THE EFFECTS OF THE COMMON ANÆSTHETICS ON THE CIRCULATION.

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For some time previous to the War great interest has been taken in the effects of general anaesthesia on the heart and circulation. All the general anaesthetics have, to a greater or lesser extent, a depressant effect on the circulation though the effect is not always noticeable at the time of operation and indeed may not show itself until several days later.

The majority of the experimental work on anaesthetics has been done on animals and requires clinical confirmation. This can only be obtained by the keeping of accurate records of all patients who have been given an anaesthetic whether the operation be a serious one or not. A knowledge of the blood-pressure and pulse reactions to general anaesthesia helps much in the early diagnosis of shock. The importance of a correct choice of an anaesthetic in cases of gas poisoning is evident.

Ether and, unfortunately, chloroform are still two of the most commonly used anaesthetics. Both have, in varying degrees, toxic effects on heart muscle and on the peripheral blood-vessels. The apparent initial stimulant effect of ether on the circulation is not maintained for long. Anyone who has by accident or design attempted to inhale an anaesthetic concentration of ether will agree that the stimulant effect on the circulation can be accounted for by the severe irritation of the air-passages and the effect is replaced later by gradual circulatory depression. The early stimulant effect of ether does not occur with chloroform and a fall of blood-pressure occurs with this drug right from the beginning. Both paralyse the heart muscle in mammals though the relative toxicity of the two narcotics, as assayed by Cushing, indicates that chloroform is twenty-five times more toxic to heart muscle than ether. The paralysis begins in the auricles (Embley) [1] and later spreads to the ventricles but vagal stimulation will cause cardiac arrest before the drug reaches lethal concentration. Here is the usual cause of death from chloroform overdosage but asphyxia due to respiratory failure complicates the picture in the case of ether. In both cases the signs of overdosage are bradycardia, an irregular pulse and a marked fall in blood-pressure. Such overdose, even in skilled hands, can occur with chloroform and this is not surprising when it is realized that in the Starling heart-lung preparation 20 to 40 mgm. per cent chloroform in the prefusing fluid will cause a marked diminution in cardiac output while 18 to 40 mgm. per cent is necessary for deep narcosis and 25 to 30 mgm. per cent is necessary for surgical anaesthesia. This margin of safety is extremely small and might easily be exceeded during induction in a robust patient (Buckmaster and Gardner) [2].

Mixtures of chloroform and other narcotics give no guarantee of safety and it has been shown by Anderson (1932) [3] that similar effects follow the use of A.C.E. mixtures. Oncometric examination of the heart under ether shows a continuous dilatation from the beginning of induction although little or no diminution in cardiac output or blood-pressure occurs until much later (Cattell) [4]. It is hardly necessary to say that no warning of the effects of this drug on the heart need be given by the pulse. Blalock [5] demonstrated, however, in dogs a distinct increase in cardiac output associated with tachycardia. This is explained as due to sympathetic stimulation and a vagal inhibition with associated liberation of adrenaline. The theory that vagal inhibition under ether does occur is supported by Samaam (1935) [6] who states that adrenaline injection does not cause bradycardia while vagal section in the neck has no influence on the cardiac rate. Cutting of the sympathetic nerves reduces the tachycardia. Tachycardia in human subjects is common during light surgical anaesthesia. Chloroform produces neither tachycardia nor a rise in blood-pressure but it has some very unpleasant side effects. The well-known experiments of Levy [7] in 1923 demonstrated the serious effects of chloroform on heart muscle. He showed that besides the ordinary effects
of overdosage a type of cardiac arrest occurs early in induction and during light narcosis. This is a ventricular fibrillation. It may, but need not always, be preceded by tachycardia and extrasystoles. There is a phase of increased excitability and the refractory period of heart muscle is shortened. It is easy to realize that under such conditions a trigger action will occur through sympathetic stimulation induced by asphyxia and struggling and this has been confirmed by experimental work on animals. The cardiac output under ether and chloroform is also reduced by occasional extrasystoles, possibly also a sympathetic effect, since Brow [8] has discovered an area in the hypothalamus stimulation of which will produce extrasystoles.

The use of the electrocardiograph has demonstrated that extrasystoles occur much more frequently than had previously been suspected. Premature beats, tachycardia of ventricular and auricular origin, sinus arrhythmia and delayed auriculo-ventricular conduction time have all been noticed but it is difficult to separate the effects of the anaesthetic drug and the effects of asphyxia during induction.

