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BE 512

Introduction to Biomaterials

Termpaper:

Are Biomaterials the Limiting Factor in the Progress of Arterial Prostheses?

Abstract:

As the title suggests this paper tries to answer the question whether biomaterials are the limiting factor in the progress of arterial prostheses. The introduction to the paper gives a brief summary of the history of vascular grafts and introduces some of the concepts of vascular surgery. Then the normal physiological situation of arteries and their relation to the circulatory system of the human body is described in some detail. Of the three different types of arteries the focus is set on the elastic and the muscular arteries, since these are the subjects of vascular surgery. The smaller arterioles are merely mentioned for completeness. The functions of elastic and muscular arteries and the relation between the function and the microscopical structure of these arteries are pointed out. Furthermore the composition and functions of the human blood are described. Special attention is paid to the mechanisms of blood clotting and inflammation, since they are of particular importance for vascular grafts.

The next step in the paper is the description of diseases of arteries, documenting the need for arterial grafts. Basic terms like thrombosis, ischemia, and embolus are defined, leading to the description of the most important form of arterial disease there is: atherosclerosis. The high incidence of atherosclerosis and its fundamental significance for the population of middle age and later life in developed countries is stressed. The less common inflammatory arterial diseases are also mentioned. A short overview over vascular surgery and its possibilities to treat arterial diseases shows that the replacement of the diseased vessel by a graft is often the only applicable solution.

The rest of the paper deals with arterial grafts. The ideal arterial prosthesis is described, followed by the currently used grafts. There are two different types of biological grafts that are in use, the unprocessed autogenous and the processed nonautogenous grafts. The synthetic materials that are in clinical use nowadays for arterial grafts are PTFE and PET. The problems that still exist with all of these possible grafts are then pointed out and compared to the ideal graft. Some of the concepts that are being applied to overcome these problems are described, and a few examples of prospective materials for arterial grafts that are subjects of current research are given.

The conclusion of the paper is, that no material that is in current use matches the requirements for an ideal arterial graft. Furthermore it is shown that the existing problems are clearly problems of the biomaterials. This means that the answer to this paper's question is definitely a "yes": biomaterials are the limiting factor in the progress of arterial prostheses.

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Chapter 1: Introduction

Arterial diseases are a major medical problem in the developed world. In fact, they are one of the main causes of death in the United States. *Surgical reconstruction* of diseased arteries does not deal with the disease processes, most of which are not fully understood at the moment. But they do solve the problems that the symptoms cause[1)].

The modern history of *vascular grafts* begins in the early part of the twentieth century with the development of suture techniques to repair arteries and veins and the proof that the transplantation of veins and arteries between animals of the same and different species was possible. In the time from 1906 to 1916 the first cases are documented where veins (popliteal vein and greater saphenous vein) were used to bypass diseased arteries in humans. Arterial *allografts*, or *homografts*, obtained from young dying persons were first introduced as vascular replacements in the late 1940s. Despite initial successes, it became apparent in the late 1950s that degenerative changes in the arterial homograft led to tremendous problems. For this reason the arterial homograft was abandoned as a conduit for arterial bypass procedures. In 1956 the bovine *heterograft*, or *xenograft* was introduced. This graft, obtained from the carotid artery of the cow was initially successful. However, the use of the graft was abandoned because of the development of complications in the follow-up period. The efforts in finding a suitable biological graft continued, and in 1976 a tanned human umbilical vein graft was introduced. This is still used today for lower extremity *revascularization*[2)].

Synthetic grafts were also tested from the beginning of this century. In World War I paraffin coated silver tubes were introduced. Later on other tube materials were tried, e.g. glass, aluminum, vitallium, polyethylene, steel mesh, and ivalon, all coated with paraffin. These materials were attractive because they were inert, lessening the tendency to thrombosis when exposed to blood elements. Nevertheless all of these grafts failed because they were nonporous and did not permit incorporation of the graft by host tissues. The importance of graft porosity, allowing fibroblasts to grow through the pores of the graft to incorporate both the inner and outer layers, was recognized in the early 1950s. Vinyon (N) cloth, a porous synthetic fabric, was then inserted successfully in patients to replace aneurysms. This was a critical turning point in the development of synthetic vascular grafts, directing attention to other fabric prostheses such as PET and nontextile synthetic grafts such as PTFE. PET and PTFE are the most important synthetic

graft materials that are used nowadays. Major advances in textile engineering allowed the creation of grafts of varying thickness, strength, porosity, and flexibility[2]. The question addressed in this paper is whether *biomaterials* are the limiting factor in the further development of arterial grafts.

Chapter 2: Normal Physiology of Arteries

2.1. The Circulatory System:

The circulatory system comprises the *blood vascular system* and the *lymph vascular system*. The blood vascular system, which distributes nutritive materials, oxygen, and hormones to all parts of the body and removes the cellular products of metabolism and carbon dioxide, includes the *heart* and a series of tubular vessels, the *arteries*, *capillaries*, and *veins* (see Fig. 1)[3].

The heart is a modified blood vessel, specialized as a double pump for propulsion. It consists of two sides, often referred to as the *left* and *right heart*. Blood from the body enters the right heart and is pumped to the lungs. The left heart receives blood from the lungs and distributes it to all other tissues and organs of the body. Furthermore the right and left heart each have two main parts, an *atrium* and a *ventricle*. Both are sac-like structures , the walls of which consist of *cardiac muscle*. The walls of the ventricles are much thicker and stronger than those of the corresponding atria. The chief function of the atria is to act as reservoirs between contractions of the heart, while the ventricles create the actual pressure to pump the blood through the two circulations[4].

Vessels that carry blood to and from the lungs form the *pulmonary circulation* and those that distribute to, and collect blood from, the rest of the body constitute the *systemic circulation*. In both circulations arteries, which by branching constantly increase in number and decrease in caliber, conduct blood from the heart to the *capillary bed*. The capillaries, where most of the interchange of elements between the blood and the other tissues takes place, form a meshwork of fine tubules. Veins return blood from the capillaries to the heart[3].

The blood pressure in the pulmonary circuit is much less than that in the systemic circuit, approximately one tenth of it. The reason for this is that no fluid should be filtered out into the *alveoli*, the air-containing cells of the lungs. The function of the pulmonary circuit is not nutrition to the lungs, its sole purpose is rather the exchange of gases. To achieve this the capillary bed of the lungs permits carbon dioxide of the blood to be released into inspired air and oxygen to be absorbed from it[5].

The lymph vascular system commences in the tissues as blind tubules. It consists of lymphatic capillaries and various-sized lymphatic vessels which return a fluid called *lymph* from tissue spaces to the blood stream via the large veins in the neck[3].

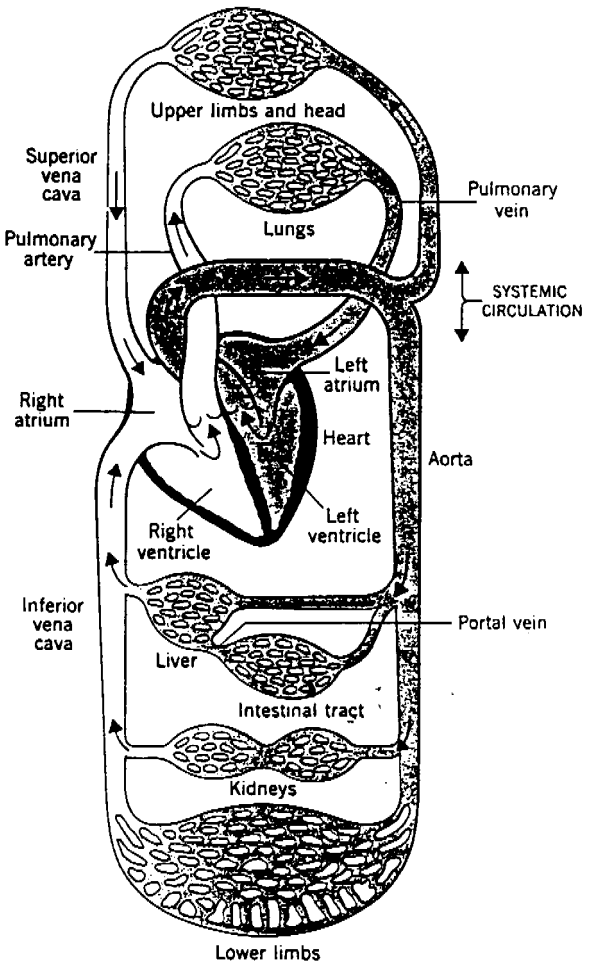


Fig. 1: The circulatory system (taken from Ref. 5).

