MICROCIRCULATION

In all forms of shock the common feature is a reduction in the perfusion of blood to vital organs (Messmer 1976). Therefore, pathophysiological changes are due, ultimately to an inadequate maintenance supply to the tissues and to alteration of normal transcapillary gradients of water-soluble metabolites and ions which owing to poor drainage, accumulate in the extra-capillary space i.e. interstitial and intracellular space (Messmer 1976). As a result, there is impairment of essential functions of microcirculation, namely transport of Oxygen and nourishment to the tissues and removal of metabolites (Messmer and Sunder-Plassmann 1974).

The microcirculation is the ultimate portion of the cardiovascular system concerned with the transfer of gas and nutrients and the removal of metabolic waste products (Zweifach 1976). It is a highly specialised, busy, sensitive and variable end organ about which the present day knowledge is very limited. But it is an established fact that the flow of blood through the microcirculation is as vital to life as that through the heart and great vessels (Zweifach 1961, Zweifach 1976). Although, Mall as far back as 1888 had examined the design of the microvascular network in the mesentery of dog, yet late 1930 represents the beginning of modern microcirculatory thinking and research. There had been a re-birth of interest largely through the works of leaders such as August Krough (1922) and
Thomas Lewis (1930). The definitive treatise on the blood capillaries was the monograph by August Krogh (1922). In his study he tried to find out the mechanism which permitted the enormous increase in the number of capillaries with an active flow of blood during exercise. He developed a concept of "recruitment" which described a contractile part by the vessels within the microcirculation proper (Zweifach 1976). According to this idea the capillary network was looked as a peripheral heart with an active role through the microscopic vessels.

Anatomy of Microcirculation

In the process of branching, large arteries after originating from the heart and aorta, divide and sub-divide till these ultimately become to smaller muscular arteries. They in turn divide into arterioles. The arteriols are only few milimetres in length and have diameters varying from 8-50 microns. Each arteriole branches many times to supply perhaps 10 to 100 capillaries (Guyton 1976-a). The smaller muscular arteries and arterioles together are classed as muscular vessels (Zweifach 1973). Some of these arterioles devide into smaller muscular walled vessels called metarterioles. The later devide into several capillaries. Some of the capillaries are very large, and they course almost directly to the venules. These are called preferential channels (Intaglietia and Zweifach 1974, Guyton 1976-b). However, most of the
capillaries, called the true capillaries (Zweifach 1973, Guyton 1976-b), branch mainly from the metarterioles and then finally terminate into a venule which constitute the beginning of the venous channel (Guyton 1976-b). The arterioles have a strong muscular coat, and the metarterioles are surrounded by sparse but highly active smooth muscle fibers. In addition, at each point at which a capillary leaves a metarterioles, a small muscular precapillary sphincter, usually composed of a single spiralling smooth muscle fiber surrounds the origin of the capillary. These minute precapillary arterioles, post capillary venules and capillaries constitute the major components of microcirculation (Guyton 1976-b).

**Muscular arteries**

They constitute the precapillary resistance vessels. The muscular wall of these vessels contain little elastic tissue and are innervated by adrenergic nerve fibers, which are constrictor in function. But in some instances the muscles of these vessels are innervated by cholinergic fibers and they dilate the vessels.

**Metarterioles**

As described before the arterioles divide into smaller muscle wall vessels known as metarterioles. This term was used first by Zweifach 1961. These vessels (metarterioles)
Diagram depicting microcirculation

Fig. No. 4

Nucleus

Endothelial cells

Capillary wall

Fig. 6
are defined as primary structural units which serve as a framework for distribution of capillaries. In some vascular beds, a metarteriole is connected directly with a venule (Fig 5), and the true capillaries are an anastomosing network of side branches of this throughfare vessel. The origins of the capillaries are surrounded on the arterial side by minute smooth muscle precapillary sphincters (usually of a single spiralling smooth muscle fiber) (Guyton 1976-b). When the sphincters are dilated, the diameter of the capillaries are normally about 6 μ just sufficient to permit red cells to squeeze through a single file. The metarterioles and precapillary sphincters are also innervated by adrenergic vasoconstrictor fibers supplying the arterioles. But this innervation is very sparse and the muscle fibers of these two structures are controlled almost entirely by the local humoral environment of the tissues, i.e., by the concentration of oxygen, carbondioxide, hydrogen ions, electrolytes and other factors in each individual tissue area (Guyton 1976).

Capillaries

The metarterioles divide into several capillaries (Fig 2). The latter may be described as endothelial tube devoid of smooth muscle and has minimum amount of supporting tissue. In the capillaries exchange of metarials between blood and tissue and vice versa primarily occur. They are generally untapered and appear in mammals as tubes some
3-15 \( \mu \) in diameter and formed by a single layer of endothelial cells, possibly held together by an intercellular cement substance but without reinforcement of elastic or collagen fibers (Krogh et al 1922, Luft 1965). The intercellular cement substance is probably calcium proteinate in nature (Landis and Pappenheimer 1963). The layer of cells is enclosed by a "basement membrane" (Fig 5) which play an important part in transcapillary molecular exchange. Longitudinal section of the wall shows a mosaic like pattern of rhomboid or polygonal endothelial cells and which are arranged in a spiral form. The thickness of the wall is 2-3 \( \mu \) at the level of maximum diameter of the nucleus and 300\( \AA \) near the edge of the cell where it overlaps its neighbour (Fig 6). Molecules up to the size of inulin (molecular weight 5200 and diameter of about 30\( \AA \)) are able to pass easily through the walls, probably by diffusion. In between the endothelial cells on the walls of capillaries narrow areas persists. These passage-ways are actually slitlike spaces between the adjacent endothelial cells where they contact each other. However, these slits are located far apart from one another, and they represent no more than 0.001 of the total surface area of the capillary. These passages are called pores of the capillary membrane. These slitpores have a width between 80 and 90 Angstroms (Guyton 1976). Normally they are very narrow but may dilate.
to permit passage of molecule up to 30 Å in diameter. A smaller number of channels of 350Å in diameter, show the presence of a second or large pore system (Landis et al. 1963). The surface exposed to the circulating blood through these capillaries is irregular and show tiny pseudopodia or fring like structures and may be coated internally with a very thin layer of protein material - possibly fibrin. But so far electron microscopic examination has not confirmed their presence. In this respect the exact anatomy of capillaries vary considerably from organ to organ. In the liver, these pores are visible on the basement membrane under electron microscope. In other organs the basement membrane is generally continuous (Guyton 1976). In the endocrine glands, intestinal villi and some portion of kidney there are definite gaps between the endothelial lining cells (Roberts 1971). Terminal vascular beds differ greatly in different regions of the microcirculation (Sobin 1966, Sobin and Tremer 1966) but are of fantastic complexity (Barman 1964), (Burton 1965). Frequently the capillaries originate from the subdivision of precapillary channels which in turn diverge from a thoroughfare channel (Zweifach et al 1976) connecting a terminal arterioles with a collecting venule so that the branching net work may be equiped with a variety of feeds and drains. The thoroughfare channels are characterised by a very sparsely distributed muscle coat having only one cell thickness and flow from them into the capillary net work is often controlled by precapillary sphincters.
The angles of branching capillaries differ in various organs and in different species. Thus in the liver and lungs they radiate circumferentially at right angles to the axis of the supplying vessels whereas in the mesentry they radiate at a less acute angle of $30^\circ - 45^\circ$ (Block 1963).

Another feature of those vascular beds is the existence of direct connections (or shunts), which short circuit the capillary system (Burton 1951, Burton 1966). They are thick walled vessels generally closed during normal tissue metabolism (Bloch 1966) and structurally more comparable with arterioles than capillaries.

Rouget (1873) described a special variety of cell placed at interval along certain capillaries. The cells are almost transparent and have long, branching threadlike processes which run round the circumference of the capillary tube. They are thought by most observers to be connective tissue cells and the suggestion that contraction of them alters the size of the capillary lumen is probably incorrect. "Rouget cells" have been described in some capillaries in certain situations in amphibia, and in some capillaries of the mammal, during certain stages of development (Zweifach 1976 b).

**Venules**

As mentioned earlier, venules originate in the post capillary side, at the appearance of the first smooth muscle
DIAGRAMMATIC REPRESENTATION OF THE MICRO CIRCULATION (Sphincters and valves have been omitted for clarity)
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cell in their walls (Guyton 1976-b). The small veins and venules constitute the post capillary resistance vessels. The venules are constituted of a single layer of endothelial cells adhering to a thin layer of collagen connective tissue which forms the outer wall. Smooth muscle cells are generally absent in the smallest venules but are present in the large ones. Here the endothelial cells are more rounded than in the arterial system and the diameter of the vessels are increased. The greatest cross sectional area of flow, and thus the lowest mean velocity of flow, is often found in this part of the circulation. Powerful constrictor control are provided by sympathetic nervous system on the smooth muscles of the venules and small veins (Guyton 1976-b). Dilatation of the sphincters of the venular side occur due to inhibition of these sympathetic fibers.

**Arterio venous anastomosis**

In some tissues short communicating vessels are present between the arterial and venous systems. These arteriovenous connections allow arterial blood to be shunted into the venous system without first passing through a capillary network (Guyton 1976-b). These arteriovenous anastomosis may be straight or coiled. On the arterial side, there is a thick muscular wall whereas a thin funnel shaped widening exists on the non-muscular venous end (Fig 4). The narrow intermediate portion has an extra thick wall which appears
to be the most contractile part (Landis E.M. and Pappenheimer J.R. 1963). The muscular tissue of the entire wall of the arterio-venous shunt is innervated by adrenergic nerve fibers (Guyton 1976-b). During dilatation, internal diameters of these shunts varies between 20 - 40 μ. When vasoconstriction of small vessels of arterial end beyond the shunt increases the resistance to the blood flow, the arteriovenous shunt may come to preferential use (Guyton et al 1972). Arterial blood will be diverted at that time to shunt which afford the path of least resistance (Guyton 1976-b).

