

1. DEFINITION AND PATHOGENESIS

Cardiogenic shock is shock occurring after myocardial infarction. It has been variously described as occurring in 6% (32), 2% (50) (65), 10% (98) (113), 17% (136) and 20% (52) of patients with myocardial infarction. Shock accompanies the onset of pain in few cases (32) and most cases occur in the first twenty-four hours after infarction (32) (113) although

80% of people developing shock after myocardial infarction die. This essay is concerned to ask why they die and what can be done about it.

Accordingly it consists of two parts: the one concerned with the definition and some relevant aspects of the pathogenesis of cardiogenic shock; the other concerned with therapy, its difficulties and its future.

In view of the difficulties in defining the criteria for diagnosis of shock, the individual criteria and the interpretations placed upon them warrant further discussion.

The pallor, coldness, diaphoresis and oliguria are taken to indicate an increase in activity of the sympathetic nervous system leading to sweating and a reduction in blood flow to the skin and the kidney respectively. Similarly, signs of anxiety, restlessness or apathy are taken to indicate a reduction in cerebral blood flow or cerebral hypoxia. Anxiety or restlessness might be expected in patients who are in pain

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Cardiogenic shock is shock occurring after myocardial infarction. It has been variously described as occurring in 6% (32), 8% (50) (63), 10% (88) (113), 12% (136) and 20% (52) of patients with myocardial infarction. Shock accompanies the onset of pain in few cases (32) and most cases occur in the first twenty-four hours after infarction (32) (113) although they may occur several days after (63).

The criteria for diagnosis of shock may vary with different authors (hence the anomalous 20% above) but, in general, it is agreed (32) (46) (50) (55) (61) (96) (148) that shock is suggested clinically by the following features: cold, clammy extremities, pallor and cyanosis, rapid, thready pulse, anuria or oliguria, anxiety, restlessness or apathy, and prolonged hypotension. The only objective assessment is of blood pressure and this alone does not define shock (148). Considerable variation may therefore be expected in diagnosis.

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for the measurement of arm (20) and cerebral blood flow (62) exist but the measurements do not yet appear to have been made in cardiogenic shock. The tachycardia also reflects the increased activity of the sympatho-adrenal system, the increased rate being due probably to an increase in sympathetic activity to the heart and to the high level of blood catecholamines in shock (158). The increase in urinary noradrenaline and adrenaline which has been demonstrated after myocardial infarction appears to be related to the clinical severity of the condition (158). The thready pulse may be taken as an indication of the reduction in stroke volume (96).

Cyanosis represents an increase in the amount of reduced haemoglobin visible in the sub-papillary venous plexuses (94) and is influenced by the haemoglobin content of the blood. So-called central cyanosis is said (46) to represent an arterial oxygen saturation of less than 90 - 95% but trained clinical observers are unanimous in their observation only when the oxygen saturation of blood is as low as 75% (106). The misleading effects of fluorescent lighting are important (79). Such cyanosis may be due to inadequate pulmonary oxygenation, increased deoxygenation of arterial blood or veno-arterial shunts. All three may be important in cardiogenic shock (see later).

Hypotension is difficult to define in view of the wide range of normal blood pressures in the general population (58) (111). Indirect measurement of brachial systolic blood pressure with a sphygmomanometer compares favourably with direct intra-arterial recording (at least at normal levels of blood pressure) within certain limitations, e.g., cuff

width and length (15) (57) (58) (77) (121) (124) (138).

Whether the agreement is of the same order in hypotension is not recorded. A systolic blood pressure of less than 100 mm.Hg. (96) or less than 90 mm.Hg. (111) has been taken as indicating shock while others feel that a systolic blood pressure of less than 80 mm.Hg. is a necessary criterion of shock (32) (50) (53) (141). Others again adhere to 80 mm.Hg. with an "allowance" of 90 (63) or 100 mm.Hg. (52) for previously hypertensive patients. Mutual agreement about the value of blood pressure taken to indicate shock is desirable if therapeutic trials are to be comparable. Hypotension in shock can be taken to indicate that the heart is unable to maintain blood pressure by an adequate output in a situation where the total peripheral resistance is normal or raised (53) (96) (151) (152). It must be distinguished from the initial hypotension often seen in myocardial infarction which is relieved by analgesics or sedatives and is attributed to pain (46). Vaso-vagal attacks (5) (153) and excessive doses of morphine, pethidine or sedatives (46) may also be misleading causes of hypotension.

The clinical definition of shock is not entirely satisfactory and since the early classical studies of Coumand (31) attempts have been made to find a haemodynamic expression of shock. Right heart catheterisation is essential in haemodynamic studies if one is to measure cardiac output, central venous pressure and pulmonary artery pressure. It is used for withdrawing samples of "mixed" venous blood for direct Fick or injecting dye for dye diffusion estimations of cardiac output (59) (147) (160). Cardiac output is traditionally

expressed as cardiac index (L/min./m<sup>2</sup>) (161) in an attempt to eliminate variations in cardiac output related to body size. The total peripheral resistance can be calculated from the relation

$$\text{CARDIAC INDEX} = \frac{\text{MEAN AORTIC PRESSURE} - \text{CENTRAL VENOUS PRESSURE}}{\text{TOTAL PERIPHERAL RESISTANCE}}$$

In animals the haemodynamic consequences of shock have also been studied after coronary embolisation with spores or microspheres (1) (12) (90), coronary ligation (28) (47) or occlusion (120).

The outstanding feature of haemodynamic studies has been the uniform demonstration of a fall in cardiac index in cardiogenic shock (148) (162). It is important to remember that this is an acute fall in cardiac index. In general, the lower the cardiac index, the more severely ill the patient is, although specific instances have recently been described (151) (152) where a very low cardiac index has been present in patients without shock. Hypotension itself is not sufficient to define shock since sympathectomised patients may have adequate tissue perfusion with a slow pulse and a low blood pressure (148). The effect of fever on the total peripheral resistance may cause a similar phenomenon (103). Although reduction of cardiac index may be present in non-shocked patients, severe reduction of stroke volume seems to be more "specific" to cardiogenic shock (96) and coupled with the demonstration of an increased cardiopulmonary blood volume indicates failure of the left ventricle as a pump.

Total peripheral resistance in shock has been described as being increased (53) (96), normal (53) (96), or decreased

(53) (55). Gunnar (53) (55) divides his cases into two groups: one with an increased peripheral resistance which is considered to represent the normal reflex response to a fall in cardiac index and one with a decreased peripheral resistance which is believed to be the result of some vascular reflex from the damaged heart. Patients with a low total peripheral resistance responded to noradrenaline by increasing peripheral resistance which is taken to indicate that the vasoconstrictor mechanism is still functional although reflex vasoconstriction is inhibited by a reflex from the damaged heart. However, in cats the vascular tree can be responsive to noradrenaline in the "shock state" long after it has ceased to respond to sympathetic nerve stimulation (89) (107).

