TREATMENT OF HAEMORRHAGE WITH GANGLION-BLOCKING AGENTS: A PRELIMINARY REPORT *

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The complex of the shock reaction has been likened[1] to a fugue, which consists of 3 parts, viz. the exposition, the response and the counterpoint; the exposition being the noxious stimulus or injury, the response the reaction of the cardiovascular system and the organism as a whole, and the counterpoint the means we adopt in treatment. It is in relation to the counterpoint, or treatment, that I shall confine my remarks.

The thesis of this paper is that, in association with adequate blood replacement, ganglion-blocking agents have a fundamental and vital part to play in the treatment of haemorrhage, especially in the more severe types. This therapy is based on the premise that vasoconstriction is often associated with deleterious and undesirable effects, and if prolonged and unrelieved constitutes a lethal factor in the development of 'irreversibility'. An analysis of vasoconstriction and its effects is therefore necessary.

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Vasoconstrictor Response

Intense peripheral vasoconstriction is the common denominator in virtually all forms of shock, irrespective of the cause, and constitutes a fundamental bodily response. It is primarily protective in nature, being designed to restrict fluid and blood loss and maintain the blood supply to the brain and myocardium. It also incidentally constitutes an effective barrier to the rapid restoration of the blood volume. A great deal of experimental and clinical work has been done in relation to this subject and can be best considered in two main groups, viz. (1) factors related to vasoconstriction and (2) factors accompanying vasodilatation. It will be shown that the former are associated with undesirable sequelae and the latter with beneficial effects.

There is an accumulation of evidence which suggests that irreversible shock may be due to excessive prolongation of the vasoconstrictor reaction, which after a time becomes self-perpetuating.[2-5] Irreversible shock has been produced by prolonged intravenous injection of noradrenaline in animals which had not suffered fluid or blood loss.[6-8]

Therefore the irreversible phase of haemorrhagic shock is not due to a low blood pressure *per se* but rather to the secondary response to vasoconstriction.[9-11]

That vasoconstriction may be so intense that it actually hinders peripheral blood flow, is demonstrated by Wang *et al.*[12] in some excellent experimental work employing cyanide which, because of its action *via* the chemoreceptors, measures central flow, and fluorescin, which measures peripheral flow in that it must leave the peripheral system in order to become visible. These findings have been confirmed by other workers.[6-8]

Zweifach[13] in his classic analysis of the microcirculatory derangements as a basis for the lethal manifestations of experimental shock has elucidated this problem further. He has shown that under conditions of moderate hypotension the operation of homeostatic mechanisms is still adequate to distribute the blood commensurately with the air requirements of tissue metabolism. But when the hypotension is protracted and severe these mechanisms become ineffective, because arterial and venous constriction has now progressed to such an extent that changes distal to the constricted vessels cannot ensure an effective distribution of blood to the tissues through the capillary vessels. Two organs which are especially vulnerable to deficient circulation during haemorrhagic hypotension are the liver and intestine. Zweifach shows quite conclusively how this deficiency of tissue flow involves these organs in the decompensatory trend leading to irreversibility.

Thus it is seen that the vasoconstrictor response, initially protective, if prolonged and severe can become a parent mechanism in the production of irreversibility. Similarly, pain perception is a highly important defence against injury, but no one would suggest that its prolongation was in any way necessary for the survival of the patient. In fact if unrelieved it may cause profound shock and exhaustion. This is an important and basic concept.

Even before vasoconstriction had been observed directly under the microscope, numerous investigators concluded that if the body were freed from the influence of the central nervous system 'marked shock' would fail to produce death in a significant percentage of cases. The influence of the central nervous system has been counteracted by spinal anaesthesia, subarachnoid injection of procaine, transection of the spinal cord, and bilateral thoraco-lumbar sympathectomy.[8,14-16]

It has been demonstrated[17-21] that the protection of experimental animals against the noxious stimuli of vasoconstriction by the pre-shocking administration of blocking agents such as dibenamine, TEA and chlorpromazine results in a significantly higher survival rate in these animals; thus showing that vasoconstriction is not necessarily an effective long-term physiological response to haemorrhage.