Cardiac depression is not confined to ether and chloroform. Ward and Wright [9], in experiments on healthy volunteers, showed that nitrous oxide given without oxygen for short periods greatly depresses the ventricular myocardium.

The danger of "Dental Gas" given to persons with a weakened heart has long been known. But ethylene, nitrous oxide with oxygen, cyclopropane, vinyl ether and avertin all produce their quota of irregularities. Indeed, during induction with cyclopropane the slow pulse makes irregularities easily detectable. However, such irregularities need not always be regarded as signs of circulatory depression (Lennux, Graves and Levine [10]). The cardiac side effects of cyclopropane are naturally of great interest as the survival of this drug as an anaesthetic depends ultimately on its freedom from cardiac damage. Kurtz [11] with the electrocardiograph noted a multiple focus ventricular tachycardia in 10 per cent of patients under cyclopropane. This abnormality is the precursor in chloroform narcosis of ventricular fibrillation. Increase in depth increases the incidence of such abnormalities and Waters has noticed a true cardiac paralysis with high concentrations of the gas. He, however, used over 50 per cent, an amount not likely to be used clinically. Hewer [12] on the other hand strongly advocates cyclopropane in severely shocked patients requiring immediate operation.

Ethyl chloride produces cardiac damage similar to chloroform (Kennedy, 1930). Ethylene and nitrous oxide apart from the arrhythmia mentioned above produce no permanent cardiac injury but avertin; although it has a much wider margin of safety than chloroform, has a somewhat similar effect on the heart (Sollman, 1936 [13]). In its cardiac effects it comes between chloroform and ether, being safer than the former and not so safe as the latter drug. In view of this it is difficult then to understand its wide use in toxic goitre.

The barbiturates have been recommended for the anaesthetization of shocked subjects and experimental work on animals by Seeley, Essex and Mann [14] indicated that amytal delays the appearance of shock following intestinal manipulation under ether, but Adolph and Gerbasi [15] have shown that this drug causes an increase in blood dilution—probably due to a transudation of lymph into the capillaries following the fall in blood-pressure. Cushing, however, states that the fall in blood-pressure under the barbiturates is due to a direct cardiac effect. Mugg [16] studying the effects of veritol on the circulation noted a 35 per cent diminution in the cardiac minute volume, raised right auricular pressure and cardiac irregularities following the perfusion with the barbiturate pernocton and similar effects have been noted in the case of evipan.

The interpretation of the experimental results in animals and their application in clinical anaesthesia is made difficult by the omission of the estimation of the depth of the anaesthesia or the blood concentration of the narcotic used.

Peripheral Circulatory Effects of Anaesthetics.—Increasing interest is being taken in the peripheral vascular effects of anaesthetics. In the case of ether there appears to be a distinct loss of vasometer tone particularly in the extremities. The lower limbs show an increase in the skin temperature and measurement by Rhein's flowmeter shows an increase in arterial blood flow. Strangely enough, under light anaesthesia, the blood flow in the peripheral
arteries is greater than under deep anaesthesia and it is presumed that the fall in blood-pressure associated with the cardiac effects of deep ether narcosis reduces the peripheral flow. Herrick [17] states that ether abolishes vasometer tone in the lower extremities. The cerebral vessels are dilated but the intestinal blood-vessels are constricted.

Chloroform, not only by its direct action on the heart but by causing peripheral arterial paralysis, causes a fall in blood-pressure. Cushing claims a direct action on the muscles of the arterioles but there is evidence of paralysis of the vasomotor centre. Avertin, depending on the depth of anaesthesia induced, has both a central and peripheral dilator action on the blood-vessels (Nowak, 1934 [18]). Nitrous oxide, ethylene and cyclopropane have no action on the blood-vessels though the last is frequently blamed for excessive bleeding during surgical operations.

Spinal anaesthesia affects the circulation, in the main, peripherally. In man the vasomotor centre is highly developed because of his erect posture and, indeed, some animals are likely to die from cardiac insufficiency if maintained for some time with their head much above the rest of the body.

The central nervous system exercises this control through two main pathways—the sympathetic and the parasympathetic. Twin chains of ganglia commence in the neck and run down on either side of the vertebral column through thorax and abdomen to the pelvis. These ganglia receive efferent fibres, white rami communicantes, from the spinal cord via the anterior roots of the spinal nerves from the 1st thoracic to the 2nd or 3rd lumbar segments and synapse with the paravertebral ganglia opposite above and below. Due to this widespread distribution in the sympathetic nerve chain blocking of even a single segmental group of such fibres can cause widespread effects.