The heart has many receptors (64). Stimulation of some of them may lead to hypotension as, for example, in the left ventricular Bezold-Jarisch reflex (64) (118) with veratrine. This may be the mechanism of the bradycardia and hypotension seen in "shocked" dogs (29) which is abolished by vagotomy. Possible receptors for such a reflex have been described (139). Agress (1) has described another possible reflex in dogs mediated by the dorsal sympathetic roots, but his attempts to identify and block such a reflex in man have not been continued and were presumably unsuccessful. The higher frequency of shock in patients with branch rather than main stem occlusions in the coronary arteries has been given as a possible indication of reflex mechanisms in human cardiogenic shock (86). However, the significance of a reflex from the injured myocardium remains undetermined. Dogs

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with denervated hearts may still be shocked after infarction. Presumably people with transplanted hearts will still be liable to develop shock after myocardial infarction. This and the slow onset of shock (32) (113) do not favour a reflex mechanism.

An acute fall in cardiac index is the basic lesion in cardiogenic shock. Shock is not associated with any particular size (32) or site (113) of infarction. In one study shocked patients had a higher incidence of previous infarction than non-shocked patients (113) whereas the post-mortem hearts examined by Cronin (32) indicated that shock cases had a lower incidence of previous infarction. Cronin suggests that a previous infarct might protect the heart through the development of significant inter-coronary anastomoses (126). The impairment of cardiac function has been briefly described by MacKenzie et al (96). In their study measurements of myocardial performance indicated "gross impairment" in cardiogenic shock.

MacKenzie's fuller and more important studies in the same paper demonstrated that in shocked patients the  $P_aO_2$  was very low (mean 47 mm.Hg.) compared with non-shocked patients (mean 67 mm.Hg.) and that whereas  $P_aO_2$  rose to expected levels (mean 391 mm.Hg.) on administration of 87% oxygen to non-shocked patients, in shocked patients with oxygen the  $P_aO_2$  still remained remarkably low (mean 119 mm.Hg.). This has since been described by others (101) (117). A markedly increased alveolar-arterial oxygen tension gradient was also described (96) and has been confirmed by others in cardiogenic shock (100) (101) and in acute myocardial infarction without

shock/

shock (65) (117) (157). A significantly increased gradient is present even six to twelve months after infarction (102). The hypoxaemia is not due to inadequate ventilation since the  $P_a CO_2$  is normal or even decreased in these cases (96) (101). The hypoxaemia is due partly to an increased physiological dead space (65) (101) (117); partly to venous admixture (101) (117) (157) and also in some patients to the presence of a true shunt (96) (117) (164). The disturbed ventilation-perfusion ratios are probably due, in part, to the fall in cardiac index observed in shock leading to perfusion changes, and, in part, to the increased pulmonary venous pressure accompanying pump failure (101) leading to pulmonary congestion (87). The rise in left ventricular end-diastolic pressure which is implied in the genesis of pulmonary congestion and oedema in cardiogenic shock has recently been demonstrated (82). Detailed investigation of the ventilation-perfusion ratio changes in different parts of the lung should be possible with the techniques which have been described (30), but investigations of this nature have yet to be carried out in cardiogenic shock. They should demonstrate more clearly the nature of the ventilation-perfusion imbalance. In some areas of the lung where there is

The presence of pulmonary congestion in cardiogenic shock probably depends partly on the enthusiasm with which it is sought and partly on the severity of the cases described. For example, Cronin found crepitations absent in most of his 140 cases (32) while Nielsen describes frank pulmonary oedema necessitating treatment with digitalis in 30% of his 34 cases (113). McNicol (101) basing his diagnosis of congestion on

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the presence of crepitations or rhonchi in the absence of a history of bronchitis found pulmonary congestion in 13 out of 15 shocked patients. Radiological criteria are also valuable (157). McNicol has demonstrated unequivocally the importance of congestion in the genesis of hypoxaemia after acute myocardial infarction. Two of his shock cases had no clinical evidence of congestion and it is suggested that in these cases the hypoxaemia is due solely to a gross disturbance of perfusion. Indeed, an increased physiological dead space was very evident in these patients. It is in such cases particularly that a regional analysis of ventilation-perfusion ratios would prove interesting.

The true shunt which has been described is thought unlikely to be due to arterio-venous anastomoses "since it disappeared on recovery in two cases" (96). The possibility of arterio-venous anastomoses as a factor in shunt at high altitude has been described in association with an elevated pulmonary arterial pressure (125) but no such relationship between presence of shunt and pulmonary arterial pressure exists after myocardial infarction (59). It has been suggested that the shunt may be due to "collapse, oedema or blockage of alveoli in some areas of the lung where there is continued circulation." (96). This is more likely.

The hypoxaemia of cardiogenic shock is associated with a significant acidosis (96) (97) due principally to a rise in the concentration of blood lactate. Kirby and McNicol (81) note that the acidosis found in acute myocardial infarction is most severe in patients with hypotension (<90 mm.Hg.) plus left ventricular failure (? shocked).

The demonstrated rise in lactate/pyruvate ratio (96) is indicative of tissue hypoxia (114a) and reflects an increase in the oxidation of  $\text{NADH}_2$  by the conversion of pyruvate to lactate in the cycle of anaerobic glycolysis. Anaerobic glycolysis is more active in hypoxia because less molecular oxygen is available for the operation of the cytochrome system and aerobic glycolysis.

The increased mortality found with severe acidosis is probably causally related and represents an association between two accompaniments of tissue hypoxia. In man correction of the acidosis leads to an increase in blood pressure in non-shocked patients (111) but this may have been related to the procedure and to the volume infused. The effect of correction in shocked patients is not documented. Other reports associate acidosis with arrhythmias in man (119), decreased myocardial contractility in dogs (25) (42), and vasopressor antagonism in dogs (155). In dogs the combination of acidosis and hypoxaemia is particularly lethal (104); the survival rate is increased by correction of both.