2.2. The Different Types of Arteries:

There are three main kinds of arteries. Although all conduct blood, the three kinds perform somewhat different and important functions, to which their structure is particularly adapted. The different types are: (1) *elastic arteries*, (2) *muscular* or *distributing arteries*, and (3) *arterioles*. These types are not sharply divided, for they merge with one another. To simplify matters, only the systemic circulation will be dealt with in the following[4].

2.3. Elastic Arteries:

The left ventricle delivers blood into the *aorta* in spurts, ordinarily slightly more than 70 spurts per minute[5]. During contraction of the ventricle, the pressure generated is relatively high. But between contractions the pressure in the arterial system would fall to zero if the walls of the arterial system were rigid, like the walls of metal pipes. However, a reduced pressure in the arterial system between contractions of a ventricle is maintained because the walls of the arteries that lead directly from each ventricle are constructed chiefly of many layers of elastic laminae. Such arteries are termed elastic arteries. Blood delivered into them by the contracting heart stretches the elastin in their walls. Then, after a ventricle has finished contracting, its exhaust valve closes, and the walls of the elastic arteries passively contract to maintain pressure within the system for the short interval elapsing before the ventricle fills and contracts again. A second important function of the aorta's elastic properties is to cushion the body from the jolting shock arising from each heartbeat[6].

The pressure within the arterial system generated during the contraction of the ventricles is called the *systolic blood pressure* (normally about 120 mmHg)[5], and it is usually about 50% higher than the pressure that is maintained by the stretched elastic tissue of the arterial walls between contractions of the heart. The latter one is called the *diastolic blood pressure* (normally about 80 mmHg)[5]. The function of maintaining pressure within the arterial system during diastole is performed chiefly by the largest arteries of the body because their walls consist chiefly of elastin. The branches that arise from the largest arteries to deliver blood to the different parts of the body have a different function and they have walls of a somewhat different character[4].

2.4. Muscular Arteries:

Since the parts of the body under varied conditions of activity require different amounts of blood, the arteries supplying them must be capable of having the size of their lumina regulated so that appropriate amounts of blood can be delivered at any given time. Regulation of the size of the lumina of these distributing arteries is under the control of the *sympathetic division* of the *autonomic nervous system*. The walls of distributing arteries consist chiefly of smooth muscle fibers, which respond to nerve impulses and other stimuli by regulating the size of the lumen of the artery they surround. If the walls of these arteries were made of elastin, which can only recoil passively, nervous control would not be possible. Because the important component of their walls is smooth muscle, distributing arteries are usually called muscular arteries. They variously regulate the flow of blood to different parts of the body according to the needs of these parts[4)].

2.5. Arterioles:

In order for man to stand erect, a substantial pressure must be maintained within the arterial system. Otherwise, blood would not be delivered in sufficient quantities to the various capillary beds such as those of the brain, for this requires that the force of gravity be overcome. However, pressure must be maintained within the arterial system in such a way that blood is delivered into the capillary beds under reduced pressure because the walls of capillaries must be thin (and therefore weak) to permit ready diffusion through them. Delivery of arterial blood into capillary beds under relatively low pressure is achieved by the arterioles. These are essentially very small arteries with a relatively narrow lumen and thick muscular walls. Since blood is of a certain viscosity, their narrow lumen offers considerable resistance to its flow, and this permits relatively high pressures to be built up behind them. The degree of pressure within the arterial system as a whole is regulated mainly be the degree of tonus of the smooth muscle cells in the walls of the arterioles and this in turn is controlled by the autonomic system and by hormones[4)].

2.6. The Microscopic Structure of Arteries:

The blood vascular system has a continuous lining that consists of a single layer of *endothelial cells*. In the capillaries this single layer of cells forms the major component of the wall. Thereafter the addition of accessory coats can be traced progressively in larger vessels. Compared to the capillaries arteries have impermeable walls and are not

involved in the interchange between blood and tissue fluid. All arteries show a common pattern of organization. The wall of a typical artery is composed of three tunics, or coats[3]:

1) The innermost coat, the *tunica intima* (or *interna*), consists of an inner *endothelial lining*, a *subendothelial layer* of delicate fibroelastic connective tissue, and an external band of elastic fibers, the *internal elastic membrane*, which may be absent in many vessels.

2) The middle coat, the *tunica media*, consists chiefly of *smooth muscle cells*, circularly arranged. Interspersed between the smooth muscle cells are varying amounts of *elastic* and *collagenous fibers*.

3) The outer coat, the *tunica adventitia*, is composed principally of *connective tissue*, most of the elements of which run parallel to the long axis of the vessel. Closest to the media there may be a definite *external elastic membrane*.

The structure and relative thickness of each of the tunics vary according to the type and size of the vessel.

2.7. The Microscopic Structure of Arterioles:

These vessels, with a diameter of 100 μm or less, have relatively thick walls and narrow lumina. They have a tunica intima that consists only of endothelium and an internal elastic membrane. No subendothelial tissue is recognizable. The internal elastic membrane is really a network of fibers which by light microscopy appears as a thin, bright line just beneath the endothelium[3].

The media is composed of one to five complete layers of muscle cells, among which are some scattered elastic fibrils. The number of layers of muscle cells decreases as the caliber of the vessel decreases, and at about a diameter of 20 μm, the muscle coat becomes a single layer[3].

The adventitia, which usually is thinner than the media, is a layer of loose connective tissue with longitudinally oriented collagenous and elastic fibers. It merges into the surrounding connective tissue. No definite external elastic membrane is present[3].

2.8. The Microscopic Structure of Muscular Arteries:

This group comprises the small and medium-sized arteries, including most of the arteries that bear names and all unnamed ones. There is a gradual transition between these vessels and the arterioles. The walls of the muscular arteries are relatively thick, owing principally to the large amount of muscle in the media (see Fig. 2)[3].

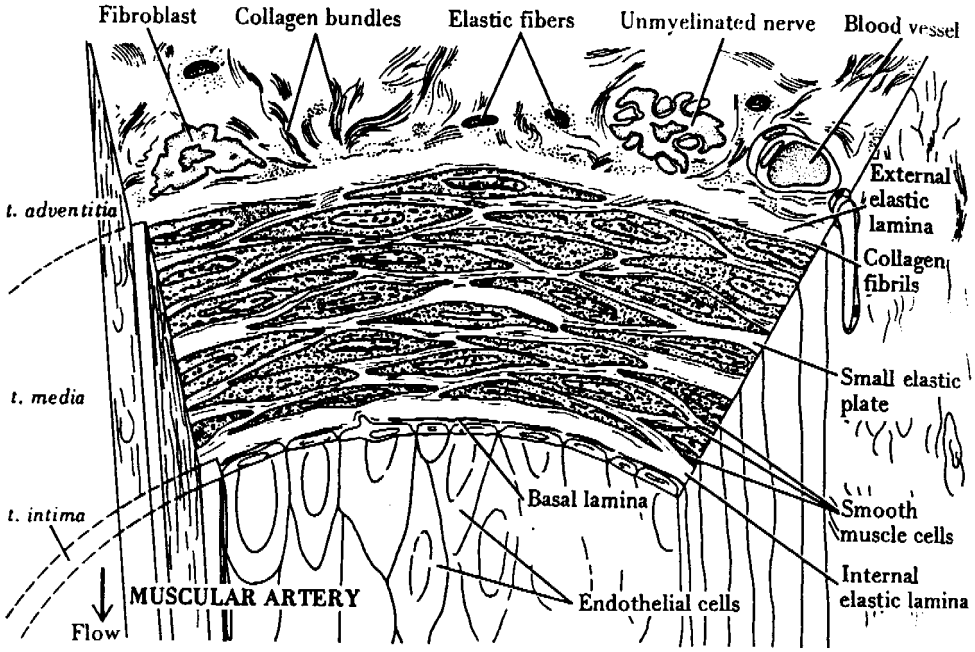


Fig. 2: Schematic diagram of the wall of a muscular artery (taken from Ref. 7).

