CHAPTER I

GENERAL INTRODUCTION

INTRODUCTION

Mathematical physiology is an interdisciplinary subject with a vast and exponentially growing literature scattered over a large number of journals belonging to different disciplines. Contributions to it have been made by mathematicians, physicists, statisticians, computer scientists, physiologists, medical scientists, mechanical, electrical and chemical engineers and many others. A large number of mathematical models have been developed to get an insight into complex biological and physiological situations. A variety of mathematical techniques have been employed to solve these models. These include techniques for solution of differential, difference integral and integro-differential equations as well as techniques of linear, non-linear, dynamics and stochastic programming, calculus of variations, maximum principle and so on.

In mathematical physiology, we study the applications of mathematical modelling and mathematical techniques to get an insight into the problems of physiology.

The science of physiology deals with the study of the functional behavior of living structures, a term which includes
all spectra of life from viruses, to plants, to unicellular organisms, to complex mammalian forms and it is the objective of physiology to establish the physical and chemical relationships that underlie such phenomena. Physiological processes range from mechanisms occurring in the microscopic organelles of the basic unit of life, the cell, to complex interactions at the macroscopic level involving whole organs.

Major advances in modern physiology have come from two principle directions: one concerned with molecular interactions within the cell, and the other with the application of systems analysis techniques to facilitate working with the extraordinary number of variables influencing the behavior of organic units.

The field of mechanics seeks to develop mathematical laws which define the common properties of an idealized body in both a static and a dynamic sense. On the basis of these laws, it derives constitutive equations which illustrate their application to different specific situations.

The interaction of physiology and mechanics is in its infancy and in all probability the substantial application of mechanics to physiological processes will require sets of axioms which have not yet been developed. The mathematical modelling and the system analysis approach become more complex. They almost by default have fallen into the domain of biomathematics. The physiologists who have relied chiefly on the
experimental approach, face an insurmountable task of attempting to reconstruct from molecular phenomena.

It is obvious that not all physiological processes lend themselves to the tools and methods of mechanics. Four areas have been investigated: the cardiovascular system including the heart; the pulmonary system including the airways, the lungs and the muscular structures involved in breathing; muscle mechanics including the material analysis of skeletal, cardiac and smooth muscle; and finally a broad category covering the supporting tissues of the body including materials such as collagen, elastin, complex polysaccharides and structures such as bone, cartilage, tendons and skin.

Applied mathematicians, approaching the problem of analyzing the circulatory systems are forced, in general, with considering the unsteady flow of a non-Newtonian, viscous, incompressible, non-homogeneous, anisotropic suspension through a complicated branching network of elastic tubes having a cross-sectional area which decreases with distance from the source. The output of the flow source (the heart) is specially non-uniform and time dependent. The tubes are curved, discrete, distorted, anisotropic, non-circular, permeable to change in compliance from external or non-mechanical stimuli. Clearly, an exact mathematical model of such a complex system is virtually impossible to construct, but even if it
were not, it is unlikely that the resulting set of equations could be solved for any of the processes involved in vitro or vivo. It is thus necessary to seek alternatives to this idealised approach and two such alternatives have been used effectively: one involves simplified mathematical modelling and the other involves careful model experimentation. The latter serves as a check on the practical validity of the mathematical modelling, preventing it from turning into mere speculation and an exercise in the abstract, while the former prevents experimentation from turning random and sterile by suggesting the types of measurements to be made and the types of experiments to be performed. While embarking upon the study of living systems, optimal progress involves the continuous and intimate interaction of precise modelling with judicious experiments - the one aiding the other in the development of a comprehensive description of life processes.

**PHYSIOLOGICAL FLUIDS**

About 56 percent of the adult human body is fluid. Some of this fluid is inside the cells and is called collectively the intracellular fluid. The fluids in the spaces outside the cells is called extracellular fluid. Among the dissolved constituents of the extra-cellular fluids are ions and nutrients needed for the cells for maintenance of life. The extra-cellular fluid is in constant motion throughout the body and is
rapidly mixed with blood by circulation and by diffusion between the blood and the tissue fluids. Although the number of physiological fluids is very large, but the fluids on which systematic study has been made in this thesis are synovial fluid and blood. Therefore, we describe about the two:

SYNOVIAL FLUID

Synovial fluid is secreted into the joint cavity by the synovium. Normally, it is a clear and colorless or slightly yellowish fluid. Aspiration of the normal human knee joint usually yields about 0.2 ml. Biochemically, synovial fluid is a dialysate of blood plasma with the addition of varying amounts of hyaluronic acid protein complex (HAP). This is an unbranched polysaccharide macromolecule whose basic dimer is a disaccharide composed of glucuronic acid linked with glucosamine. The concentration of the long chain polymer mucopolysaccharide (hyaluronic acid) is of the order 3.5 mg/g, providing a molecular weight of about $10^6$, the linear length of the long chain molecules being approximately $10^4$ Å [Ogston and Stanier (1951)]. It is the hyaluronic acid that accounts for the slipperiness and stringy quality of synovial fluid. This constituent was first isolated by Meyer et al (1939). The structure of solutions of these polysaccharides, at the concentrations in which they occur in vivo, is therefore typically a continuous network or felt of entangled molecular
chains. The nature of this structure will depend little upon whether the molecules are linear or branched, on the molecular size (provided that it is large) or upon the occurrence or absence of more specific cross-linking between parts of the molecules [Fung (1981)].

It is found also in the vitreous humor of the eye and in the umbilical cord. Passage of synovial fluid through a 0.22 µm filter removes the hyaluronate, leaving a watery filtrate [Finn and Radin (1968)]. In solution, hyaluronic acid molecules combine with protein in a weak bond. The complex possesses a high negative charge. According to Maroudas (1968, 1970), ion transport in the cartilage is important in governing flow properties and the nutrition of the cartilage. Normal synovial fluid does not clot [Lai et.al (1978)].

Just as the above hyaluronidase can result in a significant loss of lubricant properties, the phenomenon of gel formation at higher hyaluronate concentrations tend to enhance these properties. As the concentration increases (due to compaction in the narrowing intra-articular gap) the hyaluronate molecules overlap and the chains intertwine, forming a firm 'gel'. Such gels have been studied by Maroudas (1969), Lai and Mow (1978) and Collins (1982). They form by ultrafiltration of the aqueous portion of synovial fluid through the pores of the cartilage as the articular surfaces come together. Under increasing pressure, a gel concentrate is
obtained, equal to 4.5 percent by weight of the initial synovial fluid. The concentration of solids of 25 percent in the gel corresponds to 0.75 percent of solids in the initial synovial fluid. As synovial fluid usually contains only about 0.2 percent of hyaluronic acid complex, Maroudas (1969) concludes that a considerable proportion of the solids retained in the gel must consist of free protein, namely albumin. The concept of gel formation plays a central role in the present analysis of joint lubrication.

A very thorough review article on the biochemical aspects of the components of synovial fluid and cartilage has been given by Hamerman et al. (1970) and Mow et al. (1984).

Figure 1.1 represents the synovial joint configuration. Synovial joints are places where bones connect, yet may move freely relative to each other. The bone ends are connected by a tough, fibrous sheath and a capsule which encloses the joint like a sleeve and creates the joint space or cavity. Ligaments act with the capsule as elastic constraints on the relative motions of joint surfaces (articular cartilage). The interior surface of the capsules, except the articulating surfaces, is lined with the synovial membrane which secretes the synovial fluids.

**BLOOD**

Blood is a marvelous fluid that nurtures life, contains
Fig. 1.1 Schematic representation of a synovial joint.
many enzymes and hormones, knows when to flow and when to clot, and transports oxygen and carbon dioxide between the lungs and the cells of the tissue. Blood is a suspension of particles in a complex aqueous continuous phase. This continuous phase is called plasma and contains inorganic and organic salts, as well as small organic molecules. In addition about 7 percent by weight of the blood is macromolecules called proteins, which have molecular weights ranging from 44,000 to over 1,000,000. About half of the protein mass is albumin with a molecular weight of 69,000.