The following functional points are also worthy of note. The hypotension of shock will lead to a significant reduction in coronary blood flow since in the human case of infarction (but not the dog (123) and hence partly the dubious relevancy of experimental cardiogenic shock in dogs) the coronary vessels will almost certainly be atherosclerotic, arteriosclerotic or even calcified. This will limit or even eliminate any faculty for vasodilatation in response to hormonal, nervous, metabolic or any other demands. In this situation

the coronary flow becomes to a greater or lesser extent dependent on aortic diastolic pressure (54) (63) (127) since most coronary flow occurs during diastole. The existence of coronary autoregulation is still debated (7) but where demonstrated it probably ceases, like cerebral autoregulation, at pressures of 50-80 mm.Hg. The effect of degenerative arterial disease on coronary autoregulation is not known and it should be possible to study this in a suitable animal preparation with and without the complications of myocardial infarction since its effect can only be guessed in man. Arterial disease is found in a wide range of animals including snakes, lizards, tortoises and vultures (44). Disease can also be produced by altering the diet of rabbits, rats (78) and pigs (73) and this disease closely resembles that found in man. The effect of coronary artery disease on autoregulation of coronary blood flow would be most easily studied in the pig. (For similar reasons the pig would seem to be a more suitable animal than the dog for investigating the efficacy of different forms of therapy in cardiogenic shock). For the moment it is agreed empirically that a pressure of 50-80 mm.Hg. is usually adequate to maintain coronary and cerebral blood flow. Regional flow studies (62) (160) might be interesting here also. In view of the need for a minimum blood pressure difficulties arise in therapy (see later) since attempts to increase the aortic pressure by vasoconstriction to maintain coronary flow will increase the afterload of an already embarrassed heart (16).

The sympathetic vasoconstriction observed in shock leads

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to a reduction in renal blood flow, glomerular filtration rate and urine secretion (156). If this oliguria (or anuria) is maintained microscopic changes may be visible in the kidney structure (148). Similarly impairment of liver function has been demonstrated in acute myocardial infarction (21) which is probably related to hepatic vasoconstriction (43). This may be a factor in the lactic acidaemia.

The changes observed in the peripheral circulation in shock have been investigated by many workers (112). Microscopic examination of the microcirculation in shocked animal preparations (112) (165) has shown great species variation in the behaviour of the microcirculation during shock and it is difficult from the observations which have been made to indicate any consistent microcirculatory defect in shock. However, disturbances of vasomotion and of the flow patterns in exchange vessels (6) have been observed. The role of arterio-venous shunts in the microcirculation remains uncertain (112).

Coupled with disturbances of flow, pressure and exchange relationships in the microcirculation may be disturbances of the coagulation mechanism (61) which have been observed in shocked patients by the proponents of a hypothetical mechanism for disseminated intravascular coagulation (60) (61) or sludging (85). This will lead to further disturbance of the exchange and nutritive functions of the microcirculation. If present in cardiogenic shock sludging should be visible in the bulbar conjunctiva (85) (92).

Mellander (89) (107) using his technique for the indirect  
study/

study of the microcirculation in cat skeletal muscle (Figure 1)\* has noticed in shock a progressive decline in the pre-capillary resistance response to sympathetic nerve stimulation while the capacitance response remains (Figures 1 and 2)\*. However, unphysiological doses of noradrenaline will retrieve the resistance response when sympathetic nerve stimulation fails (Figure 1:Q)\*. If shock is prolonged the capacitance response to sympathetic nerve stimulation is abolished and intravascular pooling may occur. At the same time disturbances of the relationship between pre- and post-capillary resistances and hence the Starling mechanism (146) will lead to haemoconcentration. Mellander interpreted the refractoriness to sympathetic nerve stimulation as being due to the presence of tissue hypoxia and accumulated "metabolites". The nature of such metabolites remains uncertain but acidosis is probably a factor (155).

Cat skeletal muscle in haemorrhagic shock is not the human peripheral circulation in cardiogenic shock but comparisons are useful and apparently valid since recent publications (14) (90) allow the following tentative interpretation of peripheral circulatory failure in cardiogenic shock: after infarction cardiac function is severely impaired (96) and although increased sympatho-adrenal activity may be adequate at first to maintain blood pressure it is later inadequate (89) (107). If the vasoconstriction is severe or prolonged enough it leads to tissue hypoxia (45) and acidosis (81). Hypoxaemia (96) will exaggerate this phenomenon and total peripheral resistance may fall. Progressively the resistance vessels become refractory to sympathetic nervous stimuli/

stimuli (107) while maintaining some sensitivity to nor-adrenaline. Ultimately this response also disappears (63) (113) along with the capacitance response. This may lead to acidosis, loss of capillary integrity, haemoconcentration, stagnation, disruption of lysosomes (14), coagulation of blood (61) and tissue destruction with consequent loss of organ function and death. Prominent among the ultra-structural changes in shock is mitochondrial damage (67).

The role of the sympatho-adrenal system in this sequence of events is prominent enough to make one wonder what the effect of coronary embolisation or ligation might be in dogs or other animals which had either been sympathectomised or made tolerant of catecholamines. Would the same percentage of sympathectomised or catecholamine-tolerant dogs develop shock as compared with normal animals?. If so, would the mortality be altered? Would chemical sympathectomy show the same effect? If the effect was beneficial might it be applicable to human cases as a form of "preventive" treatment for cardiogenic shock? Do people who have been sympathectomised develop cardiogenic shock as often as the rest of the population? If so, do they also have an 80% mortality?

The sequence of events in shock is never seen in its undisturbed entirety since therapy is usually instituted early in the march of events and may modify the picture considerably. However, it obviously fails to alter the picture enough since the mortality remains at 80% (32) (50) (88) (127). More optimistic figures for mortality (52) are misleading and probably reflect the inclusion in the diagnosis of shock of patients with the brief initial hypotension often seen after

myocardial infarction (46).

11. THERAPY

The logic behind the therapy of cardiogenic shock is simple - the application less so. Basically it consists of trying to keep the patient alive until his heart has healed enough to function adequately. In an unknown percentage of patients this will never happen regardless of which therapy short of total replacement.

There was a time when the object of therapy was to keep the blood pressures at normal levels with vasoconstrictors (70). More recently, however, it has been accepted that to prevent the development of tissue hypoxia with its attendant fatal complications (14) it is desirable to think not only in terms of increasing cardiac index but also of protecting the periphery from the ravages of vasoconstriction.

Much of the therapy which will be described may require more facilities than the still all too rare coronary care unit (50) (88) (115) (154) can provide and is certainly as yet far removed from simple ward therapy. Facilities for cardiac catheterisation, monitoring pressures etc. (136) (151) are still limited principally to research investigations and provide useful information on the effectiveness of different therapies. In view of the high mortality of shock cases, even with intensive therapy, it would seem reasonable that they should not occupy intensive care beds to the exclusion of other patients who might more obviously benefit from the advantages offered by such a unit.

Dog experiments have been used as "therapeutic trials" in cardiogenic shock and it is worth recalling that dogs with

experimental/

experimental acute myocardial infarction (51) (in common with many surgical patients with low output shock (12)) are suffering from a condition that is superimposed on an otherwise healthy heart and not one with diseased arteries and the consequences of progressive ischaemia over the years. Dog experiments should therefore not give rise to false hope.

