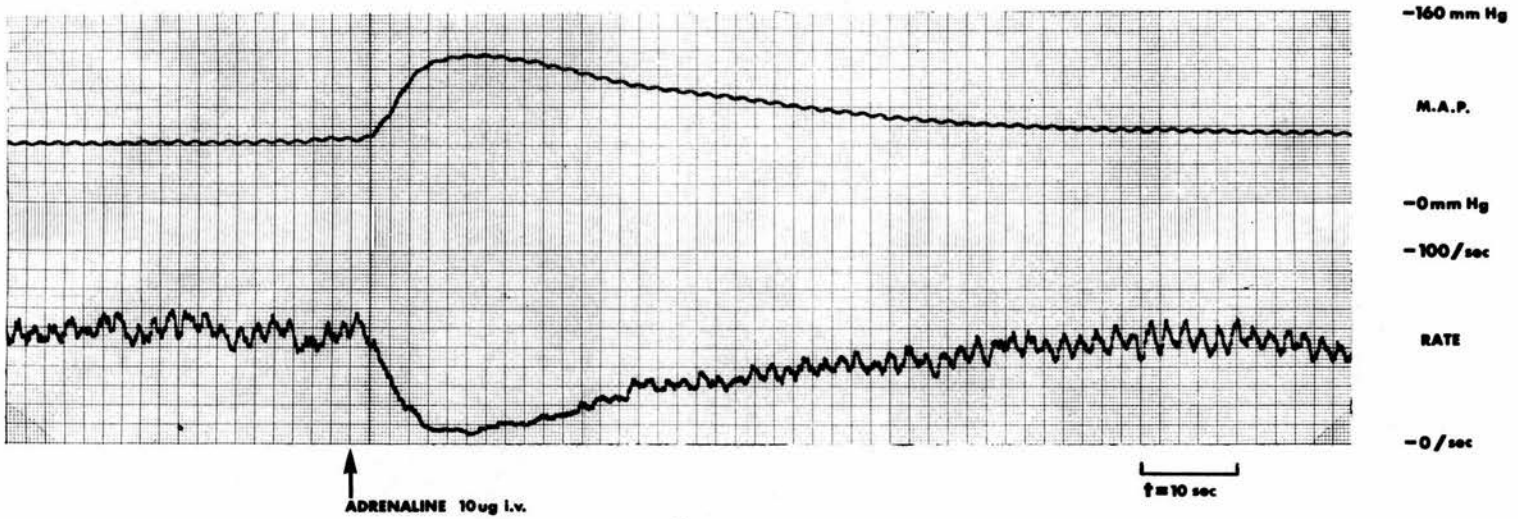

-160 mm Hg
M.A.P.
-0 mm Hg
-100/sec
RATE
-0/sec
ADRENALINE 10ug i.v.
↑=10 sec

Fig. 53

nerves in Study 2. Fig. 18 shows responses in the nerve to the carotid body.

Effects of sodium pentobarbitone. As stated under Methods, in all these studies basal anaesthesia was maintained by intermittent injections of 6 - 12 mg pentobarbitone, the required frequency being assessed during the preparative period. Lightening anaesthesia was often associated with spontaneous changes in sympathetic rate, as in the right cardiac nerve record shown in Fig. 54, there being an accompanying reduction in mean arterial pressure. In this experiment, intravenous injection of 12 mg sodium pentobarbitone produced a transient increase in the sympathetic discharge rate and a more prolonged fall in arterial pressure. The rhythmical modulation in activity persisted throughout these changes. Similarly in Fig. 55, from another experiment, spontaneous variations in hypogastric nervous discharge were abolished by injection of 6 mg sodium pentobarbitone, although this had a negligible effect on the mean sympathetic discharge rate and caused only a transient alteration in mean arterial pressure. These short-term effects of sodium pentobarbitone were characteristic, and similar to those observed in the experiments on preganglionic sympathetic fibres (Study 3).

Effects of gallamine triethiodide. These were small, and rarely as pronounced as shown in Fig. 56, where there was a brief increase in external carotid nerve activity and some fluctuation in arterial pressure after injection of gallamine 4 mg.

Fig. 54.

Spontaneous changes in arterial pressure (mm Hg), and cardiac sympathetic discharge (impulses/sec), and the effect of 12 mg sodium pentobarbitone injected at the arrow.

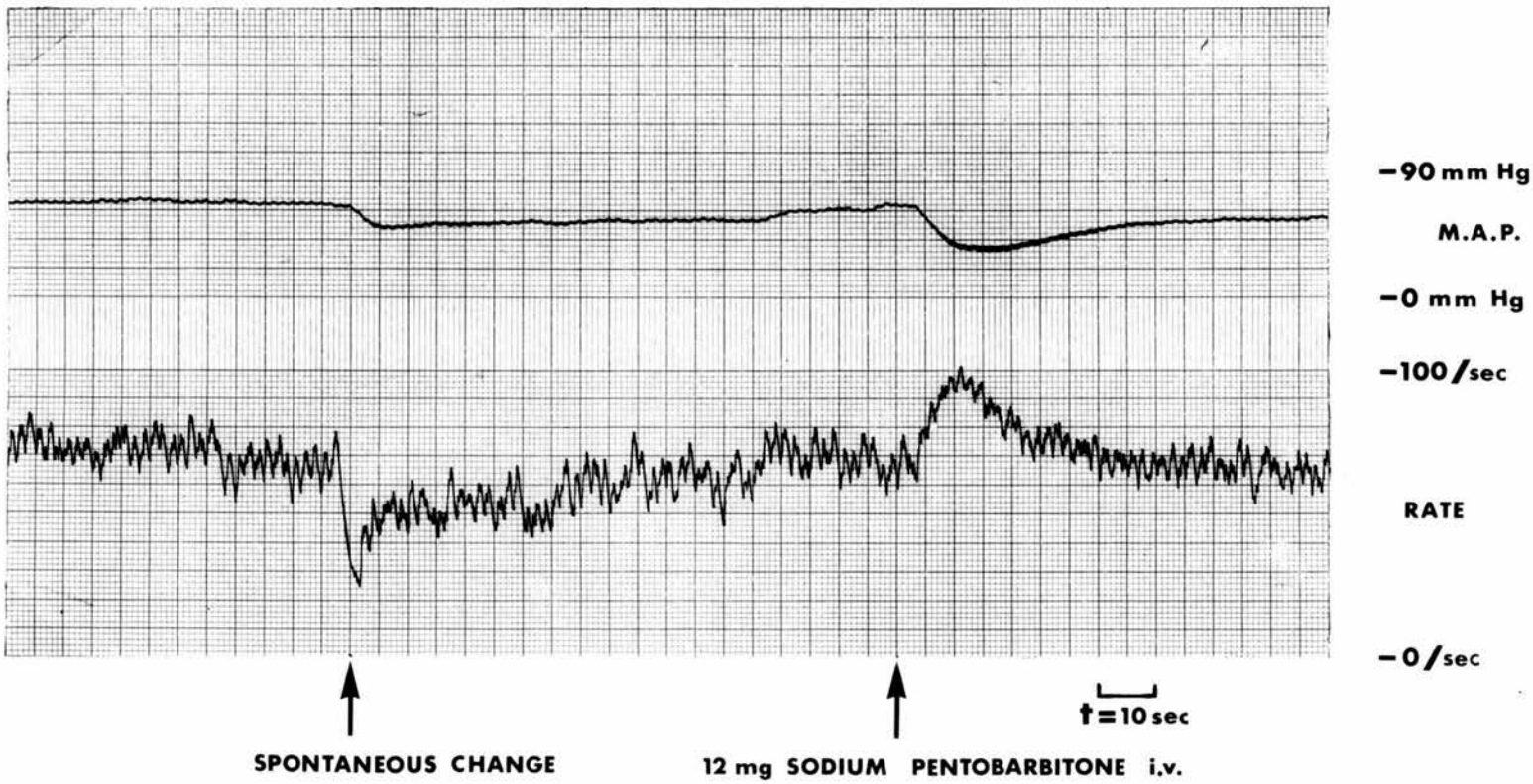

−90 mm Hg
M.A.P.
−0 mm Hg
−100/sec
RATE
−0/sec
t = 10 sec
SPONTANEOUS CHANGE
12 mg SODIUM PENTOBARBITONE i.v.

Fig. 54

Fig. 55.

Spontaneous variations in postganglionic hypogastric sympathetic activity (impulses/sec). Also shown are the effects on the discharge and on arterial pressure (mm Hg) of 6 mg sodium pentobarbitone injected at the arrow.

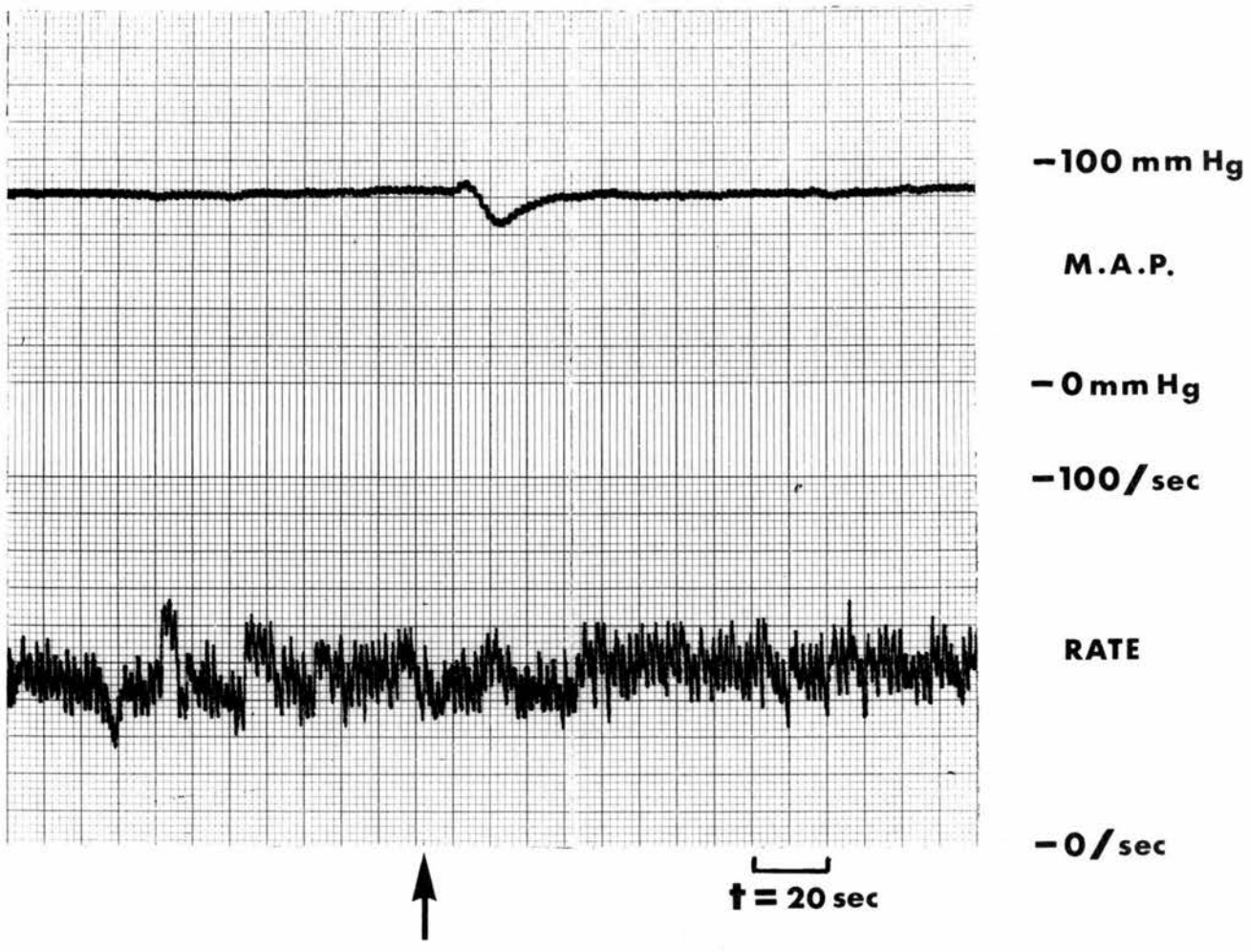

−100 mm Hg
M.A.P.
−0 mm Hg
−100/sec
RATE
−0/sec
t = 20 sec
6 mg SODIUM PENTOBARBITONE i.v.

Fig. 55

Fig. 56.

Mean arterial pressure (mm Hg) and integrated external carotid sympathetic discharge (impulses/sec). 4 mg gallamine triethiodide were injected at the arrow.

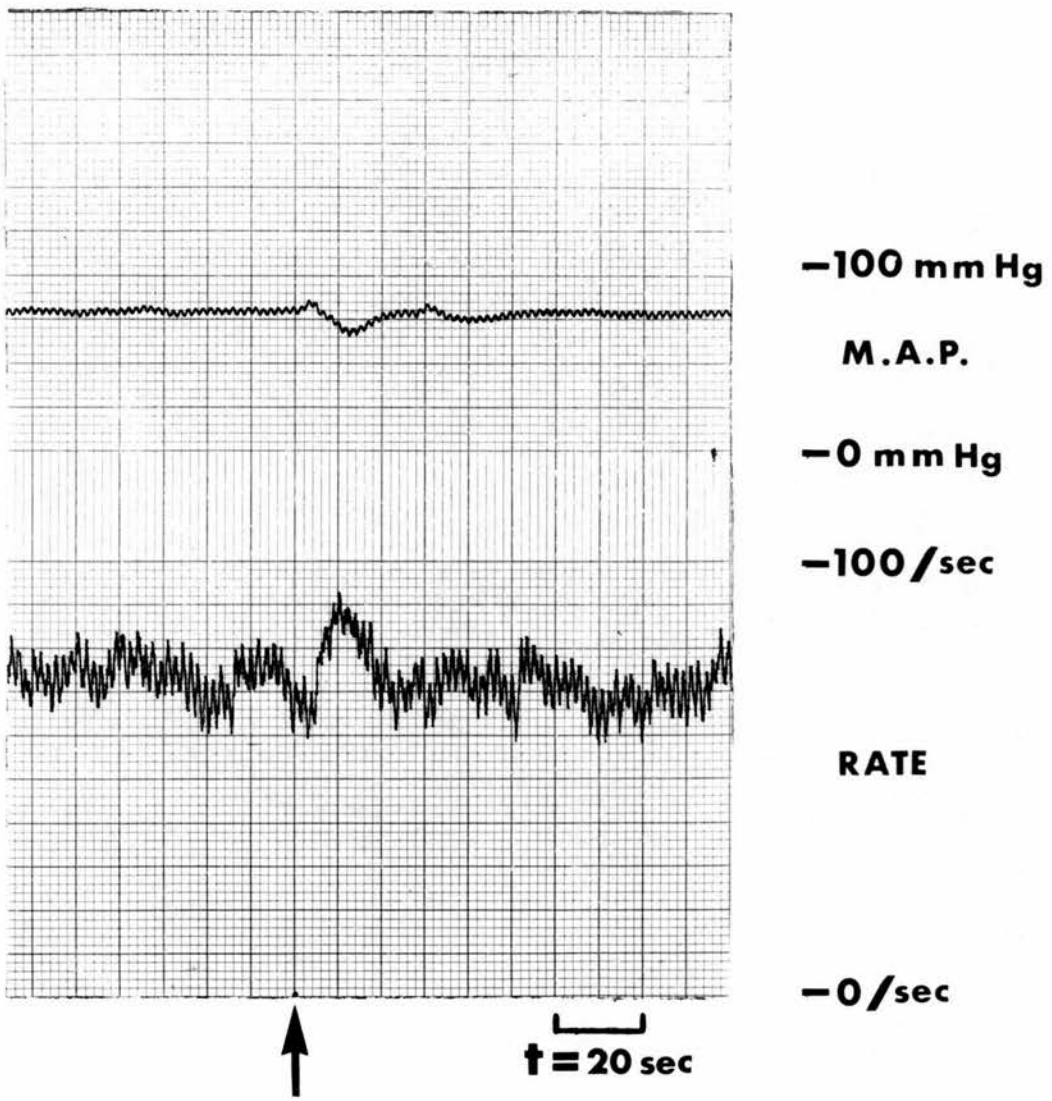

—100 mm Hg
M.A.P.
—0 mm Hg
—100/sec
RATE
—0/sec
t = 20 sec
4 mg GALLAMINE TRIETHIODIDE i.v.