The tunica intima exhibits three definite layers. Beneath the endothelium, which lies upon a thin basal lamina, there is the subendothelial layer comprising delicate elastic and collagenous fibers, occasional fibroblasts, and, in some of the larger muscular arteries, a few bundles of longitudinally oriented smooth muscle fibers. The internal elastic membrane, or lamina, is prominent and forms a thick fenestrated band composed of closely interwoven elastic fibers[3].

The media consists almost exclusively of circularly disposed smooth muscle cells. Between the layers of muscle (up to 40 in number) there are small amounts of connective tissue, the constituents of which are elastic, collagenous, and reticular fibers, and a few fibroblasts. In the larger muscular arteries, elastic fibers are prominent between the layers of smooth muscle, where they form close networks, circularly oriented[3].

The adventitia often is as thick as the media. It is composed of loose connective tissue containing collagenous and elastic fibers, most of which course helically or longitudinally. The elastic fibers are concentrated in the inner layer of the coat, where they commonly form a definite external elastic membrane. The outer layer of the adventitia blends into the surrounding connective tissue without a sharp boundary between the two[3].

2.9. The Microscopic Structure of Elastic Arteries:

This group comprises the large arteries, including the aorta and its largest main branches, the *brachiocephalic*, the *common carotid*, the *subclavian*, and *common iliac*. The wall is relatively thin for the size of the vessel[3]. To get a sense of the diameter of these arteries see Fig. 3, the structure of the wall is shown in Fig. 4.

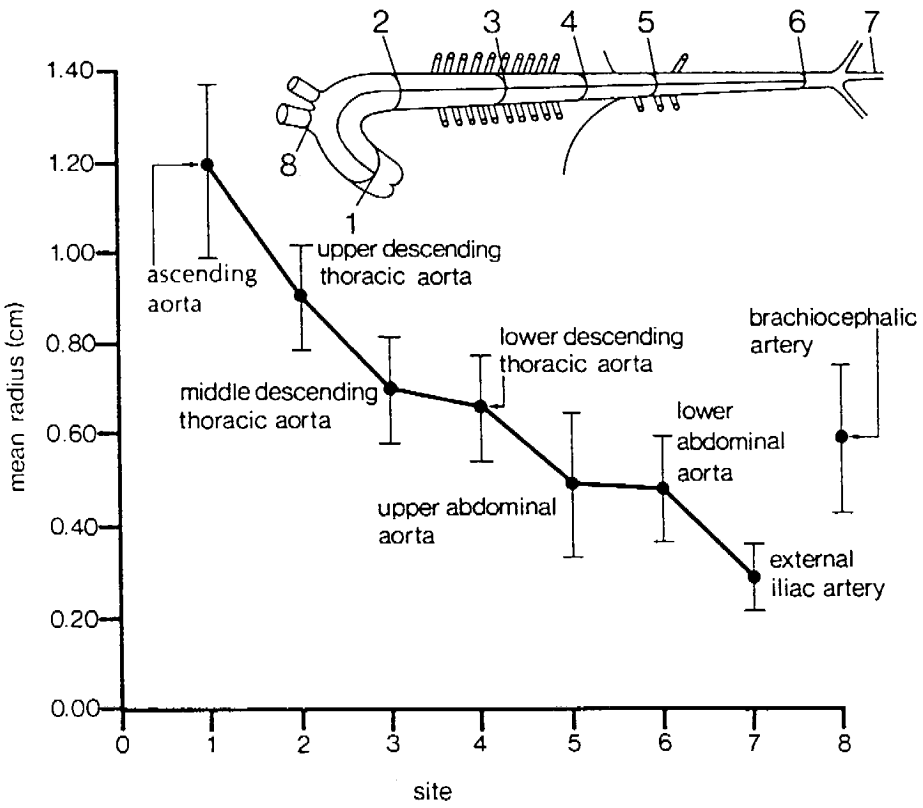


Fig. 3: Illustration of the mean radius of the branchings of the aorta and its major vessels (taken from Ref. 6).

The endothelial cells of the intima are polygonal in shape, not elongate as in the smaller vessels. The subendothelial layer consists of collagenous and elastic fibers and scattered

fibroblasts, and in the deeper portion of the intima small bundles of smooth muscle cells are present. A distinct internal elastic membrane is difficult to discern. Numerous elastic fibers, arranged mainly longitudinally, course in the deeper zone of the subendothelial layer and pass to the innermost elastic membrane of the media. This zone, by its location, corresponds to the internal elastic membrane[3].

The media is characterized by numerous distinct elastic membranes, 40 to 60 in number, which are arranged concentrically. They form a complex interlinked elastic net. Interspaces between the concentric membranes contain fibroblasts, an amorphous ground substance, a fine elastic network, and smooth muscle cells that pursue a spiral course. The smooth muscle cells have numerous short processes that are attached to the meshes of the elastic membranes[3].

The adventitia is a thin coat; it is not highly organized and cannot be distinguished sharply from the surrounding connective tissue. There is no distinctive external elastic layer or membrane[3].

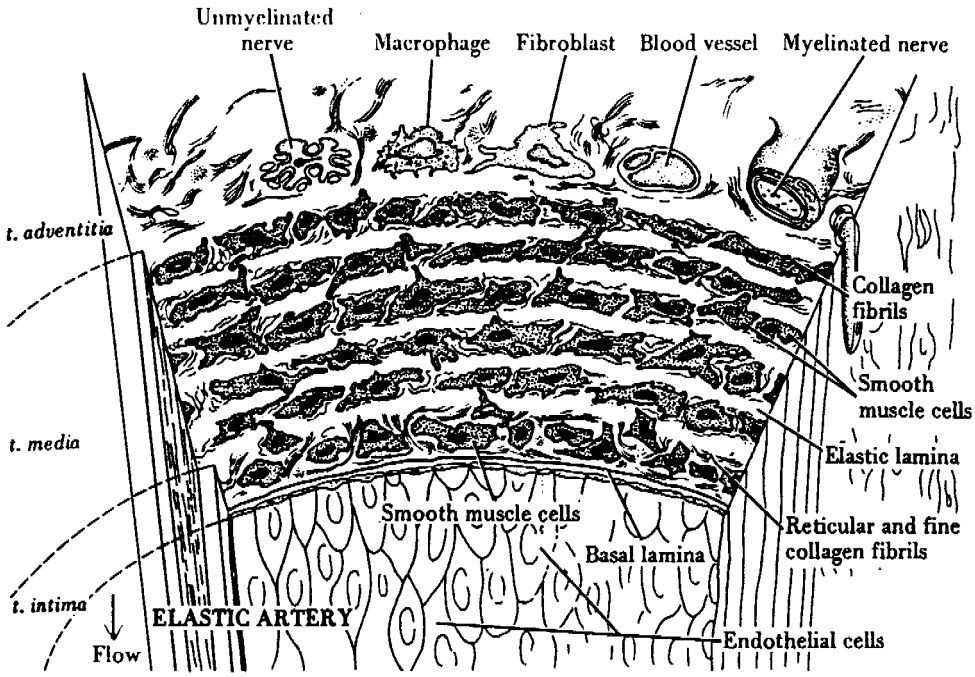


Fig. 4: Schematic diagram of the wall of an elastic artery (taken from Ref. 7).

Chapter 3: Blood

3.1. Blood in the Human Body:

The blood belongs to the group of tissues designated as *connective tissues*. It is a fluid tissue which constitutes about 7% of body weight and 5 liters in volume in human beings. The blood plays many roles in the body. It conveys nutrients and oxygen to cells; it carries carbon dioxide and waste materials away from cells; it contains *cellular* and *humoral agents* that battle infection and unwanted cells and delivers these agents to tissues as they are needed; it contains regulatory agents such as hormones that influence many activities within the body; it its thermoregulatory; and it maintains a delicate constancy of structure within certain limits, which is essential to the functional integrity of the body[8].

The blood consists of *formed elements* or *blood cells* and *blood plasma*. The formed elements are *red blood cells*, *white blood cells*, and *platelets*. Plasma is the liquid intercellular material which imparts to the blood its fluid properties. The relative volumes of cells and plasma are about 45% and 55%, respectively. This value is called a *hematocrit*. There are far more red blood cells (approximately 5×10^6 per mm^3 of blood) than white blood cells (approximately 6×10^3 per mm^3 of blood)[7].

