CHAPTER II

REVIEW OF LITERATURE
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Historical Background

French Physician Le Dran in 1743, coined the term 'Choc' to indicate a sudden collapse in the clinical status of a patient, after a serious traumatic episode. An English physician Morris in 1867, used the word 'shock' for the first time in his monograph. The experimental era in shock really began in 1899, when Crile published a book named, 'An Experimental Research in Surgical Shock'. The investigation of the pathophysiology of shock was initiated by Moon in 1938, by publishing their findings 'Shock and related capillary phenomena'. The noted cardiovascular physiologist Carl. J. Wiggers was actually the first investigator to attempt to quantify the research field of shock by establishing standardised models. The modern era of shock research had finally arrived with Wiggers' publication in 1950, 'the physiology of shock'.

Attempts to define shock have been almost as difficult as attempts to determine its mechanism. As
Ronald W. Raven (1952) stated "a complex phenomenon such as shock cannot be limited by, or contained within, a definition, and any grouping of words is incapable of defining it". None of the definitions of shock has managed to render its entire meaning at present. It is almost always characterized by hypotension and a particular overall functional exhaustion of the body. Deloyer's remark is also well known "shock is more readily recognised than described and more readily described than defined". The notion of shock immediately brings the image of a critical state. It is a well recognised clinical entity and a common cause of death. A precise definition of shock continues to change as the understanding of the surgical physiology and metabolism continues to grow.

The classification of shock is based on its etiology. Those shock syndromes caused by inadequate cardiac functions are termed cardiogenic shock. Those caused by a loss of blood volume are known as hypovolemic shock. Those syndromes which are caused due to the transudation of fluid secondary to sepsis are known as septic shock. Traumatic shock is a combination of all those shock syndromes, cardiogenic, hypovolemic and septic, produced by tissue injury. The common denominator for all these diverse forms of shock seems
to be microcirculatory hypoperfusion.

Interest in the mechanism and treatment of shock has always been stimulated by war. First world war, for the first time, brought the physiologist in contact with the battle fields. They described low blood pressure as one of the constant signs of shock. The war time experience was most enlightening, in view of the current controversies regarding the use of vasoconstrictor and vasodilator drugs. At that time the debate was between those who believed that vasomotor exhaustion with pooling of blood in great veins was the cause of shock and those who believed that vasoconstriction was the cause of deterioration.

Cannon and Baylis (1919) by using Vanslyke apparatus described a correlation between less blood pressure and reduction in alkali reserve. They noticed that the fall in alkali reserve was due to metabolic acidosis. They observed a striking improvement in shock patients after the administration of sodium bicarbonate. Keith (1919) studied blood volume in war-wounded patients and showed clearly a correlation of the severity of shock with the reduction in blood volume. Cannon (1923) defined shock as a discrepancy between
blood volume and vascular capacity. He also noticed increased lactic acid levels in hemorrhagic shock, which was later confirmed by Guttman (1941), Courmand et al (1943) and many others. Broder and Weil (1964) correlated levels of lactic acid with severity of shock. Bertilli and Bock (1970) regarded repeated estimation of lactic acid as the best index of the severity of shock.

Towards the end of world war II even when the patients with shock were successfully resuscitated, renal failure limited their survival (Baue, 1975). Trueta et al (1947) examined case reports and noted, that following heavy air raids on Britain in 1941, in which victims suffering from crushed limbs, later died of kidney failure. When this crushed syndrome was investigated in animal studies, they discovered that apparent vasospasm actually caused severe ischemia of the renal cortex with the maintenance of blood flow through the renal medulla. There is a syndrome described by Baue (1975) in which he has shown several organs begin to fail in sequential manner leading to rapid deterioration of patient. When coupled with symptoms of pulmonary, hepatic, or myocardial insufficiency, the signs of renal failure are grave (Kraman, 1979).
Experimental Hemorrhagic Shock

Hemorrhage is always impressive by the growing of its clinical nature. The intensity, rate and duration of bleeding transforms a hemorrhage, into hemorrhagic shock. It is a frequent consequence of a severe prolonged decrease in the circulating blood volume. It is characterised by a marked decrease in blood pressure, cardiac output and reduced peripheral blood flow. Sympatho-adrenal discharge also is increasing. The resultant increased levels of circulating catecholamines as well as release of angiotensin and vasopressin lead to increase in the peripheral vascular resistance and stimulate myocardium following hemorrhage. The degree of increased total peripheral resistance with hemorrhage, varies with species and within individual of a given species (Lefer and Spath, 1984).

Studies on hemorrhaged dog, cat, monkey and man reveal that one or more of the splanchnic organs undergo profound vasoconstriction, with a concomitant severe decrease in blood flow, out of proportion to the decrease in blood pressure. Significant reductions in renal and cutaneous blood flow and a
moderate to severe decrease in muscle blood flow, also appear to be a common finding in studies of hemorrhagic shock (Watts and Westfall, 1964; Chien, 1967; Bond et al, 1973 and Passmore and Baker, 1978).

Experimental hemorrhagic shock in dogs:

Since hypovolemia may affect all organic functions either directly or indirectly, it seemed of primary importance to standardize the experimental procedure as a pre-requisite for the systemic study of the factors which may cause hemorrhagic shock.

Two main experimental procedures have been used to induce shock. These are:

1) Withdrawal of a predetermined volume of blood:

Three variables can be studied by this procedure (Waleott, 1945).

1) The effect of duration of the hypotensive period on mortality.

2) The amount of blood withdrawn in one or several steps.

3) The effects of retransfusion of the blood shed
from the reservoir at the end of the experimental period or the influence of blood volume restitution by means of electrolyte solutions, plasma expanders or blood substitutes.

Forsyth et al (1970) demonstrated that the loss of 30% of the blood volume provided decreases in mean arterial pressure, central venous pressure, cardiac output and arterial pH. This procedure involved a rapid bleed-out and the immediate return of a fixed percentage of blood. The percentage of the bleed-out volume returned, determines the severity of shock. The bleed-out volume usually amounts to approximately 55 to 60% of the total blood volume. Because of the existence of some correlation between the volume reduction at the pressure levels, the use of pressure level gives an indication of the percentage of the total blood volume remaining.

2) Constant pressure reservoir method:

In this procedure an artery is connected to a constant pressure reservoir which maintains constant and predetermined systemic arterial pressure during the whole hypotensive period (Werk et al, 1942; Lamson and Deturk, 1945).
Almost all research groups working in this field use modifications of these two experimental models, or have proposed a combination of both. The reservoir procedure allows, not only good reproducibility, but also permits a thorough evaluation of the importance of the initial phases of hemorrhage, of the subsequent hypotensive period, and particularly of the predictive value of automatic reinfusion volume, prior to the reinfusion of the remaining blood, within the reservoir, at the end of the experimental period.

In the Wigger's method (1950) or it's modifications animals were bled to certain levels of arterial pressure, which were maintained for certain length of time. During the early part of such olegemic hypotension, various compensatory mechanisms are activated tending to raise the arterial pressure. Since the pressure is kept at the fixed level, further removal of blood occurs. Later during the olegemic hypotension it becomes unnecessary to remove more blood to keep the arterial pressure constant, at a fixed low level and instead some blood has to be returned to the animal, indicating the beginning of decompensatory stage.

The hemorrhaged animals that progressively lose blood into the reservoir upto a certain point,
is known as the 'maximum bleed out volume'. Within one hour, the animal begins to take back blood into the circulatory system from the reservoir. This process is known as 'uptake'. The lower the pre-set reservoir pressure, the sooner the animal begins to take up the blood from the reservoir (Lefer and Spath, 1984).

At a time determined by the experimenter, such oligemic hypotension is terminated by the rapid return of shed blood and the arterial pressure rises towards normal. Some animals may recover completely, but in many the blood pressure falls once again and death results. In these latter animals, the decompen-satory changes are not reversed by transfusion and the term irreversible shock has been often used, even though term does not indicate that it is really irreversible by all means (Gregersen, 1962).

Effect of Hemorrhagic shock on cardiovascular system

A) Heart

The functions of the heart deteriorate severely as the shock progresses and this deterioration is one of the major causes of death (Wiggers, 1947; Gomez and Hamilton, 1962; Hershey, 1964). The role of
HEMORRHAGE (SEVERE, PROLONGED)

REDUCED CBF  ACIDOSIS  SYMPATHETIC FAILURE

REDUCED O₂ SUPPLY → ENZYMATIC DAMAGE

MEMBRANE DAMAGE

MYOCARDIAL FAILURE

? MDF
?
? ENDOTOXINS

“IRREVERSIBILITY”

FIG. 3. INTERPLAY BETWEEN HYPOXIA, ACIDOSIS AND SYMPATHETIC ACTIVITY LEADING TO CARDIAC FAILURE IN HEMORRHAGIC SHOCK. C.B.F.-CORONARY BLOOD FLOW. M.D.F.-MYOCARDIAL DEPRESSANT FACTOR.
heart in shock had been neglected by many research workers, probably because cardiac deterioration was masked by the cardiac reserve. Because of this reserve, heart could maintain its pumping ability without any measurable evidence of cardiac failure. It was very difficult to detect cardiac deterioration until almost terminal conditions had ensued (Gomez and Hamilton, 1962; Hershey, 1964). The factors that might alter cardiac functions include, reduced oxygen supply to the heart, metabolic acidosis, loss of adrenergic activity and the appearance of myocardial depressant factor. These factors do not act entirely independently, but they try to potentiate their individual actions on the heart. The interplay between hypoxia, acidosis and adrenergic activity has been well documented by various studies (Figure 3).