Fig. 56

Some effects of carbon dioxide. Increases in the inspired P_{CO_2} caused increased synchronization of the rhythmic activity in preganglionic sympathetic nerves, (Study 3). The same effect was observed while recording from the cardiac nerve. Fig. 50 C, D, E are parts of a continuous record; administration of 10% carbon dioxide was started 10 sec after the beginning of record C and there was progressive synchronization of the sympathetic discharge accompanied by a fall in the mean discharge rate. The bursts of activity were in time with the phrenic activity (down-going spikes) which also showed recruitment. Fig. 57, from another experiment, also demonstrates this enhanced synchronization, although the most marked effects occurred only when 20% CO_2 was given. There was a progressive increase in mean cardiac sympathetic discharge rate throughout; thus, in A the counted rate was 10/sec, in B after 3 min of 5% carbon dioxide it had risen to 17/sec, and in C after 10 min of 20% carbon dioxide the rate was 40/sec. Mean arterial pressure was increased from 83 mm Hg in A & B to 119 mm Hg in C.

Hexamethonium tartrate. This drug was given to confirm that the sympathetic activity being studied was postganglionic in origin. Fig. 58 illustrates the action of hexamethonium (20mg/kg) on the activity in strands from the cardiac nerve (A & B), and hypogastric nerve (C & D). Fig. 52 G shows the effect on an external carotid nerve strand.

Fig. 57.

Cardiac sympathetic nerve action potentials. A: during ventilation with 100% oxygen. B and C: ventilation with 5% and 20% carbon dioxide in oxygen.

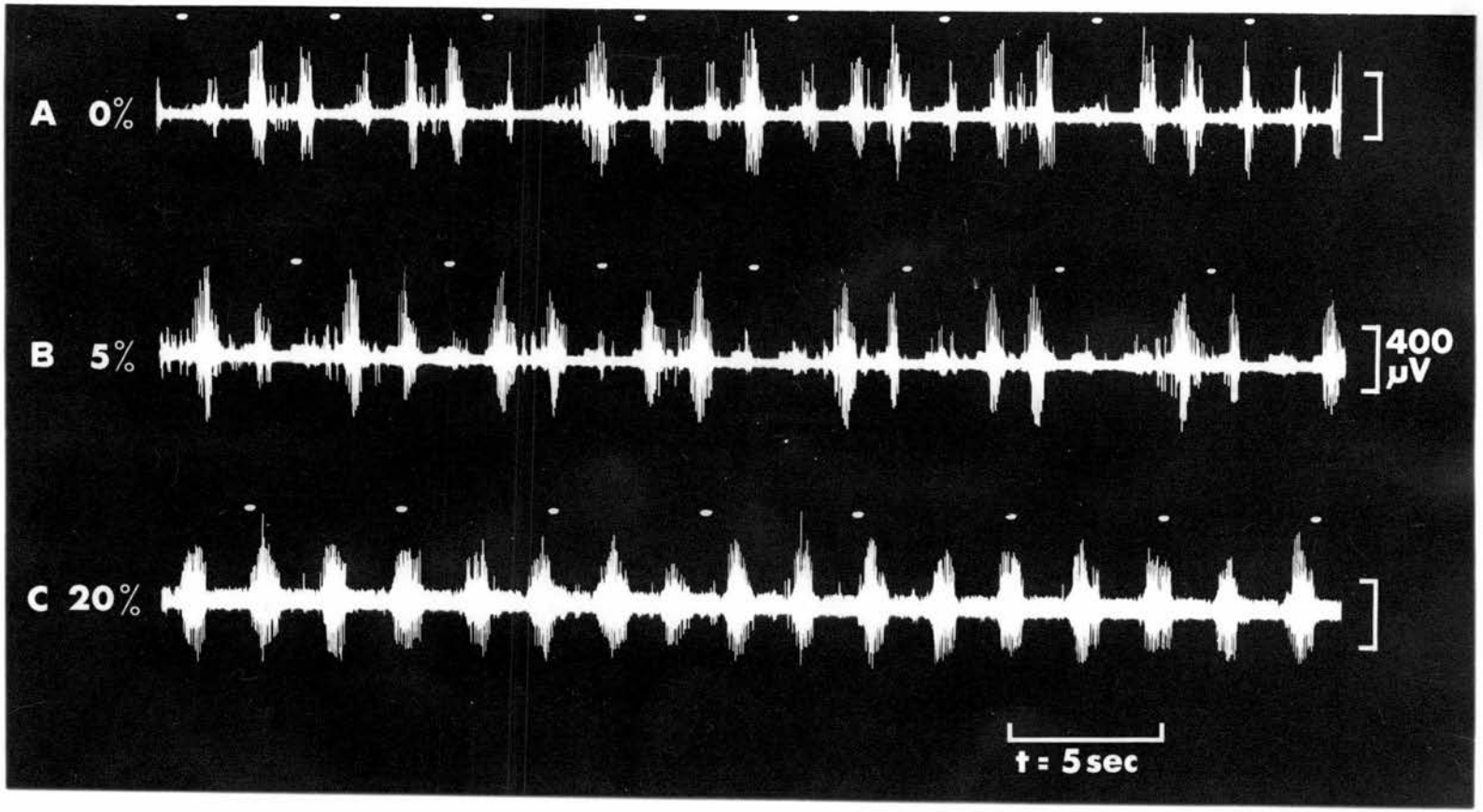


Fig. 57

Fig. 58.

Effect of hexamethonium, 20 mg/kg, injected intravenously at the first horizontal mark, and washed in at the second mark, on cardiac (A and B) and hypogastric (C and D) sympathetic nervous activity.

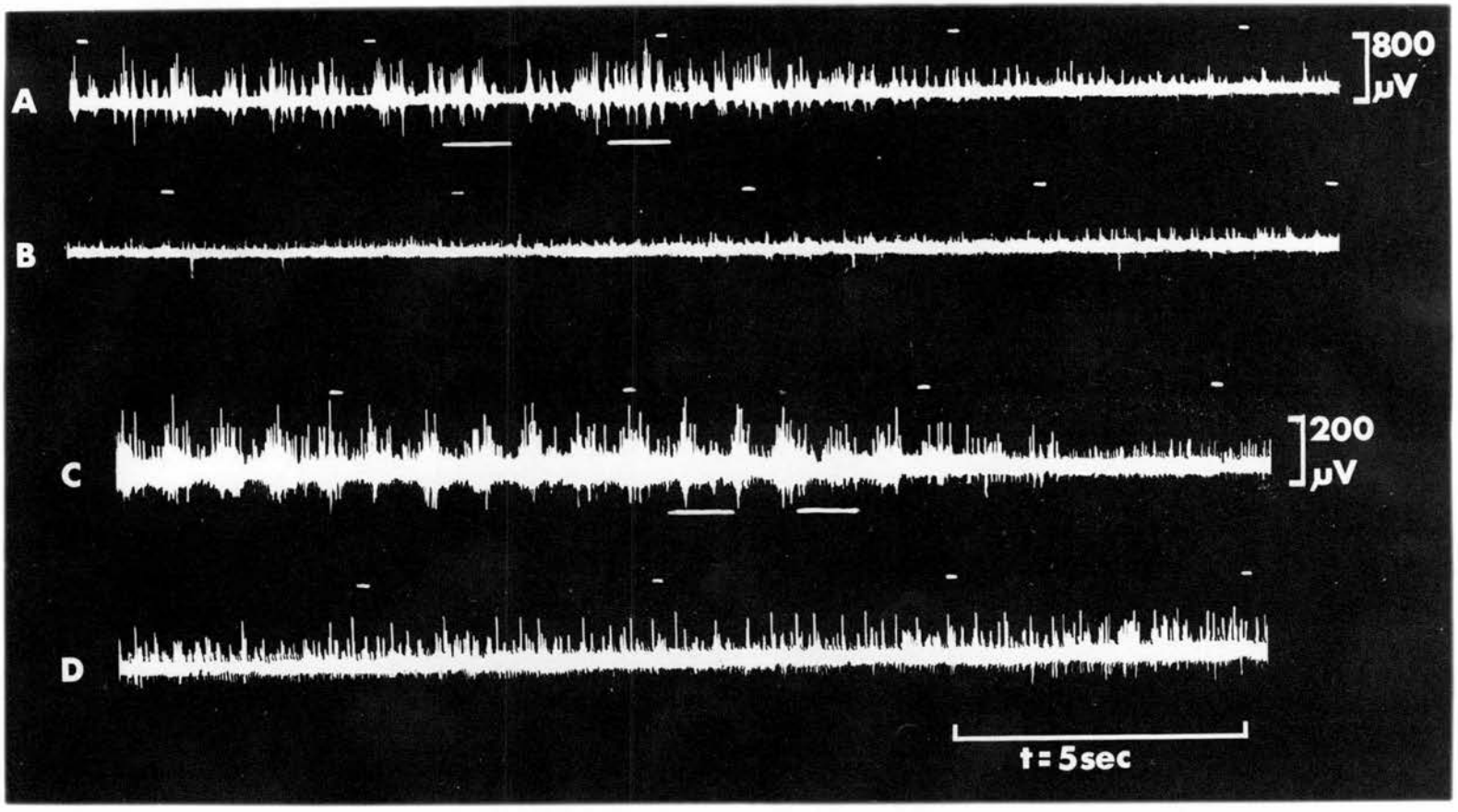


Fig. 58

Cyclopropane. Sympathetic activity was recorded from the left cardiac nerve in one rabbit, and from the right nerve in 4 rabbits, during administration of 50% cyclopropane for periods of 12 to 20 min. In 2 experiments involving the right cardiac nerve, the vagus, carotid sinus, and aortic nerves had been divided previously, and in these animals 50% cyclopropane reduced arterial pressure below control levels. In the 3 remaining rabbits, with these nerves intact, cyclopropane increased arterial pressure, by 37% above control level after 6 min in the case of the left cardiac nerve, and by 9% and 8% for the other two experiments involving the right nerve; in these animals the associated increases in cardiac sympathetic activity were by 206%, 140%, and 43% respectively. The mean maximum increase in discharge rate caused by 50% cyclopropane, for all 5 rabbits studied, was by 118% (S.E. $\pm$ 36.3; $0.05 > P > 0.025$).

Increased activity in the left cardiac nerve during cyclopropane anaesthesia is shown in Fig. 59. The mean discharge rate was 56/sec before cyclopropane (A), and was modulated by respiration; there was an increase to 168/sec after 12 min of 50% cyclopropane (B), arterial pressure was raised, and there was pulsus alternans, a common accompaniment to the ventricular arrhythmias produced by cyclopropane. Arterial pressure had returned to above the control level 53 min after discontinuing

Fig. 59.

Cardiac sympathetic action potentials, and arterial pressure trace. A: ventilation with 100% oxygen. B: after 12 min of 50% cyclopropane. C: 100% oxygen, 33 min after terminating cyclopropane. Same experiment as in Figs. 62 and 64.