Physiology of Microcirculation

At any particular time, the venous compartment contain about 85%, arterial side 10% and capillaries 5% of the blood volume (Hamilton 1963). But the last 5% is the most important part as it is across the systemic capillary walls and here oxygen, nutrients enter the interstitial fluid and carbondioxide and other waste products enter the blood stream. This exchange across the capillary wall is essential to the survival of all tissues in the body (Guyton 1976, Ganong 1967).

Local blood flow and its distribution to capillary network is largely determined by the metabolic demand of each tissue (Guyton 1976-b). In the resting stage, majority of capillaries are collapsed and blood flows mainly through
the AV shunting vessels (Roberts 1971). In active tissue, the metarterioles and the precapillary sphincters dilate and the intra capillary pressure rises. It overcomes the critical closing pressure of the vessels and blood flows through all the capillaries (Guyton et al. 1972*, Altura 1971).

Microcirculation is regulated by two mechanisms: (a) vasodilation by metabolites and hypoxia (except in the lungs), (b) extrinsic vasoconstriction tone through adrenergic nerves (Guyton 1976). Regulation of arterial pressure is maintained by the competitive influence of these mechanisms. At any time, normally only one forth of the capillary bed of a particular tissue is perfused. This quarter is not a static portion, but according to the concept of papillary auto-regulation, continuously changes in response to local tissue needs (Ledingham 1973). The changing concentration of local metabolites and oxygen tension dictates which particular capillaries need perfusion (Roberts & Laros 1971). When one observes a local tissue under microscope, he sees that the precapillary sphincters are normally either completely open or completely closed. The number of precapillary sphincters that are opened at any time is approximately proportional to the requirements of the tissue for nutrition. In some tissues the precapillary sphincters open and close cyclically several times per minute, the duration of the open phases being approximately proportional to the metabolic needs of the tissues. This cyclic opening
and closer of the sphincters is called vasomotion (Guyton 1976). The extrinsic neural control which constricts the calibre of resistance vessels, can not over ride the effects of metabolites and reduce blood flow temporarily to one organ or tissue and preserve blood flow to vital organs when the need of the animal as a whole occurs. After prolonged adrenergic activity, this vasoconstriction control over precapillary resistance vessels may be lost, while the effect on post-capillary vessels persists (Guyton 1976).

The exact mechanism of action of the metabolite on the capillary blood flow is a controversial subject (Ledingham 1978). Hypoxia has been stated as the primary cause of local depression of neurogenic activity (Guyton et al 1964). According to this postulation, concept of vasodilator metabolites is of very little value. Hypercarbia has also a significant degree of vasodilator activity on the precapillary sphincters. But this action is ten times less than that produced by hypoxia (Guyton 1976). Certain areas of the circulatory bed are particularly sensitive to changes in PCO₂ level e.g. resistance vessels of the cerebral and splanchnic circulation (Ledingham 1978). The coronary and renal circulation are, however, more sensitive to oxygen lack (Guyton et al 1972). Metabolites like potassium, histamine, lactic acid and bradykinin have been implicated as vasodilator "transmitters" (Guyton 1976-b). But none of them have the universal distribution of site of action which would characterise such a transmitter. Once
adenosine has been particularly implicated both alone and combined with mediators in the myogenic regulation of coronary blood flow (Ledingham 1978). But adenosine does not occur to any significant quantity in skeletal muscles or other tissues and hence cannot be regarded as an universal vasodilator metabolites. It is, therefore, seems that vasodilator metabolites play a secondary role to the direct effect of oxygen lack and excess of carbondioxide in the autoregulation of capillary blood flow (Lendis and Pappenheimer 1963, Guyton 1976).

Capillary pressure

Capillary pressure vary considerably. But average value in human nailbed capillaries are 32 mm of Hg at the arteriolar end and 15 mm of Hg at the venous end. The pulse pressure is about 5 mm of Hg at the arterial end and zero at the venous end (Ledingham 1978). The functional capillary pressure is measured to be about 17 mm of Hg (Guyton 1976).

Capillary flow patterns

Though the capillaries are short tubes yet blood flow through them is very slow, about 0.07 cms/second. In an average sized capillary, time taken for blood flow from arterial end to venous end is 1 - 2 seconds. The particular nature of blood is also important in determining the flow properties as the diameters of the vessels diminish. It can
no longer be treated as fluid because the RBC, which possesses some degree of rigidity, are restricted in the orientation and position which they can assume adjacent to the vessel wall. The mean haematocrit is reduced in this area and a large portion of the shearing during flow takes place in it. Nevertheless, some relative motion between the cells in the main core also occurs at normal haematocrits and assume two general forms. In the first, the cells arrange themselves in roughly concentric laminae with their disoidal surfaces orientated predominantly parallel to planes passing to the vessels axis. The central core travels more rapidly, each additional layer passing more slowly than the one inside it (Knisely 1965) and the leucocytes and platelets accompany the peripheral layer. The degree of orientation of the cells increases with the flow rate (Bloch 1966) and although some cells may move incontact with the walls during flow, a plasma layer which on an average, is between a half and one cell diameter in width, is present over a wide range of vessel diameters (Bloch 1963). The thickness of the plasma region at the wall may also be velocity dependent, and disappear when the flow ceases (Bloch, 1963, Maggio 1965). Thus, this type of flow pattern may be referred to as "laminar" (Maggio 1965) although the term has a different physical significance in this context from when it is applied to pure fluids.
In the second pattern there is a random orientation of the RBC's and every small portion of the blood mass oscillates across the tube in an irregular fashion, the cells bending, rotating, tumbling and exchanging places in a chaotic manner (Muller 1966, Maggio 1965). They make frequent intimate contact with the walls and plasma spaces not frequently extend transversely across a third or more of the cross section of the vessels (Bloch 1963). This type of flow has been called "turbulent" (Maggio 1965) and "Newtonian" (Müller 1966). But both the two terms unfortunately are liable to create confusion. In both flow patterns, however, relative movements between the red cells in the core is a common factor and appropriate name for the flow should be "shearing Core" (Whitmore 1967). As the vessel size decreases from the larger arterioles and venules to the terminal arterioles and capillaries, there is an imperceptible transition in the bulk flow patterns. There might be deformation of both these two channels to maintain the blood flow through them. Only a single file of RBC maintain the flow of blood through the narrowest arterioles and capillaries.

Flow at the junctions

At the diverging junctions in the microcirculation, the concentration of red cells may differ considerably. Here not only the concentration of cells in the feeding vessels vary from instant to instant, but also skimming of plasma occurs (Krogh 1922).
Diffusion through the capillary membranes

The transfer of fluids and solutes between blood and interstitial fluid take place across the capillary wall, (Roberts 1971). It has already been mentioned that there are gaps in some places in the cement substance filling the spaces between the endothelial cells of the capillary wall. These gaps or pores are believed to be the site of transfer of substances that are soluble in water but completely insoluble lipids (Sodium ions, chloride ions, glucose and so forth) (Mayerson et al 1960). Despite the fact that not more than 1/1000 of the surface area of the capillary is represented by slit pores, the velocity of thermal motion is so great that even this small area is sufficient to allow tremendous diffusion of water and water soluble substances through pores (Guyton 1976). The rate at which water molecules diffuse through the capillary membrane is approximately 80 times as great as the rate at which plasma itself flows linearly along the capillary (Guyton 1976).

The size of these pores depends on the nature of tissue in which they form a part. In the walls of muscle capillary the pores are about 30Å in diameter whereas in the renal glomeruli they are up to the size or 100Å in diameter. Hepatic capillaries have been larger pores and allows appreciable amount of protein through them. But these openings in the walls of the capillaries of the brain are relatively
impermeable to most substances in the blood.

By the mechanism of diffusion and filtration, movement of water and solutes across the capillary wall occur. The rate of filtration at any point along a capillary depend upon the filtration pressure (algebraic sum of hydrostatic pressure in the capillary and that of the interstitial fluid) at that point. This filtration pressure is opposed by the osmotic pressure of the plasma protein. The filtration pressure is higher at the arterial end (32 mm of Hg) than the oncotic pressure (25 mm of Hg). As a result, fluid travels from the vascular compartment to the interstitial space. But the oncotic pressure at the venular end being higher than the filtration pressure, causes the movements of the fluid back into the capillaries (Guyton 1976). The amount of fluid moving across the capillary wall is enormous. It has been estimated that an amount equal to the entire plasma volume enters the tissue and equal amount leaves them every minute (Gannong 1967).

The lipoid soluble substances (Carbon dioxide and oxygen) can travel directly through the cell membranes of the capillaries without going through the pores (filtration). Since these substances can permeate all areas of the capillary membrane, their rates of transport through the membrane are several 100 times the rate for mostly lipoid insoluble substances (Guyton 1976). Water molecules are the next to diffuse rapidly through the capillary membrane. Part of the
water diffusion occurs through the pores of the endothelial cellular membrane but the other half passes almost without any difficulty through the slit-pores between the endothelial cells (Guyton 1976).

**Relation between molecular size and pore permeability**

It is obvious that the permeability of the capillary pores for different substances will vary according to the diameters of their molecules.