3.2. Blood Plasma:

Plasma is the fluid that transports all nutritive materials. In it are found the nutritive substances derived from the digestive system, the waste substances produced in the tissues, and the regulatory substances. The composition of plasma is outlined in Table 1[3].

Component	Percentage
Water	91-92
Protein (fibrinogens, globulins, albumins)	7-8
Other solutes: Small electrolytes (Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, PO_4^{3-}, SO_4^{2-}) Nonprotein nitrogen substances [NPN] (urea, uric acid, creatine, creatinine, ammonium salts) Nutrients (glucose, lipids, amino acids) Blood gasses (oxygen, carbon dioxide, nitrogen) Regulatory substances (hormones, enzymes)	1-2

Table 1: Composition of blood plasma (taken from Ref. 7).

As seen from the table, most of the plasma consists of water which serves as the solvent for the variety of solutes. The proteins are the largest of the dissolved substances. They can be divided into three major groups designated as the *fibrinogens*, *globulins*, and *albumins*. Fibrinogens, the largest proteins, are made in the liver and function in *blood clotting*. Albumins, also made in the liver, are the smallest proteins. They are responsible for exerting the *major osmotic pressure* on the blood vessel wall. The globulins include the *immunoglobulins*, by far the largest component of the globulin fraction. The immunoglobulins are functional molecules of the *immune system*, they are the *antibodies.* The regulatory substances, the *hormones* and *enzymes*, chemically also belong to the group of proteins. Aside from the proteins, most of the other plasma constituents are sufficiently small to easily pass under physiological conditions through the blood vessel wall into the extracellular spaces of the adjacent connective tissue[7)].

3.3. Blood Cells:

The formed elements of the blood and their relative numbers are given in Table 2.

Component	Number or percentage
Red blood cells (erythrocytes)	$4\text{-}5 \times 10^6/mm^3$
White blood cells (leukocytes)	$6000\text{-}9000/mm^3$
Agranular leukocytes:	
Lymphocytes	30-35% (of leukocytes)
Monocytes	3-7% (of leukocytes)
Granular leukocytes:	
Neutrophils	55-60% (of leukocytes)
Eosinophils	2-5% (of leukocytes)
Basophils	0-1% (of leukocytes)
Platelets (thrombocytes)	$2\text{-}4 \times 10^5/mm^3$

Table 2: Formed elements of the blood (taken from Ref. 7).

Red blood cells, or *erythrocytes*, perform their functions while they are within the bloodstream. The white blood cells, or *leukocytes*, however, regularly leave the blood through the walls of capillaries and venules to enter the connective tissues, lymphatic tissues, and bone marrow where they perform specific functions. Thus, white blood cells must be regarded as transients within the blood. That is, they use the bloodstream as a vehicle for transport to specific sites within the body[7)].

3.4. Erythrocytes:

Red blood cells constitute the largest number of cells in the blood. Circulating erythrocytes are rather unusual cells in that they do not possess a nucleus. They are shaped as biconcave discs with a diameter of approximately 8.5 μm and a thickness of approximately 2 μm, and they usually display this appearance, tending to give the impression that their form is rigid and inelastic (see Fig. 5). However, the contrary is true. Erythrocytes are elastic and they readily deform, if necessary, in passing through small blood vessels. Although circulating red blood cells lack organelles, they are highly specialized and functional cells, engaged in the transport of *respiratory gasses*, oxygen and carbon dioxide. This function of the erythrocytes is documented impressively by the total surface area of all the red blood corpuscles in the human body, which amounts to 3500 m^2. This enormous area is available for exchange between the erythrocytes on the one hand and the plasma and air on the other[3].

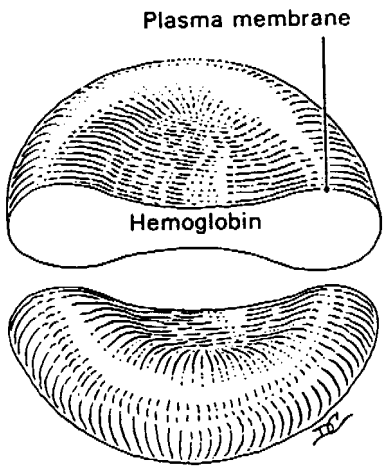


Fig. 5: Diagram illustrating the shape of a red blood cell, cut in half (taken from Ref. 4).

Erythrocytes transport oxygen from pulmonary alveoli to the tissues and carbon dioxide from the tissues to pulmonary alveoli. In the alveoli, the oxygen partial pressure is much larger than in the systemic venous blood coming from the tissues. As a result, oxygen diffuses through the alveolar wall into erythrocytes where it is loosely bound by the heme of *hemoglobin*. At the same time, carbon dioxide leaves the plasma and hemoglobin where it travels as bicarbonate and carbaminohemoglobin and diffuses into the alveoli. When blood reaches the capillaries, oxygen dissociates from the

hemoglobin and diffuses through the plasma and capillary wall and out into the surrounding tissues, while carbon dioxide diffuses from the tissues into the plasma and into the erythrocytes[8].

Hemoglobin, which constitutes approximately 33% of the weight of a red blood cell[8], consists of four polypeptide chains complexed to iron-containing heme groups. The polypeptide chains are not all alike, and depending on the kinds of polypeptide chains present, hemoglobin is designated as HbH, HbA2, and HbF[7].

3.5. Platelets:

Platelets are small cytoplasmic fragments within the circulating blood that do not contain a nucleus. They are ovoid bodies, 2 to 4 μm in diameter. Platelets are essential in preventing and staunching *hemorrhage*, the discharge of blood from the blood vessels. They seal off small breaks in blood vessels, they participate in blood coagulation, and they maintain the competence of the endothelium. If a blood vessel is cut and its endothelial continuity broken, certain proteins in the blood plasma are absorbed upon the exposed subendothelial collagen and other extracellular connective tissues. Within seconds circulating platelets establish contact with this subendothelial tissue and adhere to it. The platelets spread out over the damaged zone and their surface becomes altered, so that newly arrived platelets adhere to them and a hemostatic *platelet plug* is formed. As circulating platelets join the plug, several mechanisms are activated that further accelerate the build-up of the plug, called the *primary* and *secondary aggregation*[8].

3.6. Blood Clotting:

Directly after vascular injury, during platelet aggregation, blood clotting or *coagulation* is initiated by plasma factors and factors released from the damaged vessel. Blood coagulation is the consequence of the sequential interactions, or *cascade*, of perhaps thirteen plasma proteins. The last step in this cascade is the conversion of the monomer plasma protein fibrinogen to the linear polymer *fibrin* through the action of the plasma enzyme *thrombin*. Fibrin forms an interlacing network of slender fibers, running among the platelets and trapping erythrocytes and other blood cells. The result is a jelly-like bulky clot that, together with the platelet plug, serves to block bleeding. Although the blood clot may be initiated without platelets, the adherent platelets are essential to the production of a useful clot. They display great procoagulant activity by which they accelerate and magnify the process of blood coagulation[8].

With its injury covered by the clot, the vessel heals and its endothelium is regenerated. The clot is no longer needed. The plasma protein *plasminogen* is converted to the hydrolytic enzyme *plasmin* by *plasminogen activators* secreted by endothelial cells, and plasmin dissolves the clot[8].

There is a second way to initiate the process of blood clotting, which is provided by a part of the human immune system called the *complement system*. The complement system consists of at least 10 plasma components that, when activated, react sequentially with multifold consequences. Components of complement, in conjunction with certain antibodies, can not only initiate the coagulation of blood, but can also cause cell lysis. Other components induce the release of histamine from mast cells and basophils, are chemotactic for neutrophils, enhance phagocytosis, or induce smooth muscle contraction[8].

3.7. Leukocytes:

Leukocytes are cells that contain nuclei. There are two main types of leukocytes, *agranular* and *granular*. Agranular leukocytes have a cytoplasm that appears homogeneous and nuclei that are spherical to reniform in shape. Granular leukocytes contain abundant specific *granules* within their cytoplasm and possess nuclei that exhibit considerable variation in shape. There are two types of agranular leukocytes: *lymphocytes*, which are small cells (6-8 μm in diameter) with a scanty cytoplasm, and *monocytes*, which are slightly larger cells (9-12 μm in diameter) containing somewhat greater amounts of cytoplasm. The granular leukocytes are of three types: *neutrophils*, which are small polymorphonuclear cells (7-9 μm in diameter) whose abundant cytoplasm is filled with fine granules, *eosinophils*, which are slightly larger than the neutrophils (9-10 μm in diameter), whose cytoplasm characteristically is filled with coarse, refractile granules of uniform size, and *basophils*, who are about the same size as neutrophils (7-9 μm in diameter) and whose cytoplasmic granules are spherical, coarse, and variable in size[3].