B) Peripheral Circulation in shock:

According to Green (1944) the physiological response to hypovolemic shock include physical as well as neural and humoral compensatory and de-compensatory adjustments. Following blood loss there is a decreased intravascular volume to capacity relationship, resulting in a reduced mean blood pressure,
leading to reduced ventricular filling and decreased stroke volume. Depending on the severity of hypotension and the type of vascular bed, blood flow to the tissues may be compromised by both the fall in perfusion pressure as well as by the baroreceptor induced vasoconstriction through sympathetic nervous system (Wiggers, 1934; Green, 1961). This increased resistance to blood flow helps the maintenance of blood pressure and tends to divert the blood flow to the more 'essential' cerebral and myocardial tissues, the vasculature of which has been shown to be relatively unresponsive to central vasoconstrictor control during hypotension (Gregg, 1968; Green et al, 1980). However, the vascular beds which undergo vasoconstriction during hypotension, do so at the expense of their own nutritional well being. If flow deprivation is prolonged local and systemic accumulation of vasodepressor substances may cause some of these vascular beds to lose their tone, allowing increase of flow. Although this vasodilation is advantageous to the local tissues, it can cause even more fall in blood pressure, needed to maintain flow to the essential tissues. This vasodilation can cause vascular decompensation and in fact causes a break
down in the normal compensatory response to hypotension (Bond and Green, 1983).

1) **Myocardial vasculature:**

Wiggers and Werle (1942) were the first to suggest the possibility of a relationship between reduced coronary flow and irreversible shock in hemorrhagic shock. Gregg (1968) published a series of studies on shock that indicated a fall in myocardial vascular resistance, in spite of a moderate fall in the coronary flow.

Bond et al (1973) supported by Lee and Downing (1976) and Archie and Mertz (1978) suggested no significant reduction in myocardial blood flow during either compensatory hypovolemia or decompen-satory normovolemia. In fact there was a modest increase in flow and oxygen consumption even though there was no change in myocardial contractility. When the pressure was reduced by stepwise hemorrhage, there was a small reduction in flow at each step between 100 and 40 mmHg. This could be explained by either active vasoconstriction induced by baroreceptor
reflex or more likely, the reduced work of the heart and decreased metabolic demand during systemic hypotension. The myocardial vascular tone remains under autoregulation rather than extrinsic control.

2) Cerebral vasculature:

The cerebral vascular exhibits the most efficient autoregulation over widest range of pressure. The primary factors responsible for this intrinsic regulatory response are the tissue levels of carbon-dioxide, pH and oxygen. PO2 is the most dominant factor. Slater et al (1975) have discovered that even though total cerebral flow decreased somewhat during hemorrhage, the flow distribution pattern to the grey matter, cerebellum, hypothalamus, white matter and medulla were equally reduced during oligemia. In another study, Kovach (1972) found that the flow in the hypothalamus and frontal cortex fell more than in other areas of the brain. Even though the cerebral vasculature has been shown to exhibit good autoregulation during hypovolemic shock, there is little doubt that sustained cerebral hypotension to levels lower than 40 mmHg does result in cerebral dysfunction.
3) **Visceral vasculature:**

It has been described by Johnson (1964) that the autoregulation of blood flow to the intestine as a 'labile' phenomenon which is less pronounced than that seen in either brain or kidney. He found that the blood flow to the intestine falls linearly from 100 to 55% of the control when pressure is reduced from 100 to 40 mmHg, compared with the cerebrovascular response of only a 10% fall in flow over this same pressure change. The autoregulation in the intestine is not flow dependent. From his studies it appears that the intestine regulates its flow in response to a myogenic mechanism directed at maintaining a constant capillary pressure rather than a constant flow. Bohlen et al (1975) have suggested that the intestinal vasoconstriction is predominantly under the control of sympathetic nervous system, rather than circulatory vasoactive agents and is activated by baroreceptor mechanism during hypovolemic shock.

4) **Skeletal muscle vasculature:**

Over the pressure range of 100 to 40 mmHg, blood flow falls from 100 to 70% indicating arteriolar
vasodilation as pressure falls. In 1964, Stainsby reported a positive relationship between skeletal muscle autoregulatory capability and increased metabolic activity. Hutchins et al (1974) observed significant small artery dilatation when there was hypoxia. Thus there is little doubt that the skeletal muscle vasculature dilates in response to tissue hypoxia and that a metabolic mechanism is part of the autoregulatory response in this tissue. The relative roles played by autoregulatory, neural and humoral process in the skeletal muscle vasculature response to hemorrhagic shock were evaluated by pressure flow relationship by Bond et al (1967). Studies by Gonzale and Bond (1974) indicate a continual high sympathetic tone to the skeletal muscle during hypovolemia. About half of the total response of vasoconstriction is attributed to an increased alpha-adrenergic activity (Bond et al, 1973).

5) Cutaneous vasculature:

It is a non-autoregulatory passive vascular bed (Bond et al, 1967). The term passive vascular bed means that the vascular walls behave in a
predictable mechanical manner in accordance with the intraluminal pressure. The apparent vasoconstriction as pressure decreases is caused by a passive release of tension on the vessels as the intravascular pressure is reduced and conversely, passive diaotation as pressure is elevated. Even though the skin vasculature is known to have alpha-adrenergic vasoconstrictor fibres (Moran, 1963), these fibres may not participate in blood pressure regulation through baroreceptor reflex. The primary circulating agents responsible for the powerful instantaneous vasoconstriction during hemorrhagic shock are the catecholamines released into the circulation by both the adrenal medulla and all active peripheral adrenergic nerve terminals, with little or no effect coming from the baroreceptor activation of the adrenergic nerves innervating cutaneous vasculature (Watts and Westfall, 1964; Chien, 1967).

**Kidney in Shock:**

Renal insufficiency in shock may be associated with the renal circulatory or hormonal changes or various combinations of both which occur in shock (Passmore, 1983). The renal insufficiency can take
more than one form, depending on the renal hemodynamics or the degree of renal damage. There is a syndrome described in the literature (Baue, 1975) in which several organs begin to fail in sequential manner, leading to rapid deterioration of the patient. This when coupled with symptoms of pulmonary, hepatic, or myocardial insufficiency, the appearance of signs of renal failure are grave (Kraman et al, 1979). When crush syndrome was investigated in animal studies, Trueta et al (1947) discovered that an apparent vasospasm actually caused severe ischemia of the renal cortex with maintenance of blood flow through the renal medulla, resulting in a hypothesis of renal shunting. Subsequently, various methods have been developed to maintain renal blood flow and urine formation which help to prevent acute renal failure.

Renal blood flow changes:

Kidneys receive one of the richest blood flows of all organs of the body - approximately 3.5 to 4.0 ml/per gm/min as compared with the brain, which receives only approximately 0.5 ml/gm/min. The blood flow to the kidney is autoregulated between pressures
of 70 and 190 mmHg. The term autoregulation infers that changes in blood pressure alone do not change renal blood flow. It remains apparently constant at the flow rate determined by sympathetic tone, level of angiotensin, and other external factors.

Renal blood flow is often measured by means of clearance of para-amino hippurate (PAH). 90 per cent of the PAH is thought to be cleared from the plasma of the blood flowing through renal circulation. PAH clearance should represent 90 per cent of the total renal plasma flow. PAH clearance divided by 0.9 and corrected for hematocrit represents total renal blood flow. Selkurt (1945) reported that PAH clearance may decline to zero during hemorrhage.

The urine formation is related primarily to the blood flow to the kidney and the oxygen utilization per unit of blood flow is very low. Renal venous oxygen concentration are much higher than those of other organs. According to Thuran (1964) a decrease in blood pressure and flow actually results in a decline in oxygen consumption by the kidney because tubular reabsorption is a less active process when glomerular filtration rate is reduced. Therefore
it seems that renal plasma flow could decrease to very low values without causing renal ischemia. Focal areas of patchy renal cortical damage occur when renal blood flow is reduced to 25 per cent of normal. Hemorrhage to 70 mmHg (mean arterial pressure) reduces renal blood flow of dogs to about 50 per cent of control values (Stein et al., 1973; Passmore and Baker, 1978 and Neiberger et al., 1980). Hemorrhage to 50 mmHg reduces canine renal blood flow to approximately 20 to 25 per cent of control values (Passmore and Baker, 1973).