**Effect of oncotic pressure on diffusion through the capillary membrane**

The rate of diffusion of a substance through any membrane is proportional to the oncotic pressure difference between the two sides of the membrane. Greater the difference between the concentration of any given substance on the two sides of the capillary membrane, more will be the net movement of the substance through the membrane. As the concentration of oxygen in the blood is more than in the interstitial fluid, it flows from blood towards the tissues (Guyton 1976). Whereas difference in concentration of carbon dioxide being just its reverse, the gas moves from the tissues to the capillary lumen. The rates of diffusion through the capillary membrane of most nutritionally important substances, are sufficient to cause more than adequate transport between the plasma and interstitial fluid.
Relation between hydrostatic pressure and rate of diffusion through capillary membrane

Rate of diffusion of substance depends not only on the oncotic pressure difference but also on the hydrostatic pressure difference between the two sides of the capillary membrane. Rate of diffusion is directly proportional to the hydrostatic pressure (Kinetic energy of the molecules) (Guyton 1976).

Bulk flow through capillary pores

When measured, a rate of movement of water and low molecular weight solutes through the capillary membrane (caused either by a colloid osmotic pressure or by a hydrostatic pressure) it will be evident that this is ten times as great as can be expected on the basis of not diffusion alone. Here, these molecules move through pores that are far larger than their own diameters (i.e. slit-pores of capillary membrane), a large amount of mutual drag occurs between the molecule. So during diffusion, some of the molecules actually "flow" together. This phenomenon is known as bulk flow and it can increase the movement of both water and low molecular weight solutes many folds (Guyton 1976).

Transport through the capillary membrane by Pinocytosis

Another method by which minute quantities of substances can be transported through the capillary membrane is by Pinocytosis. In this process the endothelial cells of the
capillary wall inject small amounts of plasma or interstitial fluid and form small intracellular vesicles of the injected fluid. These then migrate from one surface of the endothelial cell to the other where the fluid is released. Transport of high molecular weight substances (Plasma proteins, glyco-proteins and dextran) might occur to a significant extent by Pinocytosis (Guyton 1976-c).
EVOLUTION IN THE THEORIES OF SHOCK

For over a century the term "Shock" has been used to describe the clinical state produced by the body's re-action to various noxious stimuli. Many attempts at an exact definition and at its causative factors have been made. Each time something new and more scientific has been discovered and thus the conception of shock changed with the advancement of science and general medicine. Before the first world war emphasis was laid on the behaviour of the peripheral circulation and changes produced in this system by nervous stimuli. Hypotension associated with marked peripheral vasoconstriction was thought as the result of body's reaction to haemorrhage and wounds. The clinical picture depicted by Fischer in 1870 of a young man with intra-abdominal haemorrhage can hardly be improved even in the present age.

As early as 1879 Mapother called attention to the presence of intense peripheral vasoconstriction in shock. But in those days crile's theory (1899) of vasomotor paralysis was widely accepted. Gradually with the advancement of knowledge in this subject the concept of shock changed and in 1905 Malcolm again confirmed the observation of the Mapother and he suggested in 1907 heat, vasodilators and saline solutions as the treatment of shock. Unfortunately, these observations did not attract much attention until the
past decade (Lillehei & Dietzman 1974).

High mortality of traumatic shock in the first world war led to further investigation. Possible dangers of excessive amounts of circulating adrenaline were emphasised by Bainbridge and Trevan (1917) and Erlanger et al (1919-a & 1919-b). Cannon in 1919 described shock further and observed the presence of acidosis in it (Cannon and Bayliss 1919).

Cannon (1919) also has shown that there was a selective vasoconstriction of splanchnic and cutaneous areas to divert the blood to heart, brain & voluntary muscles. This response was called by him as fight and flight reflex. This is what has been described later on as a part of "alarm reaction" by Selye (1946). It is probable that this response is evolutionary in origin and a part of the "survival of the fittest" suggested by Darwin (1859). Whatever its origin and original purpose may be, it can be considered as "Nature's first aid" (Lillehei & Dietzman 1974).

Later on Blalock (1930) stressed on the extent of fluid loss around the site of injury and challenge the concept of generalised vascular damage. He first gave the term "Haemato-gemic shock" to those cases of shock where fluid and blood loss occurred.

Moon (1935, 1937, 1942) put the matter in a nutshell when he remarked that the shock syndrome results from a
disparity between the volume of blood and volume capacity of vascular system. There may be a decrease in the blood volume, and increase in the volume capacity of the vascular system or a combination of both. The blood volume may be increased by haemorrhage, and by transudation of serum through the capillary walls with resulting increased concentration and viscosity of the blood and rise in the cell count and haemoglobin percentage.

Swingle et al (1933) drew attention to many points of similarity between the clinical science of animals who were subjected to adrenalectomy or who had been suffering from experimentaly induced shock. These findings suggest that the removal of adrenals may precipitate, or render a person more liable to develop shock. Freeman et al 1951 & Longerbeam et al in 1962 demonstrated prolonged infusion of adrenalin leads to shock. But it does not follow that all cases of irreversible shock are caused by adrenal insufficiency as the administration of cortical extracts could not diminish or abolish the production of shock from a wide variety of stress (Frank et al 1955).

Gilson et al (1947) suggested that the isolation of blood in the minute vessels is a dominating factor in reducing the venous return in shock. They stated that the actual volume of red cells trapped was small but could be enough to reduce the capillary flow by 20% to 40%.
Bobb and Green (1947) had shown that the kidney plays no part in the causation of ischaemic compression shock in dogs. The danger lies in the effect of hypotension upon the kidney, since if it lasts for more than an hour, readily detectable depression in renal tubular function occurs. Hayes (1957) has shown that the time of hypotension is directly related to the time it takes for maximal tubular recovery.

Harkins (1940) repeatedly attempted for an excellent definition of shock.

Wiggers (1942) placed emphasis heavily on the importance of circulatory system although other systems were not overlooked.

Boyd (1953) defined shock as a circulatory deficiency characterised by decreased blood volume, decreased cardiac output and increased concentration of blood. He divided this pathophysiological syndrome into primary shock (which follows immediately on the receipt of a severe injury) and secondary shock (which may not develop even within first 24 hours). In primary shock, nociceptive nervous stimuli was the chief factor for widespread capillary paralysis whereas in the secondary shock the capillary paralysis was thought as the effect of histamine like substances. However, later on this time oriented classification was discarded.
Afterwards Howard (1957) described shock further as a state of persisting deficiency in blood flow to tissue throughout the body and unless it is treated or sufficiently mild to be corrected spontaneously, it progresses by self-intensifying mechanism to a fatal outcome.

Change of concepts of shock in the recent years

In the recent years renewed interest have been grown in the behaviour of the peripheral vessels following experimental work on the effect of haemorrhage and administration of endotoxin on the laboratory animals. Freeman et al (1951) by giving prolonged infusion of adrenalin to mongrel dogs shown the appearance of a state of severe vasoconstriction and ultimate fatality similar to the stages seen in traumatic shock. Working with similar species of animals Lillehei (1957) found that haemorrhagic hypotension of four to five hours duration does not respond to the return of shed blood but blood pressure continues to fall until death occurs. Post-mortem examination revealed haemorrhagic necrosis of the bowel mucosa. Comparable changes were seen after the administration of bacterial endotoxin (Longerbeam et al 1962).

Lillehei et al (1962) & Nickerson (1963) observed that prolonged and intense sympathomimetic activity by either endogenous or exogenous adrenalin was very harmful for the experimental animal life.
Microscopy of the damaged gut in man (and dogs omentum and rats mesoappendix) shows capillary engorgement with arteriolar dilatation and venular contraction (Zweifach 1958, 1961). Possibly it is due to the differing ability of the pre and post capillary sphincters to maintain their tone during prolonged adrenergic stimulation (Lewis and Mellander 1962).

At first, both pre and post capillary sphincters are tightly constricted allowing little blood to enter the capillary bed. The pre capillary sphincters then lose tone due to local anoxia and cause accumulation of acid metabolites, while the post capillary sphincters remain constricted. This leads to capillary engorgement and stagnation, with extravasation of fluids. This causes further depletion of blood volume. Ultimately there is capillary destruction and loss of frank blood into the tissues. According to Lillehei et al (1964) the onset of this state during prolonged haemorrhagic hypotension or shock from any cause marks the change of the condition from "Rversible" to "Irreversible" state. The same authors also observed that organ showing most damage, vary from one species to another but haemodynamic disturbance in the peripheral vascular bed is a common feature and is the result of prolonged harmful vasoconstriction.

**Summary**

Though in shock syndrome ultimately almost all the organs of the human body are affected yet the important
features and site of involvement in different types of shock may be summarised in the following ways :-

Brain : Vasomotor collapse due to paralysis of vasomotor centre and dysfunction of peripheral vessels (Crile 1899).

Capillaries : In shock, increase capillary permeability from toxic substances liberated from the damaged tissue (Gregersen 1946), endotoxin (Bhagat 1974) and anoxia lead to loss of fluid from circulation and stagnation of blood in venous reservoirs (Gannon and Baylisis 1919, Blalock 1930). This cause further fall in cardiac out put.

The slow flowing, abnormally acid capillary blood in shock, is hypercoagulable. Thrombocytogetic agents (products of haemolysis, bacterial toxin and proximity to damaged tissue) initiate aggregation and sludging of red cells in capillaries and damage to the capillary wall. (Brill and Shoemaker 1960, Kinsely 1965 and Gelin 1956). Disseminated intravascular coagulation thus initiated causes irreversible cell death. Simultaneously there is depletion of coagulation factors from the circulating blood causing haemorrhagic manifestations. Necrosis of bowel mucosa in haemorrhagic shock (Lillehei 1957) and endotoxic shock (Longerbeam et al 1962) occur after this.
Microscopic examination of these necrosed cells show capillary engorgement, arteriolar dilatation and venular contraction (Zweifach 1958, 1961) possibly due to differing ability of the pre and post capillary sphincters to maintain their tone during prolonged adrennergic stimuli (Lewis and Mellander 1962). Ultimately there is capillary destruction and loss of frank blood which in haemorrhagic shock turns reversible to irreversible state (Lillehei et al 1964).

Small vessels:

In shock there is formation of platelet thrombi, consequently plugging of small vessels and ultimate circulatory failure (Hardway et al 1967).