These efferent nerves carry all the vasomotor impulses from the centre in the brain to the entire body so blocking of the efferent nerves from the 1st thoracic to the 3rd lumbar segments will cause vasodilatation practically all over the body.

The grey rami communicantes arise from the ganglionated sympathetic cord and proceed via the spinal nerves to their destination, the arterioles of the somatic circulation. The grey rami obviously cannot supply vasoconstrictor impulses if the white rami are blocked as occurs with a spinal anaesthetic. The number of vasoconstrictor nerves put out of action depends on the extent of the anaesthetic or motor block. Included in the sympathetic system are the three cardiac accelerator nerves. Stimulation of these nerves speeds up the heart rate and, since their origin is from the upper thoracic white rami, they may be blocked by a high spinal anaesthetic. Should this occur bradycardia might be expected as the vagal parasympathetic influence is unopposed.

Fibres from the 5th thoracic nerves downwards form the splanchnic nerves. Blocking of these nerves by spinal anaesthesia produces, among other effects, dilatation of the abdominal vessels and a fall in blood-pressure. Fibres via the upper three lumbar nerves control the vessels of the kidneys, spleen, colon and genito-urinary tract and spinal block in this region causes only a slight fall in blood-pressure perhaps because the parasympathetic nerves are simultaneously affected. The vasomotor nerves to the arms come from the 4th to the 10th thoracic segments, to the legs from the 11th thoracic to the 2nd lumbar segments.

The fall in blood-pressure under spinal anaesthesia can be most reasonably explained by the above-mentioned effect of the anaesthetic on the sympathetic nervous outflow from the spinal cord. The fall in pressure begins about fifteen minutes after injection and reaches its lowest point about half an hour later. A gradual recovery then takes place provided haemorrhage or shock do not, in the meantime, occur. The fall in pressure, other factors being equal, depends on the number of white rami paralysed, i.e. on the height of the motor block. A high spinal anaesthesia will reach the 4th or 5th thoracic segments and, since the lower cardiac accelerator segments arise from this area, bradycardia is not uncommon but this need not be alarming unless a severe fall in blood-pressure occurs (Maxson [19]). Ferguson and North [20] state that the degree of blood-pressure fall can be estimated by the degree of bradycardia. However, a severe fall in blood-pressure is more likely to produce tachycardia.

Paralysis of the intercostal muscles of the chest by embarrassing cardiac filling is, in the opinion of Maxson, a definite factor in blood-pressure fall—the less inspiratory movement the less the "vis a fronte" in the great veins and the slower the blood flow towards the heart. Heymans (1933) [21] has made an interesting study of the effects of spinal anaesthesia in dogs. He showed that with spinal block to the level of the umbilicus no appreciable fall in blood-pressure occurred but the vasomotor control by the carotid sinus was suppressed or diminished.

Loss of general muscular tone, fall in intra-abdominal tension, cerebral anaemia and absorption of the drug into the circulation may be necessary factors in blood-pressure fall.
but I think there is no doubt that the main factor is vasomotor nerve paralysis in the subarachnoid space.

Anaesthesia and Shock.—The profound effects of spinal anaesthetics on the nervous control of the arteries has been shown in some detail above. General agreement as to the cause of shock has not been reached but one effect of shock is a loss of tone in the small blood-vessels. Now ether, chloroform and spinal anaesthesia have a profoundly deleterious effect on the vasomotor system but it is also of practical importance to remember that, in the case of the first two drugs, the cardiac reserve is also diminished while the third prevents the nervous control designed to compensate for shock and hemorrhage from acting. Most authorities, therefore, rightly state that these three anaesthetics should not be used in cases of imminent or developed shock.

Shocked animals show quite a different reaction to ether from normal animals—the initial fall in blood-pressure in cats under ether anaesthesia is progressive if shock develops and the blood-pressure falls to zero (Cattell [4]). Overdosage of narcotics can cause a marked fall in blood-pressure but this effect is reversible and, if the depth of anaesthesia be reduced, a rapid return to normal occurs. Anaesthetics plus trauma have quite a different effect—the blood-pressure recovery being retarded or prevented—such a condition we know as shock. Since Crile’s work in the prevention of operative shock by local anaesthesia combined with gas and oxygen much attention has been given to the search for a general anaesthetic which will, if not prevent, at least not increase shock. We cannot say that such an anaesthetic has been found though gas and oxygen, ethylene, and cyclopropane approach nearest the ideal. Jarman advocates the use of the intravenous barbiturates in shock and there is experimental evidence for his view. Seeley, Essex and Mann (1936) [14] compared the shock producing effects of ether and the barbiturates—they report in favour of the latter and even state that amytal can delay the onset of shock produced by intestinal manipulations under ether.