It is proposed to discuss those aspects of therapy which the present author finds most relevant or interesting. The author feels justified in looking to the future in his consideration of therapy. Indeed, the present status of therapy renders such an attitude essential.

#### Initial Therapy

In cardiogenic shock the importance of immediate therapy has long been realised (52) (63). Patients should be put to bed supine unless the complications of pulmonary oedema have arisen. There is some dispute as to the incidence of this complication in cardiogenic shock but if diagnosed it should be treated in accordance with its severity (46). If administration of pethidine or morphine is needed to relieve pain then the dosage should not be excessive since both drugs have hypotensive and respiratory depressant effects (72) (133) (150). Shock patients are more liable to arrhythmias and asystoles ( a reflection of the hypoxic state?) than patients with uncomplicated infarction (50) (80). These should be treated according to standard therapy (46) (75) (133) (136). If acidosis is present this should be corrected by the administration of bicarbonate or THAM (in that order of preference): this in itself may reverse arrhythmias (119). Oxygen should be administered immediately.



## Oxygen

The administration of oxygen in cardiogenic shock has a sound theoretical basis (45) - the rationale being that the tissue  $P_{O_2}$  should be of the order of 10 mm.Hg. for metabolism to function aerobically. In cardiogenic shock the tissue  $P_{O_2}$  is probably much lower (45).  $P_{aO_2}$  in shock is low (96).  $P_a CO_2$  being essentially normal, administration of 100% oxygen is preferred (98) since the  $P_{aO_2}$  of some patients may be refractory to oxygen therapy (96) (101) (117). In acute myocardial infarction (149) and in cardiogenic shock (96) oxygen leads to no significant change in heart rate, a small fall in cardiac index and a slight rise in total peripheral resistance.  $P_{aO_2}$  will rise, the oxygen diffusion gradient will increase and there will be a slight increase in the amount of oxygen carried by the blood. In cardiogenic shock the blood should carry as much oxygen as possible (45) (77). With this in mind the possibility of hyperbaric oxygen therapy will be considered later.

"Traditionally" the next step has been to elevate the blood pressure with vasoconstrictors.

## Vasoconstrictors

The importance of elevating blood pressure to a certain minimal level in order to maintain satisfactory coronary and cerebral blood flow has already been mentioned. Certain agents e.g., angiotensin have no place in this sort of therapy (136) since they act solely on the peripheral circulation and increase total peripheral resistance and blood pressure at the expense of increasing cardiac overload and decreasing cardiac index. In a situation where cardiac index is already

too low a further decrease is not recommended. Similar arguments apply to purely  $\alpha$  adrenergic agents (95) (136). At this point it is convenient to mention that the terminology applied to the sympathomimetic drugs in this essay is that of Ahlquist (2). In his terminology  $\alpha$  drugs are drugs which act on  $\alpha$  receptors and are associated with vasoconstriction while  $\beta$  drugs act on  $\beta$  receptors and are associated with vasodilatation and myocardial stimulation.  $\alpha/\beta$  drugs combine both these actions.  $\alpha/\beta$  drugs such as noradrenaline and metaraminol (which releases noradrenaline from tissue stores (14)) have been used in classical therapy for some years. Both drugs act in small doses to increase myocardial contractility (131) and in larger doses to vasoconstrict all regional circulations except the coronary (66). Their pressor effect is predominantly due to the vasoconstriction and their action provides a high pressure-low flow system since the vasoconstriction decreases peripheral flow and the elevation in pressure increases cardiac work and hence decreases cardiac index (66) (87) (127) (133) (136) (141). Only in small doses will noradrenaline elevate the cardiac output. Difficulty is encountered in trying to weigh the merits of high pressure in increasing coronary flow against the disadvantages of increasing heart pressure work (66). In general, the use of sympathomimetic amines in cardiogenic shock is of dubious value and since they have been shown to cause shock in man (117) and dog (43) provides an interesting paradox.

There is no convincing demonstration in the literature that noradrenaline therapy has significantly affected the

mortality/

mortality from cardiogenic shock, indeed one trial hinted that the drug might have an adverse effect on the outcome of shock (132). No effect of noradrenaline therapy on mortality is seen in Cronin's 140 cases (32). Earlier reports of a halving of mortality (52) (63) have not been borne out and the patient selection procedure allows of the possibility that some non-shocked patients were included in these series. Gunnar, with his original interpretation of the pathogenesis of cardiogenic shock, is a stout upholder of noradrenaline therapy. Nevertheless, of his patients (53) (55) 65% died from shock and another 25% died shortly after recovering from shock.

Friedberg's recent statement that a pressor effect with noradrenaline is obtained in 80 - 90% of cases (46) must be contrasted with Nielson's figures (113) which show that 50% of patients are refractory to vasoconstrictors. The difference probably lies in the stage of shock at which treatment was initiated since refractoriness to noradrenaline is one of the later manifestations of shock and reflects the beginning of some of the more severe microcirculatory changes (14) (95) (107). This refractory state is almost invariably fatal (63).

Prolonged use of vasoconstrictor drugs may lead to an exaggeration of tissue hypoxia and the associated metabolic changes and ultimately to "decompensation" or reversal of the Starling mechanism (146) which causes net movement of fluid into the circulation in shock. In this state fluid may leave the circulation and haemoconcentration may occur. Decompensation is accelerated by noradrenaline and delayed by adrenergic blocking drugs.

12. Dog experiments have recently demonstrated that noradrenaline therapy alone in experimental cardiogenic shock does not significantly alter the mortality from the control value in untreated dogs (12) (35). Other therapy in dogs is more encouraging (see later).

The value of noradrenaline is limited only to the inotropic effect observed with small doses. This is almost certainly useful in some cases and in order to be of most value the vasoconstrictor effect should be minimised as much as possible.

Acceptance of the general failure of noradrenaline therapy is not yet complete. However, as an alternative to the high pressure-low flow system achieved with noradrenaline, it would seem that a low pressure-high flow system might be more successful in preventing and not aggravating tissue hypoxia. To this end the possibility of therapy with  $\beta$  drugs and  $\alpha$  blocking drugs will now be discussed. The difficulty with this sort of therapy is going to be in deciding what minimum pressure is acceptable to the system and whether at this pressure the heart can function adequately enough to maintain the required flow.