The particles consist of a variety of cells, but the red cells compose about 97% of the total cell volume in the blood. Consequently, the removal of white cells and platelets from blood does not measurably modify the experimentally determined flow properties of these suspensions. The normal white cell count is considered to be from 5000 to 8000/mm$^3$ and platelets from 250,000 to 300,000/mm$^3$. The red cells are not spherical in shape. In blood which is not flowing, the red cell has a biconcave discoid shape, with a major diameter of 8.1 microns and a maximum thickness of 2 microns. White cells are more rounded and they are in many other shapes. Platelets are smaller and have a diameter of about 2.5 µm [Fung (1981)].
The red cells, also called erythrocytes consists of a thin, flexible but essentially unstretchable envelop or membrane and an interior filled with a complex aqueous solution, which is nearly a saturated hemoglobin solution. The membrane is a specialized structure which serves as a barrier to the transfer of macromolecules is the site of metabolism-linked transfer mechanisms for particular chemical species and it permits some small molecules such as water, to transfer very rapidly. Thus the erythrocyte (red cell) is a complicated type of osmometer. In addition the red cells (as well as the protein molecules) all carry negative charges. The buffering power of the hemoglobin is also an important factor in helping to maintain consistency of blood pH. Plasma proteins exert an osmotic pressure which influences the exchange of fluid between blood and tissue. Plasma and platelets contain all the factors required for clotting. Thus, loss of blood from injury is reduced by inherent properties of blood itself.

When the blood is withdrawn from its natural environment, certain irreversible chemical and mechanical reactions occur, the cumulative effect being called 'clotting'. To prevent this from occurring various anticoagulants are added to the blood as it is drawn from the animal. If the blood is allowed to clot, a straw colored fluid called serum appears in the plasma, when the clot spontaneously contracts, serum is similar to plasma in composition, but with one important colloidal
protein, fibrinogen, is removed while forming the clot. The specific gravity of red cells is about 1.10, that of plasma is about 1.03. When plasma was tested in a viscometer, it was found to behave like a Newtonian viscous fluid [Merril et al (1965)] with a coefficient of viscosity about 1.2 Cp [Gregersen et al (1967), Chien et al (1966, 1971)]. When whole blood was tested in viscometers, its non-Newtonian character was revealed. The viscosity of blood varies with the hematocrit, H, the percentage of the total volume of blood occupied by the cells.

Blood gets reduced in the tissues and oxygenated in the lungs. Consequently, it has to pass alternatively through lungs and tissues doing opposite functions at these two places. Hence circulatory system is divided into two functionally opposite parts:

(A) The systemic circulation
(B) The pulmonary circulation

The blood after leaving the arterioles pass through the thousands of these fine vessels in order to reach the veins. The veins collect the blood from the capillaries in the tissues and carry it to the hearts. This is called 'systemic circulation' [Rushmer (1970)]. The systemic circulation is characterised as a highly controlled high pressure, high
resistance system serving a wide variety of tissues dispersed over long distances from the heart. The other circulation is called 'pulmonary circulation' which is distributed only to the lungs. The quantity of blood passing through the lungs is precisely equal to the quantity passing through the remainder of the body. In pulmonary circulation the impure blood received from various parts of the body by the right portion of the heart is sent to lungs for purification, from lungs the blood goes to the left half of the heart for being pumped to the various parts of the body [Ruch and Harry (1965)] (Figure 1.2).

The heart sends out about 5.5 litres of blood per minute of which about 0.75 litres are received by brain, 1.1 litres by the kidneys, 1.1 litres by liver, 0.25 litres by heart muscles and so on [Kapur (1980)]. The quantity of blood which the heart pumps into the arteries each minute is called the 'cardiac output'. The series of different actions which the heart performs in succession is called 'cycle or beat'. Started with any one of the separate actions or movements of the heart, the series of changes which take place until that particular action commences to repeat itself constitutes a cardiac cycle. The contraction of the heart is called 'systole'; its relaxation is called 'diastole', [Gablnick and Mitchell (1973)].
Fig. 1.2 Schematic diagram of the blood flow through the heart. The arrows are the direction of blood flow. The valves are indicated by symbols T-tricuspid, P-pulmonary, A-aortic, and M-mitral.
The human circulatory system consists of a complex network of blood vessels and performs important functions: respiratory, nutritive, excretory, protective and regulatory in human body. The internal diameter of blood vessels range from 2.5 cm to 4 microns. Circulation may be classified into two main categories: 'Macro circulation' in vessels of diameter less than 500 microns. Most of the effect in physiological flows have been directed towards the problems related to circulatory and respiratory systems. Evidently, these vessels are tapered and branched in the flow direction. Blood flow in circulatory and air flow in respiratory system take place in distensible vessels and are unsteady [Tandon et.al (1978)].

CONSTITUTIVE EQUATIONS FOR PHYSIOLOGICAL FLUIDS

There are numerous physiological fluids, out of which only two fluids blood and synovial fluid have been made the target of study here. It has been confirmed by so many researchers theoretically and experimentally, both of these fluids donot obey Newtonian law. Therefore, several non-Newtonian fluid models have been proposed from time to time in reference to each of the physiological fluids. The involved parameters have also been computed and estimated for various fluids with the help of experimental findings. But
till now there is no single most suitable model for any fluid which can fulfil the needs of researchers. The models which are frequently used for these fluids are as follows:

(I) **POWER-LAW FLUID MODEL**

Some investigators [Charm and Kurland (1962), Hershey and Cho (1966)] have suggested power law fluid model for characterising blood.

\[
T_{ij} = \mu (e_{1k} e_{kl})^{n-1/2} e_{ij} \tag{1.1}
\]

But it has been found that this equation does not hold over more than two decades of shear rates [Charm and Kurland (1965)]. Therefore this equation has limited use for application to flow analysis in capillary tubes or vessels unless shear rates in the tube are definitely within the experiments range measured with the viscometer.

The power law index varies from 0.68 to 0.80 for rotational viscometers and for tube viscometers greater than 0.9. The pseudoplastic behavior has also been represented by other fluid suspensions like, synovial fluid (i.e., the suspension of hyaluronic acid in plasma).
Picologlou et al. (1973) studied the peristaltic motion of human faces characterised by a power-law model from the point of view of pressure generation in the contracting part and concluded that the peristalsis in colon, though rare, is a major propulsive mechanism. The peristaltic motion of power law has also been studied by Raju and Devnathan (1972).

(II) CASSON'S FLUID MODEL

Casson (1958) derived a semiemperical equation to describe the flow behavior of printing ink and Keiner and Scott-Blair (1959) suggested its application to describe blood viscosity

\[ a^{1/2} = a^{1/2} e^{1/2} + b^{1/2} \]  

(1.2)

where \( a \) and \( b \) are constants.

Casson's equation is based on the behavior of mutually attractive particles subjected to disruptive forces such that particle group size is a function of shear rate. In addition, the yield stress or shear strength of the suspension must be exceeded before the structure can be broken and flow initiated.

It has been shown that shear stress–shear rate behavior of red cell suspensions can be expressed by this equation over wide range of cell concentrations and shear rates 1 to
100,000 sec\(^{-1}\) [Charm and Kurland (1962), (1965)] and 0.1 to 20 sec\(^{-1}\) [Merrill et al. (1964), Cokelet et al. (1963)]. Charm and Kurland (1965) have obtained the values of parameters \(a\) and \(b\), 0.166 and 0.35 respectively for blood. Casson equation suffices in the analysis of simple problems in which the strain rate tensor can be calculated a priori, in more complex problems it is insufficient. Casson's equation is all we need in analysing poiseuille and couette flows, for which the shear stress and strain distributions are known from kinematics and statics. But if we wish to analyse the flow of blood at the point of bifurcation of an artery into two branches, or the flow through a stenosis or the flow in aortic sinus etc, the stress and strain rate distributions are not known [Fung (1981)].

(III) MICROPOLAR FLUID MODEL

Eringen (1964) introduced the notion of simple micropolar fluids to describe the behavior of some fluids which can support stress moments, body moments and possesses local spin inertia that can influence the flow properties. Eringen (1966) gave a set of governing equations for the flow of simple micropolar

\[
\tau_{kl} = (-\pi + \lambda_\omega \omega_{r,r}) \delta_{kl} + \mu_\omega (\omega_{k,l} + \omega_{l,k}) \\
+ K_\omega (\omega_{k,l} - \varepsilon_{k,r} \nu_r) 
\] (1.3)
where $\mu_w = \mu + \mu_o - \mu_1$

$$K_w = 2(\mu_1 - \mu_o)$$

$\pi$ = the thermodynamic pressure

$\lambda_w$ = the stress moments

$\omega$ = the velocity

$\varepsilon$ = the alternating tensor.