3.8. Inflammation:

Leukocytes generally are involved in the cellular and humoral defense of the organism against foreign materials and perform their functions within the connective tissue. If chemical irritants or bacteria or other foreign substances penetrate the body, a series of reactions is initiated that constitutes *inflammation*. It is essentially a connective tissue response. Clinically, inflammation is characterized by heat, swelling, redness, pain,

and loss of function. It involves an initial constriction of blood vessels and an increase of the vascular permeability. As a consequence, the amount of interstitial fluid increases and cells enter the inflammatory site from the blood. The neutrophils are the most numerous of the first wave of cells to enter the inflammatory site, and they engage in a mechanism called phagocytosis. The first step of the phagocytosis of a foreign body, for example a bacterium, is its engulfment by a neutrophil. After the neutrophil has ingested the bacterium, the *specific granules* fuse with and empty their antibacterial agent into the phagosomes. Then, the *azurophilic granules* fuse with the phagosome and pur their hydrolytic enzymes into the phagosome, and these enzymes bring on the lysis of the bacterium. Many neutrophils perish in this process, and the accumulation of dead bacteria and neutrophils constitutes the thick yellowish substance called *pus*. Other white blood cells, especially monocytes, also quickly enter the inflammatory site. The monocytes transform into macrophages and phagocytose bacteria and tissue debris. With time the character of the inflammatory cell population changes. Macrophages remain at the inflammatory site longer than neutrophils, and thus they are the major cell type later on during the inflammation. Lymphocytes, eosinophils, and basophils also play a role in inflammation. However, their role is more specifically directed toward the immunologic aspect of the process[7)].

3.9. Immunity:

The idea of immunity is rooted in infectious disease. If an individual survives an infection, he may thereafter be resistant or immune to disease caused by the infecting organism. The immune system is a means of recognizing genetic relatedness. Thus, an individual will mount an immune response against foreign tissue but not against his own or genetically identical tissue. The two major types of immunity are *humoral immunity* and *cellular immunity*[8)].

Humoral immunity tends to be activated by invading microorganisms that live outside of host cells and by toxins released by such microorganisms. The basis of humoral immunity is the secretion of *antibodies* by plasma cells and by B lymphocytes undergoing transformation into plasma cells. *Antigens* are particulate or colloidal substances, typically foreign to the host. A large-scale secretion of antibodies is triggered by antigens, if they are i*mmunogenic* (i.e. capable of inducing an immune response). The antibodies diffuse through the blood plasma, lymph and other fluids of the body. The presence of

antibody throughout the fluids of the body constitutes a protective presence that eliminates or limits antigens[8].

Cellular immunity depends on immunologically competent cells working over short range in restricted sites where antigens are lodged. Cellular immunity is activated by microorganisms (certain bacteria, protozoa, fungi, and viruses) that do not lie free in the host but lie intracellularly within macrophages and other cells, by diffusible products created by these microorganisms, by grafts of tissue, by tumors, and by certain compounds applied to skin and other surfaces. Cellular immunity depends on *T cells*. T cells account for about 80-90% of the lymphocytes circulating in the blood and in the thoracic duct lymph. They have surface receptors that are specific for antigens. Antigens in the body are held on the surface of *antigen presenting cells* and are thus exposed to the T cells. If the antigen matches the surface receptor the stimulated T cell then undergoes clonal expansion and a portion of that clone engages in the cellular immune response, i.e. the production of *lymphokines*. The remaining cells of the clone constitute a bank of *memory cells*[8].

Chapter 4: Diseases of Arteries

4.1. Importance of Arterial Diseases:

Diseases of the arteries are among the most common causes of morbidity and mortality in people of middle age and later life. These diseases belong to two groups: those that are sometimes called *degenerative* and are represented principally by *arteriosclerosis*, and those that are *inflammatory* and are often grouped under the heading of *arteritis*. Numerically, instances of arteritis are uncommon, whereas arteriosclerosis is so universal in the western world that it is usually considered to be a concomitant of aging. Occlusions of the arterial tree causes untimely death in more than 500000 North Americans each year. In fact it is considered surprising when an elderly person is found to exhibit little or no arteriosclerosis at autopsy[6].

4.2. Thrombosis:

Clotting of the blood should occur when the blood escapes from the vessel, but not when it is flowing through the lumen of the vessel. Should this occur, it is called

thrombosis; the clot within the vessel is known as a *thrombus*. It consists mainly of platelets that adhere to the vessel wall, fibrin, and red blood cells trapped in the mesh, which gradually form a mass that may finally close the lumen of the vessel and stop the flow of blood through it, which can result in the loss of blood supply to a part. This is called *ischemia*, what designates a local loss of blood supply. The causes of thrombosis are threefold: (1) slowing of the blood stream, (2) changes in the vessel wall, and (3) changes in the blood itself. Since the first of these factors is more common in veins than in arteries, it is natural that thrombosis usually occurs in veins[6].

4.3. Ischemia:

The local loss of blood supply in ischemia leads to *anoxia*, or loss of oxygen to the part. The effect of ischemia is therefore the gradual death of the specialized cells of the body part that is affected, e.g. nerve cells in the brain, cardiac muscle cells in the heart, and so on, and their replacement by scar tissue, so that the organ loses the power to do its proper work. Closure of the arteries in the leg and, rarely, in the arm may lead to death of the parts farthest from the heart, the toes or fingers, since in them the circulation is likely to be most sluggish. This leads to another problem, for bacteria invade the dead tissue through the skin and cause decomposition of the ischemic tissue[6].

4.4. Embolism:

An embolism is usually a thrombus that has become detached and has entered the blood stream. As it is most commonly a vein that is the site of a thrombus, and as the veins become larger as the heart is approached, it follows that the embolus will meet whit no obstruction in its voyage to the heart. But no sooner has it passed through the right side of the heart and entered the pulmonary artery that carries the blood to the lungs than the chances of arrest of the thrombus increase with every millimeter the embolus travels, for the arteries become narrower the father they pass from the heart. Finally, the embolus will lodge in one of the arteries of the lung. The vessel blocked depends entirely on the size of the embolus. Indeed, the main pulmonary artery may be blocked if the embolus is sufficiently large (see Fig. 6)[6].

An embolus may originate in the heart instead of in a vein, usually on the left side of the heart. The original thrombus may have been a vegetation of a valve, or it may be formed in one of the chambers of the heart, usually the left atrium. In either case, the destination

of the embolus is now different, for it enters the aorta, and therefore the systemic circulation (see Fig. 6)[6].