Clinically, ganglion-blocking agents were primarily designed to limit bleeding during operation. But it soon became apparent that these agents afforded some protection against the development of shock during elective surgery, and attention immediately became focussed on the possibility that vasomotor activity was the essential cause of peripheral circulatory failure. Johnstone[1] holds that halothane has provided strong, if not conclusive, evidence in favour of the concept that vasoconstriction is an undesirable consequence of trauma or haemorrhage.

Vasopressor Therapy

Despite the foregoing it has been recommended,[22] and is still generally accepted, that all possible attempts should be made to maintain a normotensive head of pressure with vasopressor drugs. This recommendation is deserving of a critical analysis. In spite of the fact that the administration of a vasopressor agent is no guarantee that an adequate blood flow will be maintained in the tissues, a multitude of clinical reports on the use of noradrenaline (norepinephrine in American literature) have appeared. Very few experimental reports, however, can be found on this subject, and those that are available reject this as a rational form of therapy, viz.:

(*a*) Remington *et al.*[17] showed that noradrenaline decreased the survival rate in dogs subjected to haemorrhage.

(*b*) Foster et *al.*[23] working on renal blood flow in haemorrhagic shock, found that in spite of a normal pressure being maintained by noradrenaline 8 out of 10 dogs developed irreversible shock.

(*c*) Wiggers *et al.*[18] showed that the use of a vasopressor might transform 'impending' into 'irreversible' shock.

Why then has noradrenaline been used? It is because we have been led to believe that the irreversible phase of shock is myocardial in nature; since then, the primary and potent action of noradrenaline is believed to be on the contractibility of the myocardium, it is the drug of choice.[24] There are two objections to this, viz.:

1. Adrenaline does not increase the coronary flow and in moderate doses will decrease the flow.

2. All irreversible shock is not myocardial in nature, especially haemorrhagic hypotension, which is the variety under discussion.

How, then, can satisfactory results be obtained if we increase the work load of the heart without increasing (we may even decrease) the coronary arterial flow? The uniformly poor results of noradrenaline in controlled series do not seem to warrant the routine use of the drug in haemorrhagic hypotension.

Mural Tension and Blood Pressure

Two other facts warrant consideration, one a mechanical force and the other related to blood-pressure estimations. Burton[25] has shown that with reduction in the diameter of blood vessels the chances of closure of the lumen secondary to 'tensions forces' in the walls are greatly increased. This postulate is in accordance with the Laplace theory of the 'paradox of the elastic cylinder'. This state of affairs would not apply if vasoconstriction, i.e. the active 'tensions force', is prevented.

There are limitations to the accuracy of baumanometer estimations of blood pressure. Sharpey-Schafer[26] has pointed out that thick arms produce false readings and that this method breaks down when the mean and pulse pressures are low or the peripheral vessels are so constricted as to damp out the small pulsations needed to detect systolic level. Boba and Converse have noted that the blood pressure as measured by an intra-arterial cannula is not an index of capillary circulation. Clinical observation and experimental evidence tend to prove that tissue flow and arterial pressure cannot be directly correlated, and in fact may be completely divorced from each other. Their statement that 'meticulous and assiduous regular estimation of blood pressure is probably more for the therapy of the doctor in attendance than

for the patient' highlights this long and deep-rooted fallacy of the importance of maintaining the blood pressure at all costs.

Philosophy of Therapy

If one can conceive that an acute, severe haemorrhagic episode is an experience that the body was not designed to withstand for any length of time, then one may accept the principle that our therapeutic efforts need not mimic normal physiological responses. In a sense, we should not strive for 'fitness' of the individual in order to observe Cannon's 'fight or flight' theme, but rather for preservation of viability of tissues and organs. Viability does not of necessity imply function. This point has been carried to an extreme in hypothermic anaesthesia, where all bodily functions, including cardiac activity, are suppressed so that the body can withstand insults which are considerably beyond its normal limits of tolerance.