Vessels: In shock there is intense vasoconstriction (Erlanger et al 1919-a, Dueasting 1919) due to excessive amount of circulating adrenaline (Bainbridge & Trevan 1917, Erlanger 1919-b).

Endotoxin in septic shock due to its action on adrenal medulla or post ganglionic sympathetic nerve endings (Bhagat 1974) or by its interaction with various plasma factors & WBC (Reichgott and Melmon 1972) causes liberation of vaso active substances whose sympathomimetic actions are easy to demonstrate experimentally on kidney, bowels and lungs (Kudia et al 1958, Hinshaw et al 1961, Motsey et al 1974).
Vasoactive peptides in haemorrhagic shock causes myocardial damage (Lefer and Glenn 1974).

A-V Shunt: In severe hypotension where blood pressure is lower than the critical closing pressure of small vessels, blood flows through A-V Shunts and causes poor tissue perfusion and extensive cell damage.

Due to excessive vasoconstriction and abnormalities in the microcirculation itself, tissue perfusion also decrease by increase of oxygen demand in hypermetabolic state in severe trauma, burns and sepsis (Burton 1951).

Cells: In septic and haemorrhagic shock anoxia leads to intra cellular acidosis, causing lysis of lysosomal membrane and depletion of ATP and alteration in the biosynthesis of ribosome resulting formation of vasoactive peptide. By their action (Schumer 1972) and release of lysosomal enzyme there is generalised cell damage (Janoff 1964).

In hypovolemic shock intracellular potassium comes out causing rise of plasma potassium level. When it reaches toxic level, fatal arrhythmias supervene (Holmes 1947).

Heart: In hypovolaemic shock, reduced cardiac output with rapid heart rate (small stroke volume) causes decrease oxygen consumption and high A-V oxygen difference (approaching the oxygen carrying capacity of the blood).
This together with accumulation of fixed acids lowers the arterial pH, starts a vicious cycle and ultimate tissue death (Root et al 1947).

There is released of a specific myocardial depressor factor (Hackel et al 1974) in cardiogenic and septic shock. It may affect the myocardial microcirculation itself (Branthwaite 1978).

In shock there is acute circulatory insufficiency causing generalised impairment of vital organs (Mac Lean 1966, Dietzman and Lillehei 1968-a).

Liver: In case of associated liver failure, in septic shock from gram negative organism, entrance of bacteria and bacterial toxins are more rapid & pronounced due to visceral ischaemia (Weilkinson et al 1974).

Pancreas: Ischaemic pancreas releases vaso-active peptides (Brand & Lefer 1966, Lefer & Glenu 1974) which can cause myocardial depression.

Kidney: Effect of shock in kidney is very complicated. Generally in man there is decrease in renal blood flow (Proportionately greater than the decrease in arterial pressure) and filtration rate (Kramer 1962, Selkurt 1962). Endotoxin has got direct vasoconstriction effect on renal vessels which is independent of a fall in blood pressure (Hinshaw 1957 & 1959).
There are important species variation in this respect (Hinshaw 1961). Oxygen consumption is proportionately less in haemorrhagic shock. Several other changes are reported including increase dephosphorylation of glucose with accumulation of free glucose and lowered production of ATP.

Urine contain protein cast and urinary sodium less is than 30 mEq/L (Kramer 1962). Most of the cases, kidney gradually recovers though some renal impairment persist for few days (Lauson et al 1944, Ledd 1955). But in a smaller group of cases, urine flow does not return to normal and acute renal insufficiency starts. In this respect the concept of low and high risk types of shock is useful. Post mortem examination of acute renal insufficiency cases show agglutinated red cells in the glomrular capillaries, cloudy swelling in tubules (Selkurt 1945), dilatation of proximal, distal and convoluted tubules with cellular infiltration and oedema of interstitial cells.

Changes in acid base balance: As stated earlier, there is marked acidosis (both metabolic and respiratory) with lowering of blood pH which causes impairment of cardiac function (Henderson 1908).
Further changes in the definitions of shock

As described earlier, the term "shock" is commonly used but ill defined. Conditions to which it is applied vary in aetiology, pathology and presentation. So the value of the term even as a clinical description is frequently challenged (Block et al 1966, Thal and Kinney 1967). However, some of the definitions are widely accepted.

"Shock is reversible death, it may therefore, be considered as a general homeostatic re-action of all sorts of organisms to severe and sudden stress" (Adolph 1964).

According to MacLean (1966), Dietzman and Lillehei (1968) shock is a physiopathological syndrome occasioned by the inability to meet the needs of the tissues for oxygen and nutrients and removal of metabolites.

Roe and Kinney (1965) described that this state of circulatory inadequacy may include abnormalities of pressure, flow and distribution of blood supply and even circumstances in which excessive metabolic demand has rendered inadequate an otherwise normal circulation.

MacLean et al (1965) defined shock as a condition of circulatory insufficiency characterised by a cardiac output which is inadequate for providing normal perfusion of major organs of the body.
Shock results when tissue or organ blood flow is inadequate to sustain normal cellular activity, and that this is usually accompanied by lowered arterial blood pressure (Lillehei and Dietzman 1974).

Messmer and Sunder Plassmann (1974) have defined shock as a syndrome characterised by acute reduction in the nutritive blood supply to vital tissues, associated with a disproportion between oxygen supply and demand and inadequate elimination of acid metabolites from the tissues. As a result of this haemodynamic disturbances, functional and structural changes take place in the organs affected.

Among the Indian authors, Satoskar and Bhandarkar (1976) have described shock as a form of acute circulatory failure characterised by pallor, physical weakness, coldness of the extremities, sweating, rapid thready pulse, oliguria and marked fall in systemic arterial pressure.
SYMPTOMS

SYMPTOMATIC RESPONSE
TO TRAUMA, SEPSIS OR MYOCARDIAL DAMAGE

SHOCK

ISCHAEMIC ANOXIA

STAGNANT ANOXIA
MICROCIRCULATION IN SHOCK

The common feature in all types of shock is reduction in the perfusion of blood to vital organs due to impairment of functions of microcirculation. Invariably there is alteration in the distribution of total blood flow i.e. the cardiac output is disproportionately distributed to the tissues. This is applicable in all cases whether shock is associated with a high or a low cardiac output (Hermreck and Thal 1969, Shoemaker 1972, Weil 1972, Messmer and Sunderklassmann 1974). Oligaemic shock either due to haemorrhage or from dehydration, burns, and some of the cardiogenic shock comprises the first group i.e. low output shock. Whereas endotoxic shock from sepsis and traumatic shock may be mentioned in the second group i.e. high output shock (Messmer 1976). Further changes in the microcirculation of these two varieties of shock differ from each other.

Further changes in low output shock

An acute fall in cardiac output as a result of diminished venous return triggers a massive counter regulatory mechanism (Sympathetic-adrenal reaction of Cannon 1923, Chien 1967) by the baroreceptors of aorta and carotid sinus (fig 7). This causes release of catecholamines in the circulation at the post ganglionic sympathetic nerve endings of the vascular beds. As this effect depends on the Adrenergic innervation, circulation of blood is markedly reduced in splanchnic region, kidney and skin. On the other hand coronary and cerebral circulation being devoid of Adrenergic receptors, are spared from this
Fig. No.12
Micro circulation in Haemorrhagic shock.
vaso constrictor effect (Green and Kapcher 1959). Thus, the sympathetic adrenal reaction by increasing peripheral resistance in certain areas redistribute cardiac output and tries to save the more important organs.

Post mortem examination in dogs died after experimental haemorrhagic shock, reveals haemorrhagic necrosis of the bowel mucosa (Lillehei 1957). Similar changes are seen in the autopsy finding of dogs expired after endotoxic shock from administration of bacterial endotoxin (Longerbeam et al 1962) and in dogs expired after prolonged infusion of adrenaline (Freeman et al 1951). Microscopic examination of the damaged guts show capillary engorgement with arteriolar dilatation and venular contraction (Zweifach 1958, 1961), possibly due to the differing ability of the pre and post capillary sphincters to maintain their tone during prolonged adrenergic stimulation (Lewis and Mellander 1962). At first, both pre and post capillary sphincters are tightly constricted allowing little blood to enter into the capillary bed (fig 91c). But, inspite of arterial pressure remaining within normal range for sometime, local tissue oxygen tension falls to critical levels (Sinagowitz et al 1973). Hypoxia together with hypo-volaemia occur at this level and energy rich phosphate cannot be produced in sufficient quantity and substrates are metabolised anaerobically to an increased extent (fig 92-A, B, C). There is accumulation of the products of metabolism (H - ions, lactate and ketonic acids) associated with metabolic acidosis (fall of blood pH). Gluco corticoid
STAGES IN DEVELOPMENT OF SHOCK.
level is raised, and the cells loose potassium and take up sodium from the plasma. It leads to decrease of extra-cellular volume and enhancement of secretion of ADH and aldosterone. As a result, there is oliguria, sodium retention and potassium depletion. Neither the water soluble metabolites produced from anaerobic metabolism, nor cell ions and enzymes can be carried away in the blood stream as the capillary transport is impaired. They are incompletely removed from the interstitial space via lymphatic system. They thus accumulate in the tissues and markedly after the trans-capillary gradient (Messmer 1976). But all the changes cannot be detected in the peripheral blood at the beginning (Bergentz et al 1969).

