THE ROLE OF HALOTHANE IN THE PREVENTION OF SURGICAL SHOCK

BY

MICHAEL JOHNSTONE

Department of Anaesthetics, Royal Infirmary, Manchester, England

THE PATHOGENESIS OF "SHOCK"

The study of shock has occupied the minds of medical men for over two centuries and the documentation has reached relatively enormous proportions. Several excellent reviews of the literature have been published (Nelson, 1957; Millican and Rosenthal, 1954; Frank, 1953; Drew, 1942). These reviews indicate that most of the work to date has been done by surgeons, physicians, and physiologists who have proved conclusively that the maintenance of the blood volume is the most important single factor in the prevention and treatment of shock. Clarke (1957) suggested that the failure of response to blood transfusion was due mainly to too little blood too late. The rapid intravenous infusion of large amounts of blood has been shown to cause acute right-sided heart failure secondary to the intense vasoconstriction of the pulmonary arterioles caused by the citrate used to prevent coagulation of the stored blood, a reaction which can be prevented by the intravenous administration of calcium gluconate and procaine hydrochloride (Firt and Hejhal, 1957).

Opinions differ as to the best method of replacing blood lost in severe haemorrhagic shock; some recommend the intravenous route, others the intra-arterial, and others the intra-aortic. A fourth revolutionary method consists essentially in rapid intravenous infusions after the administration of vasodilator substances (Martin, 1955). Whilst the transfusion approach to the shock problem is perfectly logical in cases where blood loss is obvious, it must be admitted that shocked patients are not infrequently encountered in whom transfusion by conventional methods appears to be not only useless but detrimental because of the risk of pulmonary oedema. In many instances the delay associated with the restoration of the blood volume must inevitably have deleterious effects on the patient, e.g. strangulated hernia, gastric perforation and peritonitis, intestinal volvulus, mesenteric embolism, etc. It is with this latter group that my interest lies, because I am convinced that the solution to the problem is in the hands of the pharmacologist and his clinical counterpart, the anaesthetist.

There is much confusion as to the meaning of the term "shock", many different definitions having been provided. I feel that the misunderstanding derives mainly from the fact that too much attention has been paid to the finer aetiological factors, in the sense that it appears to have been assumed that different agents cause a fundamentally different type of shock syndrome—thus we have traumatic shock, haemorrhagic shock, surgical shock, obstetric shock, endotoxic shock, anaphylactic shock, histamine shock, vasovagal shock, cardiac shock, neurogenic shock, anaesthetic shock, and adrenaline shock. This picture has been further complicated by the presentation of clinical symptomatologies in which there has been little effort to differentiate between the signs of impending shock and those of established shock.

In view of this rather bewildering state of affairs I have endeavoured to simplify the issue by starting at the wrong end, that is, to concentrate on established cardiovascular collapse and to describe it as something analogous to a fugue in three parts: the exposition, the response, and the counterpoint; the exposition being the initiating stimuli or injury which provokes the shock response of the cardiovascular system; the counterpoint being the means we adopt to counteract both the initiating stimuli and the cardiovascular reaction. In the management of shocked patients, as in the fugue form of music, there is a constant inter-
weaving of these three elements which renders almost impossible the study of each as a separate clinical entity.

Figure 1 illustrates diagrammatically the cardiovascular picture of a normal man. This subject has a normal blood volume, his skin is warm and pink and the veins are visible. Circulation is at optimal efficiency in the liver, kidneys, intestines, lungs, heart, and brain. Circulatory homeostasis is maintained by the neuro-endocrine system from control centres in the hypothalamic and medullary regions. Functional integration of the neuro-endocrine and cardiovascular systems permits the circulation to adapt immediately to environmental changes and directs adequate blood supplies to the tissues with priority demands. Under conditions of acute stress, such as trauma or certain forms of anaesthesia, the neurogenic vasomotor stimuli are mediated by the chemical transmitters adrenaline and noradrenaline.

For some reason our subject suffers a profound shock and figure 2 illustrates diagrammatically the dismal state of his circulation. He may have sustained a severe crush injury or his stomach may have perforated; he may have had a coronary occlusion or a volvulus of his intestines; there may have been a sudden haemorrhage or he may have been given an overdose of adrenaline; he may have been subjected to a severe emotional crisis, or he may have undergone prolonged and deep anaesthesia with a toxic agent. The ultimate cardiovascular state is one of intense peripheral vasoconstriction, the common denominator in virtually all forms of shock irrespective of the cause. The skin becomes cold, clammy, pale, and cyanotic; the pulse is rapid, thin, and feeble, and the veins disappear; the intestines, kidneys and liver become pale and bloodless, the spleen contracts, and the rate and force of the cardiac contractions increase. This vasoconstrictive reaction is primarily protective in nature, being designed to restrict blood and fluid loss and to maintain the blood supply to the brain and myocardium. It also constitutes an effective barrier to the rapid restoration of the blood volume by either the venous or arterial routes.