The Essential Problem in Treatment

In a final analysis, therefore, the survival of the organism depends upon the supply of oxygen and nutritive materials to the tissues. This is facilitated by an adequate blood flow to the tissues, which is in essence the prime purpose for which the cardiovascular system was designed. With loss of blood the peripheral flow in many regions is reduced below the point where oxidative tissue metabolism can be effectively carried out. This reduction in flow is due to a widespread peripheral vasoconstriction compensating for the inability of the heart to maintain an effective cardiac output and blood pressure. The net result is a compensatory situation in which blood pressure is maintained at the expense of blood flow to the tissues. In this situation the relative autonomy of the terminal vascular bed becomes the dominant factor and gives rise to changes antagonistic to the initial compensatory readjustment. The longer this stage of the syndrome is allowed to progress the more refractory to fluid replacement the body becomes, and fatal circulatory collapse ensues. This imbalance of blood loss and the vasoconstrictor response is contained in Boba and Converse's apt definition of shock, viz., 'The sympathetic response to an acute reduction in cardiac output (primary or secondary) wherein the response becomes an independent noxious stimulus'. There are thus two major problems in therapy, viz.:

1. To combat the decrease in cardiac output.
2. To prevent damage from the prolonged overwhelming sympathetic vasoconstrictor response.

With haemorrhage the decrease in cardiac output is secondary to a decrease in venous return, and is treated by blood replacement.

The rational approach to the treatment of the vasoconstrictor response is fairly obvious. Firstly, it is important to interrupt the train of events progressing to irreversibility. Secondly it is desirable that the barrier against rapid blood replacement which vasoconstriction causes should be removed. Finally, the blood that is transfused should be able to reach the tissues. In other words, not only is it important to restore blood volume, but we must ensure that the blood is able to subserve its vital function of maintaining cellular integrity and viability.

Administration of a ganglion-blocking agent, by virtue of its vasodilator effect, will satisfy the above criteriae.

Ganglioplegic Effects on Special Organs

The use of deliberate hypotension in anaesthesia has stimulated a number of investigations in the field of circulation at low pressures, which serve to indicate that some of our commonly accepted concepts need re-evaluation.

In the kidney after injection of a ganglion-blocking agent very little change in renal blood flow can be observed. If the blood pressure is then raised with a sympathomimetic amine a sharp fall in renal blood flow co-existent with an increase in systolic blood pressure can be demonstrated.[23,27] Even at extremely low heads of systemic blood pressure, urinary output is maintained, though somewhat depressed.[28]

In the brain the circulation may be 'pressure regulated', or at least the calibre of an artery may be a pure function of the head of pressure to which it is exposed.[29,30] With low arterial pressures (regardless of how achieved) cerebral vasodilation is the response. With high arterial pressures vasoconstriction is the response. The vessels of the brain are apparently designed to regulate the resistance to flow in their own circulatory area. Kety *et al.*[31] defined the term 'cerebrovascular resistance', and showed that its value varies in the same direction as the arterial blood pressure. This in no way contradicts the fact that anoxia is a powerful stimulus to cerebral vasodilation. Philosophically, the cerebrovascular response to anoxia supports the concept that vasodilation affords better circulation.

As regards the heart, there are two factors operating from the administration of a ganglion-blocking agent, viz. (1) a reduction in the work of the heart as a consequence of decreased peripheral resistance, and (2) a reduction in coronary arterial flow. Hackel *et al.*[32] and Eckenhoff *et al.*,[33] working under experimental conditions, have reached the conclusion that with reduced peripheral resistance the reduction in cardiac work is relatively greater than the reduction in coronary flow.

Capillary Reinfusion or Auto-infusion

It is important to reiterate that ganglion-blocking agents should not be exhibited unless there is adequate blood available for concomitant transfusion. The quantity of blood replaced calls for comment, and Ruscoe Clark's[34] contention that what is required is 'bigger and better' transfusions needs some modification, based on the phenomenon of capillary reinfusion, sometimes labelled auto-infusion.

The reinfusion which occurs immediately after haemorrhagic shock has been observed directly by determinations of the total blood volume before and after haemorrhage,[35] and indirectly by observing the cardiovascular response to the quick reinjection of all shed blood.[20] It has also been shown that rapid transfusion of volumes equal to those removed from experimentally bled animals has produced primary cardiac failure because the post-transfusion blood volume exceeds the volume before haemorrhage.[36,37] This is responsible for the theory of partial replacement therapy which is discussed below.