Trueta et al. (1947) were among the first to show that the kidney is having two different circulation. Thorburn et al. (1963) developed a method for determining blood flow through various vascular regions of the kidney. A bolus administration of Kr\textsuperscript{85} into the renal artery is carried into the kidney where it equilibrates with the renal tissue. An external monitor is used to record the disappearance curve and to find different components. Components I, II, III and IV have been shown to represent rates of blood flow to cortex, outer medulla, inner medulla and peri-renal fat respectively. Subsequently several other investigators
like Stein et al (1973), Leffler et al (1975) using radioactive microspheres demonstrated differential blood flow rates within the renal cortex. The elegant work of Beeuwkes (1971) demonstrated the postglomerular renal vasculature of various regions of the kidney having different characteristics. The renal medulla derives its blood flow from vasa straight branches of the efferent arteriols from the inner cortical glomeruli, extend towards medulla, as a bundle (Plakke et al and Pfeiffer, 1964). Jones and Merd (1974) demonstrated that the dense vascular plexes in the outer medulla receives a blood supply that is distinct from that of vasarectae. This area is the tissue in which medullary blood flow is maintained during hemorrhage, when renal cortical, especially outer cortical, tissue is very ischemic.

Grand Champ et al (1971) have shown that sympato-adrenergic factors were primarily responsible for cortical ischemia in hemorrhagic shock. In their experiments alpha-adrenergic blockade completely reversed redistribution of blood flow in hemorrhage. However Carrier and Thorburn (1966) found incomplete protection of the renal cortical flow with alpha
blockade during hemorrhage. Passmore and Baker (1973) reported reduced outer cortical flow in hemorrhaged dogs, but demonstrated that in the late deterioration of hemorrhagic shock indicating a loss of sympathetic tone. In a later study Padsmore et al (1975) showed that hypotension in the absence of increased sympathetic tone caused little redistribution. LaChance et al (1974) reported that phenoxybenzamine, and angiotensin antagonist, and a volume expander were all needed to block the cortical ischemia caused by hypotension.

In another series of experiments by Hock et al (1982) alpha-receptor blockade and an angiotensin antagonist were used to study renal cortical vasoconstrictor mechanism during hemorrhage to 70 mmHg. Hemorrhage alone caused a 49 per cent decrease in total renal blood flow and a 70 per cent decrease in outer cortical blood flow. Inner cortical flow decreased approximately 60 per cent, outer medullary blood flow decreased 49 per cent. Renal arterial infusion of phentolamine (25 ug/kg min. for 12 min.) beginning 20 minutes posthemorrhage produced no alteration in the expected posthemorrhagic total renal blood distribution. Plasma renin activity
increased six to seven fold in the hemorrhage group as well as hemorrhage and phentolamine treated group. Saralasin treatment (2 to 4 μg/kg/min for 1 min.) beginning 20 min. posthemorrhage produced a pattern in which hemorrhage decreased total renal blood flow only slightly and cortical blood flow not markedly. The angiotensin blockade, which would block the effects of the renin-produced angiotensin II, during hemorrhage, also blocked the renal cortical ischemia of hemorrhage. Therefore, it appears that angiotensin II is a powerful renal cortical vasoconstrictor during hemorrhage.

Patterns of renal cortical blood flow distribution similar to those observed in hemorrhagic hypotension have been described by Houck (1951), with stimulation of renal nerves, and by Hoff et al (1951) with stimulation of cerebral cortex. The reported observations that nerve fibres are found mainly in the renal cortex (Mitchell, 1957) lend support to the suggestion that vasoconstriction is neurogenic in nature in the renal cortex. They have also reported that intra renal infusion of noradrenaline, adrenaline and angiotensin also produce a similar pattern of cortical ischemia, starting in the cortex but sparing the medulla.
The marked ischemia of the outer cortex may have additional physiological significance as Brown et al (1963) have shown increased renin content in the outer glomeruli many times more than that of the juxtamedullary glomeruli.

Cox et al (1974) have postulated a decrease in glomerular permeability as a primary event for decreased glomerular filtration rate after noradrenaline infusion. They observed that infusion of norepinephrine for 2 hrs into the renal artery produced diminished cortical blood flow. Electron microscopy revealed abnormalities in the epithelial structure of glomeruli following infusion of nor-epinephrine (Cox et al, 1974). The current consensus is that change in glomerular perfusion, related to afferent arteriolar constriction and/or efferent arteriolar dilatation (Hollenberg et al, 1968, 1970). Cellular swelling may also lead to diminution in glomerular capillary patency, thus impeding the blood flow through vessels (Leaf, 1970). If such a mechanism was operating, RBF and effective GFR would be reduced. Obstructed glomerular capillaries due to cellular swelling have been described by light and electron microscopic studies (Summers and Johnson, 1971; Flores et al, 1972; Johnson and Latta, 1977).
After one hour of ischemia, cloudy swelling in glomeruli was noted by light microscopy. Summers and Johnson (1971) observed decreased and incomplete filling of the lumens of glomeruli by carbon particles after infusion in the rat following induction of ischemia. Electron microscopic studies have also reported the same results (Johnson and Latta, 1977). Frega et al (1976) described a diffuse patchy ischemia as judged by silicon-rubber injection after 1 hour of ischemia. Furthermore, a structural functional correlation have been implicated involving the renin-angiotensin system. Juxta glomerular cells present in the media of the afferent arteriole are known to contain renin which is involved in the formation of angiotensin II, which is a potent vasoconstrictor. Glomeruli in the superficial cortex is known to contain more of renin when compared with those of Juxta medullary region (Cook, 1962; Granger et al, 1972). It is an observation which correlates well with superficial cortical ischemia associated with acute renal failure in shock. By using electron microscope no significant alteration was observed by Holden et al (1965) and Maza (1964) in glomeruli or distal convoluted tubule after 120 minutes of hypovolemia. There was focal intracellular edema and in some cells the brush border was deranged
with the escape of the supranuclear portion of cytoplasm into the lumen of the tubule.

**Metabolic Changes in Shock:**

Metabolic acidosis frequently present in shock, might result from the inadequate oxygen and nutrient delivery and decreased removal of acid metabolites secondary to the reduced flow in shock. Blood pH, $P_{O_2}$ and bicarbonate fall while pyruvate, lactates, phosphates and sulphates rise in hemorrhagic shock. A respiratory acidosis or alkalosis might be superimposed on metabolic acidosis. In shock renal blood flow sharply declines, urinary output decreases and finally stops. The regulating effects of kidney on acid base balance are thereby lost. Daniel et al (1978) had observed under moderate hypotension, kidney has a large functional capacity of lactate removal. During established shock, lactate uptake decreased in parallel with the renal tissue oxygen tension.

**Lactic Acid in Shock:**

Increased arterial lactate concentrations has been shown to reflect a poor prognosis in various types
of shock. Lactate metabolising organs may not be capable of removing lactate produced by peripheral tissues. The main organs for lactate removal are the liver and kidney. Hepatic lactate uptake decreases during hypoperfusion and hypoxemia. Whereas the behaviour of renal lactate uptake under similar condition is incompletely known (Nelimarka, 1983).

Kent et al (1968) mentioned that in hemorrhagic shock, there was inadequate oxygen transported to the cell to accept hydrogen ions released by the degradation of glucose to pyruvate. The lactate is formed by the reaction of excess hydrogen ions with pyruvate, this lactate is accumulated as a metabolic waste, resulting in depletion of high energy phosphate bond due to the failure to mobilise glucose beyond 3 carbon chain.

During periods in which metabolism is sustained by hypoxia, the metabolic fate of pyruvic acid is temporarily altered. Aerobic oxidation in the tricarboxylic acid cycle is blocked and pyruvic acid is converted into lactic acid. Nicotinamide adenine dinucleotide (NADH₂) provides energy for this electron exchange. The transformation of NADH₂
to NAD during conversion of pyruvic acid to lactic acid allow glycolysis to protect without obligatory rejunuation of NADH$_2$ by oxygen. The oxidation of NADH$_2$ might be blocked by hypoxia.

Beaty (1945) observed in his experiments that the control level of blood lactate usually varied from 4-20 mg%. The blood pyruvate in the controlled determination ranged between 0.8 and 2.4 mg%. He further noticed that there was marked increase in blood lactate immediately after 75% hemorrhage which was succeeded by a period during which the lactate showed no increase or the rise was very slow. In the terminal stages there was usually a rapid increase in blood lactate, which sometimes attained value as high as 160 mg%.

Ballinger et al (1962) observed excess lactate in human patients with circulatory failure. In their studies on 13 patients, they found that when the maximum arterial excess lactate was below 3 mmol/lit, (in 8 patients) there were no fatalities. When the excess lactate was above 3 mmol/lit, 3 patients died and two survived. Thus the validity of increased lactate as a metabolic index of severity
of shock and as an indicator of oxygen debt has been confirmed in human patients and experimental animals. It provides a parameter for measurement of reversibility and served as an objective clinical guide (Seligman et al, 1947; Hackel and Goodale, 1955; Broder and Weil, 1964).