### $\beta$ Adrenergic Drugs

The use of isoprenaline in cardiogenic shock is a logical consequence of the realisation that maintained peripheral vasoconstriction is an undesirable state in shock. Isoprenaline increases heart rate and cardiac index and causes peripheral vasodilatation (110) (140) and the drug is obviously suitable for the operation of a low pressure-high flow state in cardiogenic shock. It warrants further clinical trials since there

is, as yet, little reported clinical experience with the drug. In dogs the  $\beta$  effect on the heart was not maintained with prolonged infusions (85) but this does not seem to be the case in man. A suggestion that the drug may precipitate arrhythmias (136) has not been borne out (110).

#### Adrenergic Blocking Drugs

$\beta$  blocking drugs are not recommended in cardiogenic shock since they block inotropic action on the heart and lead to a fall in cardiac index (95) (136).

$\alpha$  blocking agents such as phenoxybenzamine or chlorpromazine (36) provide a suitable alternative to the use of  $\beta$  drugs. As previously described prolonged reduction of perfusion in the peripheral circulation may lead to several potentially lethal changes (14) and although noradrenaline may initially elevate cardiac index and blood pressure eventually it causes a fall in cardiac index while the blood pressure remains elevated in a high pressure-low flow system. However, low pressures may give an adequate flow provided vasoconstriction caused by circulating catecholamines and nervous activity is reduced or overcome. Pressure may have to be maintained at 50 - 80 mm.Hg. to maintain adequate coronary and cerebral blood flow although it is probable that in cases with grossly diseased arteries these pressures may not be adequate enough. This is one of the problems. In general, however, low pressures, when associated with vasodilatation, are compatible with prolonged survival if fluid balance is maintained and the patient is positioned to facilitate cerebral perfusion and venous return (this applies also to  $\beta$  drug therapy.)

The logic of  $\alpha$  blocking is that vasoconstriction will be reduced, resistance will fall, capacitance will rise and the reduction in pressure will mean less pressure work for, and a lower myocardial oxygen consumption by, the heart.

The fall in resistance will lead to increased cardiac emptying and the increased capacitance may be useful in the treatment of pulmonary oedema (14).

So far, this approach to therapy has been established mainly in dogs (12) (14) (35) (36) (90) and awaits controlled application to human cardiogenic shock (18) (87). Dog experiments have their limitations but in view of the failure of classical vasoconstrictor therapy this treatment invites application. In dogs with shock phenoxybenzamine plus intravenous fluid or phenoxybenzamine plus intravenous fluid plus noradrenaline leads to very significant increased survival from cardiogenic shock (12) (35) (36) as compared with controls or noradrenaline treated animals. In general, survival is improved when the pressure work of the heart is decreased and the volume work is increased (34). The technique has also been successful in patients with low-output surgical shock (12) (35). When using this form of therapy it is desirable to keep the central venous pressure at 10 - 12 mm.H<sub>2</sub>O with careful monitoring and infusion of fluid when required. Monitoring of pulmonary arterial pressure has been suggested as a more reliable indicator of impending pulmonary oedema (61). Dietzman (36) recommends plasma or low molecular weight dextran as the fluids of choice for administration. The success of intravenous infusions of 5% dextrose alone has been noted by one investigator (114) (114a) and it has been

suggested/

suggested that in some cases the injured ventricle can still operate on the ascending portion of its Starling curve in response to distension (16) (127).

#### Low Molecular Weight Dextran (L.M.W.D.)

The properties of L.M.W.D. are complex but consist basically of a reduction in the viscosity of the blood (8) (13) (91), an increase in the circulating blood volume and the activation of fibrinolysis (13). Its properties are such as to make it useful in the shock state particularly in view of the suggested importance of disseminated intravascular coagulation (60) (61) or sludging in the pathogenesis of shock. Block (12) (13) has found that treatment with L.M.W.D. alone in experimental cardiogenic shock in dogs significantly improves survival as compared with control untreated dogs. The same group of workers have also used L.M.W.D. with favourable results in low-output surgical shock (36).

In a situation where the cardiopulmonary system is failing to supply enough oxygen to the tissues logical therapy would attempt to increase the supply of oxygen or decrease the demand. Hypothermia is one way of decreasing demand (17).

#### Hypothermia

Reduction of body temperature to  $33^{\circ}\text{C}$  reduces oxygen consumption to  $\frac{2}{3}$  normal and reduction to  $30^{\circ}\text{C}$  reduces it to  $\frac{1}{2}$  normal. The technique has been used successfully in the treatment of septic shock (11) where patients not responding to conventional therapy were cooled by surface contact with a refrigerated rubber blanket to  $32^{\circ}\text{C}$  and progressed to a 50% survival. Shivering is a complication which raises the

oxygen/

oxygen consumption but this can be controlled by neuro-muscular blocks (10). At moderate temperatures ( $32^{\circ}\text{C}$ ) myocardial efficiency is enhanced and ventilation is augmented. Blood chemistry is not dangerously altered at  $32^{\circ}\text{C}$  (10). The only suggested danger is an increased risk of arrhythmias (10) which is particularly inappropriate in myocardial infarction. The healing of the infarct will also be delayed. This form of therapy would seem to be worth a trial at least in animals. It may be necessary to counteract to some extent the vasoconstriction associated with hypothermia to achieve maximal benefit from this therapy.

One way of increasing the supply of oxygen to the body is by hyperbaric oxygen therapy.

#### Hyperbaric Oxygen

At 3 atmospheres of 100%  $\text{O}_2$  the pulmonary capillary blood should contain  $6.8 \text{ ml. O}_2 / 100 \text{ ml. blood}$  in solution. In fact, for a variety of reasons (129), it only contains  $\sim 5 \text{ ml. O}_2 / 100 \text{ ml. blood}$  in solution as compared with  $0.31 \text{ ml. O}_2 / 100 \text{ ml. blood}$  at one atmosphere of air. This represents an increase of 25% in the total amount of oxygen carried by the blood and the accompanying high partial pressure (1700 mm.Hg.) greatly increases the gradient and hence diffusion from the blood to the tissues (129) (136). In dogs hyperbaric oxygen protects against death due to ventricular fibrillation after embolisation (84) or coronary artery ligation (159) and may decrease the size of the infarct (84). The protection increases with increasing pressures (28) (47). In dogs also hyperbaric oxygen improves survival after diffuse myocardial infarction (74). In pigs

(coronary/



(coronary circulation similar to human) 1.25 atmospheres of 100% O<sub>2</sub> increase survival after coronary occlusion by aneroid constrictor (120). In man, the haemodynamic effects are an exaggeration of those observed in conventional oxygen therapy (24) (38) and oxygen toxicity (39) does not yet seem to have been a problem. In acute myocardial infarction with and without shock hyperbaric oxygen therapy has no effect on mortality although acidosis is reversed and there is a non-statistical suggestion of a reduction in the number of arrhythmias (24). There is a suggestion that failure of therapy in cardiogenic shock may be related to technical problems of managing decompression during the therapy (22). The type of mask is important (22). Cameron (23) presents an interesting case of cardiogenic shock where 100% O<sub>2</sub> at two atmospheres failed to raise P<sub>a</sub>O<sub>2</sub> above 180 mm.Hg. This probably indicates the presence of a considerable shunt (cf. (96)).