During the past few years an accumulation of evidence has indicated that the development of the so-called irreversible stage of shock may well be due to excessive prolongation of the vasoconstrictive reaction which, after a time, becomes self-perpetuating (Paton, 1957; Boba and Converse, 1957; Zweifach and Thomas, 1957; Martin, 1955). In the earlier stages of shock the constrictor actions of circulating adrenaline and noradrenaline are intensified by a vasoeexcitor material (V.E.M.) released from the ischaemic kidneys. As the shock state persists the sensitivity of the peripheral vessels to adrenaline and noradrenaline is abolished by the vasodepressor material (V.D.M.) released by the ischaemic liver (Nelson, 1957), causing pooling and stagnation of blood in the peripheral vessels, presumably the irreversible stage—hyporeactivity and stasis with “back-flow” in the terminal vascular bed. There is reason to believe that intravascular clotting occurs at this stage, leading to the formation of multiple minute pulmonary emboli which enhance the asphyxial state of the patient and ultimately lead to his death (Crowell and Read, 1955; Adelman and Katz, 1957). Survival after prolonged or severe vasoconstriction is not infrequently followed by death from uraemia—the so-called “crush syndrome” or lower nephron nephrotic syndrome—or by death from hepatic failure in patients with established liver disease (Shackman et al., 1952, 1953; Himsworth, 1950).

The activity of the vasomotor section of the sympathetic system is largely responsible for initiating this unhappy train of events. As with all neuronal circuits the vasomotor system consists of a central station, situated in the floor of the fourth ventricle, which receives afferent signals from several peripheral receptor areas and dispatches them along the efferent pathways to the heart, blood vessels, and viscera. The afferent stimuli originate in receptors of four different types, namely, the baroreceptors, the chemoreceptors, sensory or pain receptors, and cerebral cortical influences (fig. 3).

Baroreceptors.

These are located in the carotid sinus and aortic arch and are activated by changes in blood pressure from any cause, e.g. hypovolaemia, myocardial damage, or postural pooling of blood.

Chemoreceptors.

These are situated in the carotid and aortic bodies and are stimulated by carbon dioxide and changes in the pH of the blood. Oxygen defi-
Diagram of the vasomotor centre with its afferent and efferent connections.

Fig. 3
ciency also exerts a stimulant effect on them. Probably the best example of shock due mainly to activation of these receptors is the profound collapse which sometimes follows gastric perforation in elderly males with fixation of the costovertebral joints: diaphragmatic rigidity secondary to peritonitis seriously restricts respiration causing partial asphyxia and shock which often responds dramatically to the restoration of normal tidal volumes. Chemoreceptor activity is also present in the shock which follows acute coronary occlusion and is also suspected to be present to some degree in the intense vasoconstriction due to B. Coli endotoxin liberated from ischaemic bowel in such conditions as mesenteric embolism, intestinal volvulus, and strangulated hernia. Carbon dioxide retention is a well-known cause of circulatory collapse during or following general anaesthesia.

Sensory Afferents.

It is well recognized that severe pain can cause profound shock. This has been confirmed experimentally by stimulation of sensory nerves in experimental animals. Shock from this cause is sometimes observed clinically when patients emerge quickly from anaesthesia after trivial operations such as haemorrhoidectomy, and is easily avoided by the timely administration of an analgesic. General anaesthesia, particularly the very light planes of the nitrous oxide-curare technique, does not always adequately protect the patient from this type of vasomotor activation. Drenching sweats, with pallor and vasoconstriction, are commonly encountered during abdominal surgery in inadequately anaesthetized patients (Loder, 1957). Some of the most severe degrees of shock I have seen occurred in patients undergoing prolonged neurosurgical operations under local analgesia.

Cortical Afferents.

The influence of the emotions on vasomotor activity is well known (Gellhorn, 1943). Anxiety states have been shown to cause peripheral vasoconstriction (Ackner, 1956) and the intimate relation between emotional disturbances and essential hypertension has recently been described (Boshes, 1958). The anaesthetist not uncommonly encounters quite severe degrees of vasoconstriction, sometimes with hypotension, in non-premedicated patients in the immediate pre-operative phase. Similarly, minor surgery performed under local analgesia, is sometimes associated with severe circulatory collapse in the absence of blood loss. In these circumstances the induction of sleep promptly causes a striking improvement in the peripheral circulation.

Efferent Pathways of the Vasomotor System.

Fibres arise in the centre and pass down the cervical cord to end in the sympathetic cells of the lateral grey horns of the thoracic and upper lumbar segments of the cord. The preganglionic fibres then leave the cord via the anterior roots and pass peripherally in four different types of relay system (fig. 3):

1. Most of them form synapses in the paravertebral ganglia of the sympathetic trunk and pass thence as postganglionic fibres to the peripheral vessels and viscera.

2. Some pass uninterruptedly through the paravertebral ganglia and emerge as sympathetic nerves, passing to synapses in the collateral ganglia, e.g. the splanchnic nerves and the mesenteric ganglia. Postganglionic fibres emerge from the collateral ganglia.

3. Some fibres run to the peripheral vessels with no connections with the paravertebral or collateral ganglia. These arise from the sympathetic cells of the upper dorsal and upper lumbar segments of the cord (Alexander et al., 1949).