**Acid Base Equilibrium in Shock:**

Acid base disturbances can be analysed by using measurements of arterial CO₂ tension (PCO₂), bicarbonate concentration and pH. Although there is growing consensus favouring this conceptual approach, other schemes have been developed over the years and have retained popularity in some quarters (Gennari et al, 1982). Singer and Hastings (1948) utilized measurement of 'whole blood buffer base' as well as pH, PCO₂ and plasma bicarbonate to assess acid base disturbances. Astrup (1961) devised a method to assess acid base balance by measuring 'standard bicarbonate' and 'base excess', as well as pH and PCO₂. Both of these methods have been introduced before the concept of 'whole body-titration' was established. Blood samples are titrated in vitro to separate the respiratory and
and metabolic components of acid base disturbances.

The disorders of acid-base equilibrium are classified according to which of the two physiologic variables, PCO\textsubscript{2} or bicarbonate is directly affected (Harrington et al, 1982). Those disorders initiated by a change in PCO\textsubscript{2} are referred to as respiratory disorders whereas those initiated by a change in bicarbonate concentration are referred to as metabolic disorders. Hypercapnia and hypocapnia leads to respiratory acidosis and respiratory alkalosis respectively. Hypobicarbonatemia and hyperbicarbonatemia initiate acid-base disturbances designated as metabolic acidosis and alkalosis respectively. In each of these cardinal acid-base disturbances, the initiating process not only alters acid-base equilibrium directly but sets in motion, secondary physiologic responses that change the value of the other member of the carbonic acid-bicarbonate pair. Thus metabolic disturbances evidence a secondary ventilatory response that alters the level of PCO\textsubscript{2}. Primary hyperbicarbonatemia is followed by a secondary increase in PCO\textsubscript{2}. In the same way respiratory disturbances induce secondary responses that changes the level of bicarbonate concentration. The primary hypercapnia is followed by a secondary increase
in bicarbonate concentration and primary hypocapnia is followed by a secondary decrease in bicarbonate concentration. In each case, the immediate effect is to shift hydrogen ion concentration towards normal. In view of the highly predictable pattern of response observed for each class of acid-base disorders, the secondary physiologic changes are best regarded as an integral part of the disturbance to which they are wedded and not as independent abnormality.

Any impairment in the ability to excrete CO₂ leads to an immediate increase in dissolved CO₂ and lowers PH(Pitts, 1974; Vander, 1980). The plasma bicarbonate, pH and PCO₂ obey the Henderson-Hesselbach equation.

\[
\text{PH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.030 \times \text{PCO}_2}
\]

Where HCO₃⁻ is in milliequivalents per litre and PCO₂ is in mmHg.

Metabolic acidosis is common in surgical patients, patients with renal failure, in acid loading and lactic acidosis due to cardiogenic shock, septic shock, hemorrhagic shock and tissue hypoxia.
(Moore, 1977; Reineck and Stein, 1980) and the diagnosis of metabolic acidosis is made in the setting of a decreased blood PH and bicarbonate concentration. Carbondioxide excretion by the lungs offset CO₂ production of respiring tissue. Any imbalance between production and elimination will change the body CO₂ content and PH, as more or less H₂CO₃ is produced. This change in PCO₂ immediately affect the bicarbonate buffering system (Pitts, 1974; and Vander, 1980). Renal bicarbonate handling is the primary way in which the kidney responds to PH changes. HCO₃⁻ is freely filtered through the glomerulus and is reabsorbed through H⁺ ion secretion mechanism (Vander, 1980). Since HCO₃⁻ is not easily transported from the renal tubule, tubular cells generate H₂CO₃ in presence of carbonic anhydrase, water and CO₂ and then actively transport the resultant proton into the tubular lumen. In this way tubular, CO₂ is formed as H⁺ combines with HCO₃⁻. H₂CO₃ dehydrates to CO₂, which rapidly moves into the tubular cell, so that no net cellular CO₂ change occurs. However, bicarbonate from the intracellular H₂CO₃ diffuses back into the plasma and thereby affect the net transfer of HCO₃⁻ is completely absorbed. During alkalosis less HCO₃⁻ is reabsorbed and during prolonged acidosis, increased H⁺ secretion
and ammonia synthesis occur, so that complete \( \text{HCO}_3^- \) absorption and additional \( \text{H}^+ \) excretion occur. \( \text{H}^+ \) secretion is controlled by arterial \( \text{PCO}_2 \) and the direct \( \text{PH} \) changes are produced in the tubular cell (Cohen and Kassiner, 1980 and Vander, 1980). Filtered \( \text{HCO}_3^- \) is proportional to altered renal blood flow and plasma bicarbonate concentration, so that the \( \text{HCO}_3^- \) load to be reabsorbed fluctuates with the changes of body acid-base metabolism.

It has been demonstrated, that the marked fall in \( \text{PO}_2 \) does not itself generate peripheral cellular damage (Kittle et al, 1965; Lowery et al, 1969). In shock, it seems that one peripheral release and reception of oxygen are at first obstructed and blood transport only afterwards. In states of shock, the RBC proves inadequate in the retention and liberation of oxygen to the tissues. Moreover, the large intestinal fluid pool and blocking of the microcirculation prevents the cellular extraction of oxygen, under these conditions, the usual \( \text{PO}_2 \) is no longer sufficient to supply the tissues. Hence only high pressure \( \text{O}_2 \) therapy and the intravascular administration of peroxidase are able to raise the pressure of \( \text{O}_2 \) in the tissues (Ackerman and Brinkley, 1968). Normally,
the tissues extract 28 per cent of the oxygen brought by RBC to the periphery. But in shock, there is a temporary extraction of 60 per cent or even more. But the tissular mechanisms of oxygen extraction are rapidly exhausted, especially by intraerythrocyte blocking (Suten et al, 1975). If the normal PCO$_2$ of 40 mmHg is exceeded by only 2 mmHg, the rhythm and depth of breathing increases two fold. At PCO$_2$ of 60-80 mmHg, its narcotic action begins on the cortical neurons. The mixed hypoxia- hypercarbic syndrome is constantly encountered in shock. Ventilatory compensation is not sufficient to counteract tubular acidosis (Choffat and Picard, 1970). Shock acidosis has been designated by different authors by different terms; hypoperfusion acidosis, hypoxic acidosis, stagnant lactic aciduria (Moore, 1968).

According to Nelson et al (1963) acidosis in itself is not dangerous. But PH values must obviously be brought within physiological limits, bearing in mind, however, that the PH only indirectly reflects the effects of hypoperfusion, hypoxia and hyperglycolysis which have to be corrected. The life of the tissues depends upon the removal of the causes of the acidosis (Robinson, 1969 and Nelly et al, 1970).
Hypovolemia can produce alterations in water and electrolyte metabolism. An adequate functional blood volume is the one that provides a normal sufficient circulation of the heart and peripheral circulation. The body is an aqueous solution of electrolytes and on-electrolytes and the body fluid is actually composed of two solutions, intracellular and extracellular fluids. These two solutions are separated by cell membrane. A portion of the solution outside the cell is held within the blood vessels to serve as a vehicle for electrolytes and other formed elements in plasma. The remainder of the extracellular fluid (ECF) is termed as interstitial fluid. The ECF is essentially an aquous solution of Na⁺ balanced electrically by Cl⁻ and HCO₃⁻ with smaller amounts of K⁺, Ca++, Mg++, SO₄⁻ and PO₄⁻. The concentration of electrolytes in the whole plasma is lower than the concentration in the plasma water, since proteins and other solids occupy approximately 71 per cent of plasma volume (Chaudry and Baue, 1983).

The single, most important ion is Na⁺, which is responsible, with its anion Cl⁻ for the 93 per cent
of the osmolality. Na\(^+\) controls the ECF volume by virtue of its effect on water. The ECF Na\(^+\) concentration is normally maintained at a constant level, and any change outside the normal range must be regarded with suspicion (Boyd et al, 1970).

In addition, to the stabilizing reflexes to restore blood pressure Haljamae (1978) designed an equally effective homeostatic responses to conserve and expand plasma volume. Na\(^+\) and water are conserved by kidney under the influence of aldosterone and ADH respectively. The studies of Perkle and Gann (1976) have suggested that mild hemorrhage leads to an increase in extracellular osmolarity mediated in part by increased cortisol concentration. As a result of this, there is a shift of intracellular fluid to the intestitium causing interstitial pressure to increase. The increased interstitial pressure accelerates lymphatic movement of the interstitial proteins to the vascular system, which results in a reequilibration of ECF towards the plasma. This, then completes the restoration of blood volume.

Increased secretion of renin, aldosterone, ADH, erythropoietin and renal conservation of Na\(^+\) and water also occur in shock (Skillman et al, 1967).
Interstitial fluid is decreased and is restored only by either injection or ingestion. So long as shock is not produced, a rapid arterial bleeding produces higher rates of capillary refilling (Skillman et al, 1967). Under these conditions, adrenal release of epinephrine and sympathetic nervous system release of nor­epinephrine are increased, as is cortisol secretion.