The above mentioned metabolites act from the capillary wall first and cause decrease of tone of the capillary wall. As a result the capillaries dilate. But both the pre and post capillary sphincters remain closed (Hollow capillary dilation of Roberts and Laros 1971). When the number of these hollow capillaries increase sufficiently a disparity occurs between the size of the vascular compartment and volume of fluid available to fill it. It leads to further decrease in tissue perfusion. The precapillary sphincters then lose tone, while the post capillary sphincters remain constricted. This leads to capillary engorgement and stagnation and haemorrhage within the capillaries. The ensuing rise of intracapillary pressure causes an increase of out flow of fluid into the interstitial space, resulting local haemoconcentration and further rise
Fig. No. 10
Reversible Shock

Fig. No. 11
Irreversible Shock

The extravasation of fluid thus caused leads to further depletion of the blood volume. Ultimately there is a capillary destruction as the endothelial cells of the capillaries are dependent on the oxygen supply by the blood in the capillaries. There is loss of frank blood. This cause further worsening of the tissue perfusion. The next stage evident in the evolution of shock is disseminated intravascular coagulation (DIC). The specific cause of this DIC is unknown but intravascular sludging, metabolic product with thromboplastic activities have all been suggested as contributing factors. DIC through the formation of microthrombi further diminishes perfusion (fig 11). Although clinical DIC becomes apparent only in the end stage of shock, it is suggested that it begins much earlier (Roberts and Laros 1971). According to Lillehei et al (1964) the onset of this stage during prolonged haemorrhagic shock makes the change of the condition from "reversible" to "irreversible" in other words the point at which restoration of blood volume alone is ineffective to prevent progressive deterioration and death. The same author pointed out that the organs showing most damage vary from one species to another, but that this haemodynamic disturbance in the peripheral vascular bed is a common feature and is the result of prolonged and harmful vaso constriction.
Mechanism leading to reduced cardiac output and inadequate tissue perfusion (from Hacket al. 1974)

Diagram depicting the vicious circle in shock associated with low cardiac output, owing to a feedback mechanism operating between microcirculation and cardiac output. States of shock in patients with initially high cardiac output are also caught up in this vicious circle.
Beside adrenaline and noradrenaline shock is associated with the release of other vaso-active substances like histamine, plasma-kinins and angiotensin I.

**Histamine**

Its release is characteristic in septic shock. But the failure of histamine to appear in increased quantities in the circulating blood in other forms of shock, does not diminish its importance in the micro-circulatory response to shock. This is because histamine is derived not only from the mast cell granules (preformed histamine) but also by local activation of histidine decarboxylase (induces histamine). Histamine has a predominantly vaso-dilator action and may also increase capillary permeability. Like catecholamines, histamine has been incriminated in the aetiology of refractory shock but traditional anti histamine compounds i.e. histamine $H_1$ receptor antagonist, provide little protection to animals in shock. The recent discovery has raised further interest in the role of histamine in shock (Beaven 1976). Combination of $H_1$ and $H_2$ receptor antagonists have been shown to prevent death in animals given an otherwise lethal dose of histamine (Levenson 1967, Black et al 1975).

**Plasma-Kinins**

Plasma-Kinins are vaso-active polypeptides that dilate blood vessels and increase capillary permeability. They are formed from inactive precursors (Kininogens) present in the
L₂ globulin factor of plasma proteins by proteolytic enzymes (KalliKreins) released from leucocytes and injured tissue (Ledingham 1977). Some kinin releasing proteolytic enzymes (e.g., trypsin) may be released into the circulation from the ischaemic pancreas as a result of lysosomal breakdown.

**Prostaglandins**

These are 20 carbon carboxylic fatty acid, synthesised in the body by cellular microsomes from essential fatty acids. They have wide range of pharmacological effects on smooth muscle, gastric acid secretion and cardiovascular system. Prostaglandin of the E series usually dilates blood vessels and increases capillary permeability, those of F series usually constrict blood vessels (particularly pulmonary circulation). F₂ series causes pulmonary vaso constriction, decrease in lung compliance and increase in airway resistance. Release of prostaglandins of the E series has been demonstrated following haemorrhage. It is also observed that substances responsible for prostaglandin synthesis (aspirin, indomethacin and sodium meclofenate) when administered into the persons suffering from haemorrhagic shock, cause increase peripheral resistance (Ledingham 1978).

**Angiotensin I**

This is deca peptide formed by the action of renin on a protein (angiotensinogen or renin substrate) found in L₂ globulin fraction of the plasma proteins. A converting enzyme
Carbohydrate Metabolism

- Glucose → Glycogen
- G-6-P
- Fructose 6P
- Anaerobic Glycolysis
- Alanine = pyruvate = lactate
- Acetyl CoA
- Final Oxidation
- Tricarboxylic Acid Cycle
- Citrate
- Carbohydrate Metabolism

Approx 2 moles ATP per mole glucose
Approx 30 moles ATP per mole glucose
splits of histidyl-lencine to form the octapeptide angiotensin II, which is most potent vasoconstrictor agent known. Angiotensin II has been demonstrated in considerable amount in the blood following haemorrhagic shock (Ledingham 1978). It is impossible to predict the effects, at the microcirculatory level, of the combined release of the above humoral agents. However, it is clear that a massive release of such potent vaso-active substances have important consequences in shock states. The increased peripheral resistance which is a characteristic feature of haemorrhagic and cardiogenic shock is due the release of catecholamines and angiotensin.

Disturbance in cell metabolism

It has been already mentioned that disturbance of cell function is an early feature of shock syndrome. But it is less readily recognised than haemodynamic and respiratory changes. In the absence of adequate oxygen, carbohydrate metabolism is impaired at an early stage with accumulation of lactic acid inside the cells (as they cannot form pyruvate in the same extent or in the same speed as occurs in the normal pathway via co-enzyme A into Kreb's citric acid cycle. This block in the normal glycolytic pathway leads to a tendency for glucose to leave the cell. The resultant hyperglycaemia is resistant to insulin administration and increased glycogenolysis occurs in an attempt to maintain normal levels of intracellular glucose. Formation of ATP is reduced due to failure of carbohydrate
metabolism to proceed to completion. Consequently, there is failure of normal sodium pump mechanism and diminished formation of immunoproteins (Schumer and Sperling 1968). This also leads to an accumulation of phosphates within the cell and later in the blood. The failure of sodium pump leads to extravasation of intracellular potassium and swelling of the cytoplasm. The metabolic acidosis which begins within the cell, becomes detectable first as a fall in blood pH. It originates predominantly in ischaemic muscle, but in low flow state, the liver itself may also produce lactate. Beside this, the circulating catecholamines, in the presence of β-blockade, can precipitate the production of lactate acidosis. The last reaction can be effectively prevented by β adrenoreceptor blocking agents.

Failure of the ischaemic liver to metabolise this load of lactate indicates a severe metabolic injury and sustained metabolic acidosis in shock is a grave prognostic sign.

The secondary effect of a low blood pH on organ function is less certain than formally. Opie (1965) has shown that the cardiac contractility only begins to be impaired below pH values less than 7.10. Correction of marked metabolic acidosis during haemorrhagic hypotension and after retransfusion often has little influence on myocardial function and oxygen consumption (Ledingham et al 1972).
Organ dysfunction in shock

Laboratory studies have shown that there is a large species variation in the physiological and metabolic response to shock. In baboons and probably in man, the lungs, the liver and the kidney appear particularly susceptible to shock. These observations have led over the years to the belief that the failure of specific organs may account for the eventual refractory nature of shock. But in the present era there is little evidence to substantiate this "target organ" concept since it is clear that almost every cell in the body is adversely affected by the shock process. Yet, it will be good in appreciating that the shock patients is susceptible to respiratory or renal failure and that precautions should be taken to reduce the risk of further damage to these organs. This is particularly relevant when there is pre-existing cardiopulmonary or renal diseases (Ledingham 1978).

Cardiovascular system

Cardiogenic shock as a primary event is due most commonly to myocardial infarction. Other causes are dysrhythmias or extremes of cardiac rate, pulmonary embolism, regurgitation caused by ruptured cusp, papillary muscle dysfunction or acute septal perforation, pericordial tamponade or direct myocardial trauma (Branthwaite 1978). Myocardial infarction may sometimes be followed by shock but the shock state itself may induce acute myocardial failure and thereby continue to the vicious cycle of haemodynamic changes. These changes are variable.
Hypotension, tachycardia and elevation of venous pressure are common and in most cases there is a lowered cardiac output and high systemic vascular resistance. But in a few patients with myocardial infarction, there is hypotension with normal cardiac output and low systemic vascular resistance, possibly due to vasodilating reflexes arising from afferents in the coronary bed (Dawes and Comroe 1954) or left ventricle (Brannwald 1968, Thomas et al 1965, 1966). The cause of cardiac failure in shock has evaded precise definition. Since the myocardium has a high oxygen consumption, a discrepancy is expected to occur between the availability and consumption of myocardial oxygen during severe hypotension. But the work of the heart and therefore, myocardial oxygen consumption falls in most forms of shock. Moreover, the normal heart is able to protect itself to a remarkable degree by autoregulatory vasodilatation during hypotension. But the patient with diseased coronary arteries, may be unable to dilate his vessels in response to hypotension and myocardial ischaemia of greater severity may occur in these patients than in patients with normal coronary arteries for an equivalent degree of hypotension.

However, the autoregulatory vasodilatation and fall of cardiac work and oxygen consumption in most forms of shock accounts for the difficulty in producing biochemical evidence of myocardial ischaemia. Recently detection of circulatory myocardial depressant factor (MDF) (Lefer 1973) in cases of heart failure in shock patients has become a helpful means
in their prognosis. This substance is thought to originate in the ischaemic pancreas and may reach the systemic circulation via the lymphatic system.

Lungs

Abnormalities of respiratory function are common in shock from any cause. Clinically this is manifested by increased respiratory rate and frequent dyspnoea. Biochemically there are hypoxia and hypoventilation. The later occurs independently of the presence or absence of metabolic acidosis. The hypoxia is caused by increase discrepancy in ventilation and perfusion within the lungs and low arterial \( PO_2 \) due to shunting of mixed venous blood having oxygen content lower than normal (Kelman et al 1967). Hypoventilation is probably due to number of factor like hypoximia metabolic acidosis, reflex response to stimulation of arterial or venous baroseptors and direct effects of endotoxin on the medulla (MacLean et al 1967).