$\nu$ = the gyration

and $\mu$, $\mu_o$, $\mu_1$ are the viscosity coefficients and other symbols have their usual meaning.

Various authors [Ariman et.al (1974), Kang and Eringen (1976), Chaturani and Upadhya (1979)] considered micropolar fluid model as a suitable model for blood under physiological conditions. Kang and Eringen (1976) have shown that certain observed phenomena like Fahraeus and Lindeuist effect could be explained well with micropolar fluids by introducing parameters depending on the local variation of the concentration.

Devi and Devanathan (1975) have studied the peristaltic motion by considering the fluid as a micropolar fluid.

Tandon and Jaggi (1979, 1981) have represented synovial fluid by micropolar fluid due to substructural effects. Nigam et.al (1982) have also represented synovial fluid by the micropolar fluid. But the values of the micropolar
fluid parameters for synovial fluid are still awaited and it is hoped that these parameters will be estimated in the near future.

(IV) **COUPLE STRESS FLUID MODEL**

Recently, this model was considered by Chaturani and Mahajan (1982) and they explained some of the anomalies such as Fahraeus-lindquist effect, segre-silberberg effect, blunted velocity profiles which are associated with blood flow through narrow tubes. The governing equations for the stress components are

\[ \tau_{[i,j]} = 2\epsilon (\omega_{[i,j]} + \omega_{[i,j]}) \]  

(1.4)

This theoretical study may be useful for viscometer studies of blood flow which may find applications in the diagnosis and treatment of any cardiovascular, renal and diabetic diseases, [Dintenfass (1977)].

(V) **RATE-TYPE CONSTITUTIVE EQUATION**

Simple Maxwell fluid is the simplest rate-type linear viscoelastic fluid. The constitutive equation for this fluid is

\[ \tau = -pI + \bar{\tau} \]  

(1.5)

\[ \bar{\tau} = 2\eta_0 \dot{D} - \lambda \tau^* \]  

(1.6)
where $\tau$ = stress tensor

$p$ = pressure

$I$ = identity tensor

$\bar{T}$ = extratensor for small deformations

$\tau^*$ = identified with the partial derivative $\frac{\delta \tau}{\delta t}$

and equation (1.6) reduces to, in cartesian form,

$$\tau_{ij} + \frac{\lambda}{\delta t} \tau_{ij} = 2\eta_0 D_{ij}$$

(1.7)

where $D_{ij}$ are the components of the rate of deformation tensor $D$ whose components are given by

$$D_{ij} = \frac{1}{2} \left( \frac{\delta v_i}{\delta x_j} + \frac{\delta v_j}{\delta x_i} \right)$$

(1.8)

where $v_i$ and $v_j$ are the velocity components.

This rate-type of model provides good approximation of the fluid behavior when stress relaxation function can be adequately approximated by one exponential term. The linearised Maxwell fluid involves only two material constants $\lambda$ and $\eta_o$. The parameter $\eta_o$ is the (rate independent) steady shear viscosity and $\lambda$ is known as the stress relaxation time. Lai et al (1977) have obtained the material parameters for synovial fluid.
(VI) DIFFERENTIAL TYPE OF CONSTITUTIVE EQUATIONS

The most general equation of this category is the Rivlin-Ericksen fluid given by

\[
\tau = -pI + \bar{\tau} \\
\bar{\tau} = \bar{F}(\bar{A}_1, \bar{A}_2, \ldots, \bar{A}_N)
\]

where \( \bar{F} = \) isotropic tensor function of the Rivlin Ericksen tensor \( \bar{A}_1, \bar{A}_2, \ldots, \bar{A}_N \), where

\[
\bar{A}_1 = 2D \\
\bar{A}_2 = \frac{DA_1}{Dt} + \bar{A}_1 (\nabla \mathbf{v}) + (\nabla \mathbf{v})^T A_1 \\
\vdots \\
\vdots \\
\bar{A}_{N+1} = \frac{DA_N}{Dt} + \bar{A}_N (\nabla \mathbf{v}) + (\nabla \mathbf{v})^T A_N
\]

and \( D = \) rate of deformation tensor.

In case the flow is slow and the deformation is small, an approximation of equations may be used. It is known as the second order fluid, which is

\[
\tau = -pI + \mu_1 A_1 + \mu_2 A_2 + \mu_3 A
\]

where \( A_1, A_2 \) are kinematic matrices defined by
A_1 = \| (V_{ij} + V_{j+1})\| = \| A_{ij} \| \quad (1.12)

A_2 = \| \frac{\partial}{\partial t} A_{ij} + V^t A_{ij,t} + A_{m} V^m, J \n+ A_{mj} V^m, J \| \quad (1.13)

where \( \mu_1, \mu_2, \mu_3 \) are the material constants of the fluid. The values of the parameters \( \mu_1, \mu_2 \) and \( \mu_3 \) are given by Balazs and Gibbs (1970) for synovial fluid. While equation (1.11) may be convenient to apply, it is worth noting however, that the second order fluid is not suitable for studying unsteady flow [Coleman et al (1965)].

**TWO AND THREE REGIONS FLOW MODELS**

The presence of cell-free marginal layer at the wall in small blood vessels was reported as early as the seventeenth century by Malpighi. Quantitative support for the existence of the marginal layer was first given by Fahraeus (1931) who found the average hematocrit in a tube of flowing blood was less than that in the reservoir supplying the blood. The plasma layer is apparently present in blood vessels of all sizes but only in small conductors does it comprise a significant fraction of the vessel diameter [Barbee and Cokelet (1971)].

Haynes (1960) has attempted to explain the physical basis of the Fahraeus-Lindquist effect by considering a two
layered (two fluid) model with both fluids as Newtonian but with different viscosities. Such a model is unrealistic because the experiments [Bugliarello and Sevilla (1970)] suggest that flow through small tubes leaves a clear fluid layer near the wall and a core with suspended particles. It has been further shown that plasma behaves like a Newtonian fluid [Copley and Scott Blair (1960); Cokelet et.al (1963) and Merill et.al (1964, 1965)], whereas red cell suspension behaves like a non-Newtonian fluid [Charm and Kurland (1962, 1965, Merill et.al (1963)].

Earlier workers representing two region flow models for biological fluids have considered either both consisting of Newtonian fluid of different viscosities [Shukla et.al (1980), Bugliarello and Sevilla (1970)] or both Non-Newtonian fluids [Shukla et.al (1980), Bugliarello and Sevilla (1970)]. Chaturani and Upadhya (1979) have considered two region flow by considering a core region fluid by non-Newtonian fluid and periphery layer by Newtonian fluid. In all these analysis, mentioned above, they have considered core-region viscosity to be independent of peripheral layer viscosity. The fluid in the peripheral layer is not a separate Newtonian or non-Newtonian fluid but it is actually the suspending medium of the bulk physiological fluid. Thus care has been taken in all problems of this thesis.
Some of the work has also been undertaken by developing three layer mathematical models as considered by Gupta et.al (1982) for calculating the velocity profile and wall layer thickness for the flow of blood and other particulate suspensions in narrow tubes. The model consists of a thin cell free layer, accounting for wall exclusion effect, a cell depleted one due to radical cell migration and a central core with uniform cell concentration.