The toxic variety of shock (McDonald) shows a haemoconcentration and definite changes in blood concentration occur with ether. Seeley, Essex and Mann record under ether an 18 per cent increase in cell volume, a 19 per cent increase in haemoglobin and a 15 per cent increase in erythrocyte counts with an increase in the specific gravity of the blood. As regards the permeability of the capillaries, considered so important in toxic shock, investigators into the basic action of anaesthetics agree that cell permeability is decreased by narcotics but the removal of the narcotic is at once followed by a marked increase in the permeability of the cell membrane. Since transfer of fluid from the blood to the tissues, lymph spaces and body cavities is through the cells of the capillary bed, anaesthetics, by this local activity, can, where the first effect has worn off, considerably increase this flow. Perhaps this effect has a considerable influence on the development of shock.

Blalock [22] has shown that the type of shock produced by crush injuries of the limbs can be explained as a hemorrhage or loss of plasma into the injured limb and this loss of fluid is sufficient to account for the resulting fall in blood-pressure. Compensation for this loss is fairly good at first and no marked fall in blood-pressure occurs but only because the remaining organs of the body are starved of blood by severe vasoconstriction. Anything which interferes with this vasoconstriction, e.g. spinal block, chloroform, will cause the immediate appearance of clinical signs of severe shock. Bleeding experiments have shown that not until about 60 per cent of the total blood volume is lost does a marked fall in blood-pressure occur. This marked fall in pressure occurs when the essential structures of the body are beginning to lose their blood supply and eventually the vasomotor centre fails and all control of the blood vessels is lost. Spinal anaesthesia prevents this compensation by its peripheral nervous action, chloroform and ether probably by direct action on the vasomotor centre. The blood-pressure must not be taken as an infallible guide to the degree of shock and when the fall does occur the patient has already exhausted his reserves. McDowell’s [23] opinion that “the individual who gives an anaesthetic such as ether or chloroform in obviously toxic shock is guilty of little short of homicide” has a sound experimental basis.
As long ago as 1911 Cannon and Hoskins [24] found an increased output of adrenaline in rats and rabbits following the stimulation of the sciatic nerve and noted adrenaline exhaustion as a possible factor in the production of shock but this action, mentioned also by other workers, has not been proved. The advocates of the neurogenic theory of shock suppose a long sympathetic pressor effect followed by an inhibited or depressed state due to exhaustion (O'Shaughnessy and Gloyne). Freeman (1933) [25] showed that continuous adrenal infusion in rats produces blood concentration and a reduced blood volume, two of the principal characteristics of toxic shock. It is suggested that this state is due to asphyxia of the capillaries, damage to their walls and a consequent irreversible loss of fluid. Elliott (1912) [23] demonstrated that ether alone can reduce the epinephrine content of the adrenal glands if the splanchnic nerves are left intact. Section of the nerves prevented this effect and further experiments using chloroform showed a similar action. Urethane, an anaesthetic frequently used in animal experiments, gave the same result. Maes (1936) [27] showed that ether diminished the action potential of the splanchnic nerves but Grollman (1936) [28] is of opinion that anaesthetics inhibit the reflex output of adrenaline. When it is remembered that ether and chloroform cause peripheral vasodilation certainly in the lower extremity (Herrick [17]), it can be realized that the experimental evidence is conflicting.

This summary of the pharmacology, in relation to the circulation, of the common general anaesthetics, indicates that they can aggravate or initiate shock apart altogether from the effects superimposed by a severe injury or operation. Cyclopropane, ethylene, nitrous oxide and perhaps the barbiturates if used skillfully would appear to be the least injurious to the circulation on whose maintenance recovery from severe injury so largely depends. It is necessary again to emphasize that ether, and particularly chloroform, not only cause peripheral circulatory damage but can injure the heart muscle directly. The toxic effect of an improperly chosen or badly administered anaesthetic may well lead to the loss of a patient who might have been saved by surgical intervention. Here I might mention the value of continuous blood-pressure readings being charted at short intervals during operations. Besides their statistical value an early rise in blood-pressure will often precede the fall due to shock so giving early warning that counter measures are necessary.

It is hoped that this article will convince the surgeon that the specialist anaesthetists, dislike of chloroform and ether is not wholly a prejudice but has a sound pharmacological basis.

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