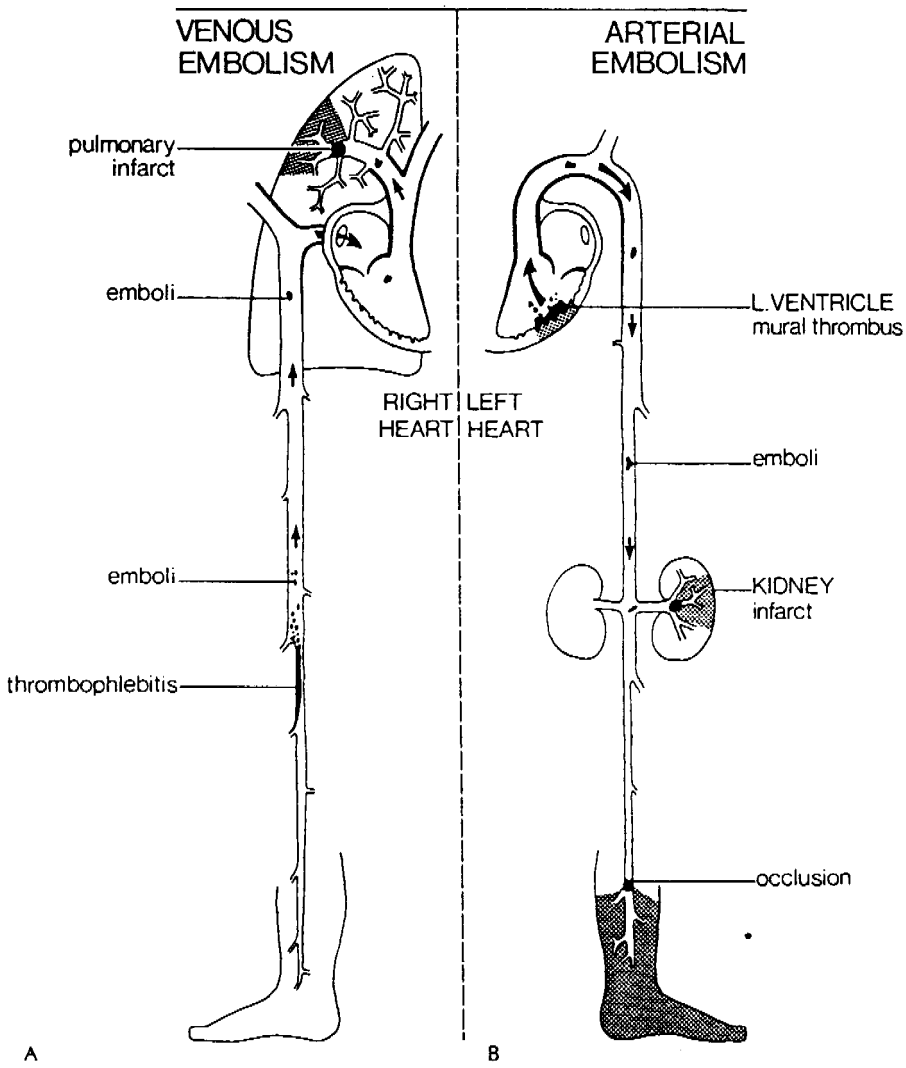


Fig. 6: Set of diagrams illustrating the complications and eventual fates of embolisms (taken from Ref. 6).

4.5. Effects of an Embolism:

When an embolus lodges in an artery, it blocks the lumen and cuts off the blood supply to the organ or part supplied by that artery. The effect depends on the size of the embolus and on the circulatory arrangements of the body part. If the embolus is large enough to block the main artery to an organ or a limb, the effect will be disastrous for the body part. In the case of a smaller embolus, the question of the vascular connections is all-

important. In most parts of the body there is what is called a *collateral circulation*, a communication between two sets of arteries. The blood to the hand for example is carried by two main arteries, one on each side of the wrist, and between the branches of these there pass numerous small communicating vessels. Should one of the main arteries be blocked by an embolus, the communications from the remaining artery become greatly dilated, so that sufficient blood can still reach the area supplied by the blocked vessel. Under these circumstances, an embolus does little or no harm. The availability of collateral circulation determines the outcome of occlusion in the systemic circulation[6].

There is another consideration, namely, that organs such as the lung and liver have a double blood supply. Each segment of the lung is perfused by blood from both the pulmonary artery (pulmonary circulation) and the bronchial artery (systemic circulation). This dual supply provides a safety factor, for if there is a small embolus to a small branch of the pulmonary artery, that part of the lung does not die, since it is also supplied by its respective bronchial artery[6].

4.6. Infarction:

It is a different matter than the case just described above, however, if the main artery to a limb, such as the femoral artery in the thigh, is blocked. Here there can be no efficient collateral circulation and the tissues are completely deprived of their blood supply and die. A similar state of affairs exists in a number of organs such as the brain, heart, kidney, and spleen. Each organ is supplied by only one major blood vessel with arterial blood. If this arterial supply is occluded by a thrombus or embolus, by mechanical means, or even by surgical intervention, the organ thus deprived of blood may be subject to what is called an *ischemic* (or *anoxic*) *infarction*, provided the interruption lasts for a significant time. This is demonstrated in the kidney and the spleen, where the infarcts appear as pale areas. The arterial blood does not reach parts of the organs and the cells become mummified following prolonged anoxemia. An infarct may be produced by thrombosis as well as by an embolism. The most frequent and important sites of infarction are the heart, lung, brain, spleen, kidney, and intestine[6].

4.7. Atherosclerosis:

Arteriosclerosis is a general term referring to a variety of entities that cause thickening and loss of elasticity in arterial walls. *Atherosclerosis* is a particular form of

arteriosclerosis, where the inner layer of the artery wall is made thick and irregular by deposits of a fatty substance that progressively narrows the lumen of the artery. The major underlying cause for the high incidence of arterial diseases is actually atherosclerosis. Atherosclerosis principally affects the large arteries, especially the aorta and its main branches, but also the small arteries, particularly the coronary and cerebral arteries. This is the form of arteriosclerosis that commonly predisposes a person to thrombosis[6].

The patchy or nodular thickening of the intima of the artery, with accumulations of lipid, often results in narrowing of the lumen. The blood supply may be cut down to the danger point, and a thrombus is apt to form on the diseased wall and to obstruct the narrowed lumen. It is worth recognizing, however, that an artery may be lined with atheromas or plaques and still be functional. The normal perfusion does not fall off until more than two-thirds of the diameter of any vessel lumen is occluded. If obstruction has been gradual, as sometimes occurs in the femoral artery, even complete occlusion may not cause symptoms, because a collateral circulation has had time to develop. Unfortunately, in some situations collateral circulation is not available, and sometimes the demands are unusual and excessive, and the narrowing due to atheromatous plaques is sufficient to result in serious or fatal ischemia. This is the mechanism of production of coronary thrombosis, cerebral thrombosis, and thrombosis in the arteries of the leg[6].

4.8. Pathogenesis of Atherosclerosis:

It is remarkable that, in spite of the frequency of atherosclerosis and the enormous amount of time and money expended in its investigation, little is known about the cause of it. Many factors influencing the formation of atherosclerosis are known, but the common mechanism by which it is produced is still unknown, also there are some hypotheses. The most important factors are (see Fig. 7)[6]:

1) Atherosclerosis increases with age.
2) It apparently progresses more rapidly in women after the menopause and seems to be more severe in men than in women under the age of 40.
3) There are worldwide differences in the severity of atherosclerosis. The disease has been characterized as being more common in highly developed societies.
4) There is a whole number of special risk factors, that may make the disease more severe, e.g. hypertension, obesity, cigarette smoking, high fat intake, and coincidental diseases such as diabetes mellitus.

A factor, the significance of which is undetermined but that may be extremely relevant to the understanding of atherosclerosis, is exercise. A sedentary occupation is clearly a risk factor, and the rise in participation in physical work or exercise may be partly responsible for the leveling off in premature deaths attributable to atherosclerosis[6].

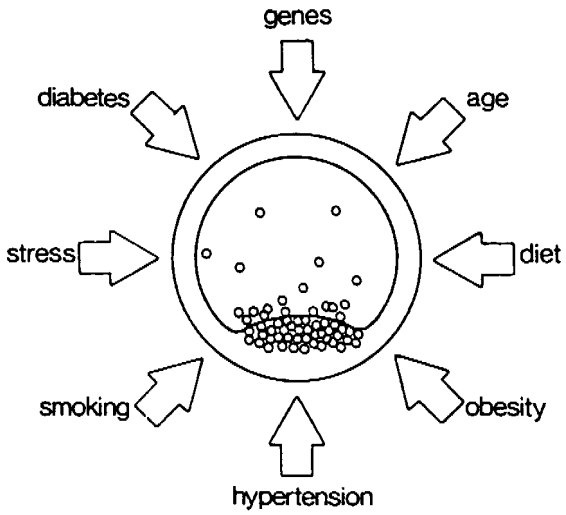


Fig. 7: Factors that influence the formation of atherosclerosis (taken from Ref. 6).

4.9. Arteritis:

Apart from atherosclerosis a *lesion* in arteries, i.e. an abnormal change in their structure, can also be produced by inflammation, although this is a much less common event than atherosclerosis. A number of these diseases appear to be manifestations of allergy or of hypersensitivity, although little or nothing is known about the substances to which the person is allergic[6].

Polyarteritis nodosa is one of the diffuse *collagen diseases*. The collective phrase collagen diseases or *collagen vascular diseases* represents an attempt to group diseases of unknown origin that manifest in morphologic changes in the histologic appearance of connective tissue. It is an acute inflammation that involves the small arteries of the internal organs. The cause is unknown, but strong evidence suggests that this disease represents a type of hypersensitivity[6].