Great interest has developed during the last two years in the syndrome of "Shock Lung" or acute respiratory distress syndrome of adults (Moore et al 1969, Pontoppidan et al 1972). Characteristically an episode of trauma is followed a few days later by dysphoea, tachypnoea and cyanosis. The life threatening hypoxia occurs and it is difficult to relieve even with controlled ventilation. A similar disorder can accompany septicaemia.
It is important to appreciate that quite considerable abnormalities of respiratory function can exist without physical signs in the lungs or the production of appreciable quantities of sputum. In early cases, there may be no demonstrable pathology on the chest X-ray, but soon diffuse mottling occurs and later there is confluent shadowing with air filled bronchi clearly visible (negative bronchogram). The pathogenesis of the syndrome is obscure. Experimentally there is evidence of pulmonary vasoconstriction affecting either the pulmonary arterioles or pulmonary veins (Hyman et al 1974; Kusajima et al 1974). Vasoconstriction may be initiated by vaso-active substances which are liberated within the circulation or are derived from damaged lungs tissue. The vascular obstruction is aggravated by the mechanical effects of platelet and white cell micro-emboli. These aggregates develop intravascularly or are derived from transfused blood and they are thought to disintegrate within the lungs liberating serotonin and lysosomal enzymes (Blaisdell 1974) which cause further local damage. An association between D.I.C. and defects in gas exchange has been suggested (Milligan et al 1974). Histologically, there is evidence of widespread damage to both pulmonary capillary endothelium and alveolar epithelium. A protein-rich exudate accumulates. It is caused by vascular damage rather than by an increase in pulmonary capillary pressure (Riordan and Walters 1968). Alveolar Collapse then facilitated by surfactant loss secondary to damage to type II alveolar pneumocytes. All these ultimately lead to pulmonary oedema.
The Kidney and Adrenal

Urine formation ceases when the systemic arterial pressure falls to 50 mm of Hg. The autoregulatory control of renal blood flow is absent during haemorrhagic hypotension (Bell 1972), and blood flow thus falls proportionately with blood pressure. This is particularly marked in the renal cortex and is not influenced by denervation or by administration of mannitol before or during experimental haemorrhagic hypotension. Circulating catecholamines contribute a part in its initiation. Glomerular filtration rate also falls in proportion to the fall in blood pressure, but the filtration fraction rises probably as a result of more marked vasoconstriction of the efferent glomerular arterioles. The changes produced by shock in the renal cortex may be patchy in character and although, in most cases, replacement of fluid deficit produce restoration of normal blood flow, in some, this patchy ischaemia may persist and may be related to acute intrinsic renal failure. Oxygen consumption in the kidney is closely related to sodium re-absorption in the tubules.

In addition to these direct sequelae of shock on the kidney, other indirect effects of renal ischaemia are, release of aldosterone by the adrenal cortex. The juxta-glomerular
The magnitude of the response to injury, urine N is expressed as g/day.
apparatus in the renal cortex responses to blood volume depletion and sodium deficiency by producing renin which acts in the blood to produce angiotensin II. This potent vaso-pressure stimulates the adrenal cortex to release aldosterone which conserve body sodium and thus blood volume. Like this both cortisol and cortecosterone are produced in excess during shock.

Liver and Gastrointestinal tract

Appearance of haemorrhagic necrosis has been seen in experimental shock in dogs. But it does not occur in man. In gram negative septicaemia it occurs with profuse diarrhoea (Borden and Hall 1951). Jaundice and impaired liver function tests are frequently seen in patients with prolonged hypotension or septicaemia. In some case, this jaundice may be of haemolytic in origin (Eley et al 1965).

High output shock

In hyperdynamic shock due to sepsis and trauma, there is also a disproportionate allocation of cardiac output (Messner and Sunder-Plassmann 1974, Shoemaker 1972, Weil and Shubin 1972). Here cardiac output is raised. The principle
cause of this rise in cardiac output is blood blow through functional arterio venous shunt (particularly in pulmonary and splanchnic areas) in the infected are and in skeletal muscle (Hermreck and Thal 1969). The other cause is the increase in the requirement of oxygen. Functionally, the result of increased shunt perfusion is a reduction in nutritional blood flow and capillary exchange surface, corresponding to the pre-capillary vaso-constriction (Fig 4).

In the septic shock haemoglobin has an increased affinity for oxygen i.e. oxygen is given up less readily to the tissues (Valeri and Kopriva 1972), so that with the overal rise in oxygen requirements, associated with elevated temperature and increased cardiac work, and oxygen deficit rapidly develops both in well perfused and less perfused tissues.

The causative organisms may be Gram positive (Streptococcus, Staphylococcus and clostridium Welchii), Escherichia coli, Pseudomonas aeruginosa and recently found bacteroides group of strictly anaerobic bacilli and more Gram negative organisms. Animal experiments have suggested that the lethal nature of gram negative septicaemia is related to the release in the blood stream of endotoxin, a large molecular weight lipopolysaccharide substance found in the O somatic antigen of the bacterial cell wall (Ledingham 1978). Different bacteria produced endotoxin of
different potency and chemical structure. The lipid fraction of endotoxin produced its toxic effects while the polysaccharide fraction produced its antigenicity. It is possible to estimate the level of circulating endotoxin by employing the limulus lysate coagulation test (Fossard et al. 1974). The precise mechanism of action of endotoxin is uncertain although it probably does not act directly on vessel walls. Its vaso-active properties may be attributable to an intermediary proteolytic substance forced in the blood causing the release of peptids (Bradykinin) amines (Catecholamines, histamine and serotonin) and probably vasoactive lipid anions from various cells. Endotoxin has direct effects on certain inter cellular enzymes and reduces oxygen consumption in rat liver mitochondria (Moss et al. 1969). The co-existence of hyper perfusion and circulatory endotoxin is particularly strong stimulus to aggregation of the cellular elements of the blood (e.g. platelets). Such platelet aggregation may set the scene for obstruction of blood flow in key vessels leading subsequently to cell death. This process has been described as disseminated intravascular coagulation or consumptive coagulopathy (Ledingham 1978). The clinical feature of some patients with septic shock differ from the more usual pattern of shock. These patients have a hyperdynamic circulation with a raised cardiac output and low peripheral vascular resistance and often described as having warm hypotension. Only at a later stage do the more classical
features of peripheral cyanosis and cardiovascular collapse emerge. Associated with these cardiovascular features there is low arterial mixed venous oxygen content difference. This distinctive clinical pattern may simply represent the response of the body to powerful circulating vaso dilator substance (Hermreck and Thal 1969) released from septic region, with redistribution of blood flow towards the area of sepsis and a compensatory increase in cardiac output (Ledingham 1978).
BIOCHEMICAL CHANGES IN SHOCK WITH SPECIAL REFERENCE TO MICROCIRCULATION

It has been stated earlier that shock whatever may be the etiology, causes some degrees of biochemical changes in microcirculation due to disturbances in cell function and consequent changes in cell metabolism. Though these features appear early in shock syndrome yet they are less rapidly recognised than haemodynamic and respiratory disturbances (Ledingham 1978).

Carbohydrate metabolism

Carbohydrate metabolism is impaired at an early stage. There is reduced tissue perfusion and fall in intracellular oxygen. Therefore, pyruvate the principal end product of anaerobic cycle, because of its inability to enter the aerobic cycle, accumulates. A greater part of the pyruvate is converted to lactic acid. As the later finds its way into the circulation, its concentration rises in the blood. So the increased concentration of lactic acid in blood is used as an index of the degree of intracellular anoxia (Lillehei and Dietzam 1974-a). Due to glycogenolysis and to some extent neoglucogenesis and increased adrenal cortical action hyperglycemia occurs in the initial phase of shock (specially haemorrhagic shock). But in the later state there is decline in the blood glucose level. Thus, lactacidemia, pyruvic
Acidemia and impaired glucose tolerance occur. As stated before, blood lactate and pyruvate increase proportionately in the early phase of shock, but in severe and prolonged shock a greater rise in blood lactate occurs. Acidosis for the same reason is a characteristic feature of shock. As pulmonary function is usually decreased in most of the types of shock, metabolic acidosis may be complicated by respiratory acidosis and anoxia.

**Water & Electrolytes**

During the period of stagnant anoxia, measurable shift of sodium ions and water molecules occurs into the cells, and corresponding number of potassium ions come out of the cells. These cause a fall in the serum sodium chloride and rise in serum potassium, and reduced exertion of sodium, chloride and water.

**Vitamins**

An abrupt fall in the blood levels of ascorbic acid and decreased excretion of ascorbic acid, riboflavin, thiamin and nicotinamide are observed in most cases of shock (Levenson et al 1946).

**Energy metabolism**

A decrease in body temperature reflecting a reduction in total energy metabolism, oxygen consumption, and heat production occur in majority of shock cases (Ledingham 1973).
But except for the severely burned patients exposed to atmospheric air, no significant increase in heat loss is usually observed (Levenson 1967 & Moncrief 1974). A poor co-relation between temperature and survival was also observed under experimental condition (Fine et al 1960). Body temperature is clearly a complex function which reflects not only the degree of injury but also the efficiency of compensatory mechanisms (Levenson 1967). It was postulated that toxic substances might have been released from the injured tissues, which caused lowering of temperature, decreasing oxygen consumption and ultimately death. At temperatures ranging from 25 to 29°C, the "toxin" was presumably inactivated by the body or excreted. However, at lower environmental temperatures it was regarded as the cause of increased fatalities. On the other hand, method: or agent which increase metabolism and raise the body temperature may also hasten the fatal outcome. There is an "optimum" environmental temperature range which favours survival following various forms of shock (Levenson 1967).