**RHEOLOGICAL STUDIES OF SYNOVIAL JOINTS**

The space between the cartilagenous extremities of the bones, known as joint cavity is filled with a viscous non-Newtonian fluid called synovial fluid [Ogston and Stanier (1950), Davis (1967)]. The normal functioning of the synovial joint is mainly governed by the characteristics of the articular cartilage and synovial fluid, [Mac-Conaill (1967), Wright and Dowson (1976)]. The synovial joints which are also known as diarthrodial joints encounter a wide range of operating conditions. They support large loads (4-5 times the body weight), [Morrison (1968)] under complicated motions and varying speeds, [Dowson (1967)]. These loads may be of fluctuating nature also, [Paul (1969)]. Moreover, the load bearing area of cartilage is very small [Walker and Hajek (1972)], i.e., it is 127 mm² for hip joints, [Thomas et.al
(1980)]. It has been suggested that the ability of joints to provide ideal performance inspite of the severe operating conditions is the result of complex interaction between the bearing components, i.e., the cartilage surface, synovial fluid and subcondral bone [Mow (1969)]. For any joint motion, one should know the exact nature of the bone which are in activity, its coverings (articular cartilage), the synovial fluid and the geometry of contact under various operating conditions. A brief description of these are given below:

ANATOMY OF SYNOVIAL JOINT

Joints are formed between bones during the growth of the skeleton. Bones are highly vascular constantly changing mineralized connective tissue which is self healing and undergoes remodelling processes in response to stress [Tanner, (1966)]. Due to this nature of the bone, it rarely undergoes to fatigue failure. The bone is poroelastic in nature and behaves like a composite material. Most of the analysis of bone consists of hard mineral fibres embedded in a soft organic matrix permeated with pores. There are many studies which relate elastic modulus with porosity [Young (1957), Currey (1964)]. Those that allow various
degrees of relative motion of the bones are called diarthrodial joints or synovial joints. The hip, knee, shoulder and finger joints are familiar examples of this type of joint. Figure 1.3 is a schematic representation of some of the principle kinematics of a human knee joint. As shown in Figure 1.1, the bone ends come together within a fibrous enclosure called the joint capsule. The inner lining of this joint capsule is called the synovium. The ends of the bones are covered by a thin layer of articular cartilage, a relatively stiff connective tissue. The joint cavity, formed by the cartilaginous surfaces and the synovium, contains a small amount of fluid known as the synovial fluid. Ligaments, tendons and other soft tissues inside and outside the joint cavity give stability to the joint and maintain it in proper alignment during motion.

The function of the knee joint is to provide flexion and extension of the leg during gait. Hence, this joint may be required to perform repeatedly complicated motions of varying speeds and to carry large (~5 x body weight) and rapidly fluctuating loads (Paul 1969). Under normal conditions, the knee provides these services without replacement or maintenance throughout the usual seven or eight decades of life. The ability of the knee joint and other diarthroidal joints
Fig. 1.3 Kinematics of the synovial joint.
to provide smooth and low-friction motion, with low abrasion of the bearing surfaces under all conditions of load and speed, is the result of a complex dynamic interaction occurring between the mating components of the joint.

**ARTICULAR CARTILAGE**

Articular surface of the bone is covered by a thin and soft layer of glistering material which provides a smooth gliding surface. These cartilage surfaces are the actual load carrying surfaces. The thickness of the cartilage layer ranges between 1-7 mm and varies from joint to joint as well as from species to species. Its physical and chemical properties are studied by several researchers [Thonar et al. (1979), Edwards (1967), Mow (1969), Wright and Dowson (1976), Lipshitz and Glimcher (1979)]. It is described as a highly specialized connective tissue mainly composed of a firm turgid water gel, [Anderson (1962)], which is rich in extracellular materials. The elastic character of the cartilage has been taken into consideration by Skoloff (1966) and Edwards (1967). The young modulus of the cartilage is found to be in the range of $10^6$-$10^8$ dynes/cms. Various techniques have been used to study the structure of the cartilage matrix. Recent electron microscopic studies pointed out the existence of some kind of regularity in the cartilage structure [Meachim and Roy (1969), Walker (1969)]. On the basis of the studies under the scanning electron microscope it has
been observed that the cartilage is a three layered porous medium \cite{Clarke(1971)}. The upper layer of the cartilage is known as superficial tangential zone (STZ) and is adjacent to the joint cavity as shown in Figure 1.4. It was a popular belief held by earlier workers that the cartilage surface is smooth. However, this was only a naked eye observation. Recent electron microscopic studies have shown that the cartilage surface is quite rough, \cite{Dowson et al. (1968), Walker et al. (1969) and Higginson (1978)}. The roughness waves show a periodic pattern with the periodicity of 20-50 µm according to Gardner and McGillivery (1971) and Clarke (1971). Below the superficial tangential zone lie middle and deep zones. The middle zone consists of coiled collagen fibres which are arranged in an open mesh work with large space between them. They are spheroidal in shape but they are arranged in columnar groups. Each column group consists of 4 to 8 cells.

It has been observed that when the cartilage is loaded for a long time, the cartilage matrix undergoes creep deformation due to the extrusion of the matrix fluid. This concept has brought up the viscoelastic nature of the cartilage \cite{Sokoloff (1966); Hayes and Mockross (1971)}. The elastic property of the cartilage has been studied in detail \cite{Fessler (1957, 1960)}. In fact, the colloidal nature
Fig. 1.4 A schematic depiction of the layer variation of articular cartilage.
of the cartilage is supposed to be responsible for the viscoelasticity [Barnett et.al (1961)].

Many experimental attempts (identification and compression tests) have been described for obtaining the young's modulus of normal human cartilage [Sokoloff (1966), Hori and Mockros (1976), Johnson et.al (1977)]. Hori and Mockros (1976) have reported that for normal articular cartilage, young's modulus is about $7.87 \times 10^6 \text{ N/m}^2$ and Johnson (1974) has reported its value of zero creep to be $20 \text{ MN/m}^2$.


Earlier single phase description (elastic or viscoelastic) of such compositionally complex, biologically active and rheologically complex tissue have been found inadequate in describing multiphase tissue in which components interact with each other during deformation. Multiphase models for such materials have been recognised due to the recent developments in the theory of interacting continua [Green and Nagdhi (1970), Craine et.al (1970), Bowen (1976)]. Mow et.al (1976, 1980) have developed binary mixture models of elastic solid and the viscous fluid. They studied that the movement
of interstitial fluid govern the mechanical as well as biomechanical functions of synovial joints and its biological integrity i.e., nutritional transport required by the chondrocytes of the adult tissue. Kuei (1978) reformulated the biphasic model for articular following the theoretical formulation of Craine et al. (1970), Green and Naghdi (1970), Bowen (1976) for mixture of an elastic body with dissipation and a linearly viscous incompressible fluid. Under the conditions of infinitesimal deformations and velocities, the stress and strain relationships of this first order theory governing the solid matrix phase (assumed to be isotropic) and the interstitial phase of mixture are given by

\[ T^s = -\alpha p I + A e I + 2N e + \lambda_s (\text{div } V^s) + 2\mu_s D^s - 2K_c \]  
\[ T^f = -p I + \lambda (\text{div } V^f) I + 2\mu D^f + 2K_c \Gamma \]  
\[ -\pi^f = \pi^s = b \text{ (grade) } -K (V^s - V^f) \]

where \( e, D^s \) and \( e \) are the strain tensor, rate of deformation tensor and dilatation \( e = F^{-1} \) of the solid matrix, respectively and \( D^f \) is the rate of deformation tensor. Note that the solid matrix stress/strain relationship \( T^s \) is given by the parallel sum of a linearly elastic body with viscous dissipation (a Kelvin body), a diffusive couple \( 2K_c \Gamma \). The
interstitial fluid $T^f$ is given by the parallel sum of a linearly viscous fluid (a Newtonian fluid), the equal but opposite diffusive couple $2K_c\Gamma$. The diffusive forces $\pi^f$ and $\pi^s$ are equal and opposite and are taken as body forces in Cauchy's equation of motion:

$$\rho^s \frac{\partial^2 U}{\partial t^2} = \text{div} \, T^s - \pi^s$$  \hspace{1cm} (1.17)

$$\rho^f \frac{DV}{Dt} = \text{div} \, T^f - \pi^f$$  \hspace{1cm} (1.18)

where $D/Dt$ denotes the material derivative $\rho^s$ and $\rho^f$ are the densities of the matrix and fluid respectively, $U$ is the displacement vector of the cartilage, $V$ the fluid velocity.