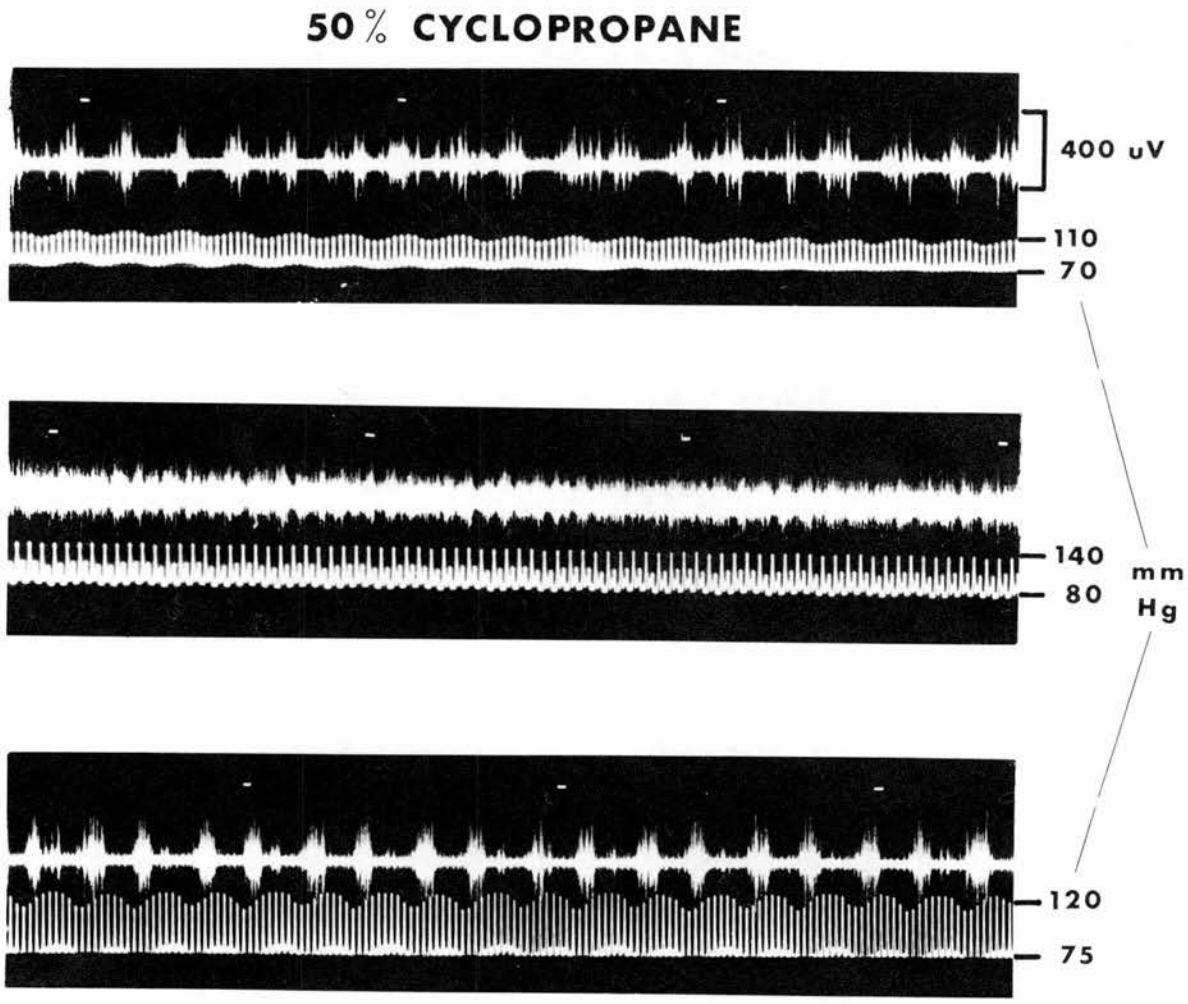


Fig. 59

Fig.60.

Graph of changes in mean integrated cardiac sympathetic discharge, ● , impulses/sec, and mean arterial pressure, O, mm Hg, against time. A: 50% cyclopropane was given (between the arrows) to a rabbit in which the vagus, carotid sinus, and aortic nerves had been divided. B: effects of 3% halothane in another rabbit in which these nerves were intact.

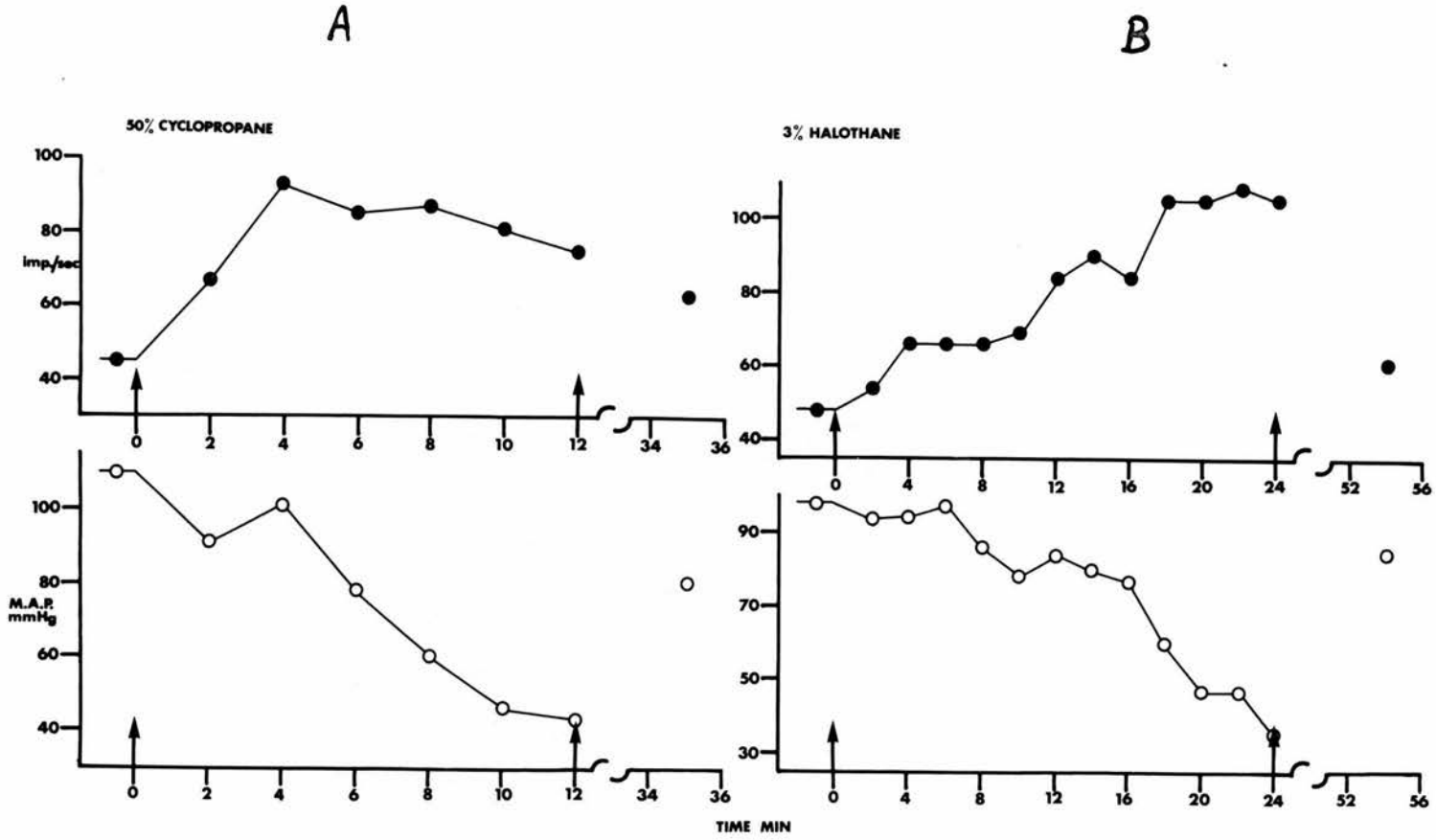


Fig. 60

cyclopropane, and the mean sympathetic discharge rate was then 60/sec (C).

Fig. 49 illustrates the changes in right cardiac nervous activity caused by cyclopropane in a rabbit in which the vagus, carotid sinus, and aortic nerves had been cut. The control record (Fig. 49E) was taken 47 min after a previous administration of halothane, and the trace F refers to 8 min of 50% cyclopropane. The sympathetic rhythm, which was of central origin (E), was less marked during cyclopropane (F) and the mean discharge rate had increased from 85/sec to 105/sec; mean arterial pressure was reduced to 27 mm Hg at this time, from a control level of 63 mm Hg. Fig. 49G shows recovery, 24 min after discontinuing cyclopropane, to a mean sympathetic discharge rate of 80/sec. The time course of the changes in cardiac sympathetic rate and arterial pressure are shown in Fig. 60A, from another experiment, in which the sinus, aortic, and vagus nerves had been cut. The unusual and progressive fall in mean arterial pressure caused by 50% cyclopropane was associated with a maximum increase in mean sympathetic discharge rate of 85%.

When cyclopropane was stopped, there was usually a transient, and sometimes pronounced rise in arterial pressure within the ensuing few minutes, while the cardiac sympathetic rate remained unchanged or was gradually declining. This effect on arterial pressure has been shown to occur in man (Price, Conner, and Dripps, 1953). An example is shown in Fig. 61 where the lower trace,

Fig. 61.

Effects of resuming ventilation with 100% oxygen following administration of 50% cyclopropane. From above down: mean arterial pressure, mm Hg; mean integrated cardiac sympathetic nervous discharge (impulses/sec); respiration, and the change from cyclopropane to oxygen, monitored by a thermistor bead placed in the airway.

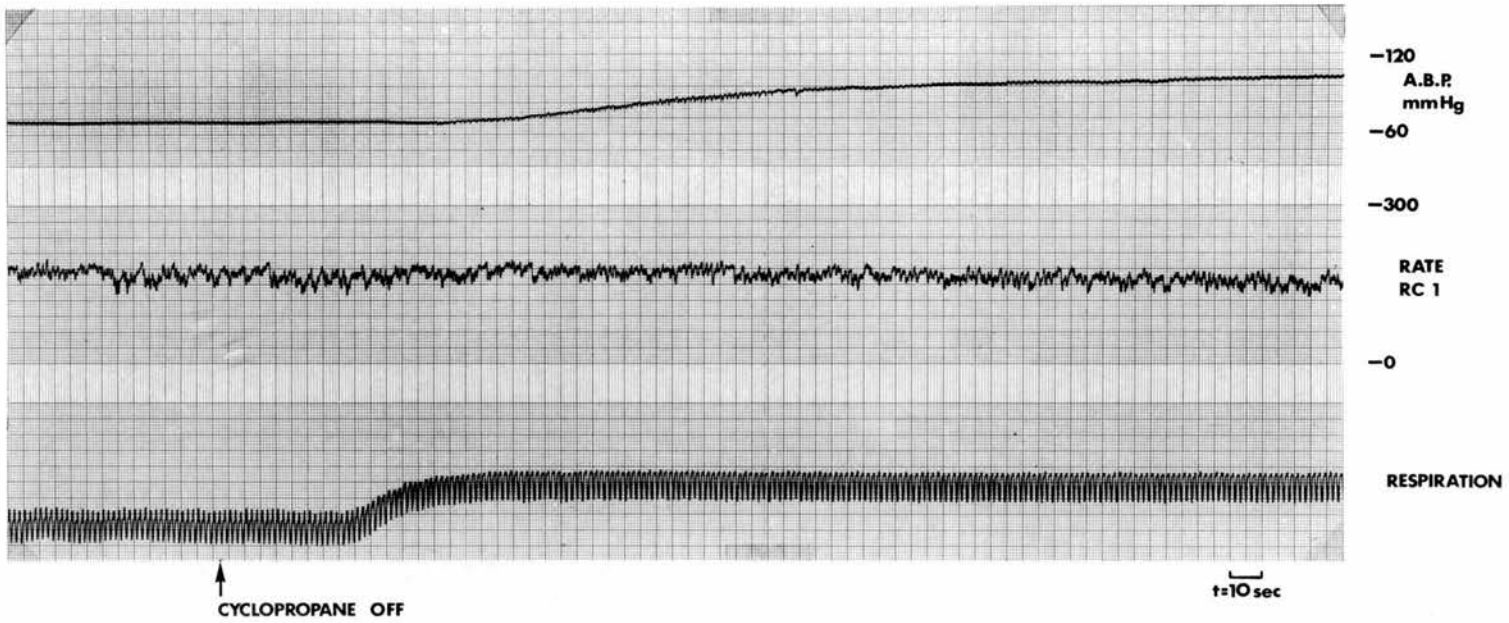

−120
A.B.P.
mmHg
−60
−300
RATE
RC 1
−0
RESPIRATION
CYCLOPROPANE OFF
t=10 sec

Fig. 61

obtained from a thermistor flowmeter (Millar and Marshall, 1963) placed in the tracheal cannula, shows the start of cyclopropane elimination; this was followed by a rise in mean arterial pressure which was only temporary, although full recovery of pressure later occurred. Similar effects were noted during preganglionic sympathetic recording (Fig. 33, in Study 3).

Halothane. Recordings were made from the left cardiac nerve in one rabbit, and from the right nerve in 5 rabbits, before and during administration of 3% halothane; the duration of anaesthesia ranged from 10 to 24 min for the right side and was 12 min for the left. As in the case of preganglionic studies (Study 3), changes in postganglionic sympathetic activity have been related to two levels of arterial pressure - 30% and 60% below control.

In two experiments involving the right cardiac nerve, the vagus, sinus, and aortic nerves had been divided bilaterally. In these animals, at a 30% reduction in arterial pressure during halothane anaesthesia, the cardiac sympathetic discharge rate was increased by 14% and by 9%; corresponding with a 60% fall in pressure, the activity was increased by 35% and by 4% respectively; the control arterial pressures were 127 mm Hg and 102 mm Hg.

When the latter results are included with those obtained in the other 4 rabbits (whose control arterial pressure averaged 90 mm Hg), the mean increase in cardiac sympathetic rate at 30% depression of pressure was by 64% (S.E. $\pm$ 22.9; $0.05 > P > 0.025$), and at a 60% pressure reduction by 84% (S.E. $\pm$ 24.9; $0.025 > P > 0.02$).

The largest increases were measured in the left cardiac nerve, and were by 160% and 174% at 30% and 60% reductions in arterial pressure respectively. Records from this nerve are shown in Fig. 62; the control level was 60/sec, with synchronized bursts of sympathetic activity (A). After 6 min of 3% halothane mean arterial pressure was reduced from the control level of 89 mm Hg, to 78 mm Hg, and the cardiac impulse discharge rate was increased to 168/sec (B). The activity was still modulated by respiration but the respiratory variations in arterial pressure were much diminished. The discharge remained essentially unchanged as arterial pressure fell to a level of 27 mm Hg after 12 min of 3% halothane. Fig. 62C shows the substantial recovery 19 min after discontinuing halothane; the mean sympathetic discharge rate was 74/sec and there was a respiratory modulation of arterial pressure. Later in the same experiment, records were obtained from a second cardiac sympathetic nerve strand. In this case, there was a 68% increase in activity after 6 min of 3% halothane, in association with a fall in arterial pressure from 104 mm Hg to 47 mm Hg.

Recordings from one of the two rabbits studied following section of the vagus, sinus, and aortic nerves, showed some evidence of enhancement of a centrally driven rhythm when halothane was administered (compare Fig. 49A with B). In this experiment the total cardiac sympathetic discharge in the dissected nerve strand was discriminated into "small spike" and "large spike" groups by means of the pulse height selector. After 4 min of

Fig. 62.

Left cardiac sympathetic action potentials, and arterial pressure trace. A: 100% oxygen. B: after 6 min of 3% halothane. C: oxygen, 19 min after discontinuing halothane. Same experiment as in Figs. 59 and 64.