Thromboangiitis obliterans is a thrombotic occlusion of the vessels of the legs in relatively young men, and results in gangrene of the toes and then the feet. The cause is unknown, but it is believed that there is a condition of allergic hypersensitivity in the arterial wall, as a result of which an acute inflammatory reaction develops. Patients seem to be especially hypersensitive to tobacco, and the sufferer is often found to be a heavy cigarette smoker[6].

Syphilis attacks two important sets of vessels: (1) the thoracic aorta, including the coronary artery ostia, more especially the ascending portion, and (2) the cerebral arteries. Syphilitic aortitis can result in an *aneurysm*[6].

4.10. Aneurysm:

An aneurysm is a localized or diffuse dilatation of the wall of an artery caused by damage to the elastic tissue of the wall. This dilatation may be saccular, an outpouching of the vessel at a single point, or *fusiform,* a uniform dilatation of an entire segment of the artery. Every aneurysm is due to weakening of the arterial wall. As a rule it is the media that is damaged. Syphilis used to be the most important cause of aneurysm of the aorta and its main branches. With the modern control of syphilis and with the increasing age of the population, atherosclerosis has come to replace it[6].

Aneurysm due to atherosclerosis occurs at a later age than the syphilitic form; it generally affects the abdominal aorta, and it usually causes diffuse dilatation of the vessel. The aneurysm may press on the lower dorsal and lumbar vertebrae, with disastrous results[6].

A syphilitic aneurysm usually involves the ascending aorta or the arch, is usually saccular, and presses on the surrounding structures, causing pain in the back, dyspnea, and difficulty in swallowing. It may rupture on the surface or internally, killing the person at once[6].

4.11. Dissecting Aneurysm:

Dissecting aneurysm is not a true aneurysm, as the vessel is not dilated. A hemorrhage occurs in the media of the aorta at a point of weakness, and spreads along the vessel, dissecting the media into two layers. The usual pattern may be a sudden sharp or excruciating pain in the chest or the abdomen. The pain passes, but in a typical case death occurs some days later from the rupture of the aneurysm into the chest or the

abdominal cavity. This clinical pattern is not the only one, since the dissection may take a number of routes. It may separate the walls of the aorta and narrow the renal arteries; it may close off the mesenteric supply to the bowel; or it may dissect retrograde to narrow the coronary arteries. Studies of collected cases show that 3% of patients with a dissecting aneurysm die immediately; 20% die within a day; 60% die whiten two weeks; and 90% die within three months. In a few lucky cases, the person may survive many years[6].

Chapter 5: Vascular Surgery

5.1. Aim of Arterial Surgery:

In many cases the arterial diseases described in the previous chapter are treated by surgical reconstruction of the arteries. This does not treat the reasons that produced the disease, but it rather deals with the symptoms that are caused by the disease. The aim of arterial surgery is generally twofold[9]:

1) To deal with ischemia resulting from arterial occlusion or interruption.
2) To correct abnormalities of the blood vessel wall that threaten its integrity and may lead to rupture and serious hemorrhage.

The basic surgical maneuvers aim at restoring the arterial surface or substituting a nonthrombogenic, nonembolizing conduit for an occluded, narrowed, or dilated thrombogenic one[9].

5.2. Surgical Treatment of Arterial Diseases:

There are five general ways to surgically deal with arterial diseases[9]:

1) Remove the diseased artery if possible.
2) Reopen an occluded or narrowed artery by *endarterectomy*. This is literally the cutting out of the inner wall of an artery.
3) Reopen an occluded or narrowed artery by *dilatation.* This concept usually employs the *balloon catheter technique,* which consists of insertion of a catheter

with a balloon at its end into the atherosclerotic lumen. The balloon is inflated to compact both thrombus and atherosclerotic debris and thus reopens the artery.
4) Develop or promote *collateral circulation.*
5) *Replace* or *bypass* the occluded or narrowed artery with an arterial substitute.

In many cases the use of arterial substitutes is the only applicable solution. There are three different ways to achieve an arterial replacement[9]:

1) Removal of the diseased artery and interposition of the prosthesis.
2) Employment of the *bypass principle* in which an arterial replacement is *anastomosed* to an open artery above and to one below the artery to be replaced. The term anastomosis generally designates the surgical connection of natural blood vessels and/or blood vessel grafts.
3) Employing an *extra-anatomical route* in which the *proximal* end (i.e. the one located closer to the heart) of a prosthesis is anastomosed to a distant artery and its *distal* end (i.e. the one located farther away from the heart) is anastomosed to the healthy part of the diseased artery beyond the obstructed segment.

Chapter 6: The Ideal Arterial Graft

There are certain characteristics that *ideal arterial grafts* need to have[1,2]:

1) The *durability* of the implant should be superior to the life expectancy of the host.
2) The insertion of the graft should not cause undesirable reactions beyond the capacity of the host to handle and correct them.
3) The inner surface must interact in a *nonthrombogenic* fashion with blood elements and resist infection. For this reason it would be ideal if the luminal surface of the graft would promote the growth of an endothelial layer on it.
4) Ideally, the patency of the graft should approach 100%. If the graft occludes, this process should not be due to intrinsic problems of the graft itself.
5) The ideal graft should exhibit and maintain the same elastic properties as the original undiseased artery to which it is sutured. In this respect especially the *compliance* and *flexibility* are of importance.
6) The ideal graft should be incorporated with and anchored to the surrounding tissue.

7) An ideal graft should be readily sterilizable with a method that does not degrade its properties.
8) The material for the graft must be readily available in a variety of sizes and lengths.
9) The graft should be easy to handle for the surgeon.
10) As a point of minor importance it would be nice if the material were inexpensive.

Chapter 7: Current Arterial Grafts

7.1. Unprocessed Biological Grafts:

If *unprocessed biological grafts* are used they are taken from the patient himself. For this reason they are also called *autogenous biological grafts*. Several blood vessels have been tried for this purpose with varying success. The ones in use today are either the *greater saphenous vein* or *arterial autografts*[1,2].

7.2. Greater Saphenous Vein:

The greater saphenous vein is the best graft available for replacement of small- and medium-sized vessels, between 4 and 6 mm in diameter. Although not the ideal conduit, it fulfills many of the basic qualities that an arterial substitute should have. It is readily available, conveniently located under the skin, expendable, and sufficiently long, averaging about 60 cm in the adult male. Unlike most other veins in the human body, which are thin walled and may become aneurysmal if exposed to systemic arterial pressure, the greater saphenous vein is structurally strong. The thickness of its wall in adults is comparable to that of medium sized arteries. This vessel develops with age to withstand normal venous hydrostatic pressures of 100 mmHg that occur in the lower extremities. Two other qualities make the greater saphenous vein unique: the presence of endothelial cells on its luminal surface and a compliance that is similar to that found in arteries[1,2].

In the use of the greater saphenous vein the *valves* inside of the vein have to be considered, which in the normal physiology of the vein prevent the backflow of blood in these low-pressure blood vessels. For this there are two possibilities[1,2]:

1) The vein is *reversed*, i.e. completely taken out of the body and turned around, so that the blood does not flow against the direction of the valves. In this case the careful dissection and anastomosis is incredibly important.
2) The vein can be used in *situ*, i.e. left in the place it is. In this case the flow of blood from the arterial bypass is against the direction of the valves. Therefore the valve destruction prior to the anastomosis is critical.

7.3. Arterial Autografts:

Arterial autografts are in many respect nearly ideal arterial substitutes. The arteries are lined with endothelium that maintains its viability when transplanted to another site. The vasa vasorum of medium-sized arteries originate from small branches off the artery itself. In transplanting an artery from one site to another the arterial autograft will carry its own blood supply, thus ensuring its viability. This living tissue then is less likely to undergo degeneration and can be implanted in an infected field. Unfortunately, the limited availability of a suitable arterial autograft restricts its clinical use. Some arteries can be sacrificed without replacements, for some the harvesting necessitates their replacement with a prosthetic graft. The need for excision of normal arteries arises when arterial reconstruction must be done in an infected field. The arterial autograft is removed from a remote clean area, replaced with a prosthetic graft, and transplanted to the infected field[2)].