Shires et al (1960) first drew attention to an apparent decrease in interstitial fluid volume during shock. In the early phases of hemorrhagic shock, the increase in the pre-to-post-capillary resistance ratio results in a net absorption of ECF mainly from skin and skeletal muscle into the vascular compartment (Johnson and Bagett, 1973). Although the decrease in the effect of circulatory volume can be due to intestinal hemorrhage as seen in dogs in shock (Werk et al, 1942), a number of studies have indicated that there is a decrease in circulating plasma volume during the later stages of oleagemic shock (Abel and Wolf, 1973).

The cell membrane is a protein-lipid complex that is freely permeable to water, but the movements of most of the solutes are restricted. The two possible
mechanisms for the passage of solutes across the cell membrane are diffusion and active transport. Concentration of unchanged particles is same on both the sides of the membrane when diffusion equilibrium is reached. The active cation transport system maintains cell volume (Tosteson and Hoffman, 1961) and restores cellular ionic composition (Woodbury, 1969). It also appears to be important for cell processes such as protein synthesis (Pestka, 1971) and mitochondrial oxidative phosphorylation (Jarhult, 1973). Diffusion and active transport processes are involved in the maintenance of normal cation concentration in the extracellular and intracellular fluid. K⁺ slowly diffuse out of the cell and Na⁺ diffuses in, but as this occurs, the (Na⁺ + K⁺) ATPase or the Na⁺ pump, pumps the Na⁺ back out of the cell and K⁺ back in. The Na⁺ pump is dependent on the intactness of the cell membrane and the availability of ATP. It is evident that cellular membrane function is disturbed during shock, as evidenced by disturbances in the electrolyte transport characteristic of single cell (Haljamae, 1970) and tissue slices (Sayeed et al, 1974).

Potential difference measurements across the cell membrane were conducted by a number of investigators
and it was found that the cellular membrane potential decreased during shock from a resting level of about -90 to a value as low as about -50 (Shires et al, 1972; Trunkey et al, 1973 and Sayeed et al, 1981). With this change in potential difference, these investigators predicted, according to the Cl⁻ space and Nernst equation, that Na⁺ and water entered the cell and K⁺ came out. It is also reported by Trunkey et al (1973) that the decrease in transmembrane potential is directly related to the cellular metabolic disturbances. There are linear correlations between the extent of the membrane potential decrease, on one hand, and tissue increase in lactate or decrease in PH or high energy phosphate on the other.

The studies of Shires et al (1972) showed that there was an increase in the intracellular Na⁺ and a decrease in the intracellular K⁺ during hemorrhagic shock. Haljamae (1970) correlated his results of depressed K⁺ transport with the severity of shock. Grossman (1968), have suggested that similar changes can occur in the neurons of the brain also in haemorrhagic shock. The results of a number of investigators (Shires et al, 1973; Horowitz, 1975;
Amuludson et al, 1979) suggest that skeletal muscle cells may be the principal site of electrolyte and fluid sequestration following severe hemorrhagic shock. Electrolyte concentration can be altered in vascular smooth muscle (Day and Friedman, 1978).

Haljamae (1978) and Shires et al (1972) used interstitial fluid around muscle from animals in shock and found that K⁺ values increased to 15 to 18 mEq/litre after 2 hours of shock. This indicates that K⁺ leaves the cell in severe hemorrhagic shock. The capacity of the liver cells to transport K⁺ was also significantly decreased in prolonged hemorrhagic shock (Baue, 1975). In late state, the liver cells lose the capability to maintain intracellular K⁺ concentrations. It was also found that cation concentration in the mitochondria was altered with activity of the transport enzyme (Na⁺K⁺) ATPase was greatly increased (Baue et al, 1974). The cation changes consisted of increased Na⁺ and loss of K⁺ from cells during shock, increased Ca++ and decreased membrane bound Mg++. These observations therefore suggested that alterations in membrane transport phenomena may be an important
Humoral toxic agents have been found in a variety of circulatory shock (Lefer, 1973b). Many of these substances fulfill the criteria necessary to qualify as a toxic factor in shock. One of the best known toxic factor is myocardial depressant factor (MDF) which is produced in several types of circulatory shock. MDF was first discovered in 1966 by Brand and Lefer in the plasma of cats in hemorrhagic shock. This observation has been confirmed by many other laboratories (Baxter et al, 1966; Williams et al, 1969; Fisher et al, 1973 and Rogel and Hilewitz, 1978). It has been identified as a peptide with molecular weight of 500 and consists of three to four amino acid residues (Green et al, 1977).

MDF accumulates in the plasma during shock and reaches the toxic levels in about 2-7 hours after the onset of shock which then induces hypoperfusion of the splanchnic region, including the pancreas. This hypoperfusion results in acidosis, hypoxia and
ischemia of the pancreas which are important stimuli for lysosomal disruption and for activation of zymogenic enzymes (i.e., conversion of trypsinoen to trypsin and chymotrypsinoen to chymotrypsin). With the result, release of large amounts of proteolytic enzymes into the cytoplasm of pancreatic acinar cells occurs. Acidosis does not appear to be directly involved in activation of these enzymes but enhances the activity of the lysosomal proteases, once they are released from the lysosomes (Glenn and Lefer, 1971a). This zymogenic and lysosomal proteases appear to accelerate proteolysis and thereby stimulate MDF production (Litvin et al., 1973). Once formed, this peptide is either transported by the capillaries or bound to a carrier protein and transported by the lymphatics to the circulation where it is able to exert its deleterious effects.

MDF has been shown to exert a variety of pathophysiological effects in the intact animal as well as in isolated organ or tissue. The best known action of MDF is its negative inotropic effect on heart during hemorrhagic shock (Wangensten et al., 1971). MDF appears to be responsible for a significant
portion of the myocardial depression observed in shock states (Glenn and Lefer, 1971a). In addition to this negative inotropic effect, MDF also tends to undermine circulatory homeostasis. MDF causes constriction of the resistance vessels in splanchnic area (Glucksman and Lefer, 1971) which in turn promotes conditions which favour the continued production of MDF. It also depresses reticuloendothelial system which in turn inactivate one of the primary avenues of clearances of foreign or native toxic materials from the blood (Lefer and Blattberg, 1968).

Basic Principles in the Treatment of Shock:

The treatment of circulatory shock has been as varied as its causes (Lefer and Spateh, 1984). In hemorrhagic shock the addition of volume in the form of whole blood, plasma, or crystalloid solution has been recommended as the best. The reduced mean arterial pressure occurring in virtually all types of circulatory shock have prompted the use of a variety of vasopressor agents in the treatment of shock. There are a variety of approaches to the treatment of circulatory shock based on correcting the recognised
abnormalities associated with shock states. Even then the treatment of circulatory shock from whatever cause it may be remains a difficult problem. A consideration of both the hemodynamic and subcellular alterations that occurs in shock is necessary in order to understand fully the basis of the therapeutics of the shock state.

Wiggers and Ingraham (1946) defined hemorrhagic shock as a progression of three physiological conditions; Simple hypotension, impending shock, and irreversible shock. The first of these states requires treatment other than removal of the immediate cause. Thus in the case of hemorrhage, cessation of blood loss would be sufficient for the return of cardiovascular function to normal. The second phase requires treatment to correct. If left uncorrected this proceeds to the third stage, irreversible shock. Thus impending shock involves cellular derangements that become irreversible and leads to death despite generally accepted therapeutic modalities.

Irreversibility of Hemorrhagic Shock:

In the classic wigger's hemorrhagic shock model, reinfusion after a hypotensive period of about
EARLY PHASE

HEMORRHAGE

↑HISTAMINE  ↑β-ENDORPHINS

ARTERIAL SMOOTH MUSCLE RELAXATION

↓TOTAL PERIPHERAL RESISTANCE

↑CARDIAC OUTPUT

FIG. 1. SHOWS IN A GRAPHIC FORM THE IMPROVEMENT OF CARDIOVASCULAR FUNCTION BY THE TIMELY RETURN OF LOST BLOOD VOLUME.
90 minutes produces a short but definite increase in cardiac output (CO). This increase in CO may be due to a decrease in TPR (Figure 1), which may result from histamine acting peripherally and from centrally acting endorphins. The decrease in TPR readily explains the ensuing hyperdynamic state with its increase in CO, increase in total body oxygen consumption and thus increase in myocardial oxygen consumption. Measurement of cardiac function at this stage need not show any significant impairment. However, with the progression of shock from the early to the late phase of shock via an increase in venous capacitance causing a failure of venous return, this increase in venous capacitance can lead to a decrease in CO. With timely volume replacement CO might still be maintained. But after a critical point, CO can no longer be maintained and the system enters into a high-resistance, low output state. Sympathoadrenal system is activated along with the vasoconstrictor prostaglandins. This compensatory mechanism leads to an increase in both TPR and pulmonary vascular resistance. This hypotensive period contributes to pulmonary damage which further leads to a total body ischemia. The decrease in renal flow activates the renin-angiotensin-aldosterone system
and also contributes to the increase in TPR. The total decrease in tissue perfusion produces acidosis and helps the formation of myocardial depressant factors which in turn depresses the myocardial function, which leads to decrease in CO resulting in the observed mortality of irreversible hemorrhagic shock.