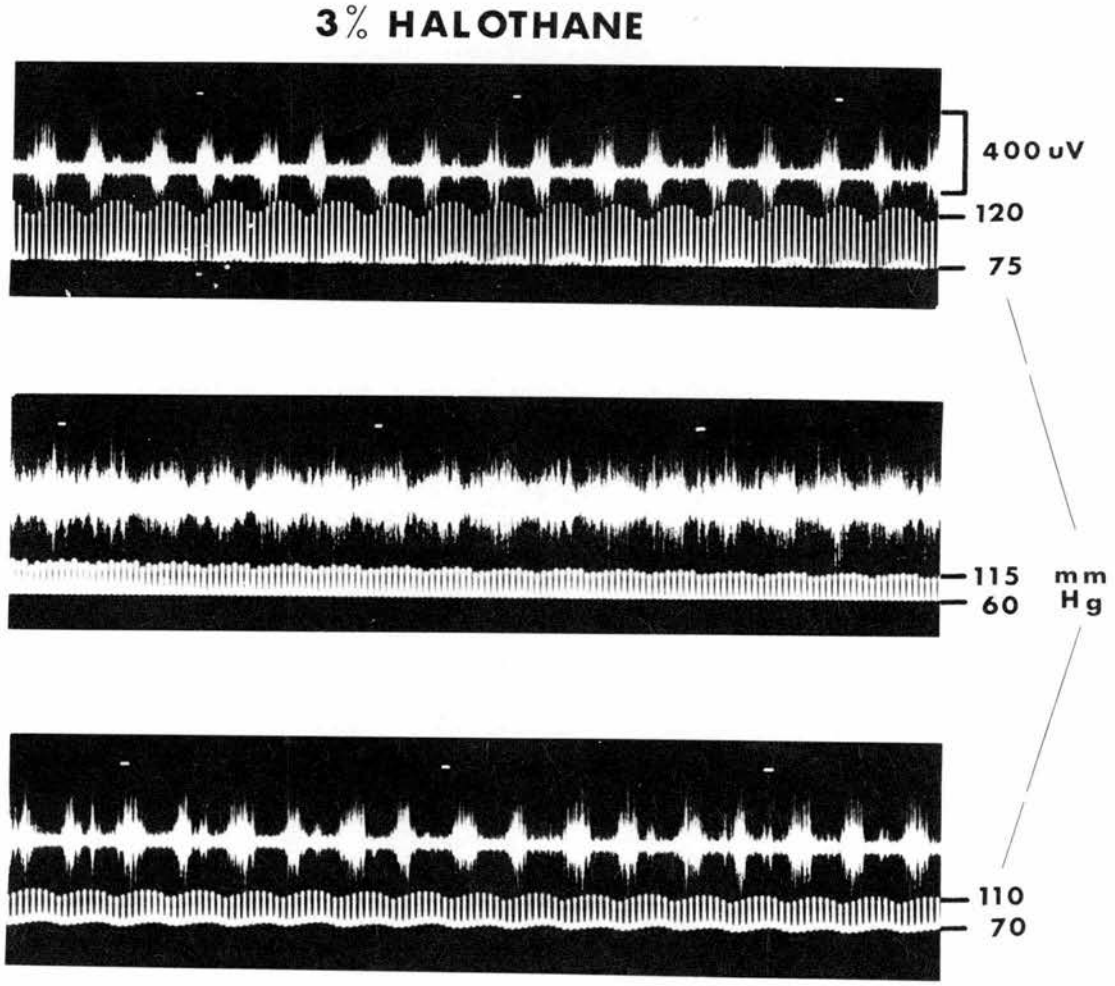


Fig. 62

halothane (Fig. 49B), when arterial pressure had fallen from 102 mm Hg to 30 mm Hg, the large spikes had increased in rate from 46/sec to 48/sec while the small spikes had decreased from 40/sec to 32/sec; there was, therefore, a 7% reduction in the total discharge rate being counted. After 10 min of halothane (Fig. 49C), the large and small spike counts were respectively 45/sec and 33/sec and the sympathetic rhythm was more pronounced although mean arterial pressure was only 16 mm Hg. There was no discernible rhythm after 15 min of halothane (Fig. 49D), when the large and small spike counts were 50/sec and 54/sec respectively. Subsequently, mean arterial pressure recovered to 68 mm Hg and the total firing rate, both large and small spikes, was 85/sec. Thus, this experiment on a baroreceptor-denervated rabbit showed that after early increases in cardiac sympathetic rate within the first 4 min of halothane, and some dissociation in the time course of the responses of two groups of action potentials, a progressive fall in sympathetic rate was reversed only when arterial pressure had reached very low levels. In fact the arterial pressure after 4 min was below 60% depression, so that these later rates were not included in the statistical calculations already presented.

The time course of the effects of halothane on cardiac sympathetic activity is illustrated in Fig. 60B where the impulse discharge rate was inversely related to the pressure and both changes were largely reversed when the anesthetic was discontinued. In this animal the baroreceptor nerves were intact.

Further evidence that halothane occasionally enhanced a central sympathetic rhythm is found in the records of Fig. 63. The spasmodic activity shown in A (from the same experiment as Fig. 51) became well synchronized after 19 min of halothane (B); the bursts do not have the same period as the end-tidal CO_2 record and their rhythm is probably of central origin. Later (C), there is a return to the earlier spasmodic activity, although it is more rhythmic.

Ether. 5 rabbits were studied, in 4 of which recordings were made from the right cardiac nerve and in one from the left cardiac nerve. In two right cardiac nerve experiments the vagus, aortic, and sinus nerves were divided. The ether concentrations were in the range 7 - 15%.

The left cardiac nerve showed increases in impulse discharge frequency of 48% and 116% after 4 min and 10 min of 9% ether, respectively. The corresponding changes in arterial pressure, from a control level of 91 mm Hg, were a rise to 103 mm Hg at 4 min, and a fall to 57 mm Hg at 10 min.

The right cardiac nerves from the rabbits in which the sinus, aortic, and vagus nerves had been divided, showed increases of 5% and 10% after 4 min, and of 32% and 36% after 10 min of ether; the control arterial pressures were reduced from 119 mm Hg and 63 mm Hg, to 90 mm Hg and 35 mm Hg respectively after 4 min, remaining at these levels after 10 min of ether.

When all the ether data are grouped together, the mean increase in cardiac sympathetic activity after 4 min of ether was

Fig. 63.

From above down: end-tidal P_{CO_2}, mm Hg; mean arterial pressure, mm Hg; mean integrated cardiac sympathetic discharge rate, impulses/sec; cardiac sympathetic nerve action potentials. In this experiment the vagus, carotid sinus, and aortic nerves had been divided. A: ventilation with 100% oxygen. B: after 19 min of 3% halothane. C: after return to oxygen.

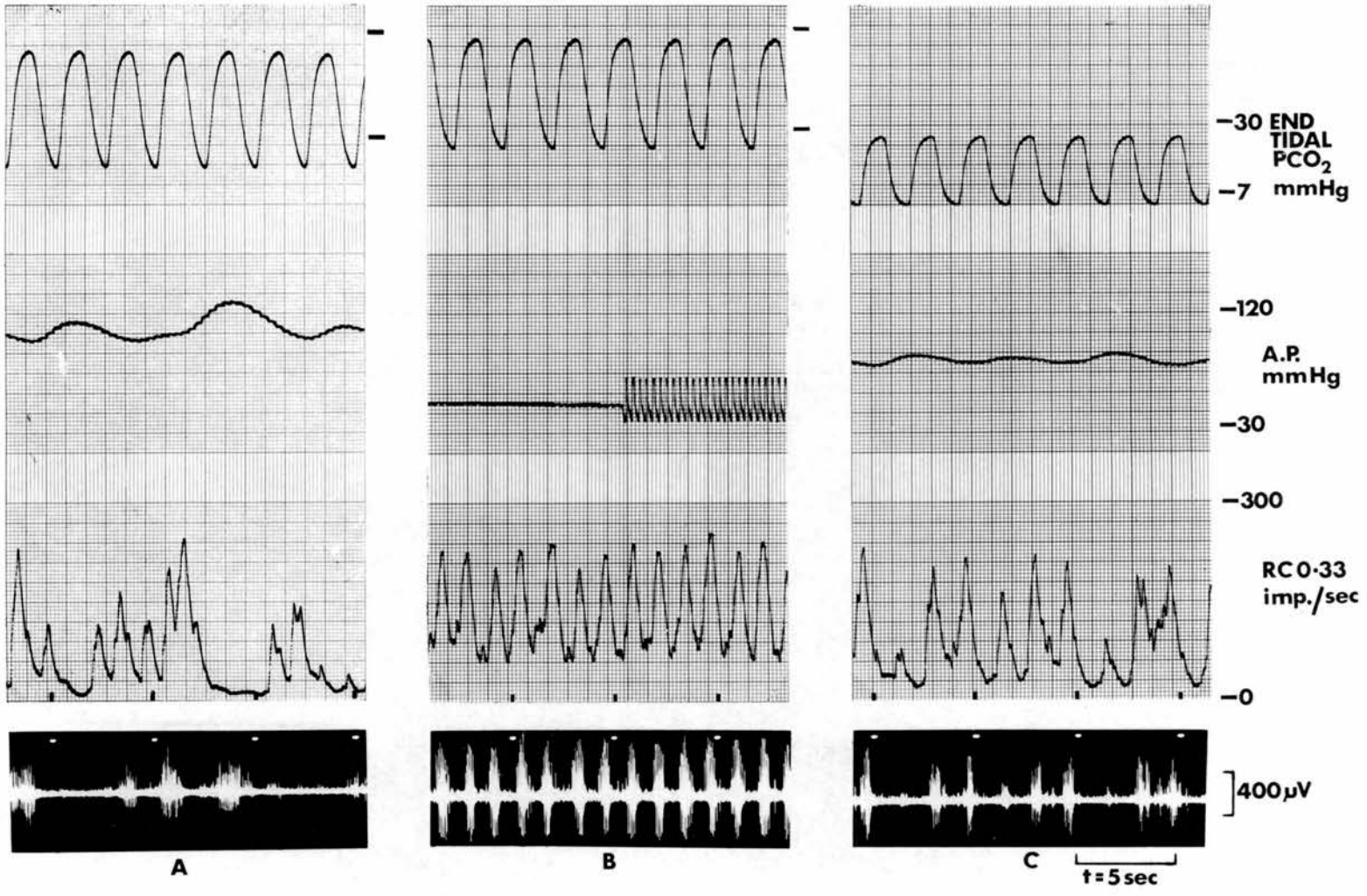

-30 END TIDAL PCO_2
-7 mmHg
-120
A.P. mmHg
-30
-300
RC 0·33 imp./sec
-0
400 μV
A
B
C
t = 5 sec

Fig. 63

by 24% (S.E. ± 8.9; $0.1 > P > 0.05$), and after 10 min the mean rise was by 64% (S.E. ± 22.1; $0.05 > P > 0.025$).

The effect of 9% ether on left cardiac sympathetic activity is illustrated in Fig. 64. The mean control discharge rate was 72/ sec (A) and the activity shows a respiratory modulation; after 9 min of ether (B) the sympathetic discharge was 156/sec and the frequency of the respiratory rhythm was increased. This may be compared to Fig. 62, where a similar increase in the rate of sympathetic discharge occurred after 6 min of halothane, but without a change in the frequency of the respiratory modulation. When ether had been discontinued for 33 min, the discharge rate was reduced to 96/sec (Fig. 64C), and the bursts of impulses were more clearly defined although still at a higher rate than in the control record (A).

Fig. 49 illustrates responses of the right cardiac nerve during ether anaesthesia in one of the two rabbits studied following vagotomy and division of the sinus and aortic nerves. Trace G shows the control discharge rate of 70/sec, 24 min after a previous study of cyclopropane. After 10 min of 11.5% ether the sympathetic rate was increased to 95/sec (Fig. 49H) and the synchronized bursts had become more discrete; the mean discharge rate was further raised, to 110/sec, after 22 min of ether (Fig. 49I) and there was continuous firing between the bursts of activity, which also reached a higher peak frequency. Subsequent recovery is shown in Fig. 50.

Fig. 64.

Left cardiac sympathetic action potentials, and arterial pressure. A: ventilation with 100% oxygen. B: after 9 min of 9% ether. C: 33 min after discontinuing ether. Same experiment as in Figs. 59 and 62.

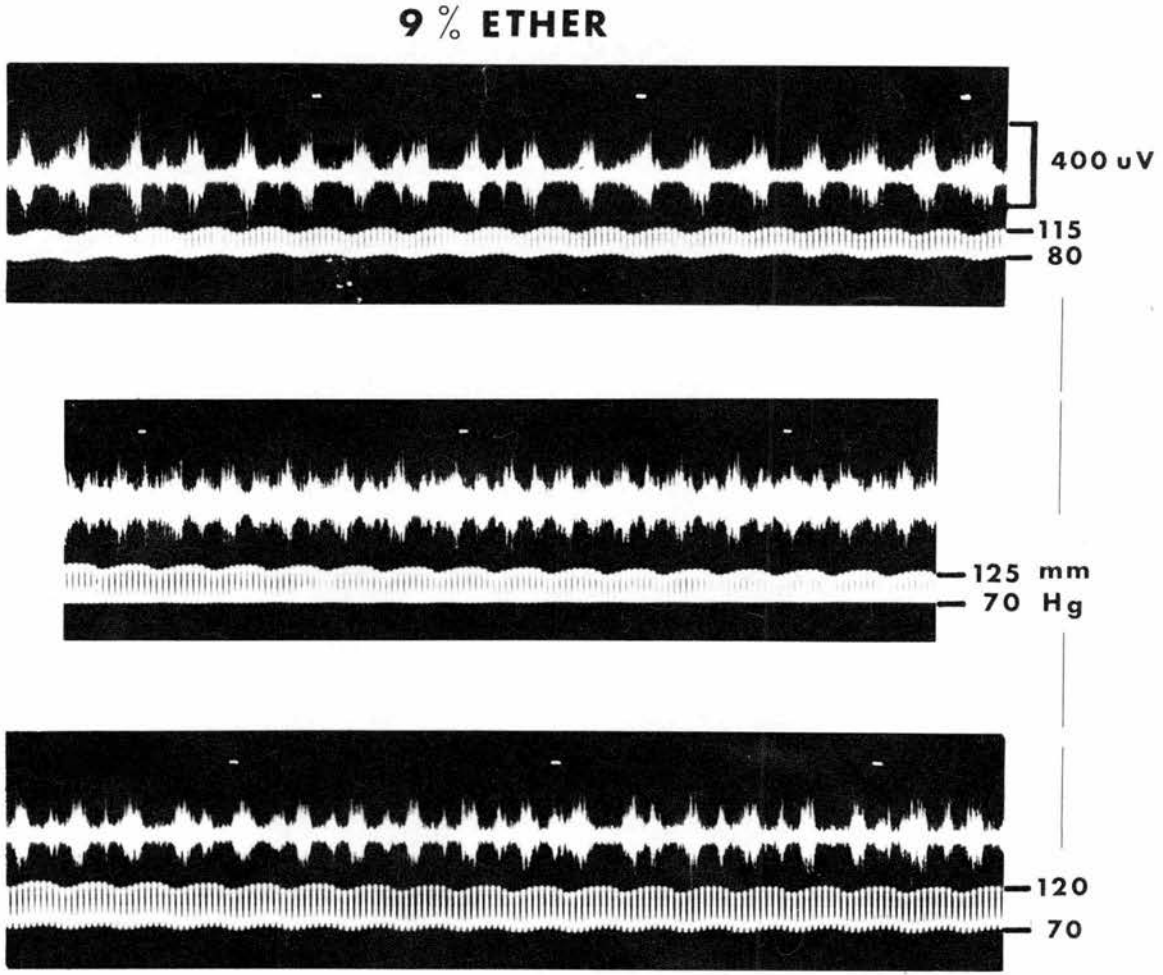


Fig. 64

Cyclopropane. Responses were recorded from the branch of the superior cervical ganglion to the carotid body in 2 rabbits, the results from two strands in one nerve being included, and from the external carotid branches of the superior cervical ganglion in 5 rabbits. The anaesthetic was given in a concentration of 50% for periods of 4 to 20 min. The baroreceptor nerves were intact in these experiments.