4. The sympathetic nerves to the suprarenal medulla are preganglionic all the way, the cells of the suprarenal medulla being regarded as postganglionic sympathetic cells resistant to the action of ganglionic blockers (Hollinshead, 1936; Hall, 1957).

In addition to these central and peripheral sympathetic connections there also exists the phenomenon known as the "peripheral autonomy" of the sympathetic system (Rothlin and Berde, 1949-53) by means of which circulatory homeostasis can be maintained after destruction or inactivation of the peripheral connections of the vasomotor system. This phenomenon is associated with the development of hypersensitivity to the vasoconstrictor effects of adrenaline and noradrenaline (Gellhorn, 1943). All these factors and variations have to be taken into account when
assessing the activity of a ganglionic blocking drug or technique.

**TO WHAT EXTENT IS ANAESTHESIA INVOLVED IN THE PATHOGENESIS OR IN THE PREVENTION OF SHOCK?**

Those who have been in practice long enough will have little difficulty in recalling the profound circulatory collapse which not infrequently followed prolonged and deep anaesthesia with chloroform, ether, cyclopropane, or thiopentone. It has been repeatedly demonstrated that these agents have a depressant effect on the myocardium which is more than adequately compensated by an increased production of adrenaline and noradrenaline brought about by sympathetic stimulation (Watts, 1955; Brewster et al., 1953). Prolonged sympathetic stimulation ultimately causes intense peripheral vasoconstriction with hypotension, tachycardia, and sweating (Freeman, 1933; Paton, 1957), with delayed recovery of consciousness due to the difficulties of excretion of the anaesthetic agent created by the impaired circulation. The afferent stimuli which provoke the vasoconstrictor reaction probably arise in the baroreceptors secondary to the myocardial weakening, but there is also the possibility of direct stimulation of the vasomotor centre (McAllister and Root, 1942). Chemoreceptor activity may also be involved as some degree of asphyxia must have been the inevitable consequence of prolonged and deep anaesthesia, most of these agents being highly irritant to the air passages, causing excessive secretions and bronchiolar constriction not always amenable to the effects of atropine. In the surgical management of shocked patients it is illogical to use anaesthetic agents which of themselves are capable of inducing shock.

**Spinal Anaesthesia.**

The introduction of spinal anaesthesia was the first attempt to control the peripheral circulation by blocking the vasomotor efferents. Labat (1931) observed that patients with crush injuries of the lower extremities were improved by spinal anaesthesia provided a head-down position was maintained and vasopressors were not used. This approach was extended by Griffiths and Gillies (1948) with their “total spinal” technique and recently epidural block has been used successfully in the treatment of severe refractory shock due to coronary occlusion (Agress, 1958). Loder (1957) has called attention to the effectiveness of blocking the collateral sympathetic ganglia in the prevention of shock during elective abdominal surgery. The spinal block proved to be of limited use because it did not influence, or perhaps even intensified, the emotional and asphyxial factors, as well as having other technical disadvantages. It should be noted, however, that it is still the only method of sympathetic block which completely isolates the vasomotor centre from the periphery.

**Muscle Relaxants.**

The arrival of the muscle relaxants was a major step in the elimination of shock from elective surgery, due mainly to the fact that they abolished the need for the toxic inhalational agents (Harron et al., 1946; Gray and Halton, 1946; Cullen, 1944). It is doubtful whether the relaxants have any direct effect on vasomotor function because they have not by any means completely eliminated the incidence of shock during elective surgery (Loder, 1957). The asphyxial basis of vasomotor overactivity has, if anything, been intensified by some of the relaxants because the need for positive pressure inflation of the lungs has, in certain circumstances, disastrous effects on the normally low impedance of the pulmonary circulation (Maloney et al., 1951; Johnstone, 1956). All accepted methods of controlled respiration are but the crudest substitutes for the beautifully integrated movements of blood and gas so constantly effected by spontaneous respiration (cf. Rodbard, 1953).

**Ganglion blocking drugs.**

Then came the ganglionic blockers. Although primarily designed to limit bleeding during operations (Rollason, 1953) it soon became apparent that these agents afforded some protection against the development of shock during elective surgery. Attention immediately became focussed on the possibility that vasomotor overactivity was probably the essential cause of peripheral circulatory failure and several important papers supporting this concept have now been published (Martin, 1955; Boba and Converse, 1957; Paton, 1957). The ganglionic blockers hexamethonium and trimetaphan act mainly on the parasympathetic
synapses and on the synapses of the paravertebral and collateral sympathetic ganglia and do not appear to exert any significant effect on the synapses within the suprarenal medulla (Hall, 1957; Kurnick, 1956; Moe and Freyburger, 1950: Freyburger et al., 1948). The sympathetic connections between the periphery and the sympathetic cells of the upper dorsal and upper lumbar segments may be uninfluenced by ganglionic blockers because not only does ganglionic blockade fail to block the hypertensive response to carbon dioxide (Payne, 1958) but bilateral adrenalectomy also fails to do so (Von Euler and Franksson, 1957; Johnstone, 1958); the rise in blood pressure under the latter circumstances is presumably due to the release of noradrenaline by activation of the vasomotor system.