If the source of the additional fluid is the extravascular space, and if the shift occurs at the capillary bed, certain corollaries should follow:

(*a*) The amount of blood that can be shed with one maximal bleeding must be unpredictable because it is related to the functional status of the animal, including fluid reserves and the ability to mobilize these reserves. This has been demonstrated experimentally.[35,36]

(*b*) If the source of the fluid is the extravascular compartment and if this reservoir is not replenished, a succeeding lethal haemorrhage should not yield as much blood as it would under normal conditions. Foreman[37] has shown that the bleeding volume of dogs subjected to a shocking procedure 1 hour before the lethal haemorrhage was consistently lower than the bleeding volume in a series of normal control dogs.

Because the extravascular fluid spaces must supply a reservoir of fluid for withdrawal into the intravascular compartment the use of intravenous glucose in water or normal saline to replace this reservoir is of some importance.

With intense precapillary vasoconstriction the hydrostatic pressure of the capillary will drop, and a level will be reached where the osmotic pressure of the plasma is higher than that of the hydrostatic pressure, and thus the flow of fluid will be reversed and pass into the intravascular compartment. It has been stated that the beneficial effects of the ganglion-blocking agents are due to the fact, that by preventing vasoconstriction, a greater surface for reinfusion is afforded.[18]

CASES TREATED

Six cases, 3 treated with chlorpromazine and 3 with arfonad, will now be described. This series is very small, which is due to the fact that only cases that were severely shocked and might have succumbed to conventional therapy were treated—in an endeavour to assess the merit of the clinical applications of this concept and not to be lulled into a false sense of security and success by treating milder cases that would have responded to simpler means.

Most of the published work on the use of ganglion-blocking agents has been done in experimental animals, and very little in human beings.

Chlorpromazine

Case 1

A 20-year-old Bantu male, admitted comatose, pulseless and with cold extremities, Cheyne-Stokes breathing, and blood pressure 80/0 mm. Hg. Bright red blood was catheterized and there was marked bruising over the right loin. A diagnosis of ruptured kidney was made; in addition displaced fragments of the pelvis could be felt *per rectum*.

Blood transfusion was immediately commenced and 12·5 mg. of chlorpromazine was given intravenously 35 minutes after admission. A noticeable effect following the chlorpromazine was the greater speed with which the blood could be administered. The extremities became warmer and the blood pressure rose to 90/25. In 2 hours 6 pints of blood, 1 pint of dextran, 1 pint of plasma and 1 litre of dextrose-saline was given. The patient, however, never recovered consciousness, and he died on the way to the operating theatre.

Case 2

An obese 65-year-old Malay female, admitted with a 14-hour history. She was grey, exhibited marked pallor, and had cold extremities and a very thready pulse. The abdomen was distended and rigid, and X-ray revealed the presence of gas under both sides of the diaphragm. ECG showed evidence of a posterolateral cardiac infarct, probably not of recent origin. In spite of the indications for surgery she was not considered a good candidate, because the exact diagnosis was in doubt.

Blood and plasma were administered and also 25 mg. of chlorpromazine intravenously. An apparent improvement was noted in that the extremities became warmer and pink. Laparotomy was performed 3 hours later, when a duodenal perforation was sutured and 5 stones removed from the gall-bladder. The patient made an uneventful recovery and was discharged 10 days later.

Case 3

A Bantu male aged 22 years, assaulted. Examination revealed multiple stab wounds as well as a large left haemothorax with mediastinal shift. The patient was pulseless and cold and had no recordable blood pressure. Blood transfusion was commenced and he responded; but 1 hour after admission he collapsed, and the wound in his chest began to expand with blood. Largactil 25 mg. intravenously, was given at this point, and the chest wound was opened in the ward, clot evacuated, and a bleeding intercostal vessel clamped and ligated. He was given further transfusion and made a good recovery.

Chlorpromazine has shown to have beneficial effects as a pre-shocking procedure.[21] This is borne out by the response in case 2 and to some extent in case 3. Case 1, being an already established case of shock did not respond, which supports the conclusion from the experimental work of Hershey *et al.*[21] that the administration of chlorpromazine after the onset of haemorrhage does not afford protection. Furthermore, chlorpromazine has various mechanisms of action and has the undesirable effect of increasing the pulse rate.