The time course of the postganglionic carotid responses to cyclopropane was similar to that recorded in preganglionic cervical nerves (Study 3). The peak increase in sympathetic activity was usually reached after 4 - 8 min, and the discharge rate fell slightly thereafter; in only a single instance, which involved one of the 3 tests on the carotid body nerve, was the activity reduced below the control level, and then only after 14 min of 50% cyclopropane. In all experiments recovery to control levels occurred 8 - 20 min after discontinuing the anaesthetic.

The rise in arterial pressure produced by cyclopropane reached a maximum averaging 28% above the control level in 7 of the 8 tests, and there was an associated increase in sympathetic discharge, by a mean of 71% (S.E. $\pm$ 19.3; $0.02 > P > 0.01$). The peak increase in sympathetic activity usually occurred about 2 min later, averaged 82%, and was also significant; at this time arterial pressure was increased by 17%.

In one animal the responses were quite atypical; the arterial pressure fell quickly after starting cyclopropane, then after about 3 min showed some recovery. The sympathetic discharge rate was at that time 29% above the control level, although early in the administration the activity was reduced in parallel with the arterial pressure. Later, the animal responded similarly when 25% cyclopropane was given. Because of these atypical changes in arterial pressure, and since this rabbit failed to survive a subsequent administration of halothane, the data have been excluded from the statistical calculations.

In 3 experiments, with the aid of the pulse height selector, the responses of nerve fibre spikes of different amplitudes were examined on film. All the fibres tested showed an increase in activity during cyclopropane anaesthesia, and the time courses were similar to those of the whole nerve strands.

Fig. 65 shows action potentials recorded from the external carotid nerve; A is the control record and B shows the effect of 16 min of 50% cyclopropane. After 6 min of anaesthesia the sympathetic discharge rate had increased to 120/sec from the control level of 77/sec, in association with a rise in mean arterial pressure to 127 mm Hg from the previous level of 95 mm Hg. In Fig. 65B the discharge rate and pressure were respectively 100/sec and 90 mm Hg; this level of sympathetic activity persisted for the remaining 20 min of administration, with eventual recovery as shown in trace C.

Halothane. Recordings were made from the carotid body nerve in 2

Fig. 65.

Sympathetic action potentials recorded from the external carotid branch of the superior cervical ganglion. A: during ventilation with 100% oxygen. B: after 16 min of 50% cyclopropane. C and D: return to oxygen after cyclopropane. E: after 21 min of 3% halothane. F: return to 100% oxygen.

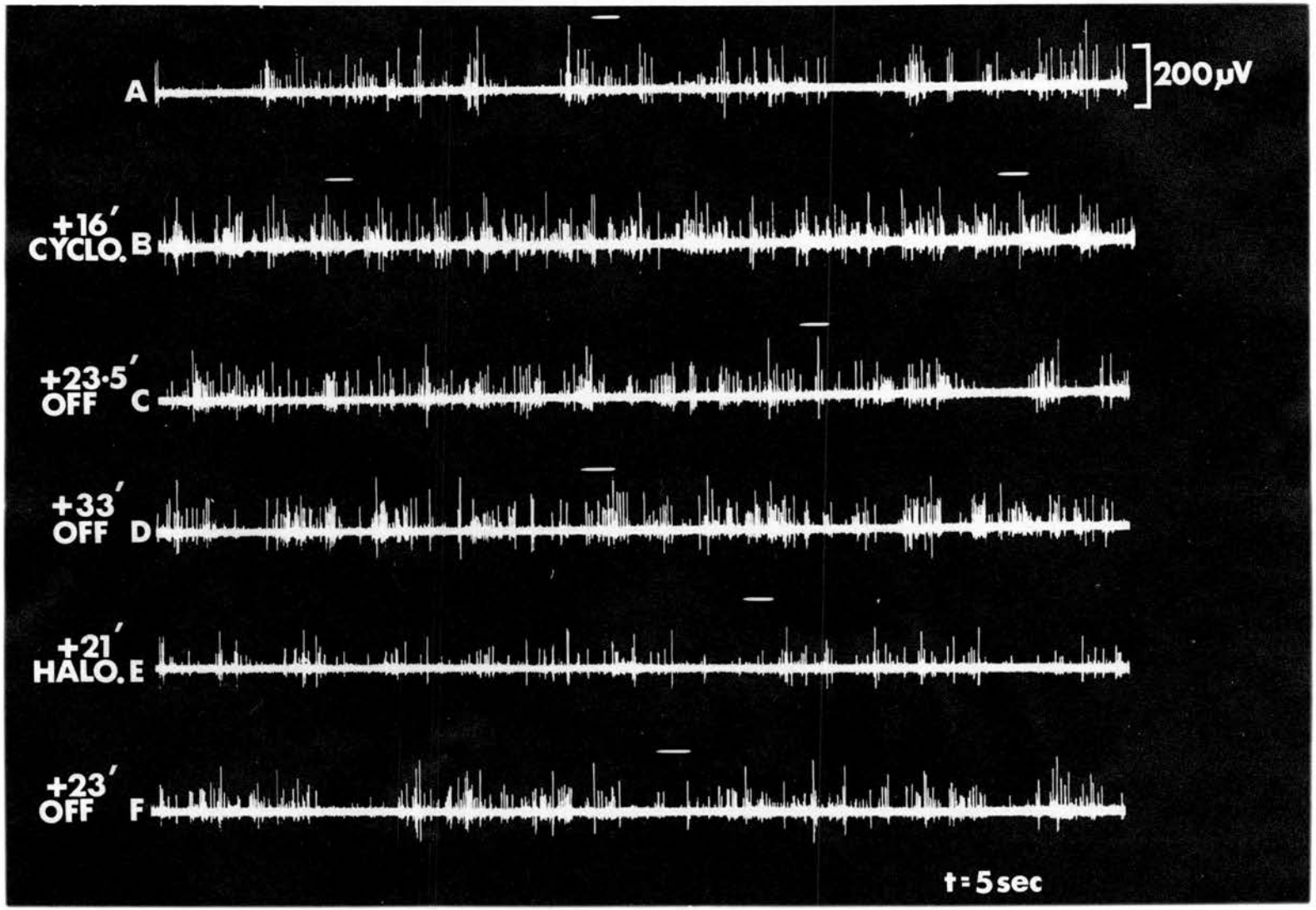


Fig. 65

rabbits, and from the external carotid nerve in 5 rabbits. Two different nerve strands were studied in one of the carotid body nerve experiments.

Arterial pressure fell steadily during halothane anaesthesia, and the postganglionic sympathetic discharge usually showed a coincident increase in rate, as with preganglionic fibres (Study 3). However, there were exceptions to this sympathetic response, as described below. Also, the rabbit which had responded to cyclopropane with a progressive fall in arterial pressure did not survive 12 min of 3% halothane; arterial pressure had fallen rapidly to very low levels, and there was also an initial reduction in the external carotid sympathetic discharge rate, which was reversed after 8 min. After 12 min of halothane, as arterial pressure failed, the rate of postganglionic sympathetid discharge reached a level 74% above control. This response was excluded from the statistical summary.

The changes in sympathetic activity during halothane anaesthesia were assessed, as before, at arterial pressure levels of 30% and 60% below control. In 5 nerve recordings from 5 animals, excluding the experiment discussed below, at a 30% reduction in arterial pressure, there was a mean increase in postganglionic discharge rate of 75% (S.E. $\pm$ 22.2; $0.05 > P > 0.025$). Four measurements were obtained at a 60% reduction in pressure, when there was an average increase in sympathetic rate of 59% (S.E. $\pm$ 14.1; $0.025 > P > 0.02$). Mean arterial pressure before administration of halothane averaged 98 mm Hg for these 5 animals, and all showed

subsequent recovery to near control levels after discontinuing the anaesthetic.

In the remaining rabbit studied, there was a reduction in external carotid sympathetic discharge during halothane anaesthesia; the control arterial pressure was 92 mm Hg, and the usual hypotensive response occurred. The nerve strand was tested with 3% halothane and then, after recovery, with 4% halothane; a second strand was tested subsequently during a further administration of 3% halothane. At a 30% fall in arterial pressure the reductions in postganglionic discharge rate in these 3 administrations of halothane were by 15%, 12%, and 10% respectively; at 60% depression of arterial pressure, sympathetic activity was reduced by 55%, 81% and 43% respectively.

Fig. 65 illustrates film strips from the second external carotid sympathetic strand dissected from this nerve. As previously described, there was a rise in activity in the typical manner with cyclopropane (A, B). In the interval between traces C and D, 15 ml of dextran in saline was given intravenously. Trace E shows the postganglionic carotid sympathetic discharge after 21 min of 3% halothane, when the rate had fallen from the control level of 80/sec (D), to 59/sec (E), and mean arterial pressure was reduced to 45 mm Hg from the control level of 92 mm Hg. The sympathetic rate had been largely unchanged for the first 8 min of administration of halothane as arterial pressure fell to below 70 mm Hg. When halothane was discontinued, recovery of the postganglionic discharge rate occurred to 72/sec (Fig. 65F),

at a mean arterial pressure of 100 mm Hg.

A similar, and unusual, contrast between the effects of cyclopropane and halothane in this rabbit was apparent when the preganglionic cervical sympathetic responses were studied subsequently on the same side. Cyclopropane produced a maximum rise of 106% in the mean preganglionic discharge rate, while during halothane anaesthesia there was little change in sympathetic activity although arterial pressure had fallen from 100 mm Hg to 50 mm Hg after 10 min. At this time the discharge rate declined, and was reduced by 17% below the control level after 20 min of halothane, when the arterial pressure was 40 mm Hg. This response is atypical, since in 8 measurements reported in Study 3, 3% halothane increased preganglionic sympathetic activity significantly by a mean of 45% at a 60% reduction in arterial pressure.

In 2 other rabbits a fall in the discharge rate of large spikes was observed in film strips taken during halothane administration, although this was concealed on the ratemeter record which showed increases in the total activity being counted.

Increases in external carotid sympathetic discharge during halothane anaesthesia are shown in Fig. 52, where the activity of all the spikes appears to be increased. The first trace, A, illustrates partial inhibition of activity by intravenous adrenaline and in B, the discharge rate had increased after 6 min of halothane to 62/sec from the control level of 47/sec; after 13½ min (C) the rate was 79/sec. There was a reduction

to 43/sec 15½ min after discontinuing halothane, D. Trace B of Fig. 52 suggests that the sympathetic respiratory rhythm was at first provoked by halothane, but this effect was lost in trace C.

Ether. Four rabbits were studied before and during anaesthesia with ether in concentrations of 10 - 12%. The nerve to the carotid body and the external carotid nerve were studied in 2 animals each. There was a progressive increase in post-ganglionic discharge rate over periods of 16 to 26 min, without evidence of depression in any of the nerve strands tested. The mean increase in rate after 4 min was 19% (S.E. ± 3.3; $0.02 > P > 0.01$), and after 10 min the increase was by 68% (S.E. ± 12.8; $0.02 > P > 0.01$). The control mean arterial pressure averaged 92 mm Hg, and there were average increases of 4 mm Hg and 3 mm Hg after 4 min and 10 min respectively. Fig. 52 D - G illustrate an increased discharge frequency in the external carotid nerve during exposure to 11% ether. Record D was taken after recovery from a previous 3% halothane administration, the mean discharge frequency being 43/sec and the mean arterial pressure 77 mm Hg. After 8½ min of ether (E) the sympathetic rate was 66/sec and after 17 min of ether it had risen to 105/sec (F). The mean arterial pressures were 82 mm Hg and 53 mm Hg at these times. When ether had been discontinued for 31 min, carotid sympathetic discharge had returned to 68/sec (Fig. 52G) and mean arterial pressure was 76 mm Hg.

Hypogastric nerve

Cyclopropane. Responses were recorded from 6 sympathetic strands in 5 rabbits, during administration of 50% cyclopropane for periods of 8 to 10 min. The baroreceptor nerves were intact in these experiments. In the case of 5 nerve strands studied for 10 min in 4 animals, arterial pressure increased to a maximum averaging 30% above the control level of 87 mm Hg after 4 to 8 min; the associated increase in hypogastric discharge was by 59% (S.E. ± 13.1; $0.02 > P > 0.01$). The maximum increase in sympathetic activity occurred about 2 min later, and averaged 73%, which was also a significant increase; at this time arterial pressure was 22% above the control level.

The fifth rabbit to receive cyclopropane during hypogastric nerve recording showed an initial fall in arterial pressure from the control level of 88 mm Hg, but this increased to 105 mm Hg after 6 min. A similar arterial pressure response was seen in two of the other rabbits. However, in this experiment the change in postganglionic discharge was quite atypical, showing only a reduction which persisted throughout the 8 min of cyclopropane anaesthesia. This nerve strand also showed unusual responses to halothane and ether, as described below. The data are therefore excluded from statistical evaluation.

Recovery to near control levels of sympathetic discharge and arterial pressure occurred after discontinuing cyclopropane in all these experiments.