When some of the technical difficulties have been overcome (22) (129) it may be possible to estimate more accurately the importance of this form of therapy for the future.

Two more drugs merit brief mention.

#### Digitalis

Digitalis is recommended for the treatment of left ventricular failure in cardiogenic shock (55) (130) (136). MacKenzie's suggestion that the inability of digitalis to increase cardiac output in shocked patients (97) is related to the metabolic acidosis invites further examination. The danger of arrhythmias may be greater in the infarcted heart (75) (136). Nevertheless, the benefits of the drug probably

outweigh/

outweigh this disadvantage. (144). This has not been

Hydrocortisone since the heart is ejecting against the

This drug has been given a control trial and seemed to have no significant beneficial effect in cardiogenic shock (132). More recently, however, the use of massive doses of glucocorticoids (30 mg/Kg. methyl prednisolone, 150 mg/Kg. hydrocortisone sodium succinate) has been successful in experimental cardiogenic shock in dogs and in low-output surgical shock in man (37). The glucocorticoids decrease peripheral resistance by an unknown mechanism and it is suggested that they may help to maintain the integrity of cell membranes and sub-cellular particles such as lysosomes (37). withdrawal of blood during systole which

The use of such large doses in cardiogenic shock proper is not yet recorded and may prove to be beneficial.

Although in some patients the therapy which has been outlined so far may be of value, in others the impairment of cardiac function and its consequences will be too severe to be resolved by administration of the appropriate drugs, oxygen etc.. For these cases the hope must lie in the future in the possibility of some sort of assisted circulation used in association with vasodilator therapy - or in the transplantation of real and artificial hearts. ischemic

Assisted Circulation refractoriness to norepinephrine

Among the numerous bypass techniques and artificial devices which have been used to assist the circulation are the following:- three others showed transitory improvement

1. Veno-arterial shunts - in which blood from the venous side of the circulation is asynchronously pumped to

oared state of their vessels.

the/

the femoral artery (27) (144). This has not been successful since the heart is ejecting against the pressure of the bypass pump and myocardial oxygen consumption is increased. If an oxygenator is used the blood is liable to haemolysis.

2. Left-atrial to femoral bypass (27) (33). Left ventricular work and oxygen consumption are only reduced when an almost complete bypass is used and a simple technique has yet to be perfected (33).

3. Synchronous assistance or diastolic augmentation

by (a) Counterpulsation. This procedure involves cannulation of the femoral artery and the withdrawal of blood during systole which is pumped back during diastole. This markedly reduces systolic pressure and increases diastolic pressure with subsequent beneficial effects on myocardial

oxygen consumption and coronary blood flow (27) (142). Proper phasing is essential

(142). Embolised dogs have a 40% greater survival after counterpulsation (71). The

technique is now being tried on patients with a 30 hour history of cardiogenic

shock and refractoriness to noradrenaline therapy (144). So far there is one sur-

vivor out of seven very old patients. Three others showed transitory improvement

in their condition. The withdrawal of blood by the pump was limited by the dis-

eased state of their vessels.

It seems that the effect on coronary blood flow may be retained some time after the procedure is terminated (144). The advantages of this technique are that no massive surgery is needed and that blood haemolysis does not seem to be a problem. The difficulty of phasing the pump is a disadvantage.

(b) Synchronous external assistance, (116) (143) effectively uses the vascular tree of the lower limbs or body as the pump in counter-pulsation. The lower limbs are enclosed in a pressure suit or chamber and subjected to appropriately phased pressure variations. So far the technique has been used only on animals but as it is atraumatic it holds promise for the future.

4. Implantable prosthesis. The notable developments in this field have been in the in-series, air-powered, prosthetic auxiliary ventricles of Scroff (9) (49) (92) and Kantrowitz (26). In the infarcted dog heart these reduced the pressure work of the heart by 47%, rendered the elevated right atrial pressure to normal and produced a 40% increase in coronary blood flow and a 54% increase in aortic outflow (26). This device has been tried on two patients with severe congestive heart failure (76). One patient died within 24 hours but the other responded favourably before dying from a cerebrovascular accident 10 days after

the operation. A considerable amount of clotting was present on the prosthesis post mortem and this led to further modifications in design (76). The solution of the clotting problem would be a major advance in this field. The prosthesis may ultimately be of use in cardiogenic shock.

5. Artificial intracorporeal hearts. Twenty-six different mechanical hearts have been reported since 1958 (68). Most of them are air-driven and so far no animal has survived more than 30 hours with a functioning artificial heart. A haemodynamically sound heart has not yet been produced and the problems still remain those of clotting, haemolysis (3) (48) (56) and unbalanced perfusion (4). With further development and research the artificial heart may become a real prospect for the therapy of cardiogenic shock. Indeed, World Health Organisation has gone so far as to prophesy heart factories for the future in a recent report.

For the moment, however, attention is directed towards another surgical procedure namely that of cardiac transplantation.

#### Cardiac Transplantation

Surgical technique is not the limiting factor in cardiac transplantation (41) since autograft transplants have survived for up to two years (40). The limiting factors with homograft transplantation are tissue typing (108), the graft vs. host reaction, catecholamine hypersensitivity (41), the homograft rejection phenomenon, its detection (108) and

control with immuno-suppressive therapy (109). In dogs homograft transplants have survived 1 to 3 months with intermittent immuno-suppressive therapy (93) and at the time of writing Dr. Blaiberg is nearing the end of his third month with a transplanted heart. The problem of preserving the heart between donor and host seems recently to have been resolved by the use of hyperbaric oxygen and hypothermia which may preserve the heart for 48 hours with complete return to function. The possibility of heart banks is now being considered but such a development must await the solution of the many other technical problems involved in transplantation before it will bear full fruit.

Moreover, transplantation of the heart raises many interesting ethical and social problems (122) which have yet to be resolved. More particularly the definition of death requires a long awaited modification and this problem is now to be considered by the British Medical Association (19). Whether the development of a successful artificial heart will precede the breakthrough in the problems of cardiac homograft transplantation remains to be seen. Meanwhile, there is adequate time to consider the implications of either (122).

#### SUMMARY AND CONCLUSIONS

The difficulties of defining cardiogenic shock have been discussed in the text.