As we have seen the synovial fluid in a macromolecular solution that exhibits a diverse array of non-Newtonian rheological behaviors. The articular cartilage is a permeable biphasic material whose interstitial fluid is freely exchangeable with the surrounding milieu under normal circumstances, the rise of the HAP macromolecules in the synovial fluid prevents them from entering into the articular cartilage, since in solution they form highly negatively charged macromolecules with each macromolecule occupying a large spherical solvent domain of approximately 4000 Å in diameter. Thus only the solvent of the synovial fluid, i.e., water is freely exchangeable with the interstitial water of
cartilage. In early stages of osteoarthritis [Redler and Mow (1974)], disruptions of the densely Woven Collagen fibrous network at the surface such as fissures, clefts and other microsurface defects take place. It is possible that these microdisruptions to the superficial tangential zone of the cartilagenous surface could destroy its efficiency as a filtering membrane. Thus, the surface porosity and surface permeability of the articular cartilage and the specific physical nature of the HAP complex are important factors to be considered during the dynamic articulation process.

Ultrafiltration is caused by the forced flow of a solution through a semipermeable membrane. Starting with a thick layer of a synovial fluid interposed between two layers of porous permeable and deformable tissue. It can be argued that during squeeze film action the viscous resistance of the side flow of the bulk fluid out of the gap is much less than that of the flow of the solvent component into the articular cartilage. As the gap width decreases, the viscous resistance of the bulk flow increases and could become greater than the resistance offered by the permeability of the cartilage. At this point, ≈1 µ, Maroudas (1969) argued that solvent flow into the tissue will dominate, thus resulting in the ultrafiltration of the synovial fluid.
The next three chapters, present the effects of ultrafiltration in lubrication of synovial joints. Based on the recent studies on mixture theory of interacting continue [Torzilli and Mow (1976), Collins (1982)]. We modelled the cartilage as composite of elastic solid and viscous fluid freely exchangeable with the suspending media of the lubricant in the joint cavity. Most of the earlier anomalies observed in various studies in this direction have been taken care of in these studies. In Chapter III, we have considered visco-elastic fluid model for synovial fluid and realistic values of parameters representing cartilage, synovial fluid and diffusion coefficients. In Chapter IV, an attempt has been made to generalize the problem of ultrafiltration leading to the gel formation. The model identifies a normally loaded human knee joint during jumping or prolonged standing. The results presented in the IIInd, IIIrd and IVth chapters, conclude some of the results observed experimentally for normal, old and diseased synovial joints in difference to physiological lubrication characteristics and gel formation on the surfaces of the articular cartilage depending on parameters involved in the analysis for normal, old and diseased joints.

MICROCIRCULATION

The blood reaching the tissue which it is to supply is
distributed through an extensive network of fine vessels seemingly in a haphazard manner. The majority of the capillary distribution channels arise on side branches of the main stem which, in turn, itself becomes smaller and smaller until even the parent vessels are of capillary dimensions. The average capillary is about $10^{-3}$ cm in diameter, 0.1 cm long and with a capillary wall one endothelial of cell thickness (about $1 \times 10^{-4}$ cm). A variety of patterns of distribution are seen in the different tissues of the body — each with structural and functional peculiarities imposed by the make up of the different tissues of the body [Zweifach and Thomas (1961)]. In some, the arterial extensions can be traced into the venous, providing the ground work for potential shunting of blood. In others, only terminal capillary ramification are found. Generalizations are thus difficult to make but presumably an analysis of these unique structural designs should provide a clue to their basic significance with respect to flow, pressure distribution of blood, surface area for exchange etc.

Fundamental to an analysis of transcapillary exchange is an understanding of how a membrane which is a mosaic of living cells can behave as if it were a sieve with a given range of porosity. Originally the permeability properties of the barrier were attributed to the endothelial cells
themselves, a point of view which was not compatible with known properties of cell membranes in general. To date only two ultrastructural features have been described which may serve to explain the unusual type of permeability of the capillary wall. Ultrastructural studies of endothelial cells show large number of vesicles whose disposition and appearance suggest a possible transport system [Palade (1961)]. In addition the cells are so extraordinarily thin along their outer reaches that the membrane from both sides of the cell fuse into a large number of button-like structures [Elfuin (1965)]. Such sites could conceivably serve as preferential paths for fluid exchange without involving the cell proper.

Careful analysis indicate that the barrier between the blood and the tissue cells is made up of at least five separate structural elements [Zweifach (1965)]. The capillary tube itself consists of a layer of flattened endothelial cells joined together along their contiguous edges to form a continuous membrane. Immediately outside of the endothelial tube is a thin layer, some 500-700 Å thick, of an amorphous fibrillor material referred to as the basement membrane which varies in thickness and density in different vessels and tissues, where the cell edges join one another, a space of about 100-200 Å is regularly found and this is
filled with an amorphous material which is believed to be continuous with the outer basement membrane. The intercellular material was referred to in the past as a cement [Florey (1961), Karnovsky (1967, 1970)]. Many physiological reactions suggest that the inner luminal aspect of the endothelial tube may be lined with a material which in part is derived from the endothelial cells and in part from the blood. The presence of such an endocapillary layer has been verified by electron microscopy [Luft (1965)] and it appears to be polysaccharide-protein complex.

In as much as the capillary wall behaves passively in transcapillary exchange, the major forces involved are diffusion, ultra-filtration and osmosis. The free movement of water in and out of blood stream [Henessey (1940)] would seem to indicate that there is no physical barrier of any consequence to the diffusion of water molecules [Flexner (1948)]. The movement of water solute materials must occur along aqueous channels in continuity with the blood and tissue compartments. Diffusion movements of ions and small molecules are believed to occur across the entire capillary surface. Ultrafiltration occurs through the intercellular regions [Pappenheiner (1948)].

In contrast large-sized molecules are found to be transported at relatively slow rates [Hayerson (1960)]. It has
been shown, for example, that a water molecule can exchange by diffusion some 200 times back and forth across the capillary wall during a single passage of blood along the length of a capillary. Isotope tracer studies show nearly 100 percent of the water in the blood can exchange in one minute. On the other hand, the total plasma albumin in the blood, only one thousandth part is exchanged per minute.

The term permeability has meaning only when applied to the movement of a particular substance, since the mechanisms involved in the exchange of different types of materials may not be the same. For example, lipid-soluble materials — including gases — exchange much more rapidly and apparently over a larger portion of the surface than water-soluble materials [Renkin (1953)]. Water moves freely without any significant hindrance, but other solutes are exchanged in relation to their molecular size. Macromolecules such as proteins are transported primarily by ultra-filtration, probably through leaks or large pores, other macromolecules may be taken up by the endothelial cells lining the vessel and transported across the other surface inside the small membrane bound vesicles [Crone (1963)].

There is good evidence that movement of gases, water and small water-soluble molecules occurs each across the walls of the terminal arterioles and precapillaries. Furthermore, many macromolecules, including plasma proteins, pass
freely through the walls of extensive collecting venoles. The various vessels differ in size, in wall thickness and even in their intrinsic physical characteristics.

The blood capillary barrier can be visualized as consisting of three concentric tubular layers: endocapillary, endothelial and basement membrane. The endothelial tube which is the living portion of the system represents the skeletal framework. The material forming the endocapillary layer is tightly attached to the inner or lumen side of the endothelium. The outer layer is only loosely attached to the outer surface of the endothelial tube, since colloidal particles, proteins and blood platelets can enter a potential space [Majno (1964)].

The actual exchange occurs between the sub-endothelial space and the general ground substance across the basement membrane. However, the actual concentrations available for exchange will depend on the endothelial cell, i.e., whether it forms a tight membrane barrier, the relative number of leaks or gaps between cells, whether the cell is flattened out and thin or thickened and compressed. The endothelial tube can thus serve as a buffer between the moving blood and the connective tissue compartment. Diffusional movements occur uniformly across the whole outer surface of the
capillary wall depending on the concentration gradients which are built up.