Thus an acute decrease in volume results in the release of the mediators, histamine and betaendorphin causing an increase in venous capacitance. With prolonged hypotension, the venous capacitance system becomes unable to respond to excess transfusion and leads to diminished CO. Since the arterial pressure is the product of both CO and TPR, this also declines. Both short term and intermediate-term compensatory mechanisms are then initiated. The short term mechanism is sympathoadrenal mechanism. This is an attempt by the body to maintain the perfusion pressure. However, the effect of catecholamines at the pre and postcapillary resistance vessels causes the movement of fluid into the intestinal space. This further decreases the blood volume. The intermediate compensatory mechanism is the renin-angiotension-aldosterone mechanism. Angiotensin produces an increase in TPR by constriction of arterioles. This results in decreased
FIG. 2. SHOWS THE PROGRESSION OF THE IRREVERSIBLE PHASE OF HEMORRHAGIC SHOCK LEADING TO CARDIAC FAILURE.
blood flow to the tissues and causes total body ischemia resulting in the formation of MDF like materials. The increase in TPR also affects the left ventricular ejection and further decreasing CO. The autoregulatory ability of the coronary system is over ridden, resulting in decreased coronary flow and increased coronary vascular resistance. The heart must then attempt to overcome increased after load in the face of the negative inotropic effects of MDF, H⁺ and decreased oxygen delivery effecting acute myocardial failure and irreversible hemorrhagic shock (Hess et al, 1983; Figure 2).

**Therapeutics of Circulatory Shock:**

The use of pharmacological agents to normalise hemodynamic parameters in shock has been largely directed towards modifying the autonomic response of the cardiovascular system to the shock state. Thus, vasoconstrictor and cardiotonic agents have been given to augment the response of the sympathetic system, whereas alpha and beta-adrenergic blocking agents have been administered to inhibit sympathetic activity in various types of circulatory shock. The rationale for the use of sympathomimetic drugs in shock is to
support adequate blood flow to the brain and heart by increasing mean arterial blood pressure and cardiac output. However pressor agents like nor-epinephrine with strong vasoconstrictor activity increases vascular resistance and arterial pressure. This pharmacologic increase in total peripheral resistance is deleterious to local organ function, since it exacerbates the already reduced tissue perfusion and increased total peripheral resistance that occurs in many types of shock. These findings suggested the use of alpha-adrenergic blocking agents to improve tissue perfusion in low-flow states. In addition, the use of adrenergic agents has been advocated in those situations where mean arterial pressure and total peripheral resistance decrease late in shock. In contrast, inhibition of beta-adrenergic activity would act to increase TPR and, therefore, increase systemic arterial blood pressure. Thus the rational therapeutics, require evaluation of the physiologic state prior to the treatment and pharmacological response to sympathomimetic agents and sympathetic blockers used in the treatment of shock depend on it.

**Sympathomimetic agents in Hemorrhagic shock:**

The use of sympathomimetic agents and...
particular nor-epinephrine has long been advocated in cases of hypovolemic shock in which restoration of volume fails to return the MAP to an acceptable level. Although nor-epinephrine increases myocardial contractility, its effect on cardiac output is variable. Furthermore, total peripheral resistance is significantly elevated after the commonly administered therapeutic dose levels. Moreover, even if the cardiac output is increased, the magnitude of the increase may not be sufficient for a beneficial action in shock. Although nore-epinephrine may transiently improve coronary or cerebral blood flow, it does not improve survival (Rush, 1967). In fact, administration of nor-epinephrine to hemorrhaged dogs has been associated with increased hemorrhagic lesions in the gastrointestinal tract, splanchnic viscera and kidneys (Rao, 1968). These lesions arise as a result of prolonged tissue hypoxia, secondary to tissue hypoperfusion. The beneficial role of nor-adrenaline in the treatment of shock, has been questioned by many workers. Frank et al (1956) observed that although nor-adrenaline infusion increased coronary and cerebral blood flow in shocked animals, it reduced the renal blood flow and could not prolong the survival time or
their recovery. Schummer and Durani (1963), working on dogs, observed that nor-adrenaline actually quickens the onset of irreversibility in the animals and concluded that nor-adrenaline has no place in the treatment of olegemic shock. Hardway et al (1962) went a step further and stated that nor-adrenaline should be contraindicated in the treatment of shock.

Noradrenaline infusion, initially produces a marked improvement in the shock state as shown by elevation of blood pressure and slowing down of pulse rate and respiratory rate. Frank et al (1956) and Simeone (1963) have attributed this initial beneficial effect to increased cardiac output as a result of improved coronary artery perfusion and a direct inotropic effect on the myocardium. The average survival time in the noradrenaline infused dogs was approximately twice as that of control animal (Simeone, 1963). However, all the animals receiving noradrenaline ultimately died. Histopathological examination of animals showed extensive hemorrhagic necrosis in the gastrointestinal tract and the liver, and marked cortical hemorrhages and congestion in the kidneys (Frank et al., 1956). Lister and his colleagues
(1963) have explained the genesis of visceral changes in shock. When vasoconstriction is allowed due to sludging of red blood corpuscles and increased intravascular clotting. This failure of capillary circulation produces anoxia, and accumulation of tissue metabolites and increased capillary permeability. Plasma, and later on whole blood extravasate into the tissue and the lumen of the intestines. Cortical congestion and tubular necrosis are known to occur in dogs subjected to hemorrhagic shock (Lillithel et al, 1964). The lowered urinary output and markedly enhanced tissue changes in the kidneys of noradrenaline infused animals indicate that noradrenaline infusion worsens the damage in the shock kidney. Similar degenerative changes of the convoluted tubules of the kidneys were reported by Boughten and Sommers (1957) in autopsy findings of eight patients of irreversible shock treated with noradrenaline.

It seems that noradrenaline has an initial beneficial effect due to enhanced cardiac output. It has a deleterious effect if its infusion is prolonged unduly. It accentuates the hemorrhagic necrosis in the intestinal mucosa of the liver and kidneys. The raising of blood pressure and prolongation of survival
time are falacious indications because the irreversible changes in the tissues progress unabated due to prolonged vasoconstriction (Rao, 1968).

It seems likely that norepinephrine possesses both beneficial and detrimental effects, depending on the dose and time of its administration. The beneficial effects can probably be obtained when small doses of noradrenaline are administered early though such early administration is often impossible in clinical practice (Chien, 1967). An excessive increase in heart rate due to noradrenaline infusion can be detrimental to cardiac performance (Rushmer, 1965). In association with the tachycardia after hemorrhagic shock, Hackel and Goodale (1955) found lesions in the myocardium.

Aggravation of anaerobiosis by noradrenaline would be expected to be detrimental to survival. The exaggeration of metabolic acidosis as a result of norepinephrine induced vasoconstriction can exert many deleterious effects. The aggravation of metabolic acidosis and elevation of circulating catecholamine
may constitute a vicious cycle since catecholamines intensify metabolic acidosis, and acidosis and accumulating lactate can provoke a further release of endogenous catecholamines (Woods et al, 1956; Nahas et al, 1960; and Darby and Watts, 1964). The fate of experimental animals in hemorrhagic shock can be correlated well with the excess lactate, low pH and decreased arterial bicarbonate concentration (Nastuk and Beatty, 1949; Weinstein et al, 1960 and Broder and Weil, 1964).

In later stages of hemorrhagic shock, a reduction in plasma volume due to noradrenaline administration may be expected from the alteration in vascular activity, since noradrenaline causes a preferential increase in post capillary resistance and an elevation of capillary hydrostatic pressure (Lewis and Millander, 1962 and Mellander and Lewis, 1963). The constriction of post capillary resistance vessels would also tend to cause capillary stagnation and a reduction in venous returns. A reduction in lethal bleeding volume after noradrenaline infusion, probably reflects transcapillary fluid loss (Remington et al, 1950 and Schumer and
FIG. 4. SHOWING DELETERIOUS EFFECTS OF NORADRENALINE WHICH CONSTITUTE A VICIOUS CYCLE LEADING TO PERIPHERAL VASCULAR COLLAPSE AND PLASMA LOSS IN HEMORRHAGIC SHOCK.
High hematocrit values and high blood viscosity have also been correlated with poor survival rate in canine hemorrhagic shock (Crowell and Guyton, 1962 and Seligman et al, 1946). The detrimental effects of noradrenaline and excessive sympathetic activation through vasoconstriction metabolic acidosis and plasma loss are represented in Figure 4.