The major part of energy required for the greater portion of endothermic biological processes is supplied by ATP and creatine phosphate. It was observed that a marked decrease in tissue levels of high energy phosphate compounds and their precursors occurred particularly in the liver and kidneys of rats subjected to hemorrhagic, tourniquet and drum shock (McShan et al 1945). Blood concentration of pentose and inorganic phosphorus were increased. On these observations it was suggested that a critical depletion of
energy reservoirs accompanies shock. But studies carried out afterwards fail to demonstrate energy depletion as a critical factor in shock (Rosen & Levenson 1953).

During the terminal stages of shock resulting from freezing the hindlimbs of rats with liquid air, a decrease in cerebral adenosine triphosphate, adenosine diphosphate, phosphocreatine and adenine nucleotides are observed (Kovach & Fonyo 1960).

**Hormonal Factors**

Hypothalamic – pituitary adrenal activity is increased, as indicated by increased of secretion of ACTH, adrenal cortical and adrenal medullary hormones (Melby 1967).

**Protein metabolism**

Initially there is increase amount of amino acid and fatty acids into the energy production cycle in the liver as available glucose and glycogen are used up. At a time when the liver (principal source of deamination) becomes unable to handle the excess amino acids, there is increase in amino nitrogen in blood.

The rise in plasma amino nitrogen was stated to be due to increased liberation of amino acids from various tissues, particularly those were damaged. In shock, arrest of the circulation to the liver is followed by progressive failure to remove amino acids from the blood.
Blood ammonia concentration may be elevated in the course of severe shock, but intoxication due to ammonia is not usually observed except in patients with severe gastrointestinal bleeding and liver disorder.

Plasma protein concentrations are altered either because of alteration of fluid volume and electrolytes or because of changes in plasma protein themselves (Levenson 1967). Plasma protein may be lost in haemorrhage, burns (from the surface) or in the injured tissue (sequestered) (Millican 1954). After haemorrhage, mild hypoproteinemia develops as a result of the direct loss of protein and shift of protein poor extravascular fluid in the vascular compartment. Plasma prothrombin and fibrinogen are reduced (Tagnon et al 1946).

Fat metabolism

There is also increased mobilisation of fatty acids with formation of considerable quantity of ketone bodies. Usually in shock, these substances are produced only in small amounts and metabolised by liver and peripheral tissues. Ketone bodies together with anoxia cause further metabolic acidosis (Lillehei and Dietzman 1974-b). Beside this, fatty acid molecules may coalesce and form fat emboli (Ledingham 1978, Lillehei & Dietzman 1974-c) which may lodge in the lungs leading to further oxygen deprivation. This has been supported by clinical observations that fat embolism following trauma is decreased by administration of high concentration of exogenous glucose (Fleck 1976).
Enzymes

In shock from burns, there is increase in proteolytic, lipase and phosphatase activity. There is increase of plasma fibrinolysis (Tangon et al 1946) lactic dehydrogenase and a change in tissue histidine decarboxylase activity (Vesell et al 1959). There is increased sensitivity to exogenous proteolytic enzymes (Miles 1961).

In respect of biochemical changes, the main difference between haemorrhagic & endotoxic shock lies on the length of time they require to develop stagnant anoxia. In haemorrhagic shock there is slow progress from ischaemic to stagnant anoxia in the microcirculation, which may take several hours. But in endotoxic shock the biochemical changes may be evident within minutes depending on the dose of endotoxin liberated and the susceptibility of the host animal. In both these two types of shock additional evidence of increase in anaerobic metabolism is manifested by increase in lactic acid and pyruvic acid level, entrance of sodium ions and water molecules inside the cells and exit of potassium ions from the cells. Some biochemical changes are also seen in traumatic shock.

There is decrease in protein formation (immunoglobulin). There is early appearance of DIC with consequent depletion of some of the coagulation factors like fibrinogen, platelets factor II, V & VIII. This type of bleeding diathesis may be seen in endotoxic shock. Some biochemical changes also occur in Traumatic shock.
Lillehei & Dietzman in 1970 worked on endotoxic shock with animals subjected to fungus infection (Candida albicans). Their important findings were (a) decrease in arterio-venous oxygen difference, (b) low oxygen consumption and (c) severe lactic acidosis.

Numerous techniques have been tried to produce myocardial damage and experimental Cardiogenic shock thus produced has shown resemblance with the cardiogenic shock seen during severe cardiac diseases. Practically, these techniques have been mainly confined to dogs and ranged from direct myocardial damage to coronary artery occlusion by plastic microspheres.

Immediately after production of myocardial damage there is marked reduction in cardiac output and fall in arterial blood pressure. Blood pressure then rises but stabilises below the control level. But it has been observed that cardiac output does not return towards normal in the same proportion. Hence increase in blood pressure has been explained to be due to secondary to increase in total peripheral resistance. Catechoalamines elaborated by the sympathetic nerve endings and adrenal medulla stimulate the S receptors in the microcirculation of skin, lungs, liver, intestine and kidney. Thus reducing blood flow through brain and heart is maintained at normal levels. Urine volume also decreases due to rise in the total peripheral resistance, the work load to the heart which is already decreased is increased, causing further oxygen demands and formation of a new infarct (Braunwald et al 1969).
In the visceral microcirculation, the initial ischaemic anoxia may progress to stagnant anoxia with all its disastrous haemodynamic and metabolic consequences and does not differ significantly from those described from traumatic or endotoxic shock.
BIOCHEMICAL STUDIES IN SHOCK SPECIFIC MICROCIRCULATION BY DIFFERENT WORKERS

Most of the studies of shock have been carried out at times of major wars. This statement is specially applicable for investigations in respect of metabolic changes associated with shock. The largest number of such studies were made in early 1940's at the time of World War II. At that time a number of outstanding biochemists joined hands with physiologists, surgeons and physicians in several collaborative animal and patient studies. Later on during Korean and Vietnam Wars another flurry of such studies occurred. The majority of studies so far carried out have been largely descriptive in nature and have dealt mainly with biochemical changes in the blood and urine. On several occasions, measurements of chemical composition of organs and their functions have been made. But a limited number of studies have been carried out about the problems at the cellular, subcellular and molecular levels (Levenson 1967).

Studies in general

Henderson (1908) has shown the significance of estimation of acid-base changes in shock. Cournand et al (1943) made the first clinical use of cardiac catheterisation and opened a new era for investigation of shock. Friedmann and Haugen (1943) worked on volunteers at rest after 3-5 minutes subsequent to their meals and reported that the mean concentration
of blood pyruvic acid in this subject was 0.77 mg/100 ml. Mean lactic acid level was 8.5 mg/100 ml of blood and lactate/pyruvate ratio was 11 : 3. He concluded that food, exercise and anoxia are most important factors influencing the concentration of lactic and pyruvic acids in blood.

Tabor and Rosenthal (1947) found that the tourniquet shocked mouse died from injection of potassium ion in an amount one eighth that required to kill a normal mouse. The accentuation of toxic effects of potassium in shock may be due to concomitant hyponatremia and acidosis in shock.

In 1948 Goldsmith tried to find out a relationship between blood lactate and pyruvate in various physiological and pathological states. In his study the levels of pyruvic acid and lactic acid under conditions of physical and mental rest were 1 mg and 9.3 mg per 100 ml of blood respectively. The lactate/pyruvate ratio was 9 : 3 with SD + 1:7. In patients with heart diseases, mean pyruvic acid level was slightly increased and mean lactic acid level decreased.

Huckabee (1958) estimated levels of blood lactic and pyruvic acid in subjects breathing low oxygen gases. He also shown rise of blood lactate and pyruvate levels with epinephrine injection and change in blood pH. He formulated the "Excess lactate" (which is the calculated amount of lactate that accumulates above the amount expected for the measured
blood pyruvic concentration) by the equation \( X_L = (L_t - L_0) - (P_t - P_0) \frac{L_0}{P_0} \) where \( X_L \) was used for excess lactate, \( L_0 \) & \( P_0 \) as the normal lactate and pyruvate levels and \( L_t \) & \( P_t \) were the observed lactic and pyruvic acid levels. According to his calculation 1mMol of excess lactate is equivalent to an oxygen debt of approximately 11.2 cubic centimeter.

Rührman (1960) raised the question whether the systemic response of shock as evidenced by entrance of sodium & exit of potassium from the cells (Hyponatremia and Hyperpotassiumia) depend on the metabolic failure of sodium pump.

Guyton and Crowell (1961) proposed a formula for calculating the time required for a state of irreversible haemorrhagic shock to develop. It was \( T = \frac{120}{x-a} \) where \( x \) is the oxygen consumption before haemorrhage (expressed as cubic centimeter/mg/Min) and \( a \) is the quantity of oxygen available to the tissues during the period of hypovolaemia (also expressed in cubic centimeter).

Guyton et al (1961) demonstrated by animal experiment that oxygen debt pe se is a limiting factor in the survival of dogs suffering from haemorrhagic shock. Accordingly, excess lactate estimation was thought to be a method for obtaining an index of the severity of shock. Same result was found by Rosenberg et al (1968) in experimental haemorrhagic shock. But they did not find corresponding results of Broder and Weil (1964). The later found relation with levels of blood lactic acid and survival rate.
Rosenburg et al (1968) in their same study shown direct relation between oxygen debt and clinical state and haemodynamics of the patients. The blood lactate level was not so high in septic shock as seen in haemorrhagic shock. Lipmann (1963) pointed out that a breakdown of Pasteur effect, the inhibition of Glycolysis and lactic acid production by oxygen, could also result in a relative increase in blood lactate.