The interplay of ultrafiltration and solute osmotic pressure was recognized by the famous English physiologist Starling [Starling (1896)], be recognized the simple restrictive action of the capillary membrane; it was freely permeable to crystalloids and water but retained plasma colloids. On this basis he formulated the concept that direction and rate of transfer of fluid between the blood and tissue compartments is determined primarily by the difference between the hydraulic pressure and the colloidal osmotic pressure across the capillary barrier water and solutes are transported in bulk across the capillary system by virtue of the fact that the hydraulic pressure of the blood (between 20-30 mm Hg) will tend to filter fluid across the vessel wall into the surrounding tissue. This force is opposed by an osmotic pressure (19.5 mm Hg) which exists in blood plasma because of the relative impermeability of capillary membrane to protein. The net effect of these two opposing forces is to permit exchange and yet to maintain the volume of blood in the circulation as a whole at a fixed level. Since the transfer of water across capillary walls influences flow in the microcirculation, it is appropriate to consider this phenomenon briefly. Passage through pores in the capillary
wall is a favored mechanism for the transport of water across the wall. The capillary pore, which is thought to be at the junction of the endothelial cells making up the wall, as a radius of about $4 \times 10^{-7}$ cm. The thickness of capillary wall is $0.5 \times 10^{-4}$ cm [Landis and Pappenheimer (1963)]. The volume flow of solution across the capillary wall (filtration flow) is given by

$$Q_V = [(p - p') - (p_o - p'_o)] L_p$$  \hspace{1cm} (1.19)

where

- $p$ = hydrostatic pressure in capillary
- $p'$ = hydrostatic pressure in tissue
- $p_o, p'_o$ = osmotic pressures in capillary and tissue
- $L_p$ = filtration coefficient.

The water flow is in the opposite direction to the osmotic pressure gradient, however, water flow will always be in the direction of its partial pressure gradient or its chemical potential gradient. The filtration coefficient can be represented as

$$L_p = \frac{\pi}{t_p} \frac{R_p^4}{8\mu}$$  \hspace{1cm} (1.20)

where

- $\mu$ = viscosity of water
- $t_p$ = pore length
- $R_p$ = radius of pore.
The filtration coefficient for a porous membrane in the forearm capillary 5x10^{-5} cm thick is 5.7x10^{-3} ml/min/(mmHg)/(100 g of tissue). [Landis and Gibbon (1933); Wiener and Silberberg (1968)].

Using an osmotic pressure of 7.6 mm Hg and a filtration coefficient of 0.0816 µ^3/(µ^2)(sec)(mm Hg), pressures in the frog mesentery capillaries are calculated to be about 12 mm Hg at the arteriolar end and 7 mm Hg at the venous end [Intaglietta and Zweifach (1966)]. The filtration rate per unit area is in the order of 0.05 µ^3/(µ^2)(sec)(mm Hg) with vessel diameter between 22 µ at the arteriolar end and 17 µ at the venous end. Of the capillaries tested, 70 to 80% lost fluid because their blood hydraulic pressure was higher than colloidal osmotic pressure.

Equation (1.19), known as Starling's hypothesis applies to ideal membranes that donot allow solute to leak. However, the capillary wall is not an ideal membrane and the solute passes through. Under these circumstances, the volume flow rate of solution and the flow of solute are related to the osmotic pressure and hydrostatic pressure by principles of non-equilibrium thermodynamics [Katchalsky and Curran (1965)]

\[ Q_V = \frac{\pi}{8\mu_p L} R_p^4 \left[ (P_j - p') - \sigma(p_o - p'_o) \right] \]  

(1.21)
where $\sigma$ is the reflection coefficient of protein in plasma.

The flow rate of solute across the wall is

$$Q_D = C_s (1-\sigma) Q_V + \omega(p_o-p_o')$$  \hspace{1cm} (1.22)

where $C_s = \text{concentration of solute}$

$\omega = \text{solute mobility or permeability coefficient}$.

Through discussions of restricted and free diffusion of molecules across capillary walls are given by Landis and Pappenheimer (1963) and Dick (1966).

By assuming a set of pore dimensions suggested by electron microscope studies, the pore model of Pappenheimer et.al (1951) has been modified by Lifson (1970) and Tosteson (1970) to include irreversible thermodynamic treatments of parallel pore, cell pathway and constricted pore effects [Perl (1971)].

Since water transfers across the capillary wall, the protein concentration must vary along the capillary causing a change in the osmotic pressure difference along the capillary. The transmural pressure will be influenced and consequently capillary radius and flow through the capillary pore will be effected.

The internal pressure at any point in the capillary is effected by the mechanical properties of the wall and the
mechanical properties of the wall and the cells and by the plasma viscosity. These properties also influence the absorption or expulsion of fluid from the capillary by hydrostatic osmotic pressure, which is determined in part by energy loss due to flow in the capillary.

Measurements of transcapillary fluid exchange in single capillaries reveal that the venous capillary has a higher filtration, than the arterial segment [Zweifach and Intaglia (1968)], coupled with the observation that the venous capillary is larger. This finding suggests that the midpoint of capillary fluid exchange in the context of the classical Starling hypothesis is well into the venous side of the capillary [Johnson (1972)].

Wiederhielm (1968) carried out computer analysis of fluid balance in capillary flow. He considered four fluid fluxes into and out of the interstitial space: filtration, reabsorption, plasma leakage through large pore system, and removal of tissue fluid by lymphatic substances. The program also took into account changes in tissue fluid protein concentration as determined by differences in the protein fluxes into the interstitial space through the large pore system in a capillary, as well as, protein removal by the lymphatics. He did not consider the effect of red cell or
vessel wall elasticity characteristics on capillary hydrostatic pressure.

The first interest in mathematical modelling of the microcirculation developed from experimental investigations to determine the arrangement of blood vessels in tissue. These experiments were being conducted as a result of interest in the mechanism by which oxygen was transported from blood to tissue and how this transfer could be controlled, Ranvier (1874) and Spalteholz (1888) had determined the geometric arrangement of blood vessels in striated muscle, but the work of Krogh [(1919), (1929)] is credited with motivating and laying the basis for the first conceptual model of microcirculation. Krogh theorized that the rate of oxygen transported was related to the number and distribution of capillaries in the tissue and to the permeability to oxygen of the capillary walls and surrounding tissues. His first experimental effort was aimed at obtaining an adequate knowledge of the number, distribution and surface area of the capillaries in muscle tissue. Krogh's investigations showed that, in a cross-section of striated muscle, open capillaries were distributed quite uniformly. Based on this observation, he concluded that each capillary could be regarded as running parallel to the muscle tissues and supplying concentric region of tissue surrounding the
capillary, and this tissue region was independent of the other parallel capillaries and the tissues they supplied. He determined the average radius of a hypothetical tissue cylinder by counting the capillaries in each cross-section and dividing the cross-sectional area by the number of capillaries he found. Krogh recognized that such an ideal physical geometric arrangement, shown in Figure 1.5 was amenable to a mathematical description. Though not a mathematician, Krogh persuaded a colleague, the Danish mathematician Erlang, to describe his conceptual model in terms of mathematics. Although a highly simplified model, Krogh's tissue cylinder model was a major step in the study of substrate supply to living tissue. He not only initiated the analytical but set the course for its study from 1919 to the present day.

Following Krogh's initial studies, several investigators considered the diffusion of oxygen, lactic acid and other metabolites through tissues. Hill (1928) derived equations which extended the steady state models of Krogh to the unsteady state. However, Hill did not apply his model to geometries or conditions representative of living tissues, thus his results contributed mostly to the formulation of concepts and equations describing the diffusion process rather than applications to actual circulatory systems.
Fig. 1.5 Krogh cylinder arrangement.
In the early 1950's Roughton (1952) and Thews (1950) developed steady and unsteady state equations for a Krogh tissue cylinder. Thews treatment obtained a number of solutions for cases of physiological interest. He presented graphical displays of substrate diffusing from a supplying capillary with an assumed oxygen profile into tissue spaces with different geometries.

Roughton (1952), in his work considered that oxygen combined with a substance in the tissue through a reversible reaction. Several special cases of his model were treated, but the solutions of the completely general equations were not obtained. The first attempt to include intra-capillary conditions seems to have been Kety (1970). Kety hypothesized that under certain conditions the oxygen content of the capillary blood should fall linearly from arterial to the venous end. He obtained this hypothesis with the non-linear oxygen hemoglobin dissociation curve to give the first model including oxygen distribution both within the capillary and in the Krogh tissue cylinder. He generated nomographs from which capillary and tissue oxygen could be determined.