The blocking action of hexamethonium and of trimetaphan on the cardiac parasympathetic ganglia constitutes a major and perhaps dangerous obstacle to their safe use in clinical anaesthesia. The combination of hypotension due to sympathetic blockade with tachycardia due to parasympathetic blockade may have disastrous effects on the cardiac output, particularly in the presence of organic disease of the coronary arteries: the short diastolic times may prevent complete ventricular filling at low blood pressures. At best these agents produce only a partial block of the vasomotor efferents and have no effect on the afferent stimuli which will still be relayed to the cardiovascular system through the efferents unaffected by the blockade. There is no doubt, however, that they can be used effectively and beneficially during anaesthesia in patients without organic disease of the cardiovascular system, provided non-toxic narcotic agents are used, respiration controlled with extreme care and complete oxygenation and efficient elimination of carbon dioxide are ensured. Controlled respiration by intermittent positive pressure during ganglionic blockade should be regarded as hazardous because of the abolition of the vascular compensatory mechanisms which normally counteract the raised intra-alveolar gas pressures (Barer and Nusser, 1957; Hubay et al., 1954; Saklad, 1954; Finnerty and Freis, 1950).

Chlorpromazine.

Chlorpromazine (Laborit et al., 1952) was the next drug to be used for the control of shock and was used in an attempt to suppress both the afferent and efferent vasomotor stimuli. It effectively modifies the emotional and sensory afferents and induces a peripheral vasodilatation by blocking the vasoconstrictive actions of adrenaline, noradrenaline, and other vasopressors (Dripps et al., 1955). The antipressor action of chlorpromazine, and of the various other adrenergic drugs, would appear to be a contra-indication to their use either before or during operative surgery. Patients under sympathetic blockade at any site are notoriously liable to disastrous degrees of hypotension following sudden haemorrhage or abrupt changes of posture. In these circumstances the unimpaired effectiveness of a peripherally acting vasopressor such as methoxamine can be life-saving. A further disadvantage of chlorpromazine is that it combines hypotension with tachycardia which, as with hexamethonium, may have serious effects on the cardiac output and coronary circulation.

Halothane.

Halothane is the latest anaesthetic to be used for the control of shock during elective and emergency surgery. It was discovered by Suckling (1957, 1958, 1958a) as the result of an investigation into the synthesis of nontoxic, nonexplosive, volatile anaesthetic compounds, a synthesis based on the physical and chemical principles described by Ferguson (1939, 1951). Subsequent pharmacological observations (Raventos, 1956; Raventos and Spinks, 1958; Spinks, 1958) gave every indication that it was the compound most likely to succeed in clinical practice. During the past few years extensive clinical trials have been reported (Bryce-Smith and O'Brien, 1956; Marrett, 1957; Brennan et al., 1957; Robson and Sheridan, 1957; Hudon et al., 1957; Robertshaw, 1957; Hartung, 1957; Reinhold et al., 1957). These reports indicate that an outstanding feature of halothane anaesthesia is the excellent condition in which it leaves the patient after major surgery under prolonged and deep anaesthesia. Pope (1957) has demonstrated that it may well be the anaesthetic of choice for surgery in elderly patients with advanced cardiovascular and pulmonary diseases, a group which has been particularly refractory to most other agents and techniques; his reason for this claim is that halothane, in addition to pro-
viding ideal operating conditions, appears to prevent shock and circulatory collapse.

I have now anaesthetized with halothane over 2,500 patients undergoing major surgical operations of all kinds and I have not seen any evidence of shock as manifested by tachycardia, sweating, pallor with vasoconstriction, impaired response to intravenous transfusion and to methoxamine, and delayed recovery of consciousness, even after severe accidental haemorrhage during the operations. In all cases vasodilatation with dry and warm peripheries and normal pulse rates have persisted throughout the period of anaesthesia. Profound hypotension may be encountered as the consequence of haemorrhage or of postural influences and is easily corrected by the appropriate treatment—transfusion, methoxamine, or both. Particularly good results have been obtained in patients shocked by intestinal catastrophes such as prolonged obstruction, mesenteric embolism, strangulated hernia, etc. These patients are almost invariably severely dehydrated and the intense vasoconstriction is a major obstacle to the restoration of blood volume, tissue hydration, and oxygenation. It these cases anaesthesia is induced and maintained with halothane with either oxygen or nitrous oxide-oxygen mixtures. As soon as venous dilatation appears—two to three minutes—fluids can be very rapidly administered intravenously till the blood pressure reaches reasonable levels. There has been no evidence of pulmonary oedema from the rapid infusion of fluids, presumably because the dilated state of all the blood vessels facilitates the rapid distribution of the fluid throughout the tissues of the body—needless to say, a head-down tilt should be maintained until the blood volume is deemed to be restored. With this technique, patients can be resuscitated whilst the surgeon operates and valuable time gained, and it is hoped that this will be the answer to many of the problems associated with emergency surgery in shocked patients.