Halothane. Six hypogastric strands were studied in 5 rabbits. The effects on sympathetic discharge were assessed, as before, at 30% and 60% reductions in arterial pressure during halothane anaesthesia. In the case of 5 nerve strands in 4 rabbits, the mean arterial pressure averaged 83 mm Hg before administration, and halothane was administered for periods of 8 to 16 min. Three strands, from three rabbits, showed increases in the postganglionic discharge rate of 9%, 14%, and 16% at the 30% reduction in arterial pressure; in the other two nerve strands, from the fourth rabbit, there were decreases in activity of 8% and 23%. These responses all occurred between 2 and 4 min after starting administration of 3% halothane, and the mean increase for the group of 5 nerve strands, by 8%, was not significant. Thereafter, however, the sympathetic rate consistently increased above the control level, and at a 60% reduction in arterial pressure the mean rise in postganglionic hypogastric activity in the five tests was by 45% (S.E. ± 14.9; $0.05 > P > 0.025$).

The fifth rabbit responded unusually during halothane anaesthesia, as was the case with cyclopropane noted above. Arterial pressure fell from a control level of 79 mmHg, to 24 mm Hg after 6 min of 3% halothane, and there was a coincident reduction in sympathetic activity from 137/sec to 48/sec with at no point a rise above the preanaesthetic level.

In all these experiments, recovery of arterial pressure and hypogastric activity occurred to near-control levels.

Ether. Recordings were made from 6 nerve strands in 5 rabbits

during administration of 10 - 12% ether. In the case of 5 strands studied in 4 rabbits during 12 to 18 min of ether anaesthesia, the average control arterial pressure was 81 mm Hg. After 4 min of ether there was a mean increase in postganglionic hypogastric activity of 11% (S.E. ± 2.35; $0.01 > P > 0.005$); after 10 min the increase was by 35% (S.E. ± 8.08; $0.02 > P > 0.01$). Arterial pressure usually showed a small decline, although in one rabbit there was an increase above the control level after 6 to 12 min of 10% ether.

The remaining animal, not included in the preceding statistical assessment, showed a fall in arterial pressure from 78 mm Hg to 59 mm Hg after 10 min of 11% ether, and there was a simultaneous reduction in the sympathetic discharge rate from 126/sec to 90/sec. Thus, this rabbit showed uncharacteristic reductions in postganglionic sympathetic activity during ether anaesthesia, in a manner similar to the responses evoked by cyclopropane and halothane (see above).

Recovery to near control levels occurred in these experiments when ether was discontinued.

Fig. 66 illustrates changes in hypogastric nervous activity in response to 10% ether. The discharge rate before ether, counting all spikes, was 56/sec (A), and mean arterial pressure was 109 mm Hg. After $6\frac{1}{2}$ min the rate had risen to 76/sec (B), and after $11\frac{1}{2}$ min it was 90/sec (C). Mean arterial pressure was almost unchanged from the control level at the time of records B and C.

Fig. 66.

Sympathetic action potentials recorded from the post-ganglionic hypogastric nerve. A: ventilation with 100% oxygen, 5 μg adrenaline hydrochloride injected intravenously at the first horizontal mark and washed in at the second mark. B: after 6½ min of 10% ether. C: after 11½ min of ether.

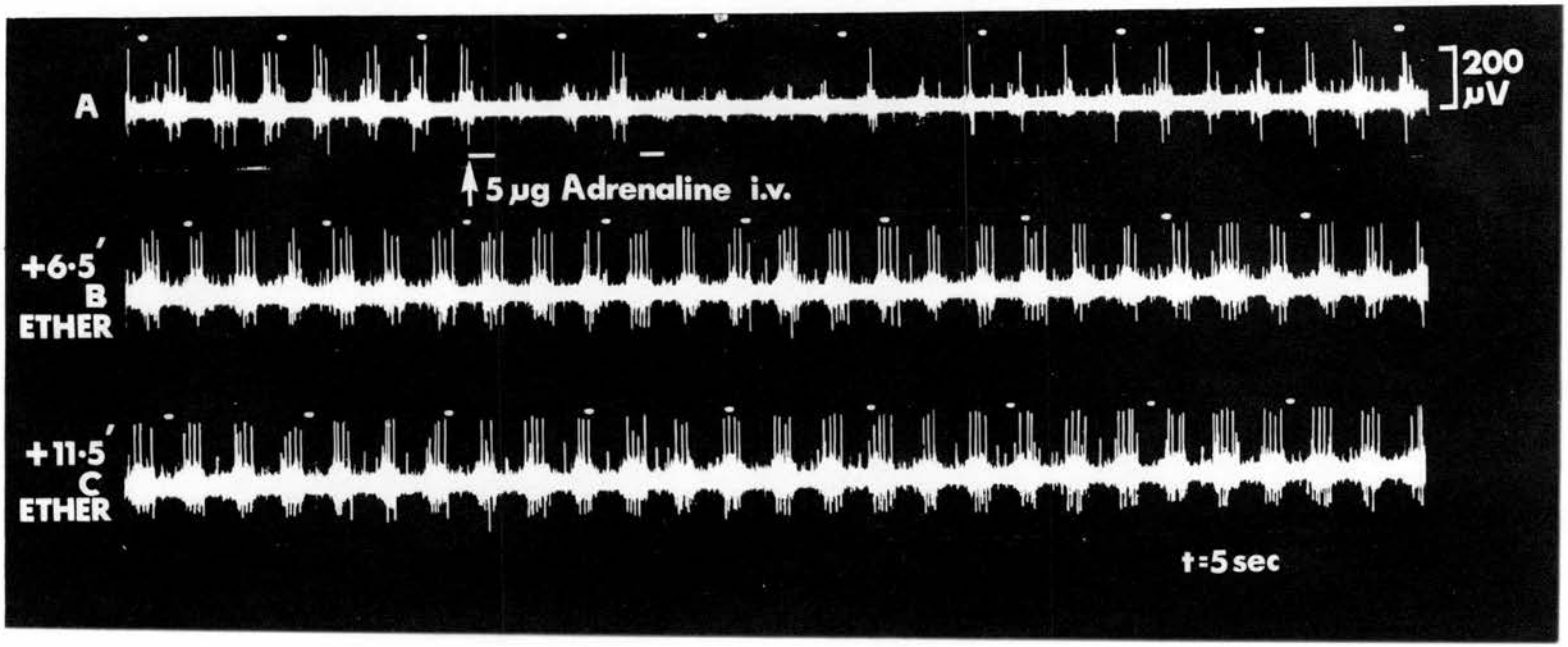


Fig. 66

Discussion

Postganglionic sympathetic nerves have been shown to resemble preganglionic fibres in regard to respiratory rhythms, and in the relation of the discharge to changes in arterial pressure whether these are spontaneous or evoked by intravenous adrenaline or by electrical stimulation of baroreceptor afferents. The responses demonstrated in the cardiac nerve of the rabbit were similar to those described in cats by Bronk et al. (1936) and by Pitts, Larrabee, and Bronk (1941). It is interesting that Bronk et al. found an increased cardiac sympathetic discharge during expiration, in mechanically ventilated cats, as was the case here in rabbits. Iggo and Vogt (1960) described a predominantly inspiratory rhythm in preganglionic fibres in the cat breathing spontaneously, and this has also been observed in the present studies. It appears, therefore, that the type of ventilation may largely determine whether the peak sympathetic discharge occurs in inspiration or expiration.

Pulmonary ventilation with carbon dioxide increased the synchronization of cardiac sympathetic activity, and usually raised the mean discharge rate. While it is possible that variations in the rate of change within the bursts of activity could be as important, or more so, in determining transmitter release at postganglionic nerve endings than are alterations in the mean level of discharge, this crucial question remains speculative at present.

There was usually a slower recovery of postganglionic activity, following injection of adrenaline, than was noted for preganglionic fibres; this effect might be attributable to ganglionic effects of adrenaline (Marrazzi, 1942).

A rhythm synchronized with the heart rate was always present in cardiac sympathetic strands, and also appeared to be more frequent in branches of the superior cervical ganglion than in preganglionic cervical fibres; it was not found in hypogastric branches. Cardiac rhythms appear to depend largely on afferent baroreceptor activity, although partial synchronization with the heart rate may persist after sino-aortic denervation (Bronk et al., 1936).

Satisfactory evidence that the nerves under study contained mainly postganglionic fibres was obtained by the abrupt inhibition of impulse discharge produced by intravenous hexamethonium, although there was often a partial return of activity within the ensuing few minutes; occasionally, continued discharge of a few identifiable single units suggested that the number of preganglionic fibres in the nerves studied was too small to influence the results presented.

In spite of readily demonstrable ganglionic effects of the inhalation anaesthetics (Larrabee and Holaday, 1952; Study 4), there is clear evidence from the present experiments that postganglionic sympathetic excitation accompanied cyclopropane or ether administration in the rabbit, and was usual during halothane anaesthesia. The changes recorded in the cardiac, carotid, and

hypogastric nerves resembled those described for preganglionic fibres (Study 3). Further consideration of the effects of the inhalation anaesthetics will be continued in the General Discussion which follows.

Summary of Study 5

1. Postganglionic cardiac, carotid, and hypogastric sympathetic nervous discharge was recorded before and during administration of the inhalation anaesthetics cyclopropane, halothane, and diethyl ether, in rabbits ventilated with oxygen; gallamine triethiodide was injected, and the background anaesthetic was pentobarbitone.

2. Except for a delayed recovery from the inhibition caused by intravenous adrenaline, greater synchronization of the discharge, and a more frequently observed cardiac rhythm, the physiological responses of sympathetic postganglionic nerves resembled those of preganglionic fibres.

3. Cyclopropane increased arterial pressure and postganglionic cardiac, carotid, and hypogastric discharge; the changes were similar to those recorded in preganglionic fibres.

4. With the exception of a few external carotid sympathetic units which showed depression, an increase in postganglionic sympathetic activity accompanied the arterial hypotension caused by halothane.

5. Postganglionic sympathetic discharge was increased by ether.

6. The increases in the mean integrated discharge rate, caused by the anaesthetics, were associated with inhibition of the respiratory rhythms normally present in postganglionic sympathetic fibres.

A comment on the use of rabbits for prolonged neurophysiological experiments.

The results presented here were largely obtained in the rabbit, which is generally regarded as a less hardy experimental animal than the cat. Initially, during the period when techniques of nerve dissection were being practised, a number of rabbits were anaesthetized with a single intravenous injection of urethane, approximately 1.5 g/kg. Acid-base determinations were carried out on arterial blood samples, and it was noted that in many instances a metabolic acidosis became progressively more severe as the experimental time increased. In these animals respiration was spontaneous, without added oxygen. Standard bicarbonate levels (Siggaard-Andersen et al., 1960; see Methods) so low as 12 mM/l. were sometimes measured.

Similar findings resulted when the experiments described here were started. When intravenous pentobarbitone sodium was used for the initial anaesthesia, it became very obvious that rabbits were more readily depressed by this agent than were cats; not notably in regard to depth of anaesthesia but rather to respiratory effects. The initial dose had to be carefully regulated for each animal, with mg/kg assessment an approximate guide only. Relative overdose resulted in severe respiratory depression and death. These effects could be regulated only up to a point, and this fact may have prevented previous more widespread use of intravenous pentobarbitone in the rabbit.

However, if tracheal cannulation was carried out quickly, and the lungs were then mechanically ventilated with air or oxygen, the ability of the rabbit to withstand many hours of experimental procedures was greatly increased. It is believed that the use of intravenous pentobarbitone for the present studies, with the advantage of a short action in the rabbit, would have been impossible without the aid of mechanical ventilation.

In most instances, the lungs were ventilated with 100% oxygen for 1 - 3 hours before the period of actual measurement. This was probably an important additional factor enabling long experiments to be continued in the rabbit. Disturbances of ventilation/perfusion ratios in the lungs are to be expected when animals are kept in the supine position for long periods; this may be pronounced in the rabbit, which apparently never adopts the supine position. 100% oxygen will prevent reductions in arterial oxygen tension from reaching dangerous levels.

Mechanical ventilation of the lungs, and 100% oxygen, helped to delay the development of a severe metabolic acidosis, but such acid-base changes were not prevented. For example, in 17 experiments there were 2 or more determinations of arterial pH, P_{CO_2}, and standard bicarbonate at intervals of one hour or longer. The average differences in standard bicarbonate were as follows:

Up to 1 hour between samples (n = 9) 1.7 mM/l.

1 - 2 hours between samples (n = 7) 2.8 mM/l.

2 - 3 hours between samples (n = 12) 3.6 mM/l.

3 - 5 hours between samples (n = 7) 3.7 mM/l.

These changes, although progressive with time, were generally smaller than those found in random measurements made in rabbits anaesthetized with urethane and breathing spontaneously.

In addition to control of pulmonary ventilation, the level of arterial pressure was observed over the initial hours of preparation. When the mean pressure was below about 100 mm Hg, intravenous injections of dextran in saline were given. Usually 10 - 20 ml. sufficed to raise the arterial pressure, the animal subsequently remaining in good condition.

An initial measurement of standard bicarbonate was made in each of 33 experiments, approximately 3 hours after the first dose of pentobarbitone. This group comprised 27 rabbits which survived for the duration of the experiment (approximately 12 hours) and another 6 animals all of which died in spite of close attention to ventilation and blood volume. Standard bicarbonate in the survivors averaged 21.5 mM/l. In the animals which died, within the 1st 6 hours of the experimental procedure, standard bicarbonate averaged 15.5 mM/l. These values were significantly different (S.E. $\pm$ 1.1, d.of f. 31, t = 5.5, $p < 0.001$). Apparently, therefore, failure to survive long experiments in the rabbit is associated with severe metabolic acidosis. Whether this is a cause or effect relation is not known. However, it might be possible, by measurement before

the start of physiological experiments, to exclude those animals showing a reduced standard bicarbonate.

The metabolic acidosis which develops during laboratory experiments is not confined to the rabbit, although it may be more marked in this species. It has also been observed in cats, dogs, and goats, and may be at least partly related to the effects of the operative procedures. In all species, it appears to be limited by efficient ventilation of the lungs with 100% oxygen, blood volume replacement with dextran, and maintenance of body temperature close to 37°C.

GENERAL DISCUSSION

The findings presented here demonstrate widespread effects of the three inhalation anaesthetics on the neurocirculatory pathways represented in Figure 1. Although the complexity of these actions clearly precludes a comprehensive analysis at this stage, an attempt will be made in this discussion to suggest the possible or probable role of the effects demonstrated, and their interrelations, in the overall circulatory picture presented by each anaesthetic.