Broder & Weil (1964) correlated excess lactate with severity and duration of shock in human subjects. It is considered to be the result of anaerobic glycolysis, which in turn is attributed to low perfusion hypoxia. In their study the largest group of patients were of hypovolaemic shock. The other patients belong to cardiogenic, septicaemic, neurogenic and endocrine dysfunction shock. The control subjects have a mean blood lactic acid level of 0.732 mMol/Lit. Those patients in whom the excess lactate was 1 mMol/Lit or less had survival rate more than 80%. As the excess lactate level rose to 2 mMol/Lit, survival rate declined to 60% and at the level of 2-4 mMol/Lit survival rate came down to 25%. When it exceeded 4 mMol/Lit, only 11% survived.

Schweizer and Howland (1968) did a review of 248 patients of shock in whom lactate, pyruvate, acid base and other parameters were recorded. He observed that the no mortality occurred in 158 cases where arterial lactate level
was between 3 mEq/Lit (27 mg/100 ml). In the next group 42 patients had lactate level above 5 mEq/Lit (45 mg/100 ml). 29 of this 42 patients survived and 13 died. The main factor responsible for significant elevation of lactate in the majority of cases was inadequate tissue perfusion secondary to haemorrhage, sepsis or hypoprotenaemia from other causes. With one exception, lactate level above 10 mEq/Lit (90 mg/100 ml) carried a fatal prognosis. Between 5 - 10 mEq/Lit (45-90 mg/100 ml), lactate level was of no significant prognostic value except in those cases where $P_{O_2}$ is relatively more (who usually survived). There was highly significant decrease in $P_{O_2}$ in the non-survival groups. Although the pH and standard bicarbonate levels were significantly lower in the expired group, their metabolic acidosis was not life threatening due to effective treatment with sodi-bicarb solution.

Haemorrhagic shock

Claude Bernard in 1977 observed that haemorrhage causes hyperglycaemia. An early rise in blood sugar is one of the most constant findings in all types of shock, both experimental and clinical. The blood sugar remains high as shock progress until the late stage when hypoglycaemia supervens. It was seen that this hyperglycaemia in shock is not reversed by administration of insulin.
McShan et al (1945) observed that a marked decrease in tissue levels of high energy phosphare compounds and their precursors occur particularly in the liver and kidney of rats subjected to haemorrhagic & tourniquet shock. Blood concentration of pentose and inorganic phosphate were increased, but more recent works fails to demonstrate energy depletion as a critical factor in shock (Rosen and Leverson 1953). Rosenbaum et al (1957) found that the hepatic pyrophosphate level is markedly elevated after transfusion of blood to the animals subjected to haemorrhagic shock and it improves the arterial blood pressure. Blood levels of lactate, pyruvate and amino acids were found back to the normal levels.

Tagnon et al (1946) estimated plasma fibrinogen level in normal & haemorrhagic shock patients. They observed that it rises with the severity of shock.

Vesell et al (1959) estimated plasma lactic dehydrogenase activity in rats subjected to experimental haemorrhagic shock.

Sayer et al (1945) by using colorimetric method estimated plasma amino nitrogen (both free & conjugate amino compounds) in rats subjected to haemorrhagic shock and found that it was an index of the gravity of haemorrhagic shock. The same parameter was estimated after-wards by Wilhelmi (1948) in the liver of rats subjected to haemorrhagic shock.
Frank et al (1952) found more rapid fall of blood sugar levels in rats & mice kept starved and subjected to haemorrhagic or tourniquet shock. These animals survived shorter periods than controls which has been adequately fed. However, when the blood sugar levels were maintained at normal levels, the fatal course of haemorrhagic shock in dogs not changed.

Engel & Hewson (1953), Bloom & Ward (1961) estimated blood ketone bodies in experimental severe haemorrhagic shock animal and shown that it decreases in severely shocked rats.

Selkurt and Brecher (1956) observed a reduction in oxygen consumption by the gastrointestinal tract in dogs during haemorrhagic shock.

Nahas and Mittleman (1960) gave experimental evidences to suggest that neither correction of acidaemia by infusion of buffers nor inhalation of 100% oxygen decrease the death rate of dogs subjected to haemorrhagic shock.

Orkin (1965) after working on the biochemical changes in haemorrhagic shock patients showed that measurements of lactate and pyruvate loads increased as high as 9 - 10 mEq/Lit and still the standard bicarbonate was normal, even it had a tendency to go towards metabolic alkalosis. It was also shown that a patient might have excess lactate as high as 6.1 mEq/Lit but there was a normal pH of blood due to buffering
of the citrate in the stored blood that was transfused and administration of sodbicarb solution. He further commented that myocardial depression is dependent on blood pH level and not upon the amount of acid present in the blood.

Schumer (1966) shown that the lactic acid concentration found in the irreversible haemorrhagic shock (blood volume less than 35%) was 7.99 mMol/Lit (71.1 mg/100 ml) of body fluid. When lactic acid was infused in normovolaemic dogs, it produced irreversible microcirculatory changes and caused death in every case.

Lundsganrd (1966) conducted enzyme analysis of lactate and pyruvate in arteriole and coronary sinus blood during experimental haemorrhagic shock. Mean systolic blood pressure was 128 mm at the start and 103 mm of Hg at the end of operation. Mean pressure during shock was 32.1 mm of Hg. There was no arterial hypoxia during these studies. The arterial lactate level was 2.58 ± 0.25 mMol/Lit at the start and rose to 6.22 ± 0.75 mMol/Lit. After retransfusion the level remained elevated above the control values. Pyruvate level rose significantly from 0.228 ± 0.015 mMol/Lit during
shock in a group if animals whose hypotension was maintained at foregoing level for 40 minutes before retransfusion. In the other group (blood pressure 30-35 mm of Hg) the pyruvate level did not change during shock but rose significantly after retransfusion. The change in lactate/pyruvate ratio for arterial to coronary sinus blood was 1.51 ± 0.29 for all normotensive and 0.70 ± 0.132 for all shock samples. Overall average was 1.31 ± 0.40 and differed significantly from zero. The average excess lactate production by the heart was 0.139 ± 0.104 mMol/Lit. There was no significant difference between the normotensive and shock averages.

Rosenburg et al (1968) in his work in haemorrhagic shock in dogs found a significant correlation between oxygen deficits, blood lactic acid level and clinical state of the subject. But the level of blood lactic acid cannot be correlated with the haemodynamic changes or clinical deterioration of the animal in endotoxic shock. The blood lactate was never as high as was obtained in dogs in haemorrhagic shock. In dogs in haemorrhagic shock, the mean lactic acid levels rose progressively after onset of shock until it reached a maximum to 9.7 mMol/Lit at 3 hrs after the onset.
of shock. Mean lactic acid level fell somewhat after this, but never went lower than 8.7 mMol/Lit. Excess lactate value was parallel to the lactic acid concentration. Three hours after the onset of shock, excess lactate was at its maximum value of 9.6 mMol/Lit. In contrast to this, the dogs in endotoxic shock demonstrate a moderate rise in mean lactic acid and excess lactate to 3 mMol/Lit and 2 mMol/Lit respectively after 30 minutes. Both measurements remained at this general level for the remainder of the experiment but fell somewhat before the dogs died.

Dillon et al (1966) in their study on haemorrhagic shock with dogs found that serum sodium fell to a mean of 3.4 mEq/Lit during hypotension. The mean drop was 4.2 and 2.9 mEq/Lit among the dogs that lived and expired respectively.

**Cardiogenic shock**

Yanof (1943) and Torre et al (1950) worked on the levels of blood pyruvic acid during exercise and in cases of congestive cardiac failure respectively. They made a conclusion that blood bisulphate binding substance i.e. intermediate product of carbohydrate metabolism, increased in subjects with heart failure.
Again in 1950, Amatauzio and Nesbitt followed by Kluberg and Gitelson (1954) studied the blood pyruvic acid levels in patients with various heart disease. They reported that the increase in blood pyruvic acid level in cases of heart failure, was due to liver damage caused by prolong stasis and anoxia.

Ballingear et al (1961, 1962) measured excess lactate in patients with circulatory failure and who were undergoing cardiac surgery, fitted with heart lungs bypass. They found that there was no fatality when arterial blood excess lactate was below 3 mMol/Lit. The importance of these studies are two folds. It is a reliable index of severity of shock and vigorous effort is necessary to prevent or to replenish it urgently.

Wolfgang et al (1968) examined the tissue content of energy rich phosphate and glycolytic metabolites and activity of myocardial enzymes in dogs after producing myocardial infarction by ligaturing branches of coronary arteries. In ischaemic muscles 30 minutes after onset of ischaemia the mean lactate level was 20.41 μMol/g with SD ± 0.95, mean pyruvic acid was 0.30 μMol/g with SD ± 0.10.
and mean lactate/pyruvate ratio was 96.18 µMol/g with SD ± 34.37 when the control animal showed mean lactic acid 2.34 µMol/g with SD ± 0.86, mean pyruvic acid 0.45 µMol/g with SD ± 0.11 and mean lactate/pyruvate ratio 5.33 µMol/g with SD ± 1.24.

Burns shock

Madden (1950), Blocker et al (1957) and Levenson et al (1959) observed that the protein content of liver in rats following burns, change little from the control. But the protein content of the same organ from the carcases (expired from burns) decreased markedly. Mathematical calculation accounted for almost the entire increase in urinary nitrogen excretion (estimated from the urine collected from the test animals before their death) against the above mentioned decrease in liver protein content. They also shown the rise in urea and uric acid levels of these animals were in proportion to the severity of initial and subsequent shock.

Rosen and Levenson (1953) estimated the plasma concentration of amino conjugate fraction in burnt rats. They found that it rose to a degree proportional to the plasma
urea and protein nitrogen.

**Traumatic shock**

Levenson et al (1955) estimated the plasma concentration of amino conjugate fraction in traumatic shock patients.