There has been much controversy concerning the cause of the vascular hypotension induced by halothane. Raventos (1956) indicated that it was due mainly to sympathetic blockade, particularly of the mesenteric ganglia, and he demonstrated a selective affinity for certain ganglia. The failure of Burn et al. (1957) to find much evidence of complete blockade in the superior cervical gan-

**BRITISH JOURNAL OF ANAESTHESIA**

lion of the cat does not exclude a block of other ganglia. Paton (1952) has stated that the superior cervical ganglion of the cat can be very resistant to blockade and selectivity is a feature of all ganglionic blockers, the response of different ganglia to different blockers being considerably influenced by the "background tone" and by individual variations in sensitivity.

The suggestion that the hypotensive effect of halothane is due mainly to myocardial weakening (Burn et al., 1957) is incompatible with the persistence of the sensitivity of the peripheral circulation to the hypertensive action of methoxamine (Brewster et al., 1953) and of carbon dioxide; nor is it consistent with the rapid and persistent rise in blood pressure which follows intravenous transfusions during halothane anaesthesia. It has been conclusively demonstrated that a hypotension due to myocardial depression is uninfluenced by methoxamine (Brewster et al., 1953). The isolated heart-lung preparation (Burn et al., 1957) has revealed a distinct myocardial depression with halothane; this observation is not strictly relevant to and is of little help in explaining the effects of halothane in clinical practice, the heart-lung preparation being in no way comparable to the intact cardiovascular system with its intricate compensatory mechanisms. It should not be forgotten that surgical concentrations of ether, widely regarded as a "safe" anaesthetic, have a deleterious effect on the heart-lung preparation (Brewster et al., 1953) whereas in the intact animal the cardiac output is increased (Blalock, 1927). The rather complex clinical experiments of Severinghaus and Cullen (1958) from which it was deduced that the halothane hypotension was due to myocardial depression, are difficult to interpret owing to the fact that unspecified concentrations of the drug were administered by the artificial inflation of the lungs of patients paralysed with suxamethonium, a manoeuvre which, quite apart from halothane, has been shown to have serious effects on the cardiac output (Johnstone, 1956). One of the outstanding advantages of halothane anaesthesia is that major surgery, including abdominal but excluding thoracic, can be performed for the most part whilst the patient breathes spontaneously. It is not improbable that spontaneous respiration does much to maintain the efficiency of the pulmonary circu-
THE ROLE OF HALOTHANE IN THE PREVENTION OF SURGICAL SHOCK

The role of halothane in the prevention of surgical shock involves the venous return to the heart, particularly in the presence of hypotension with sympathetic paresis. Halothane combined with controlled respiration either by relaxants or by central depressants can be used effectively for thoracic surgery, satisfactory results in large numbers of cases having been obtained by Hartung (1957) and by Robertshaw (1957). In using halothane with controlled respiration considerable care should be exercised in limiting the concentration of halothane vapour to the minimal surgical requirements.

The clinical picture of halothane anaesthesia has a striking resemblance to the picture of the “hexamethonium man” described by Paton and Zaimis (1952) and again by Paton (1957). The hypotension with the dry, warm, and pink skin with dilated veins; the suppression of salivary, bronchial, and gastric secretions; the tendency to postural hypotension and the pooling of blood in dependent parts; the absence of the usual sympathoadrenal response to trauma and hemorrhage; the atonic bowel; the persisting sensitivity of blood vessels to peripherally acting vasopressors; the sensitization to the autonomic transmitter substances, and the immediate response to intravenous transfusion. The disappearance of the shock syndrome as a result of halothane anaesthesia is in keeping with Paton’s concept of a “controlled circulation” effected by sympathetic blockade at ganglionic level.

There is no doubt that halothane, in common with other anaesthetic agents, depresses the emotional and sensory afferents of the vasomotor system and, in addition, it inactivates the baroreceptors and leaves intact the chemoreceptor mechanism. The hypertensive response to carbon dioxide retention is unimpaired by halothane, and may even be exaggerated (Johnstone, 1958). Direct depression of the vasomotor centre by halothane, or by any other anaesthetic drug in clinical use, is almost certainly out of the question as the classic experiments of Hill and Macdonald (1933) revealed that this centre is amazingly resistant even to the direct application of such powerful protoplasmic poisons as procaine and cinchocaine.

The persistence of the hypertensive response to carbon dioxide retention during halothane anaesthesia indicates efficient conduction in the efferent sympathetic pathways within the spinal cord (Steck and Gellhorn, 1939). The hypertensive response to carbon dioxide retention does not occur in patients under halothane narcosis combined with high spinal anaesthesia. There is considerable evidence to indicate that the efferent sympathetic nerves to the suprarenal medulla are resistant to the effects of ganglionic blockers because stimulation of them by either direct methods or by carbon dioxide after the administration of ganglionic blockers, results in a rise of blood pressure due to the release of adrenaline and noradrenaline (Hall, 1957; Enderby, 1956). The hypertensive response to carbon dioxide retention during halothane anaesthesia in man cannot be regarded as being completely due to the release of adrenaline from the suprarenal medulla because it is still present after bilateral adrenalectomy (Johnstone, 1958). The rise in blood pressure is unlikely to be of cardiac origin as both systolic and diastolic pressures are equally involved suggesting that it is probably mediated by noradrenaline released at sympathetic nerve endings in some as yet unidentified part of the body, possibly the sympathetic connections of the upper dorsal and upper lumbar segments (Alexander et al., 1949).