It requires emphasis that in the present experiments the anaesthetic concentrations used were usually sufficiently high to be considered as induction rather than maintenance concentrations, under clinical conditions. In the normal (non-experimental) situation the induction concentrations of cyclopropane, halothane, and ether might (as an approximation) be reduced after 5, 10 and 15 min respectively. This was avoided here, both to ensure consistency and to demonstrate the full effects of each anaesthetic. Because of the constantly efficient pulmonary ventilation (assisted by the use of the muscle relaxant gallamine) and the relatively high inspired concentrations employed, the arterial blood concentrations of each anaesthetic were likely to be above those which would exist, at the same time, in an animal or human anaesthetized normally and breathing spontaneously. The constancy of the inspired anaesthetic concentration meant also that a steady state of anaesthetic uptake was not attained; to achieve this continuous measurement of the alveolar (end-expired) concentration

of each anaesthetic would have been required, and facilities for this were not available.

A further point is that the various times of anaesthetic administration presented under Results, and discussed here, include the delay of about 1 min due to the capacity of the "inspiratory" tubing between the respiration pump and the animal.

Cyclopropane

No effect of cyclopropane on carotid sinus baroreceptor discharge was shown by Robertson, Swan, and Whitteridge (1956) but Price and Widdicombe (1962) found that 25 - 33% concentrations of this anaesthetic increased by approximately 20% the discharge rate of single baroreceptor fibres exposed to static carotid sinus pressures of 120 and 160 mm Hg. This effect occurred in the dog and cat, and persisted when preganglionic cervical sympathetic fibres were inactivated by cooling, suggesting that the action was a direct one on the carotid sinus wall or nerve endings. The lack of effect noted by Robertson, Swan, and Whitteridge (1956) might have been due to the very brief (2 min) duration of cyclopropane administration in their experiments.

The following comments relate to the possible role of baroreceptor sensitization in the circulatory effects of cyclopropane. During cyclopropane anaesthesia in the unsedated dog, heart rate is increased (Robbins and Baxter, 1938); in unpremedicated man, the changes are inconstant (Jones et al. 1960). The common occurrence of bradycardia during certain studies of cyclopropane anaesthesia appears to depend on the preliminary administration of morphine and other drugs (Price, Conner, and Dripps, 1953; Li and Etsten, 1957). In the presence of gallamine, and a background of pentobarbitone anaesthesia, cyclopropane increased the heart rate in the rabbits studied here. This is of interest since it was shown in the dog that another barbiturate, amytal, did not prevent the increase in heart rate

caused by cyclopropane (Robbins and Baxter, 1940).

Responses of arterial pressure during cyclopropane anaesthesia also depend on whether opiate drugs have been given beforehand. Without sedation, cyclopropane causes arterial hypertension in the dog (Robbins and Baxter, 1940) and in man (Jones et al.,1960). In the presence of morphine, an already reduced arterial pressure is lowered further by cyclopropane (Robbins and Baxter, 1940), but in man arterial hypertension is usual, even after premedication (Price, Conner, and Dripps 1953; Jones et al., 1960). Again, it is interesting that preliminary administration of amytal did not result in a lowering of arterial pressure when cyclopropane was given (Robins and Baxter, 1940).

These findings suggest that the physiological responses which on theoretical grounds might result from baroreceptor sensitization, arterial hypotension and bradycardia, do not in fact accompany cyclopropane administration except in the presence of other drugs, most notably morphine. On superficial grounds, namely those of occasional measurements made during surgical operations, arterial hypotension (systolic pressure levels below 100 mm Hg) are a rarity during the clinical administration of cyclopropane in man. The evidence seems to show that baroreceptor sensitization during established cyclopropane anaesthesia is of academic interest and unlikely to be an important element in the cardiovascular changes observed. There remains, inevitably, some doubt about the induction period; in 2 experiments reported here (Study 3) the initial response to cyclopropane was a

simultaneous decline in arterial pressure and preganglionic sympathetic discharge.

Study 2 demonstrated that cyclopropane produced early and pronounced depression of impulse transmission between baroreceptor afferent and preganglionic sympathetic efferent nerves. The early onset of this action further precludes the attachment of pharmacological importance to baroreceptor sensitization by cyclopropane, except perhaps within the first 2 - 3 min of induction. Under clinical conditions, accurate measurements of arterial pressure have probably been made infrequently during the first few min of cyclopropane anaesthesia, but there is no evidence from these sources, nor from the literature (Robbins, 1958; Price, 1960), that arterial hypotension has occurred in this period.

The significance of the potent action of cyclopropane on central baroreceptor pathways (Study 2) extends beyond the counteraction of baroreceptor sensitization, to an apparently almost complete removal of the inhibition normally exerted by afferent baroreceptor discharge on efferent sympathetic activity.

Division of the carotid sinus and aortic nerves causes an immediate increase in arterial pressure, and tachycardia (Hering, 1927; see Heymans and Neil, 1958); preganglionic cervical (Iggo and Vogt, 1962) and splanchnic (Gernandt, Liljestrand, and Zotterman, 1946; Dontas, 1955) sympathetic activity is greatly enhanced. These effects all accompany cyclopropane anaesthesia in the rabbit, as shown here. Considered alone, therefore,

inhibition of transmission through central baroreceptor pathways, by pharmacological action, could be at most an important cause of an increased arterial pressure, or at least could result in a state wherein arterial pressure is rarely lowered below control levels as a result of afferent stimuli. Before discussing this further, the effects of cyclopropane on preganglionic sympathetic discharge measured in the present studies will be related to relevant observations made more indirectly by other workers.

Robbins (1958) reviewed the pharmacological actions of cyclopropane, but did not attempt to examine their basis. It seems clear that in all species studied - which include the dog (Robbins and Baxter, 1940), man (Jones et al., 1960), the monkey (Shackell and Blumenthal, 1934), the cat (Millar, unreported observations), and the rabbit (present investigations) - cyclopropane raises arterial pressure at some stage in the administration. There are two obvious mechanisms which could be responsible; firstly, increased sympathetic discharge, and secondly a direct excitant action on the heart and/or blood vessels, or some combination of both these effects.

Martin and Marrazzi (1940) failed to show any effect of cyclopropane on preganglionic cervical sympathetic discharge, but their experiments receive only brief mention. Other evidence, although indirect, suggested that sympathetic excitation occurred during cyclopropane anaesthesia. Elmes and Jefferson (1942) showed that this anaesthetic depleted the adrenaline content of the adrenal gland. Increases in the plasma concentrations of

adrenaline and noradrenaline were measured during cyclopropane anaesthesia in man (Price et al., 1959; Millar and Morris, 1961). When unsedated dogs were given cyclopropane, the plasma adrenaline level increased (Deutsch, Linde, and Price, 1962). The indirect and circumstantial nature of deductions from changes in plasma catecholamine concentrations is revealed by the findings (Price et al., 1959) that intravenous infusions of noradrenaline in man produced significantly higher plasma concentrations during cyclopropane anaesthesia than in the conscious state; it could be, therefore, that the anaesthetic inhibited the metabolic transformation of catecholamines. Theoretically, increases in plasma noradrenaline during anaesthesia might result from levels of sympathetic activity not greatly different to control.

The present experiments in the rabbit (Study 3) have shown that the rise in arterial pressure produced by cyclopropane (to a peak of 21% above control after 4 - 8 min with the 50% concentration) was associated with proportionately greater increases in preganglionic sympathetic discharge (by 80%). When plotted together, the two responses seemed to be closely related, although only up to the time of the maximum increase in pressure. This association, while highly suggestive, does not of course prove a specific correlation between these effects in view of actions of cyclopropane on effector organs, to be considered below.

In the rabbits, failure of arterial pressure to remain

elevated for longer than about 10 min after induction with 50% cyclopropane, in spite of a persistently increased sympathetic discharge, points to depressant effects exerted distal to preganglionic neurones. Such actions were clearly demonstrated by the pronounced, transient, rise in arterial pressure which was usually observed in the early moments after discontinuing cyclopropane. This occurred without any increase in preganglionic discharge rate, and was observed similarly when recording from postganglionic neurones (Study 5); it is therefore definite evidence that increases in sympathetic activity were eventually overcome by depression of the cardiovascular effectors - heart and/or blood vessels - or of impulse transmission to these effectors. Presumably, under the conditions of study (with especial emphasis on the background anaesthesia with pentobarbitone), depression at sites distal to postganglionic neurones occurs after approximately 10 min of 50% cyclopropane in the rabbit.

It was noted, however, (Study 3) that arterial pressure could be maintained above the control level for up to 30 min when 25% cyclopropane was given; there was then a striking parallelism between the levels of pressure and of preganglionic cervical sympathetic discharge (Fig.32). The apparent discrepancy between the relatively brief arterial hypertension evoked in the rabbit by cyclopropane, in contrast to the more prolonged response described in man (Jones et al., 1960), is probably attributable in large measure to the use of a high, and fixed, inspired concentration in the present studies. Reference to

records published in the review by Robbins (1958), and clinical observations during surgery, shows that arterial hypotension occurs in the dog and man when the appropriate limits of concentration and time are exceeded.

Returning now to the mechanisms whereby cyclopropane increases preganglionic sympathetic discharge, there are in theory at least three obvious possibilities. Firstly, there may be direct excitation of sympathetic pathways in the spinal cord, medulla, or hypothalamus. Except for the finding that decerebrate dogs showed the usual hypertensive response to cyclopropane, and that transection through the medulla prevented any rise in pressure (Price et al., 1963), there is no other or more direct information available. Secondly, there may be stimulation or sensitization of systemic receptors - for example, chemoreceptors - afferent impulses from which might produce central sympathetic excitation (Heymans and Neil, 1958). In one publication it has been stated that cyclopropane produced no change in carotid body chemoreceptor discharge (Price and Widdicombe, 1962) but work currently in progress (Millar, unreported observations) suggests that cyclopropane alters chemoreceptor responses in the direction which could result in sympathetic excitation.

Thirdly, cyclopropane may increase sympathetic discharge by depressing physiological mechanisms which normally cause inhibition of preganglionic activity; the most important of these, the systemic baroreceptor reflex, has been shown here (Study 2) to

be markedly depressed through an action of cyclopropane on central baroreceptor interneurones. Since the present investigations were started in 1963, Price et al. (1963) have described findings in support of those described in Study 2. In dogs, the carotid sinus area was distended either by static or pulsatile pressure, and the depression of systemic arterial pressure caused by this manoeuvre was said to be "essentially abolished at cyclopropane concentrations of 40 - 50%". These workers reasoned that cyclopropane caused arterial hypertension and sympathetic excitation by "selectively depressing 'depressor' neurones in the medulla oblongata."

The experiments in Study 3 showed that preganglionic discharge was significantly increased (average 55% after 4 - 8 min) by 50% cyclopropane in rabbits in which the major systemic baroreceptor areas had been denervated. The degree of change was less than in the animals with intact carotid sinus, aortic, and vagus nerves, but the findings show clearly that removal from central sympathetic neurones of the influence of the systemic baroreceptor (and chemoreceptor) areas is not the sole mechanism responsible for sympathetic excitation by cyclopropane. It is worth noting that a different conclusion might have been drawn from consideration of the arterial pressure responses alone; the arterial pressure, which was raised after baroreceptor denervation, was usually lowered when cyclopropane was given to these animals. It seems likely, from these findings, that a "pharmacological baroreceptor denervation" by cyclopropane is only partly responsible for its

characteristic circulatory effects. Specific analysis of the responses after surgical section of the carotid sinus, aortic, and vagus nerves is complicated by the inevitably associated chemoreceptor denervation.

Study 5 showed that cardiac, carotid, and hypogastric postganglionic sympathetic discharge was increased by cyclopropane. The responses were similar in magnitude to those in preganglionic nerves, indicating that the central sympathetic excitation evoked by cyclopropane is transmitted effectively to the cardiovascular end-organs. This was surprising in view of the ganglion-blocking action of cyclopropane demonstrated in Study 4; the effects were more pronounced than those described for this anaesthetic by Norman and Löfström (1955). There may be several explanations for the apparent contradiction revealed by an increased postganglionic sympathetic discharge in the presence of partial ganglionic blockade. The ratio of postganglionic to preganglionic fibres is of the order 30 : 1 (Billingsley and Ranson, 1918; Ebbesson, 1963). If it is assumed, from the decrement in the compound action potential produced by cyclopropane, that a proportion of the ganglionic synapses are blocked completely, the remaining functional pathways might still produce sufficient amplification for an increased postganglionic discharge to occur. If all the ganglionic pathways are partially blocked, spatial facilitation of the subliminal fringe, and temporal facilitation, might largely overcome the block. Such facilitation was shown to occur (in the absence of inhalation anaesthetics) in the superior cervical ganglion (Eccles, 1935).

It seems possible that the test for ganglion block used in the present studies and by other workers, namely stimulation by a single shock, may be inappropriate. A more suitable test, but requiring more elaborate apparatus, might be a series of shocks having a random time sequence and random amplitude distribution and whose mean frequency could be modulated.

The possibility that the inhalation anaesthetics exert direct actions on sympathetic ganglion cells, producing an increased postganglionic discharge in the presence of ganglion block, must be mentioned. No information on this has yet been obtained. Large doses of hexamethonium have been shown to excite sympathetic ganglion cells (E. A. Bower, personal communication).

As stated above, definite evidence was obtained in Studies 3 and 5 that the hypertensive action of cyclopropane was counteracted (after about 10 min, under the conditions used here) by depressant effects exerted distal to postganglionic sympathetic fibres. When arterial pressure is raised by cyclopropane, earlier in induction with high concentrations, or throughout the administration of lower concentrations, the mechanism cannot yet be attributed with absolute certainty to an increased discharge rate in sympathetic vaso-constrictor fibres. The evidence is strong, however: whereas the force of the denervated dog heart was reduced by cyclopropane (Price and Helrich, 1955), the increases in cardiac output and heart rate evoked by cyclopropane in man were reduced by blockade of the stellate ganglia with local anaesthetic (Price et al., 1962). This infers that the cardio-

vascular response to this anaesthetic is dependent, at least in part, on impulses carried in the cardiac nerve. The present experiments (Study 5) demonstrated increases in cardiac nervous activity averaging more than 100%.

Local effects of cyclopropane are exerted on smooth muscle. Isolated strips of rabbit aorta have shown an enhanced contractile response to noradrenaline (Price and Price, 1962). Potentiation of adrenaline-induced contractions of the cat nictitating membrane has also been reported (Gravenstein, Sherman, and Andersen, 1960). In man, cyclopropane reduced blood-flow in the nerve-blocked forearm (McArdle and Black, 1963). Vascular constriction, induced directly, or as a sensitization response to locally liberated or humoral vasoconstrictor substances, may therefore be important in initiating or maintaining arterial hypertension during cyclopropane anaesthesia.