Arfonad

Arfonad (d-3,4 (1′, 3′-dibenzyl-2′-ketonim-idazolido-1,2-trimethylene thiophanium d-camphor sulphonate) is a thiophanium derivative which has the characteristic ganglionic blocking and hypotensive effect of tetra-ethyl-ammonium bromide (TEA),[38] and its main action in man is assumed to be primarily ganglionic blockade. Sarnoff *et al.*[41] state that the continuous graded intravenous administration of arfonad appears to 'provide a quantitative method of diminishing peripheral vascular resistance, in a gentler and more promptly controllable manner than has been possible by other means', and they suggested its use in the treatment of pulmonary oedema. Arfonad has assumed an increasingly important place in the production of deliberate hypotension during surgery.[40-43]

Arfonad was first used in the treatment of haemorrhagic shock by Converse *et al.*[29,44] They treated 8 cases with 'heartening' success in 25%. In all cases the haemorrhage occurred in the operating theatre. This had the advantage that the blood loss could be accurately estimated, and also that therapy could be undertaken relatively early. The 3 cases treated in the present series are as follows:

Case 1

A Bantu male aged 56 years, who had undergone 5 operations for tuberculous peritonitis and adhesions with obstruction. He was still left with a faecal fistula of the small bowel, and a distal block in the caecal area. Laparotomy was undertaken, the fistula closed, and a right hemicolectomy performed.

He recovered from the anaesthetic and was returned to the ward. One hour later he suddenly deteriorated. He was now cold, pulseless and cyanotic, with no recordable blood pressure. In addition his dressings were soaked with blood and, on removal of these, blood was found to be gushing out of his drainage tube.

He was immediately taken to the theatre, where blood transfusion was commenced and arfonad administered at the same time as a 0·1% solution in normal saline. The response was satisfactory in that the patient became warm and pink and the bleeding did not increase. The abdomen was reopened and unfortunately no single bleeder was found. Instead a widespread and diffuse ooze was present, which it was impossible to control, despite adequate blood replacement. The abdomen was packed, but the patient died, and the cause of death was thought to be a disorder of coagulation.

Case 2

A Bantu female 49 years old, admitted with a history of having been kicked in the abdomen 20 hours before admission. On examination the abdomen was found to be rigid. Laparotomy was performed and gross peritonitis due to a traumatic perforation of the terminal ileum was dealt with. Just as the peritoneum was about to be closed cardiac arrest supervened. A left thoracotomy was immediately performed and cardiac massage instituted. With the return of the cardiac beat arfonad infusion was commenced. The patient recovered and was returned to the ward. She regained consciousness completely and was perfectly rational She still showed signs of toxaemia and 28 hours after operation there was, if anything, some deterioration in her condition. Levophed was then administered. She died 20 minutes later.

Case 3

A female Bantu aged 38 years, admitted to the gynaecological ward. She was suffering from stage-III carcinoma of the cervix, which had been treated with radium 6 weeks before admission. She was extremely pale, with a very thready pulse, dry tongue and shrunken eyes, and extremely restless, and there was profuse bleeding from the vagina. The blood pressure was 50/0 mm. Hg and the haemoglobin 4·5 gm.%.

She was plugged vaginally and 5 pints of blood immediately transfused. As her blood pressure began to rise and as the last pint of blood was running in, another profuse vaginal haemorrhage occurred, with extrusion of the plug. She was now again very pale and pulseless, no blood pressure was obtained, and she was very thirsty and drowsy. Arfonad infusion of 0·1% in normal saline as well as further blood transfusion was commenced. The patient improved and the arfonad was continued over the next 24 hours, a total of 800 mg. being administered. Blood replacement was continued, a further 4 pints being given.

The patient recovered; she was no longer thirsty or restless and her blood pressure rose to 90/60, which she tolerated without any ill effects; the daily output of urine was 700 c.c. The vaginal pack was subsequently removed with no recurrence of bleeding, and she was discharged from hospital without any cerebral complications.

In these cases shock had been present for some time and was very well developed when arfonad was administered. Although 2 out of the 3 patients finally died, they died of other factors and not because of the administration of arfonad.

The survival rate in the 6 cases reported is not statistically significant, but it does appear that a ganglion-blocking agent with the attributes of ready controllability and speed of action is of considerable value in the treatment of haemorrhage.