In spite of the absence of clinical evidence to indicate a depressant effect on the heart it would be wise to assume, in the present state of our knowledge, that concentrations of halothane in excess of those required for surgical anaesthesia may have toxic effects on the myocardium. Reasonable care should therefore be exercised to ensure that the dose is limited to the surgical requirements of each patient. After two years of intensive clinical experience with halothane I see no reason to modify the previous statement to the effect that the occurrence of cardiac arrhythmias in the anaesthetized patient reflect more on the management of the patient than on the drugs used to induce and to maintain anaesthesia (Johnstone, 1955).

For the present it would seem reasonable to assume that halothane suppresses sympathetic activity at some level presumably ganglionic. As with all ganglionic blockers, the sensitivity of the ganglia to the blocking action varies from patient to patient and is selective in regard to the ganglia affected and to the degree in which they are...
blocked. The cardiac parasympathetic ganglia appear to be completely spared by surgical concentrations of halothane because Bradycardia, amenable to atropine, is invariably encountered during halothane anaesthesia; it is not known whether the slowing of the heart is due to activation of parasympathetic reflexes or to the abolition of the buffering action of the sympathetic system such as occurs in high spinal anaesthesia. This sparing of the cardiac parasympathetic ganglia is in one way a fortunate occurrence as it ensures ample diastolic times for complete ventricular filling at low systolic pressures.

Another reason for the excellent condition of patients during and after surgery under halothane-oxygen anaesthesia is that the development of hypoxia and anoxia is physically impossible in the presence of a clear airway, the oxygen uptake being almost completely independent of the tidal and minute respiratory volumes, being effected by the phenomenon known as apnoeic diffusion oxygenation (Holmdahl, 1956). During halothane-oxygen anaesthesia the oxygen uptake by diffusion is usually as efficient during apnoeic states as in normal respiration (Johnstone, 1958). The elimination of carbon dioxide is still dependent on the respiratory movements but this can be accomplished with ease because of the ideal state of the air passages—perfectly dry and relaxed with complete dilatation of the bronchioles in all patients including those with bronchiolar constriction due to pulmonary or cardiac disease. The ease with which patients ventilate during halothane anaesthesia is consistent with an autonomic blocking effect, Paton (1952)—having postulated a similar action during autonomic blockade with hexamethonium. Several investigators have demonstrated the beneficial effects of sympathetic blockade on the respiratory functions of patients whose vital capacities were seriously diminished by cardiac and pulmonary disease (Bromage, 1956; Ellestead and Olsen, 1956). The importance of adequate oxygenation in the control of experimental shock has been described by Schenedorf and Orr (1941) who observed that oxygen inhalations caused a 70 per cent increase in the duration of life in dogs subjected to severe traumatic shock; similar observations were also made by Wood et al. (1940).

ILLUSTRATIVE CASE REPORTS

CASE 1. Male, 54 years. Severe haematemesis due to gastric ulceration. Heart and lungs normal. Blood pressure 70/50 mm Hg, pulse rate 125 beats a minute, sweating. Conservative treatment and blood transfusion restored the blood pressure to 110/70 mm Hg in 12 hours. Twenty-four hours later the patient collapsed again and immediate laparotomy was decided upon. Premedication, atropine 0.5 mg. On arrival at the operating theatre the blood pressure was 60 mm Hg systolic, the pulse rate 135 beats a minute, and the respiratory rate 35 a minute.

Anaesthesia was induced with nitrous oxide, oxygen and halothane and maintained with halothane and oxygen. During the first 20 minutes of anaesthesia the blood pressure was restored to 110/70 mm Hg by the rapid intravenous transfusion of 2 pints (1 l.) of blood and 1 pint (500 ml) of saline. The pulse rate dropped to 90 beats a minute, and the skin became warm and pink. A partial gastrectomy was then performed under halothane-oxygen anaesthesia with a total dose of 150 mg of suxamethonium to facilitate the initial exploration and subsequent closure of the peritoneal cavity. Throughout the operation which lasted 80 minutes, the blood pressure remained at 110 mm Hg systolic and the pulse rate gradually dropped to 80 beats a minute, a further pint of blood and 1 pint of saline being administered. Twenty minutes after the conclusion of the operation the patient recovered consciousness, the blood pressure being 120/80 mm Hg, and the pulse rate 90 beats a minute. The blood pressure did not fall subsequently and recovery was uneventful.

CASE 2. Male, 64 years. Gastric ulcer perforation of 12 hours duration. Chronic bronchitis with emphysema. Very collapsed, cyanosed, sweating, and dyspnoeic. Blood pressure 100/80 mm Hg, pulse rate 125 beats a minute, respiratory rate 65 a minute. No response to the intravenous transfusion of 2 pints of saline. Premedication, atropine 0.5 mg.