**Dopamine:**

In the selection of vasoactive drugs for the treatment of various types of shock, the physician searched for an agent which restores blood flow to vital areas, without compromising normal perfusion pressure. It appeared that dopamine had satisfied these criteria. Although dopamine is a biochemical precursor of norepinephrine, its exact role in the adrenergic system is not elucidated. Carvalho (1968) reported that average mean arterial pressure and cardiac output rose markedly when surgical and hemorrhagic shock were treated with dopamine. The average total peripheral resistance was moderately reduced. The increase in the mean blood pressure was mainly due to the increased cardiac output. Coronary
flow increased markedly, whereas coronary resistance decreased. The mean renal blood flow was markedly increased in hemorrhagic and traumatic shock but the renal resistance decreased. The marked increase in renal flow probably was principally accomplished by the increased perfusion pressure. McNay et al (1965) demonstrated that when dopamine was used in a dosage that did not increase mean arterial pressure, it was a renal vasodilator (Mesenteric flow also increased markedly in surgical and hemorrhagic shock). This is in contrast to the usual increase in renal resistance which occurs with norepinephrine.

The increase in cardiac output and coronary blood flow produced by dopamine was abolished by the administration of β-receptor blocking agent propranolol, without significant effect on blood pressure (Carvalho, 1968). This suggested that it was the beta adrenergic receptor action of dopamine which caused dilatation of the coronary circulation and increase in the myocardial contractility. Probably the maintenance of blood pressure at this time was due to the unopposed alpha adrenergic receptor activity of the drug. It's pressor effect could be partially abolished
by the administration of alpha-blocking agents like phentolamine. However, it is of interest that when pressor effect was abolished by the alpha-receptor blocker, the increase in coronary, renal and mesenteric flow due to dopamine were only slightly changed, because the beta-action continued unopposed. From this they concluded, this drug dopamine appeared to have an almost ideal proportion of alpha and beta adrenergic activity since it substantially maintains blood pressure as well as systemic hemodynamics. The β-action caused dilatation of coronary, renal and mesenteric circulations. Its pressor effect is due to a slight alpha action causing peripheral vasoconstriction, and chiefly beta inotropic action.

Dopamine has well-defined chronotropic and inotropic effects on the heart (Maxwell et al, 1960). The effects on blood pressure vary. At low doses (less than 7 μg/kg/min), it decreases blood pressure and at higher doses a pressor component is evident (Maxwell et al, 1969; Shanbour and Hinshaw, 1969). Beta-adrenergic blocking agents prevent the inotropic effects on the heart, but not the depressor component
Dopamine as suggested by McDonald and his associate (1963), produced a few favourable effects in normovolemic persons and in patients with congestive heart failure. These favourable effects include increased CO, decreased TPR as well as increased GFR and renal flow. This is ideal and, no doubt, beneficial to the hypovolemic patients. However according to Daugher and Harrison (1970) these favourable effects of dopamine in normovolemic conditions are lost during hypovolemia, and severe hemorrhagic shock, despite replacement of all the shed blood.

Studies evaluating the effects of dopamine on renal blood flow and function during shock have shown that dopamine further decreases an already depressed blood flow (Shanbour and Parker, 1972). The levels of norepinephrine and epinephrin rise in shock, but there is decreased responsiveness to these catacholamines (Jacobson et al, 1964).

Neiberger et al (1980) observed that plasma renin activity and outer cortical blood flow were significantly greater in the group of dogs receiving
dopamine. Total renal blood flow, Na⁺ and K⁺ excretion were similar in both groups, however, the ratio of urine Na⁺ to K⁺ concentration closely followed the plasma renin activity. In addition increased plasma renin activity produced by dopamine infusion during hemorrhage tends to offset, the expected increases in renal blood flow and Na⁺ excretion. Hemorrhage is a potent stimulus for increased plasma renin activity according to Blaine et al (1970) and Brown et al (1966).

ROLE OF ENDOGENOUS OPIOIDS AND THEIR RECEPTORS:

Opiates have been a fascination for medical scientists and laymen alike. This interest reflects the unique therapeutic value of these agents and the mystery surrounding their mode of action. The discovery of opioid peptides has opened up scientific areas and posed questions many of which are still in an early stage of exploration. An enormous amount of information has accrued and is still accruing on opioid mechanism (Hughes and Kosterlitz, 1983).

The term opioid refers to any directly acting
compound, the effect of which are stereospecifically antagonised by naloxone. This definition does not take into consideration that, the possibility of an opioid or a part of an opioid may have actions not antagonized by naloxone. In this case the effects are, by definition, not mediated by opiate receptors (Hughes and Kosterlitz, 1983). Originally, the term endorphin was suggested for the newly discovered peptides. However, endorphin was used to refer specific sequences within beta-lipotropin and the less ambiguous term opioid peptide is now generally used.

It is now clear that there are at least three different families of endogenous opioid peptides.

1. Enkephalins
2. Endorphins
3. Dynorphins

These peptides may function as neurotransmitters, neuromodulators or hormones. The receptor mediated actions of these opioids show a considerable overlap in view of their structural relationship.

Major endorphins and their amino acid sequences are given in the table I and a comparison of the
# Table 1. Major endorphins and their amino acid structures

<table>
<thead>
<tr>
<th>Name</th>
<th>Amino acid sequence</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met-Enkephalin</td>
<td>Tyr Gly Gly Phe Met</td>
<td>573.8</td>
</tr>
<tr>
<td>Leu-Enkephalin</td>
<td>Tyr Gly Gly Phe Leu</td>
<td>555.7</td>
</tr>
<tr>
<td>a-Neo-Endorphin</td>
<td>Tyr Gly Gly Phe Leu Arg Lys Arg Tyr Pro Lys</td>
<td>1228.6</td>
</tr>
<tr>
<td>Met-Enkephalin-Arg&lt;sup&gt;6&lt;/sup&gt; Phe&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Tyr Gly Gly Phe Met Arg Phe</td>
<td>877.1</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>Tyr Gly Gly Phe Leu Arg Arg Ile Arg Pro Lys Leu Lys Trp Asp Asn Gln</td>
<td>2147.8</td>
</tr>
<tr>
<td>a-Endorphin</td>
<td>Tyr Gly Gly Phe Met Thr Ser Glu Lys Ser Gln Thr Pro Leu Val Thr</td>
<td>1746.2</td>
</tr>
<tr>
<td>B-endorphin (human)</td>
<td>Tyr Gly Gly Phe Met Thr Ser Glu Lys Ser Gln Thr Pro Leu Val Thr Leu Phe Lys Asn Ile Ile Lys Asn Ala Tyr Lys Lys Gly Glu</td>
<td>3465.6</td>
</tr>
</tbody>
</table>
endogenous opioid peptide systems, by considering their origin, distribution, receptor affinities and duration of action are given in table II.

Enkephalin containing neurons have been identified throughout the brain with the help of immunohistochemical studies (Hughes et al, 1977 and Simantov et al, 1977). In the medullary region they are found in plenty (nucleus tractus solitarius, nucleus ambiguus and dorsal vagal nucleus). The region around area postrema near the obex is rich in opiate receptors and this locus is critical to cardiovascular control, since all afferent baroreceptors fibres pass through this region (Korner, 1971; Young et al, 1980).

The cell bodies of beta-endorphin-positive neurons are largely restricted to the arcuate nucleus of the hypothalamus, with long axonal projections extending to the nucleus tractus solitarius as well as reticular, mid brain and limbic regions. The anatomical distribution of beta-endorphin containing neurons is also consonant with action that may affect circulatory function (Watson and Barchas, 1979). Moreover, these neurons are immunoreactive for
Table II. Comparison of endogenous opioid peptide systems

<table>
<thead>
<tr>
<th>Endorphin family</th>
<th>Enkephalin family</th>
<th>Dynorphin family</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type and nature</strong></td>
<td>Endocrine cells; neurones restricted and discrete.</td>
<td>Mainly short neurones, neurones diffuse and widespread; some endocrine cells.</td>
</tr>
<tr>
<td><strong>Particular associations.</strong></td>
<td>Co-synthesized with corticotrophin + melanotrophins.</td>
<td>Co-stored with catecholamines in chromaffin tissue.</td>
</tr>
<tr>
<td><strong>Actions at opioid receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long acting at ( \mu ) receptors</td>
<td>( \beta )-endorphin</td>
<td>Possibly ( \xi )-endorphin or dynorphin</td>
</tr>
<tr>
<td>Long acting at ( \delta ) receptor</td>
<td>( \beta )-endorphin</td>
<td>Possibly ( \beta )-neoendorphin</td>
</tr>
<tr>
<td>Long acting at ( \kappa )-receptors</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Short acting at ( \mu )-receptors</td>
<td>No</td>
<td>(Met)enkephalin</td>
</tr>
<tr>
<td>Short acting at ( \delta ) receptors</td>
<td>No</td>
<td>(Leu)enkephalin</td>
</tr>
<tr>
<td>Short acting at K-receptors</td>
<td>No</td>
<td>Dynorphin</td>
</tr>
<tr>
<td><strong>Non opioid receptor interactions</strong></td>
<td>( \beta )-endorphin and immune system.</td>
<td>?</td>
</tr>
</tbody>
</table>
adrenocorticotrophic hormones (ACTH) and beta-lipotropic hormone, two peptides that show the common pre-opiocortin precursor with beta-endorphin (Eipper and Mains, 1980).