The immediate and obvious lesion in myocardial infarction is a damaged heart and haemodynamic studies indicate that the mechanical function of the heart is most severely damaged in those patients who develop cardiogenic shock (96) (162).

The consequences of impaired cardiac function are twofold.

Firstly, the fall in cardiac index ("forward failure") (148) (162) means that the heart is unable to maintain blood pressure and to supply all the tissues adequately with oxygenated blood. The sympatho-adrenal response effects a redistribution of blood flow which favours the coronary and cerebral circulations although the coronary flow is likely to be pressure dependent (54) (63) (127) and therefore still in danger. The reduction in tissue blood flow in general (due to vasoconstriction and decreased cardiac index) leads to tissue hypoxia as indicated by the rise in the lactate/pyruvate ratio (96). All tissues are affected by the hypoxia but some probably more than others. In the kidney, e.g., structural changes may be seen eventually (156) whereas functional changes are described in others, e.g., liver (21). The higher incidence of arrhythmias and asystole in cardiogenic shock compared with uncomplicated myocardial infarction is probably a reflection of the hypoxic state of cardiac muscle (50) (80).

Secondly, the heart is unable to cope with the load placed upon it and pressures rise behind the left ventricle (82) with resultant pulmonary congestion (87) (101) and impaired lung function (65) (101) (117) ("backward failure") which leads to further hypoxaemia and exaggerates the tissue hypoxia.

The state of reduced flow and tissue hypoxia leads to a progression of events involving the development of hypotension, refractoriness to noradrenaline, microcirculatory defects, coagulation defects, capillary damage, haemo-

concentration/

haemoconcentration, metabolic changes and, ultimately, tissue and bodily death.

The therapy of shock should be determined by the individual characteristics of each case taking into account the severity of shock, length of time in shock and various complicating factors such as pulmonary oedema and arrhythmias (124) (130). The aim should be to improve or assist cardiac performance.

Initially, there was belief in the adequacy of administering noradrenaline and elevating blood pressure in therapy of shock but with fuller understanding of the pathogenesis of shock and the haemodynamic consequences of administering noradrenaline the general failure of noradrenaline therapy is understandable. For the few patients who are responsive to inotropic doses of noradrenaline there is no problem. For the majority there is no adequate therapy and it ill befits the physician to send his patient to the grave with ever increasing doses of noradrenaline.

The logical arguments for hypothermia and hyperbaric oxygen therapy invite their further controlled application. However, it would seem that some immediate hope may lie in "vasodilator therapy". ( $\alpha$ block or  $\beta$  drug + L.M.W.D.). Low molecular weight dextran is probably useful in treating the coagulation which may be seen in shock. The infusion of 5% dextran alone as standard therapy for cardiogenic shock (114) (114a) is not recommended since most cases of shock have evidence of pulmonary congestion and it is unlikely that the heart is operating on the ascending portion of its Starling curve. If, as will probably be the case, the main-

tenance/



maintenance of adequate pressure and flow with vasodilator therapy is only possible in a small percentage of cases then this form of therapy could be combined with a form of assisted circulation. The relative simplicity of external and internal counterpulsation recommends them but it may be that when the clotting problems of the auxiliary ventricle have been overcome that it will occupy an important place in the therapy of cardiogenic shock. Some patients will need only temporary assistance until cardiac function improves but others will need permanent assistance and there is scope for much development in this field.

Ultimately, in this increasingly material-orientated world the possibility of intracorporeal hearts for all will have to be considered. The difficulties attaching to cardiac transplantation may not be fully resolved before the artificial heart is perfected. In any case, if this line of therapy is exploited for the treatment of cardiogenic shock or any other disease certain moral and social problems remain to be resolved.

At the moment it is probably not inaccurate to describe cardiogenic shock as "a momentary pause in the act of dying" (163). The present essay has tried to indicate the reason for this state of affairs and to outline the course which advances in therapy may take to remedy it.

ADDENDUM.

The inotropic action of paired pulse stimulation.

Since completing this essay the details of some work concerning the above have been published.

The paper confirms the inotropic action of paired pulse stimulation in the normal dog heart. In dogs with myocardial damage, however, although paired pulse stimulation produced an initial inotropic effect, after 30 minutes there was evidence of more marked left ventricular failure than was present initially. The damaged ventricle recovered its original function on reverting to single pulse stimulation.

The authors suggest from the evidence available that the increased myocardial oxygen requirements with paired pulse stimulation cannot be met by an appropriate increase in coronary blood flow to the damaged left ventricle.

It would seem from this study that paired pulse stimulation is not the answer to the problem of improving the function of the infarcted and failing heart.

Reference: King, A.J. and Taylor, D.E.M.:

The inotropic action of paired pulse stimulation in the normal and failing heart: an experimental study.

Cardiovasc. Res. 2: 122-129 (1968)

1. The studies of Mellander & Lewis. (89) (107).

The preparation consisted of the hind part of a cat isolated from the fore part leaving only the abdominal aorta, the inferior vena cava and the lumbar sympathetic nerves intact. The skin was removed in some animals to give a "pure muscle" preparation. Some animals were eviscerated. Arterial pressure was measured in the inferior mesenteric artery; venous outflow by a drop recorder in the inferior vena cava and volume changes of the lower limbs by a water filled, temperature regulated plethysmograph. The lumbar sympathetic trunks were sectioned at mid abdominal level and stimulated at supramaximal voltage at 3 m.sec. duration within the range of 1-20 impulses/sec. Haemorrhagic hypotension was induced by bleeding the animal until the blood pressure stabilised at 40-50 mm. Hg.