Anaesthesia was induced with nitrous oxide, oxygen and halothane. Three pints of glucose-saline were administered intravenously during the next 15 minutes. The skin became warm, dry, and pink and the blood pressure varied between 110 and 140 mm Hg systolic and the pulse rate 65 a minute. A laparotomy was then performed under halothane-oxygen anaesthesia and the gastric perforation repaired, a further 2 pints of glucose-saline being administered. The blood pressure varied between 110 and 140 mm Hg systolic during the operation and increased to 150 mm Hg systolic immediately afterwards. Recovery was uneventful.

CASE 3. Female, 81 years. Right femoral hernia strangulated for 7 days. Chronic bronchitis. Collapsed, dehydrated, cyanosed, respiratory rate 45 a minute, pulse rate 135 beats a minute, peripheral vasoconstriction, tongue dry and shrunken, blood pressure 110/80 mm Hg (known to have been 230/130 mm Hg before the intestinal strangulation). Premedication, atropine 0.5 mg.

Anaesthesia was induced with nitrous oxide, oxygen, and halothane. Three pints of glucose-saline were
THE ROLE OF HALOTHANE IN THE PREVENTION OF SURGICAL SHOCK

administered intravenously (forearm vein) during the next 15 minutes. The skin became pink and warm and the blood pressure increased to 130 mm Hg systolic. Anaesthesia was then maintained with halothane and oxygen and, during the next 75 minutes, the hernia was reduced and repaired and 3 inches of gangrenous intestine excised followed by an end-to-end anastomosis. A further 2 pints of glucose-saline were administered during the operation. At the end of the operation the blood pressure was 150 mm Hg systolic, the pulse rate 110 beats a minute, the respiratory rate 30 a minute and the tongue had become moist and of normal size. Consciousness returned in 10 minutes and the blood pressure gradually increased to 170/100 mm Hg during the next 3 hours. Recovery was uneventful.

Case 4. Male, 62 years. Right renal tumour. Heart and lungs normal. Blood pressure 190/110 mm Hg. Premedication; pethidine 50 mg and promethazine 50 mg.

Anaesthesia was induced with thiopentone 250 mg (with atropine 0.5 mg) and an endotracheal tube inserted during suxamethonium paralysis. Anaesthesia was maintained with halothane and oxygen, no relaxants or other supplements being necessary. The blood pressure after premedication was 150/100 and dropped to 110/70 mm Hg during halothane anaesthesia. Spontaneous respiration persisted throughout with a respiratory rate of 30 a minute. Before induction the pulse was 85 beats a minute, and dropped to 70 beats a minute when anaesthesia was established with halothane.

Exploration of the right renal area revealed a large retroperitoneal neoplasm investing and infiltrating the kidney and several large blood vessels including the inferior vena cava and the right common iliac artery and vein. Fifty minutes after the start of the operation and during an attempt to mobilize the tumour the right common iliac artery and vein were torn; torrential haemorrhage followed and the blood pressure immediately dropped to zero in the arms but a feeble pulse was palpable in the carotid artery at 70 beats a minute. The haemorrhage was controlled by direct pressure on the bleeding area. During the next 10 minutes 1 pint of saline and 2 pints of blood were administered intravenously and caused the blood pressure to rise to 90 mm Hg systolic. An attempt was then made to apply haemostatic ligatures but this resulted in more haemorrhage and the blood pressure again dropped to zero; a further 2 pints of blood and 1 pint of dextran restored the blood pressure to 100 mm Hg systolic in 8 minutes. Attempts to control the haemorrhage occupied 65 minutes during which time 10 pints of blood, 3 pints of glucose-saline and 3 pints of dextran were administered intravenously. The entire transfusion was administered through a vein on the dorsum of the right hand, using the standard giving-set and a Martin's pump. Whenever necessary the response to the transfusion was increased by diminishing the depth of anaesthesia and by 5 mg doses of methoxamine (total dose 20 mg)—this drug is particularly effective in counteracting any tendency to pooling of blood in the dependent parts of the body. Throughout the operation the pulse and respiratory rates remained unchanged at 70 beats a minute and 30 a minute respectively, and the skin remained warm and dry. During the more critical hypotensive periods, none of which lasted more than 5 minutes, cyanotic patches appeared on the dependent parts of the body, and the uppermost areas became very pale; restoration of the blood pressure caused the skin to regain its normal pink appearance immediately.

The operation was completed in 3½ hours. The patient recovered consciousness 15 minutes later and was returned to the ward in good condition, his brachial blood pressure being 190/110 mm Hg and pulse rate 65 beats a minute. At the conclusion of the operation pulsation was absent in both femoral arteries and did not return subsequently. The patient remained in good condition for 24 hours after the operation, fully conscious and rational, his blood pressure remaining around 150/100 mm Hg. A few hours later he died rather suddenly from causes unrelated to anaesthesia.

Case 5. Male, 58 years. Obese. Left hypernephroma, 2 cm approximately in diameter. Blood pressure 170/90 mm Hg. Premedication pethidine 30 mg and atropine 0.6 mg.