In 1950, Optiz and Schneider (1950) applied Krogh's concept to a determination of oxygen supply to nerve cells of the brain. Since this application was in a tissue quite
different than that of striated muscle, their analytical modelling work was necessarily accompanied by extensive experimental investigations which are related to brain microcirculatory anatomy and oxygen metabolism. Their findings led to the inclusion of additional terms in the equations describing the Krogh tissue cylinder which accounted for axial diffusion as well as the previously considered radial components. Analytical solutions for these expanded equations were obtained by Decker and Thews and were later described by Thews (1960) in a summary of article. Thews also considered oxygen gradients in the capillary as well as in the tissue cylinder.

Two additional features were added to the Krogh's cylinder by Blum (1960). He considered a finitely permeable or semipermeable capillary wall, and a non-linear metabolic rate in the tissue space. Since he did not consider any blood substrate in the capillary blood, his results would not apply to the substrate oxygen or the by-product carbon dioxide. Such results would describe the passive transport of substrates such as glucose, bilirubin, or any other dissolved, flow transported, and diffusable substrate. Salathe and Tseng-Chan (1980) considered the mathematical analysis of a model for substrate concentration in tissue. Their model
consists of a single capillary from which substrate diffuses into the surrounding cylinder of tissue. The equations governing this model were derived by Blem (1960).

With the development of numerical approximation techniques and the increasing availability of electronic digital computers by the 1960s, several investigators became interested in the mathematical description of substrate supply to tissue. This interest centered on more complete description of the Krogh cylinder as well as other model geometries. These extended systems described substrate movement from supplying arterioles to the capillaries by time dependent flow, with a non-linear kinetic reaction occurring in the capillary blood, followed by diffusion with the capillary vessels, then movement across a finitely permeable wall, and finally movement into a tissue space, where it diffused and was bound and/or consumed. The metabolic functional dependence on substrate level could be zero order (constant), first order (linear) or Michaelis-Minten (non-linear) Reneau et al. (1966, 1967, 1969, 1970) considered the Krogh cylinder model with some generalizations. This work was followed or paralleled by several new modelling studies, including the steady state models considered by Thews (1968) and Fernandez and Atta (1968), and later the time dependent effects studied
by Fletcher (1972, 1973, 1975), and most recently analysis of capillary-tissue diffusion in Multicapillary systems [Popel (1978), Salathe (1981, 1982)].

A mathematical analysis of capillary tissues fluid exchange had been studied by Apelblat et al. (1974) in much detail. Salathe and Tseng-chan (1980) studied in detail, the mathematical analysis of capillary-tissue substrate exchange. They considered a single capillary from which substrate diffuse into the surrounding cylinder of tissue. They did not consider transport equation in the capillary and tissue region separately. Thus, in Chapter V we have studied the problem of capillary-tissue solute exchange by introducing a two region flow and diffusion model as a channel surrounding symmetrically with tissue. Viscosity of the blood in the capillary is dependent on local variations of the concentration of substructures and only the suspending medium takes part in fluid exchange and diffusion. A more general Brinkman's equation [Brinkman (1947)] supported by Tam (1969) and Lundren (1972) has been introduced for flow through porous media instead of Darcy's equation.

**CARDIOVASCULAR DISEASES**

Each year, diseases of heart and blood vessels claim more lives of human beings in the world than any war, including world wars. This startling fact emphasizes the seriousness
of the world's number one killer, which accounts for some 55% of all annual deaths from all cases. During last 25 years, tremendous studies have been made towards cure of some forms of cardiovascular diseases but still the killer is at large. It is, therefore, desirable and important, to evaluate systematically fundamental concepts related with cardiovascular diseases, is an effort to define clearly potential mechanism which may be responsible for subsequent vascular pathology.

'Arteriosclerosis' is hardening of arteries. Generally, this hardening results from accumulation of fat particles in the innermost layer of the arterial wall. The disease in this case is known as 'atherosclerosis'. The accumulation of particles in the intima causes a gradual thickening and hardening of arterial wall, forming atherosclerotic plaque or lesion and resulting in a consequent narrowing of the vascular channel. Eventually, the artery may be sealed off completely by tissue growth or by the blood clot in the narrowing opening, a condition known as thrombosis. The tissues receiving their blood supply via the occluded artery are thus deprived of their vital nutrients, so that they undergo a degenerative death called necrosis and become what is termed as infarct.

Although atherosclerosis is found at numerous
predilection sites in the body, it takes most serious toll when it strikes with the arteries of the heart or of the brain. In the former case, blood supply through the coronary arteries to the muscles which cause the heart to contract (the muscles of myocardium or middle layer of heart) is cutoff—a condition known as coronary thrombosis. This results in myocardial infarction, which, in turn, leads to one form of the heart attack when the brain is involved. Cessation of blood supply generally results in a stroke.

Clinical and autopsy observations reveal that one of the reasons for the initiation of arterio-atherosclerosis is mechanical injury of vascular endothelium. There is general agreement among investigators in the field that, at sites which are susceptible to atherosclerotic plaque development, the earliest observable lesion is that so called fatty streak, but the mechanism by which this streak develops is unknown. There are various opinions in this regard, the prevailing theory today is that this process follows a submicroscopic injury to the vascular wall-lesion forming as a result of repair process which follows biologic trauma [Chaturani (1978)].

In view of the finding that arterio-atherosclerosis can be produced solely by including a submicroscopic injury to vascular endothelium and taking into consideration the
observed localization of the plaques in vivo at well defined regions of changing geometric configuration. There is a strong suggestion that local fluid mechanics phenomenon plays an important role in the genesis and localization of atheromata and, clinical findings which continue to point clearly in this direction. The fluid mechanics approach to atherogenesis is receiving progressively under public acceptance by the scientific community, with the acceptance of this hypothesis, however, it becomes increasingly important to examine carefully the mechanics of flow of blood through the cardiovascular system, so that specific mechanism involved in the disease process may be isolated and studied in greater detail.

It has been known for many years that atherosclerosis and other arterial lesions donot occur randomly in the systematic vasculature but that certain arteries and arterial geometric configurations have a significantly higher probability for developing the disease. In particular, the prediction for such lesion occur at bends and bifurcations is the biological basis on which many of the theories of the importance of fluid mechanics in atherogenesis have been built. From engineering fluid mechanics, it is known that regions of bends and branches may experience localised areas of both elevated and reduces wall shear stress, boundary layer separation, secondary flows and so on. Whether any or
all of these factors, are important in atherogenesis has yet to be resolved, however, the postulates on which such theories are based clearly require that detailed quantitative studies of the localisation of the arterial lesions be carried out [Nerem and Cornhill (1980)].

The classical illustration of the characteristics of flowing blood is that of Poiseuille flow. Unfortunately, flow in large arteries of interest in atherogenesis in general is not of a simple Poiseuillian nature, i.e., it is not fully developed viscous flow characterised by a parabolic profile. The most obvious complicating factor is the unsteady or pulsatile character of flow. The distensibility of the blood vessels, which deform in a viscoelastic fashion in the presence of the pressure variation, associated with the pulsatility of the flow, also add to the complexity of the situation and the possible existence of turbulence represents another potential complication with regard to the latter and with exception of aorta, in a large arteries where the geometry has not been deformed by disease flow turbulence or even the transition to turbulence has not been observed. With the exception of flow pulsatility, however, the major complication involved in determining the detailed nature of flow in the arterial system is the geometry. One way in which this manifests itself is the presence of entrance effects. The
entrance effect, or the existence of any entry length is well known problem of fluid dynamics. In general, when a flow passes from a tube or chamber of large diameter into a much smaller one, the velocity distribution at the entrance to the smaller tube is found to be radically altered with result being a rather blunt velocity profile. Furthermore, in an entry-length region the flow development is accompanied by wall shear stress which exceed those of fully developed flow of the same mean velocity.

A second major geometric complexity of the arterial system is branching and curvature of vessels which quite naturally produces asymmetries in the velocity patterns. For example, at a bifurcation the flow in the upstream parent vessel divides into the two daughter vessels so as to bring relatively high velocity blood at the centre of the parent vessel in close proximity to the wall of the flow divider. As a result, the flow divider would, in general, be expected to be exposed to a higher wall shear stress at the lateral walls. Skewing of the velocity profile also occurs in a curved vessels. The nature of this skewing depends on whether the flow is largely inviscid or fully viscous. By largely inviscid, is meant a flow such as present in the ascending aorta of a medium size dog or large mammal. Here the flow is that of an entrance region where viscous effects are confined to
a thin layer adjacent to the wall. In this case velocity profile is skewed towards the inner wall and the wall shear stress should thus be higher on the inner wall on the other hand, in the fully viscous case-examples of this, are the flow in the left common coronary artery of man or in the aorta of small animals - the flow is skew towards the outer which then would be expected to experience the higher wall shear stress.