DISCUSSION

No undue emphasis was placed on blood-pressure estimations, the colour and temperature of the extremities being used as an index of beneficial response. Nor was any attempt made to replace the blood loss volume for volume.

Converse *et al.*[44] have demonstrated, by estimations of blood volume made with radiochromate-51, that induction of hypotension in animals with arfonad results in an autoinfusion of 7-12% of the control volume. Thus, if the small clinical experience here reported, together with the work of Converse *et al.* is integrated with the laboratory experience of others, it would appear that controlled vasodilation produced by drugs takes advantage of the beneficial fraction of the normal response to loss of intravascular fluid, while blocking those responses which in themselves may become pathophysiological stimuli. In other words, part of the normal mechanism for defence against blood loss is maintained, viz. low capillary pressure allowing reinfusion from extravascular fluid spaces to take place, while vasoconstriction with its attendant anoxia is effectively blocked. The previously mentioned concept of maintaining blood flow to all organs—temporarily permitting viability but not function—appears to be satisfied. It must again be stressed that ganglion-blocking agents should on no account be administered without adequate and similtaneous blood replacement.

There must be limits to this method of therapy. It is obviously of some importance to give quantitative expression to these limitations in regard to the parameters of blood volume in which this approach can function. In age groups in which atherosclerosis produces a rigid vascular system, the haemodynamic responses postulated for this mode of treatment probably do not obtain. It also appears to be essential to use gravity as an aid to cerebral blood flow in the presence of very subnormal pressures.

The Physiological Significance of the Autonomic Nervous System

The study of the above-mentioned pathophysiological states, if followed to a logical conclusion, leads to the rather disconcerting conclusion that the autonomic nervous system may be a liability to the body.[2] This trend of thought makes the concept of ganglion blockade in haemorrhage less incongruous than it at first might appear.

The usual teaching about the sympatho-adrenal system is based on Cannon's work[45] and is expressed in the classical statement that it is a system which confers an advantage on the organism when it meets emergency of some sort, resulting in the need for staying to fight, or taking flight, or expressing fright. It is fairly obvious from experimental and clinical evidence that this system is not essential for ordinary life. Cannon himself showed that after the sympathetic nervous system had been ablated a cat could still lead a relatively normal life.

The sympathetic system does not play the vital role in survival of the organism that the adrenals, pituitary, kidneys and liver play. It becomes apparent that however important the autonomic nervous system may have been for some lower organism, it no longer occupies such a key position for mammalian life, or in particular for human life. Indeed, its presence may in fact amount to a liability, in that it makes possible the play of emotion of all sorts on our viscera, and so, perhaps, gives rise to the psychosomatic disorders. It is interesting, philosophically, to balance the physiological loss which would be incurred by abrogating our right to an autonomic nervous system against the clinical gain in the diseases from which we should be freed.

However, Cannon's view was that the sympathetic played its role not in normal life but under emergency conditions. If this were true it would be difficult to see how inactivation of the sympathetic by drugs could favour survival in haemorrhage, tourniquest shock, or poisoning with anticholinesterases. It would also be impossible to accept that the human organism is made ready for elaborate and taxing surgical procedures when all the autonomic defences are shattered by refrigeration and whole batteries of paralytic cocktails.

The impression is thus gained that the autonomic nervous system is an evolutionary heritage which, however useful in our ancestral past, now seems to be out of gear with the requirements of human life, with its continued and varied emotional pressures.

SUMMARY

1. Evidence is submitted of the lethal part that vasoconstriction can play in the development of 'irreversibility'.

2. The deleterious effect, and the irrational basis for the use, of vasopressor therapy is detailed.

3. The beneficial effects of counteracting the vasoconstrictor response by destroying nervous pathways and by means of ganglion-blocking agents is demonstrated.

4. The fallacy of a direct relationship between blood pressure and tissue flow is indicated.

5. The concept of concentrating on viability rather than on function as an initial measure by using ganglion-blocking agents (in addition to blood transfusion) is elaborated.

6. Certain characteristics and effects of these agents are noted.

7. A small series of 6 cases treated is presented.

8. The philosophy that the autonomic nervous system has outgrown its usefulness to man and represents an evolutionary heritage is suggested.

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