Anaesthesia was induced with thiopentone 300 mg and the patient intubated during suxamethonium paralysis. Anaesthesia was then maintained with halothane-oxygen with adequate spontaneous respiration and muscular relaxation throughout. With halothane anaesthesia the blood pressure settled at 100 mm Hg systolic with a pulse rate of 84 beats a minute. A large hypernephroma was mobilized without difficulty. During the removal of the tumour the haemostatic clamp slipped from the atherosclerotic renal artery with the immediate loss of from two to three pints of blood before the clamp was satisfactorily reapplied. The radial blood pressure immediately became unrecordable and the carotid pulse rate dropped to 60 beats a minute. Methoxamine 10 mg was injected intravenously (per salino intravenous drip already in situ) followed by 1 pint of dextran and 5 minutes later the blood pressure was 75 systolic and the pulse rate 70 beats a minute. Two pints of blood and 1 pint of saline were administered during the next 15 minutes, using a vein on the dorsum of the left hand with a standard giving-set and the systolic blood pressure promptly increased to 120 mm Hg, the pulse rate remaining unchanged at 70 beats a minute. At the end of the operation, which lasted 90 minutes, the blood pressure was 150/100 mm Hg, the pulse rate 80 beats a minute, and full consciousness returned 30 minutes later, the skin remaining warm, dry, and pink. No subsequent drop in blood pressure occurred and the patient made a complete and uneventful recovery.

CONCLUSION

Halothane has provided strong, if not conclusive, evidence in favour of the concept that vasocostriction is an undesirable consequence of trauma or haemorrhage in the subject under medical care. Constriction of the peripheral vessels in response to haemorrhage or other stimuli is undoubtedly designed by nature as a protective
mechanism but it is difficult to perceive how this reaction fits into the efficient management of patients undergoing elective or emergency surgical operations in conditions where adequate facilities are available for the maintenance of blood volume by transfusion methods. It should not be forgotten that pain perception is also a highly important defence against injury but no one would suggest that it is in any way necessary for the survival of patients undergoing surgical treatment.

The abolition of the vasoconstrictive reaction to injury, although of fundamental importance in the control of surgical shock, carries serious and perhaps dangerous risk to the patient if it is not fully realised that the sensitivity of the patient to the cerebral and cardiac complications of hypovolaemia and hypotension are increased. Unlike all the other vasoplegic drugs introduced into clinical practice, however, halothane provides a vasoparesis which is completely under the control of the anaesthetist and which can be varied momentarily in either direction by altering the concentration of the inhaled vapour. The restoration of vasomotor tone, when it becomes necessary, can be effected so rapidly either by stopping the administration of halothane or by giving methoxamine that the threat to the cerebral and coronary circulation is reduced to a minimum, if not completely eliminated. The unusually high proportion of oxygen which is administered with the drug without impairing its narcotic and relaxant properties is undoubtedly a major factor in the increased tolerance to generalized vasodilatation.

The necessity for narcotic and relaxant supplementation of the other ganglionic methods greatly increased the dangers of these methods, survival from the effects of many of the conventional narcotics and relaxants being dependent to a large extent on the integrity of the vasomotor system and the efficiency of the respiratory movements. Halothane, on the other hand, not only provides rapidly reversible narcosis and muscular relaxation but preserves the vital function for which no complete substitute has been found and which is the most satisfactory index of anaesthetic dosage—spontaneous respiration.

It can be concluded that halothane is an efficient anaesthetic agent which ensures the immediate effectiveness of resuscitative measures, thereby eliminating the dangers of peripheral circulatory collapse during surgery. The only problem which it has presented has been the difficulty in finding explanations of its unusual and beneficial effects. The clinician is strictly limited in the means to be adopted in investigating these effects but it should not be forgotten that, in the final analysis, the only satisfactory criterion of the value of any anaesthetic agent is the condition of the patient throughout and after the operation—and in this respect halothane has not been found wanting.

ACKNOWLEDGMENTS

I am indebted to my surgical and nursing colleagues for their encouragement; to Drs. E. Falkner Hill and Alexander Stewart for their stimulating and critical interest; to Mrs. Zeta Stead-Blackburn, medical artist, and to the Department of Medical Illustration, Manchester Royal Infirmary. I am also indebted to the Imperial Chemical Industries Limited (Pharmaceuticals Division) for defraying the cost of the coloured illustrations.

REFERENCES


THE ROLE OF HALOTHANE IN THE PREVENTION OF SURGICAL SHOCK


Pope, E. S. (1957). A report on the use of halothane in twenty-five selected cases of pulmonary or cardiac disease. Anaesthesia, 12, 405.


ROYAL SOCIETY OF MEDICINE, SECTION OF ANAESTHETICS

Registrars' Prize.

The Anaesthetic Section of the Royal Society of Medicine is able to offer a Prize of £30 for the best paper submitted by medical practitioners of Senior Registrar and Registrar status in the National Health Service holding a clinical appointment in an anaesthetic department or hospital. Fellowship of the Royal Society of Medicine is not necessary for entry.

The subject will be of the author’s choice but must be connected with anaesthesia. All papers for the 1959 award must be submitted by January 1, 1959. Further details and rules of the Prize can be obtained from the Honorary Secretary, Anaesthetic Section, Royal Society of Medicine, 1 Wimpole Street, London, W.1.