Associated with the flow in a bifurcation or a curved vessel is the secondary helical motion, induced by the curved path the fluid must follow. Secondary flow is characterised by a swirling component superimposed on the main streamwise velocity along the tube axis. The most familiar example is that of steady flow in a pipe bend. The secondary motion super-imposed on the main axial flow here is related to the centrifugal pressure gradient associated with the curvature of the flow secondary motions are also produced by branchings where, just as in a curved pipe, the change in flow direction is accompanied by transverse pressure gradient. Furthermore, the pressure of secondary flow will alter the spatial variation in wall shear stress from that which otherwise would be expected.

One additional complication introduced by the geometry of the arterial system is that the flow may actually separate
from the wall giving rise to a recirculating, dead-water region which can be slowly moving among stagnant fluid. For a bifurcation, flow separates because of the adverse pressure gradient associated with the deceleration of the fluid as it passes from the parent tube into daughter tubes whose combined cross-sectional area exceeds that of the parent tube. Downstream of the bifurcation the flow will reattach to the wall. The separation 'bubble' or recirculation region located between the points of separation and reattachment contains recirculating fluid. The occurrence of flow separation is pulsatile flow, is an extremely complex phenomenon. In a pulsatile flow, the recirculation region is itself unsteady in nature and flow separation and reattachment points can change location or even disappear and then reappear as the flow pulses. Flow patterns and shear stress distributions for oscillatory flows obviously will be more complicated than for steady flow, and very little is yet known about the details of the many of the phenomena discussed here for arterial blood flow conditions [Nerem and Cornhill (1980)].

In the interaction of flow with the arterial wall and in particular with the endothelium consider the influence of arterial pressure. Pressure acts as a normal force on the wall and its role may be viewed as being two fold, first
because of the higher hydrostatic pressure within the lumen of the artery, that at its outer surface, there exists the potential to drive a bulk flow across the endothelium and through the wall. The extent to which this occurs will depend on the magnitude of the pressure difference and on the resistance offered by the wall. Osmotic pressure may combine with the hydrostatic pressure in controlling this process. Secondly, pressure may interact with the arterial wall through the distension or stretching of the wall. This produces stresses and strains within the wall but may also influence the endothelium.

In addition to differences in pressure along the vascular tree, there are also large variations in wall shear stress and a number of investigators have studied the role of wall shear in any hydrodynamic interaction with the endothelium. These results in general indicate that the transport of certain materials is enhanced by increasing wall shear. There is also an evidence that at extremely high levels of wall shear stress, endothelial damage any result. The most complete overall picture of this has been presented by Fry (1969) based on a series of in vivo experiments. These results indicate that for wall shear stress value (4000 dyne/cm²), the endothelial cellular elements remain histologically normal. In this subcritical yield stress range, however, variations in wall
shear stress may still influence the rate of transport of certain blood elements, e.g., albumin and various lipoproteins. At the critical yield stress level and above, endothelial cells begin to yield, deform and swell slightly. Here Fry noted that the cells had significantly altered staining properties which are indicative of chemical changes. Furthermore, in this range not only was protein transport enhanced by increasing wall shear stress, but transport of cellular elements and artificial chylomicrons was also increased. Finally, as further increases in wall shear were produced and the erosion stress (1000 dynes/cm²) of the endothelial cells was exceeded, denudation of the endothelium, invasion and deposition of lipid material, adherence of cellular elements, and deposition of fibrin occurred.

The abnormal and unnatural growth in the lumen of an artery is called 'stenosis'. As an obstruction develops in an artery, one of the most serious consequences is the reduction in blood flow to the distal vascular beds supplied by the artery. The nature of this reduction has been the subject of numerous past studies [Mann et al (1938), Shipley and Gregg (1944), May et al (1963), Weale (1964), Brice et al (1964), Fox and Hugo (1966), Rodbard (1966), Fry (1968), Young (1968), Kindt and Youmans (1969), Eklof and Schwartz (1970), Forrester and Young (1970), Lee and Fung (1970)], in
which a particular artery was gradually constricted and the resulting change in the blood flow rate measured. Experiments of this type revealed that there was little effect until some critical reduction in lumen area was reached, and beyond this point flow was reduced sharply. The concept of the 'critical stenosis' has been widely used, with the critical stenosis generally defined as one for which a small further reduction in lumen area will cause a significant reduction in blood flow. Typically, it is found that under resting flow conditions the lumen area must be reduced dramatically (approximately 80 percent or more) before the stenosis has much effect on flow.

In recent years considerable attention has been given to the study of blood flow characteristics due to the presence of stenosis in the lumen of an artery [Young and Tsai (1973), Nerem (1974), Rodkiewicz (1974), Caro et.al (1974), Morgan and Young (1974), Logan (1975), Young et.al (1975), Deshpande et.al (1976), Daly (1976), Giddens et.al (1976), Tobin and Chang (1976), Talukder et.al (1977), Back et.al (1977), Mates et.al (1978)]. Recently, the effects of peripheral layer viscosity on physiological characteristics of blood flow through the artery with mild stenosis have been studied by Shukla et.al [1980(a), 1980(b)]. Fukushima et.al (1982) have investigated the structure of flow through
arterial models with one or two sinusoidal stenoses under the assumption of quasi-steady flow of blood. Numerical analysis was performed by an integral-momentum method. The two fluid models for the blood flows in small diameter tubes have recently gained more attention due to the observed cell free region enclosing a centrally core.

**VISCOSITY AND DISEASES**

It has been observed that in most of the diseases e.g., cardiovascular, hypertensive and renal, the viscosity of blood is abnormal [Dintenfess (1977)]. A number of factors can influence the viscosity of blood including the plasma viscosity, hematocrit, aggregation of red cells internal viscosity of red cells flow velocity and lumen of blood vessel. These factors, in turn, can be affected by variety of entities, from clinical diseases to cigarette smoking or emotional trauma. The important point is that an abnormality of any one or more of the blood viscosity factors can produce an elevation of blood viscosity. Had it been just an increase in the blood viscosity, perhaps body could have taken care of, but multitudinous vicious circle set in which keep increasing the blood viscosity and keep harming and destroying tissues. And it seems, alone internally, body cannot cope up with this ever increasing viscosity, external methods have to be brought into reduce the viscosity—bed rest is one.
If not, then this ever increasing viscosity leads to slow down in circulation and is, therefore, intimately linked up with the pathogenesis of myocardial infarction (cardiovascular disease known as heart attack) as well as hypertension. It is, therefore, clear that the elevation of blood viscosity is a significant factor in the development of cardiovascular hypertensive and renal disorders. It is rather fortunate that the abnormality of the blood viscosity is a cause and not the result of these diseases. It is, therefore, possible to diagnose the diseases through viscosity abnormalities much before the clinical symptoms appear. Further, once the physician recognises the existence of this risk factor, he can take steps to decrease the viscosity and hence interpret at the very initiation.

In the usual study of cardiovascular diseases, doctors, commonly are concerned with cholesterol levels, the abnormalities of blood pressure, the formation of atherosclerotic plaques and so forth. Most of these measures are to fight the heart disease, the number one killer, are of remedial nature, that is, once it occurs, how to cure it. Even after all these efforts, the killer is still at large - even now 55% of all annual deaths from all causes are due to these diseases. To fame the killer, perhaps, the strategy has to
be changed. We have to adopt preventive measures, that is diaganose these diseases much before their clinical symp­
toms appear and interpret the cause of disease.

Chapters VI and VII are therefore devoted to the stu­
dies of flow and diffusion in microcirculation with mild
stenosis. The blood has been represented by two constitu­
tive models one representing the viscosity depending on
the local variations of the concentration of the suspended
cells and the other by Casson's fluid model. Where para­
meters have already been discussed and the various values
have been obtained for normal and diseased blood. The
results pertaining to apparent viscosity, resistance to
flow, wall shearing stress and Taylor diffusion coefficient
have been brought out and discussed.