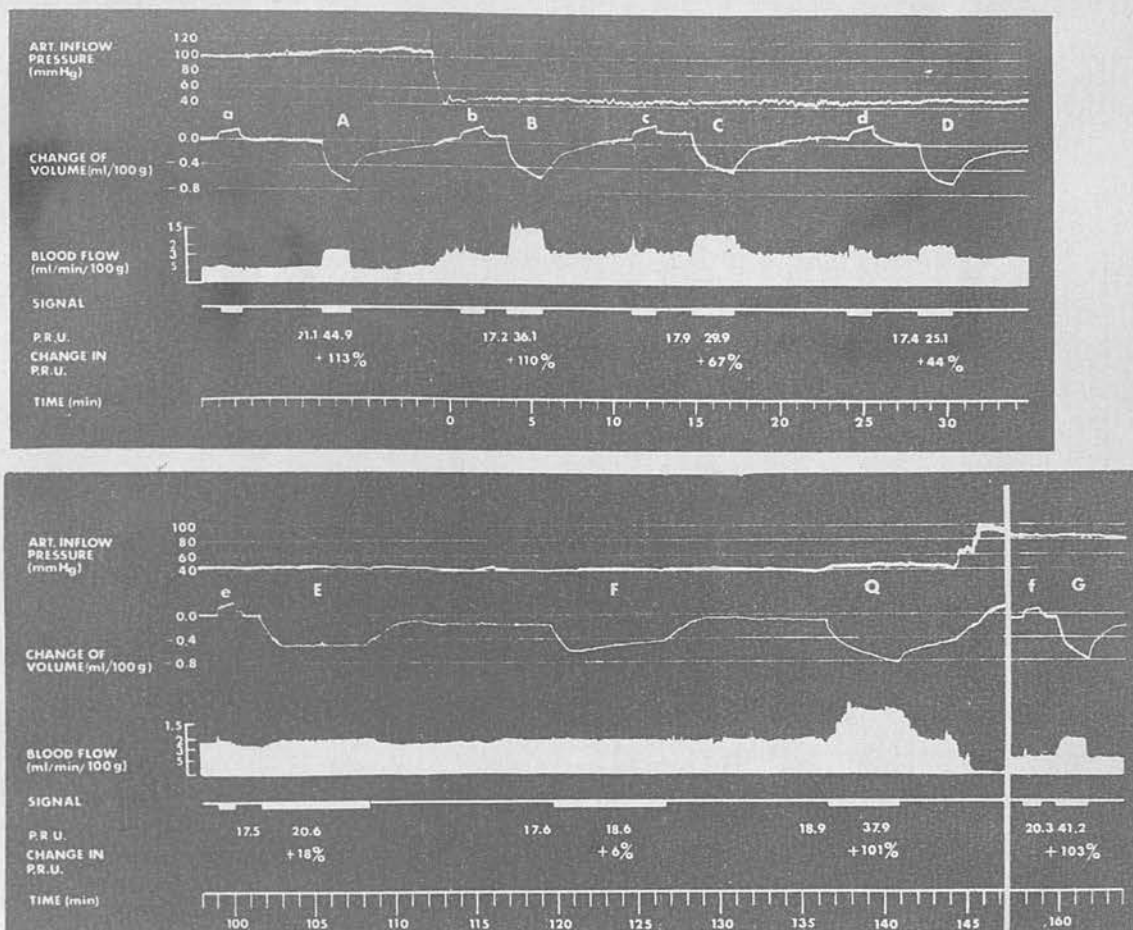
For further details of experiment and analysis see Mellander, S. : Comparative studies on the adrenergic neurohormonal control of resistance and capacitance blood vessels in the cat.

Acta. Physiol.Scand.50:

Suppl.176: 1.(1960)

Figs. 1 and 2 are taken from ref. (89) and are referred to in the text.

**FIGURE 1.**



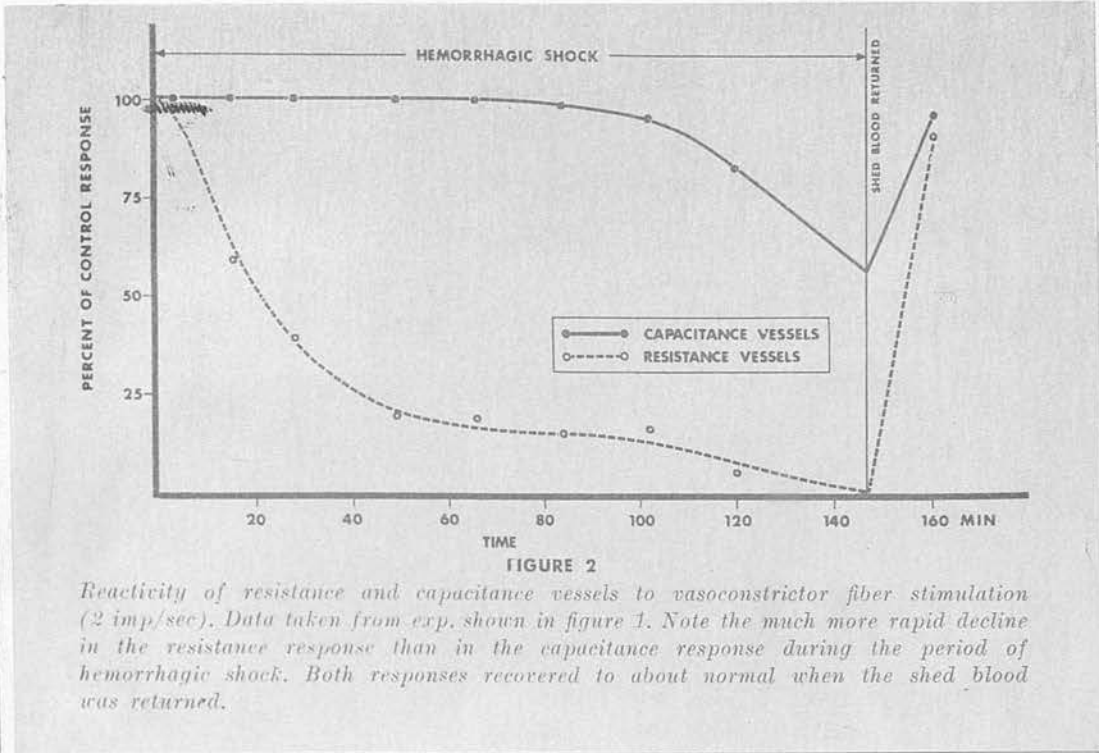
**FIGURE 1**

Cat 3.1 kg, skeletal muscle preparation. Chloralose-urethane. Effect of hemorrhagic hypotension on resistance and capacitance blood vessels and net transcapillary filtration exchange to regional sympathetic vasoconstrictor nerve stimulation at 2 imp/sec (A-G). At Q, l-norepinephrine in supraphysiological dose (12  $\mu\text{g}/\text{kg}/\text{min}$ ) infused. Responses of resistance vessels indicated by PRU and change in PRU. Responses of capacitance vessels demonstrated by the initial rapid decrease in the volume curve, and the effects on capillary filtration by the later, slower and continuous change in the volume curve during stimulation. Hemorrhagic hypotension maintained for 145 min. After this the shed blood was returned (record from 36 to 98 min omitted). Note the declining reactivity of resistance and capacitance vessels during the period of hemorrhagic hypotension. At B-D there is declining rate of inward movement of extravascular fluid, at E there is no change in capillary filtration and at F there is outward filtration on sympathetic stimulation. The large dose of norepinephrine given at Q was able to evoke a distinct response of the resistance vessels and to produce inward filtration. With return of shed blood there was almost complete recovery of all vascular responses to nerve stimulation (G). Filtration coefficient determined at a, b, c, d, e, and f.



**FIGURE 2.**

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