The peripheral nervous system and endocrine organs also contain opioid peptides. Enkephalins have been shown in the superior cervical ganglia, inferior and superior mesenteric ganglia, and chromaffin cells of adrenal medulla, whereas, beta endorphin in the circulation originates from anterior and intermediate lobes of pituitary (Schultzberg et al, 1978 and Viveros et al, 1979).

Localization of opiate receptors in the periphery is less well resolved as compared to the opiate receptors in the central nervous system. Young and his colleagues (1980) have shown that the vagus nerve contains opiate receptors that are transported along axons from the neurons in the nodose ganglia to the brain as well as to the periphery. Pharmacological evidences suggest that pulmonary 'J' receptors in the lung may contain opiate binding sites (Sapru et al, 1981). Vascular beds may also contain opiate receptors (Altura et al, 1979).
Opiate receptors were identified in 1973 (Snyder et al, 1973) in the brain and subsequently in the kidney intestine, adrenal medulla, heart and lung. The search for their ligands led to the discovery of several endogenous morphine like substances (endorphins). Since their discovery, endorphins have been implicated as the mediators of numerous physiological and pathological processes.

**ROLE OF OPIOID ANTAGONIST NALOXONE IN SHOCK:**

Since opioids produce hypotension and plasma levels of \( \beta \)-endorphin rise during stress (Guillemin et al, 1977), Holaday and Faden (1978), postulated that endogenous opioids released contribute to the cardiovascular supression seen during shock. They tested this hypothesis by administering the opiate receptor antagonist naloxone to rats in endotoxic shock. Naloxone increased mean arterial pressures and pulse pressure, thereby supporting their hypothesis. Subsequently naloxone was shown to be beneficial, when given intravenously to treat other species subjected to endotoxic, hemorrhagic or spinal shock.
Naloxone also improves hemodynamic function when given intra-cerebroventricularly. Therefore, it appears that naloxone administered intravenously may act within the central nervous system to increase cardiac performance, perhaps by reducing vagal inhibition of cardiac function (Faden and Holaday, 1979) or increasing sympathetic activity (Koyama et al, 1983b).

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Naloxone increases cardiovascular performance by acting at cardiac opiate receptors and potentiates the cardiovascular effects of adrenergic stimulation (Lechner et al, 1985). In the absence of stress, catecholamines binds to B-adrenergic receptors located on myocardial cells, and this binding results in increased production of adenosine 3',5' cyclic monophosphate. During stress B-endorphins are released from the anterior pituitary, binds to opiate receptors located on the myocardial cells, and presents the
increase in CAMP seen with B-adrenergic stimulation. They postulated further that naloxone exists its beneficial effects by binding opiate receptors, thereby preventing opioid mediated attenuation of adenyl cyclase activity (Leehner et al, 1985). Which endogenous opioid is involved in the pathophysiology of shock? Beta endorphin is a likely candidate, since its plasma levels increase during hemorrhagic shock in dogs (Vargish et al, 1984) and in baboons (McIntosh et al, 1985). It appears that B-endorphin secreted by the pituitary is the opioid involved since prevention of B-endorphin release by hypophysectomy blocks the response to naloxone during haemorrhage (Holaday et al, 1981). This evidence is not conclusive, however, since plasma levels of corticosteroids were presumably low in these animals, due to lack of ACTH and physiological levels of corticosteroids are required for naloxone to exhibit its beneficial hemodynamic effect (Patton et al, 1983). Additional evidence suggesting a role for B-endorphin in cardiovascular depression, is the finding that pharmacological doses of corticosteroids attenuate the hemodynamic response to naloxone (Vargish, 1982).
Beta endorphin and ACTH are synthesised from the same macromolecule (Mains, 1977) and the release of both are controlled by corticotropin releasing hormone. Since corticosteroids, suppress the release of ACTH, it is possible that corticosteroids attenuate the response to naloxone by blocking the release of β-endorphin. Recently Machuganska and Zaharieva (1985) also tried to elucidate whether pituitary beta endorphin contribute to the hypotension and cardiodepressor changes in hemorrhagic shock. The role of central nervous system opioid receptors for these effects, and the mechanism of action of naloxone have been derived by them. The studies were performed in hypophysectomised rats with hypovolemic shock treated with naloxone either intracerebroventricularly (ICV) or intravenous (IV). Neither ICV or IV administration of naloxone on hypophysectomized rats prevented the cardiodepressor changes during shock. The beneficial effect of naloxone was manifested only on animals with intact pituitary glands, suggesting that its therapeutic effect is centrally mediated and pituitary beta endorphin may potentiate the hypotension during hypovolemic shock through an action on opiate receptors in the CNS.
They further explained that in hypophysectomised rats
naloxone did not stimulate aldosterone secretion,
in hemorrhagic shock, as it did in rats with intact
pituitary, which indicated that this effect is secondary,
accomplished by stimulation of the secretion of both
ACTH and beta-endorphin.

It could also be argued that enkephalins released
from the adrenal medulla during hypovolemia may be the
opioid responsible for the suppression of cardiovascular
performance. This is not likely since naloxone exerted
its beneficial hemodynamic effects in adrenalectomised
dogs (pre treated with mineralocorticoids) that were
incapable of secreting medullary enkephalins (Patton
et al, 1983).

If in pentobarbital anaesthetised dogs, naloxone
acted within the central nervous system to improve
cardiovascular performance, then one would expect to
see either increased sympathoadrenal stimulation of
the heart or decreased vagal nerve activity. Naloxone
does not appear to increase sympathoadrenal stimulation
of the heart, since sectioning of the cardiac
sympathetic nerve supply does not attenuate the
response to naloxone (Lechner et al, 1985) and
plasma levels of catecholamines do not increase after treatment with naloxone (Lechner et al, 1985). If naloxone caused decreased vagal effects on the heart, then vagotomy or methylatropine should have attenuated the hemodynamic responses to naloxone. However, acute cervical vagotomy had no effect. Therefore, it appears that naloxone acts outside the central nervous system in reversing canine hypovolemic shock. Lechner et al (1985) also is of the opinion that naloxone improves cardiovascular function in hemorrhagic shock by potentiating the effect of released catecholamines and not by increasing sympathoadrenal discharge. Their study tests the hypothesis, that naloxone acts by potentiating the effects of neurally and adrenally released catecholamines. If this hypothesis is correct, blockade of endogenous catecholamines, release should attenuate the response to naloxone. In their study (Lechner et al, 1985) catecholamine release was attenuated by a combination of surgical adrenal denervation or ganglion blockade by chlorisondamine.

Naxolone also moderately increases circulating lysosomal hydrolase activity and total plasma proteolysis (Curtis and Lefer, 1980). Curtis and Lefer (1980)
also found myocardial depressant factor significantly reduced in naloxone-treated hemorrhaged cats compared to control group of cats. Inhibition of proteolysis and stabilization of lysosomal membranes appear to be involved in the protective action of naloxone along with the well known opiate-antagonist action. Except in large doses, naloxone has no direct effects on myocardial contractility either in vitro (Curtis and Lefer, 1980) or in non-shocked animals in vivo (Vargish et al, 1980). These effects may or may not be related to specific effects of opiate receptors. It is of some interest that cathepsin-D, which is released into the plasma in experimental shock, splits beta-endorphin into smaller peptide units, and it is possible that one of these fragments, containing the active opioid sequence, possesses the ability to depress myocardial function.

Naloxone has also been shown to reverse, the hypotension, hypothermia and respiratory depression in spinal shock in rats (Holaday and Faden, 1980).

Endogenous opioids strongly affect gastrointestinal motility such as gastric and intestinal contractions, gastric emptying, gastric secretory activity and raise
gastric incubation. They inhibit pancreatic bicarbonate and enzyme secretion, probably via suppressing the release of intestinal hormones cholecystokinin. These action can be reversed by opiate antagonist naloxone (Stanislan, 1980). Morane et al (1984), evaluated naloxone as a gastric cytoprotective agent during hemorrhagic shock. They found naloxone has no apparent effect on local gastric vascular resistance during hemorrhagic shock.

Thus to conclude, though naloxone has proved to be effective as a narcotic antagonist, there are no definite, conclusive evidences of its usefulness in non-narcotic coma and shock. At present the use of naloxone in pathological conditions is limited to experimental studies, with only a few clinical trials in septic and spinal shock in human beings. In experimental hemorrhagic shock, the role of naloxone in improving cardiovascular function is well documented but hardly any study of its effect on renal function.