Halothane

Halothane consistently produces arterial hypotension and slowing of heart rate (Burn et al., 1957). Baroreceptor sensitization, shown in Study 1 to accompany the administration of halothane in the cat, dog, goat and rabbit, would be expected to produce these two effects. The experiments of Study 2, concerning central baroreceptor pathways, have a special relevance to this possibility, therefore. It was shown that while halothane produced significant inhibition of the arterial pressure and preganglionic sympathetic responses to baroreceptor stimulation, it was still possible to reduce further an already

low arterial pressure by aortic nerve stimulation during halothane anaesthesia. The degree of inhibition of transmission through the central baroreceptor interneurones seemed sufficiantly great to counteract the effects of baroreceptor sensitization, although exact quantitative analysis is not possible from the studies described. The findings of Study 2, together with the other direct actions of halothane to be considered below, make it unlikely that baroreceptor sensitization plays a major role in established halothane anaesthesia. There remains the induction period, when it seems evident that direct effects on systemic baroreceptors might be important. This possibility is again offset by the fact that in 3 of 6 administrations of halothane to baroreceptor-denervated rabbits there was an initial decline in sympathetic rate in parallel with the usual fall in arterial pressure, within the first 2 min of administration. Thus, early effects similar to those resulting from baroreceptor stimulation (or sensitization) occurred in the absence of afferent baroreceptor connections, while such changes were not observed when halothane was given to rabbits with intact baroreceptor nerves. The role of baroreceptor sensitization in the cardiovascular response to halothane must therefore be seriously questioned, although it cannot be excluded on the basis of the present experiments. In agreement with the conclusion of Robertson, Swan, and Whitteridge (1956) in regard to ether and chloroform, baroreceptor sensitization remains a possible contributory cause of sudden cardiovascular depression early in induction of anaesthesia.

In the absence of an adequate definition of anaesthetic potency, the comparison of "equipotent" concentrations of different anaesthetics is largely based on a superficial correlation of several experimental and clinical observations. So far as general anaesthesia for surgical operations is concerned, it seems valid to consider 25% cyclopropane, 2 - 3% halothane, and 5 - 8% ether as roughly equivalent in potency, although in accord with their relative solubilities in blood the order given is also one of decreasing speed of onset of anaesthesia. In terms of cardiovascular effects, such comparisons contain obvious fallacies - for example, in the concentrations mentioned above, halothane is obviously the most potent circulatory depressant; on the other hand, the fact that reductions in arterial pressure may still be induced by baroreceptor stimulation in the presence of severe hypotension caused by halothane renders precise considerations of potency irrelevant, since a further increase in the inspired halothane concentration would be likely only to cause circulatory collapse rather than produce any measurably greater effect on the central baroreceptor pathways. Such a situation did not exist during cyclopropane anaesthesia, with inspired concentrations high enough to completely abolish the baroreceptor responses. It seems a valid conclusion, therefore, that the depression of impulse transmission through central baroreceptor pathways caused by halothane is less than that produced by cyclopropane.

It may now be asked whether such quantitative differences

between halothane and cyclopropane could depend on their relative effects on sympathetic discharge and arterial pressure. This cannot be answered with certainty, but pronounced inhibition of the depressor response was noted in a decerebrate rabbit which responded to cyclopropane with progressive arterial hypotension; in other animals when sympathetic discharge and arterial pressure were lowered transiently within the first 2 - 3 min of cyclopropane anaesthesia (Fig. 29a); and in several administrations of halothane when arterial pressure had at the time scarcely changed from control levels. It did not appear that inhibition of the depressor response by the anaesthetics was dependent on the associated changes in arterial pressure produced by each agent; however, the increased state of excitation of sympathetic neurones produced by the anaesthetics could antagonize simultaneous inhibition by baroreceptor stimulation, in a similar way to the effects of hypothalamine stimulation described by Bronk et al., (1940). Such antagonism would probably be greater with cyclopropane than with halothane, in accord with the actions of each anaesthetic on preganglionic sympathetic discharge.

Many reports have attempted to explain the hypotensive action of halothane. A central effect was suggested in pharmacological studies (Burn et al., 1957; Paton, 1959), and as a result of complex head perfusion experiments in the dog it has been affirmed that most or all of the circulatory effects of halothane depend upon depression of central sympathetic discharge (Price, Linde, and Morse, 1963). In the absence of a species difference, the present

results do not support this; concentrations of halothane which produced arterial pressures so low as 20 - 30 mm Hg were nevertheless associated with an increased preganglionic sympathetic discharge. This was a surprising but consistent finding in the rabbit (Study 3); the reason might lie either in direct central excitation of sympathetic neurones, in a reflex increase in sympathetic discharge secondary to a reduced arterial pressure, or to a combination of these factors.

When halothane was given to baroreceptor-denervated rabbits, preganglionic cervical sympathetic discharge showed increases of about 20% at arterial pressure levels 30% and 60% below control, compared to an approximately 40% increase at the same levels of pressure in the animals with baroreceptor nerves intact. These findings suggest that direct central sympathetic excitation (more explicitly, excitation which is not mediated through afferent baroreceptor mechanisms) is responsible in small part for the preganglionic changes measured in the present studies. The remaining increase in sympathetic activity could be induced reflexly, as a result of the arterial hypotension caused by halothane. This conclusion is supported by the persisting activity in central baroreceptor pathways during halothane anaesthesia, as shown in Study 2.

Measurement of plasma catecholamine concentrations during halothane anaesthesia have failed to demonstrate any except slight, variable, and statistically insignificant rises (Price et al., 1959; Millar and Morris, 1961). This is curious, particularly in view of the large increases in adrenal nervous

discharge measured in the present experiments (Study 3). Several explanations may be suggested: that the presence of a particular "background" anaesthetic may influence the responses to halothane; that sympathetic activity is not increased during halothane anaesthesia in species other than the rabbit; that concurrent effects distal to preganglionic fibres prevent the release of increased amounts of transmitter substance at post-ganglionic nerve-endings; that transmitter release is poorly correlated with changes in the mean integrated rate of preganglionic discharge, or that methods of assaying plasma catecholamine levels have been unable to detect increases below a certain gross order of magnitude. This last possibility seems most likely, although species differences cannot be ruled out from the present studies.

Another consideration remains, which would apply to any inhalation anaesthetic studied in the manner described; this arises from the transient arterial hypotension, and fall in preganglionic sympathetic discharge, which occur readily when, for example, the incised skin edge is touched in rabbits which appear otherwise to be adequately anaesthetized (whether respiration is spontaneous or controlled). This response (which is infrequent in species such as the dog and cat) suggests that during experimental procedures in the rabbit afferent stimuli resulting from the experimental procedures, could induce continuous sympathetic inhibition. Administration of inhalation anaesthetics in amounts sufficient to prevent central effects of such stimuli might then be responsible for a rise in sympathetic activity which

is non-specific for individual anaesthetics and based on an analgesic action. The importance of this is doubtful, since in a few experiments the addition of either 80% nitrous oxide or 1.5% trichlorethylene in oxygen to the background anaesthesia with pentobarbitone, in order to increase analgesia with only slight deepening of anaesthesia, produced only small changes in preganglionic activity.

These doubts can scarcely influence a major conclusion from the findings of Study 3, that halothane lowers the arterial pressure in spite of increases in central sympathetic discharge, and that the cause of the hypotension lies distal to preganglionic neurones. It should be noted also that in one study involving plasma catecholamine measurements, the sympathetic responses to an increased arterial carbon dioxide tension, and to haemorrhage, appeared to be essentially unaffected during halothane anaesthesia (Millar and Morris, 1960).

The role of ganglion blockade in halothane hypotension was emphasized by Raventos (1956), although this was not confirmed when ganglion blockade was induced in the course of complex studies by Severinghaus and Cullen (1953). Study 4 shows here that although halothane produces inhibition of ganglionic transmission, so also do cyclopropane and ether, which do not usually reduce the arterial pressure except in overdose. Also, postganglionic sympathetic discharge was usually increased during halothane administration (Study 5).

In the absence of contrary evidence it is assumed, when measuring changes in

measuring changes in the mean rate of postganglionic sympathetic discharge, that partial inhibition of the physiological sympathetic rhythms by the anaesthetic under study is not in itself as important an influence at postganglionic transmitter sites as are alterations in the mean level of sympathetic activity. On this assumption, halothane hypotension is not attributable to a reduced postganglionic sympathetic discharge.

Burn and Epstein (1959) described a small increase in sympathetic activity during halothane anaesthesia in cats. They also showed that this anaesthetic caused vascular dilatation in the perfused limb of the dog. This and other work (Beaton, 1959) suggested that halothane caused direct depression of vascular smooth muscle. Similar direct actions might underlie reported reductions in the contractile force of the myocardium (Mahaffey et al., 1961; Morrow and Morrow, 1961; Price, Linde, and Morse, 1963) and in cardiac output (Deutsch et al., 1962). Such changes have also been measured following cardiac denervation Morrow, Gaffney, and Holman, 1961). The finding, in man, that halothane did not cause further vascular dilatation when the limb vessels were denervated (Black and Mc. Ardle, 1962) may not prove that the anaesthetic acted by lessening sympathetic tone, but may indicate only that denervation produced near-maximal dilatation.

The foregoing evidence, therefore, which is supported by the experiments described here, indicates that a critical circulatory action of halothane is exerted either directly on cardiac and vascular muscle, or at sites of transmission of postganglionic impulses to these effectors. Although it cannot

be asserted that depression of sympathetic activity plays no role in halothane hypotension in species other than the rabbit, and while there may remain slight uncertainty in this species because of the few postganglionic fibres which were depressed by halothane, the results show that this anaesthetic can lower arterial pressure profoundly in spite of sympathetic excitation.

Diethyl ether

Robertson and Swan (1957) obtained evidence from experiments involving carotid sinus perfusion and the sudden administration of high inspired ether concentrations to cats, that baroreceptor sensitization was capable of exerting systemic effects in the early period of induction with this anaesthetic. In the course of Study 3, parallel reductions in arterial pressure and preganglionic sympathetic discharge (effects to be expected from baroreceptor stimulation and sensitization) were not encountered in rabbits given up to 15% ether in oxygen. The role of baroreceptor sensitization by ether (Robertson, Swan, and Whitteridge, 1956) is therefore difficult to assess, but its possible importance during the induction period cannot be denied at present. The results of Study 2 show, in accord with the slow onset of anaesthesia with ether, that depression of central baroreceptor transmission occurs progressively with time and that the effect becomes pronounced when inspired concentrations of 10 - 15% are given. Such depression would be likely to inhibit the transmission of afferent stimuli resulting from baroreceptor sensitization.

Sympathetic excitation by diethyl ether has been recognized for many years. For example, in 1912 Elliott showed that the anaesthetic depleted the adrenaline content of the cat's adrenal gland, and that this change was prevented by splanchnic denervation; similar findings were reported by other workers (Elmes and Jefferson, 1942). A reduction in the noradrenaline content of the hypothalamus and mid-brain of the dog was shown to follow ether anaesthesia (Vogt, 1954). Increases in plasma adrenaline and noradrenaline have also been measured, in the dog and man (Millar and Morris, 1961).

In a classical paper which attempted to resolve the apparent contradiction between the directly depressant actions of ether in the dog heart-lung preparation (Bhatia and Burn, 1953; Prime and Grey, 1952) and the increases in cardiac output measured in intact dogs (Blalock, 1927), Brewster, Isaacs, and Waing-Andersen (1953) regarded stimulation of the vasoconstrictor outflow and the adrenal medulla as vital reflex mechanisms in the maintenance of circulatory homeostasis during ether anaesthesia. In bilaterally adrenalectomized dogs in which a total sympathetic block had been induced with local anaesthetic, ether produced myocardial depression which could be antagonized by the intravenous infusion of adrenaline and noradrenaline. These workers concluded that direct depression of vascular and cardiac depression by ether was antagonized quantitatively by release of adrenaline and noradrenaline at rates of liberation approximating to 1 μg/kg/min. While the general conclusions of Brewster and his colleagues are

convincing, it is probably not possible to draw comparisons on a quantitative basis between the actions of infused catecholamines and those of adrenergic nerve stimulation (as a result of which only small quantities of liberated transmitter are likely to reach the circulation).

The present experiments confirm by direct measurement that diethyl ether increases preganglionic sympathetic discharge, but the site of action remains unidentified. As with all 3 inhalation agents studied, the increase in sympathetic activity was smaller in rabbits in which the systemic baroreceptor (and chemoreceptor) areas had been denervated. The effect was still present to a significant extent, however, which precludes the possibility that ether increases preganglionic discharge solely by pharmacological blockade of central baroreceptor pathways.

Because of the notably irritant properties of ether, reflex effects arising from peripheral receptors, for example in the respiratory tract, may influence sympathetic discharge; in addition to systemic baroreceptors (Robertson, Swan and Whitteridge, 1956), ether has been shown to exert excitatory effects on pulmonary stretch receptors (Whitteridge and Bulbring, 1944) and muscle spindle nerve endings (Matthews, 1933). In recent studies carried out by the author, carotid sinus chemoreceptor activity was increased by ether. However, an action of ether on the spinal cord was implied by Bhatia and Burn (1933), who demonstrated sympathetic stimulation during ether anaesthesia in spinal cats.

As in the case of cyclopropane and halothane, the ganglionic

effects of ether failed to prevent increases in postganglionic sympathetic discharge. Since it is unusual for arterial pressure to rise above control levels during anaesthesia with ether, and in view of the ease with which cardiovascular collapse can be caused by a relative overdose, it can be presumed in accord with the deductions of Brewster, Isaacs and Wainó-Andersen (1953) that depression of the cardiovascular effectors accompanies sympathetic excitation during ether anaesthesia. It is possible, in certain stages of anaesthesia, that this may involve vascular smooth muscle to a greater extent than the heart; in a recent study in man, for example, cardiac output increased as ether administration continued, whereas total peripheral resistance declined (Jones et al., 1962). The haemodynamic actions of diethyl ether are numerous and at present remain too complex for detailed analysis.

In concluding this discussion, the following point deserves re-emphasis. The studies undertaken have shown that in association with the typical hypotensive action of halothane, and in the case of relative overdose either with a rapidly acting gas such as cyclopropane or a more slowly acting vapour such as diethyl ether, preganglionic sympathetic activity continued at a discharge rate above that existing before administration of the anaesthetic. It is a common text-book statement that anaesthetics cause central vasomotor depression, but this requires a more precise explanation in view of the lack of any such effect in the experiments described, even in the presence of severe arterial hypotension.

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