7.4. Processed Biological Grafts:

Nonautogenous biological grafts are those that are harvested outside of the patient. The problems associated with their use are much more severe than for autogenous biological grafts, since the immune system of the patient is likely to attack the foreign cells. They therefore have to be processed chemically and tanned, thus becoming a form of leather. The problems of antigenicity, procurement, and storage can, for the most part, be solved in this way, but the treatment of the blood vessel usually weakens the structural integrity of the graft, leading to additional problems. The only clinically successful nonautogenous biological graft is the *human umbilical cord vein*, which is harvested from human newborns. The vein is subjected to a tanning process using glutaraldehyde. This agent establishes effective cross-links of collagen molecules which reduce immunological recognition and rejection. The treated graft is usually further covered with a netlike PET mesh, which increases its structural strength. The product of this process is currently

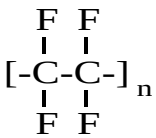
used for lower extremity revascularization. Patency rates are inferior to the autogenuous saphenous veins but acceptable if an autogenous vein is not available[1,2].

7.5. Synthetic Grafts:

Of the various synthetic materials, only *PTFE* and *PET* have proved to be sufficiently resistant to degradation in the body and are currently being used. Other materials that were considered, like for example Nylon, Orlon, or Ivalon, among many others, now belong to history. Several other synthetic materials are subject of current investigation and might become important in the future, especially *polyurethanes*[1].

7.6. PTFE Grafts:

Polytetrafluoroethylene (PTFE) is a synthetic material known in the commercial world as *Teflon*. It is one of the most biologically inert nonreactive substances known. The chemical repeat unit of the PTFE polymer chains consists of two carbon atoms surrounded by four fluorine atoms[10]:



The inertness of the material is due to the fluorine atom, which is highly electronegative and thereby hydrophobic. Two forms of PTFE have been used as prostheses, the textile type and the microporous type. *PTFE textiles* can be either *woven* or *knitted*. There is some objection against these grafts, the main one being their tendency to fray at the cut edges, i.e. at the anastomotic line. However, some of the cases of disruption at the anastomotic line may have been due to the silk suture material used, which is partially biodegradable. PTFE as such does not deteriorate and thus the use of this material especially as warp knit should be reconsidered[1].

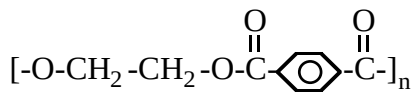
Microporous PTFE is extremely popular for replacement of medium- to large-sized vessels, of diameters approximately 6 to 10 mm[11]. This material, which is also called *expanded PTFE* (*ePTFE*), is manufactured through a unique process in which the PTFE is extruded through a die to produce structures of various sizes and shapes. It is available as vascular grafts under the trade names of *Gore-Tex* or *Impra*. Microscopically, PTFE

exhibits a semiporous material that is 85% air. The structure consists of nodes connected together by fibrils. The distance between the nodes can be varied, creating pores of different sizes. The fibrils are arranged in a longitudinal alignment, accounting for tensile strength in this direction, but poor strength in the circumferential direction[1,2].

Although the results of bypasses with these grafts have been very satisfactory, the material appears to function against all logic. It lacks compliance, it heals very little or not at all, and very often it presents on its inner surface a biofilm of glycocalyx frequently incorporating some bacterial colonies capable of being reactivated under special conditions. The numerous attempts to correct these deficiencies have proved disappointing. On the other hand, the in situ stability of reinforced Gore-Tex is impressive if manipulated with care[1,11].

7.7. PET Grafts:

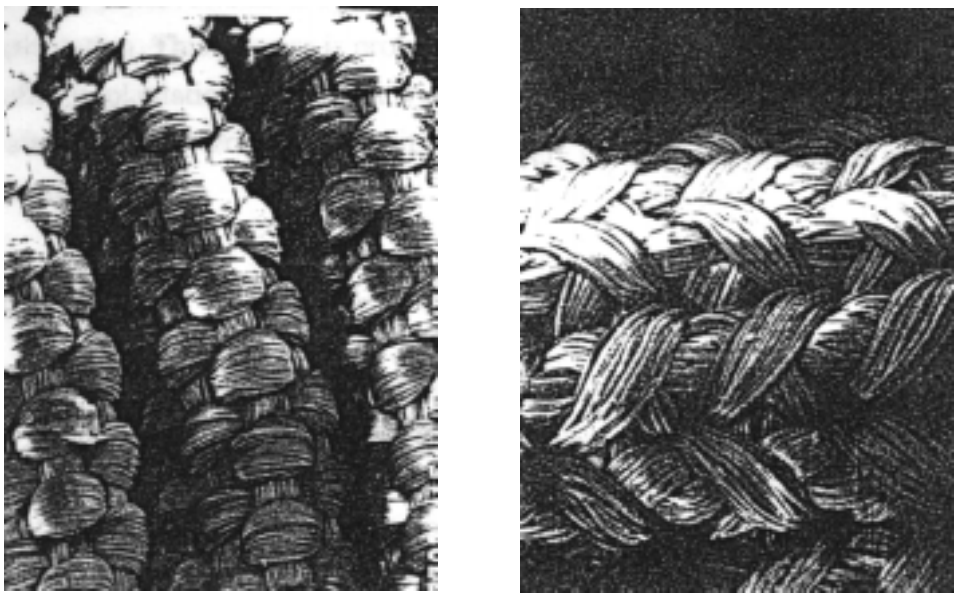
Poly(ethylene terephthalate) (PET) is known by the trade name of *Dacron*. It is the most popular material for arterial prostheses, at least for replacement of large and medium-sized vessels. It has endured the test of time, although a large number of types and various forms have been devised or proposed to improve the clinical results. PET is a p*olyester* and has the following chemical structure[10]:



For the use as prosthetic graft PET is processed as small continuous filaments made into a yarn. A typical yarn may consist of 20 to 54 filaments. To keep the yarn together, the filaments must be twisted or fabricated in a certain pattern. For vascular prostheses the pattern may be woven or knitted. A woven fabric has the yarns constructed in an over-and-under pattern (see Fig. 8). This creates a tight pattern with low porosity and little stretch. The graft is durable, but stiff and difficult to handle. Since the pores are tight, this graft will not leak blood after implantation and therefore does not need *preclotting*[1,2].

In a knitted fabric, the yarn is looped around a needle to form a continuous chain (see Fig. 8). This creates spaces between the yarns, allowing for a fabric with a higher porosity than a woven fabric but with less strength and durability. By varying the number of needles and the thickness of the yarn, fabrics of increased porosity and decreased weight

can be constructed. The knitted fabric is light, elastic, and easy to handle. Since the porosity is high, bleeding occurs through the graft after implantation unless it is preclotted. Proper preclotting that fills the interstitial spaces with fibrin usually prevents intraoperative bleeding[1,2].



(a) (b)

Fig. 8: (a) Woven PET, (b) knitted PET, magnification x50 (taken from Ref. 2).

Chapter 8: Problems Associated with Current Arterial Grafts and Concepts of Possible Solutions

8.1. Rapid Aging of the Autogenous Greater Saphenous Vein:

Although the greater saphenous vein is the best for peripheral arterial vascular reconstruction, it has significant liabilities. For femoral popliteal bypasses, approximately 35% of vein grafts will occlude over a three to five year period of time. Structural changes in the vein graft itself account for these occlusions, which are usually attributed to a *rapid aging* of the vein. The changes might result from the initial preparation of the vein, other degenerative changes perhaps relate to host factors. Furthermore the healing

capacity of the autologous saphenous vein is only limited. The *harvesting technique* used to obtain the vein has been proved to be of great importance for its long-term patency[1,2].

8.2. Degeneration of the Processed Human Umbilical Cord Vein:

The processed human umbilical cord veins undergo a marked *degeneration* about five years after implantation. This process is probably due to invasion by lipids, which starts already shortly after implantation. Treatment with *heparin* might improve the thrombogenicity of these grafts on a short-term basis, but it is unfortunately unlikely to prevent the resorption of the vessel wall[1].

8.3. Problems of Synthetic Arterial Grafts:

Synthetic arterial grafts are rather successful today for the replacement of large diameter, high-flow arteries, primarily in the thoracic and abdominal aorta. Bypasses of long segments of arteries with less than a 6 mm internal diameter presents a more challenging problem of long-term patency. To date no solid wall synthetic graft has been fabricated that will function as a small diameter graft. The paramount consideration for success of small diameter peripheral reconstructions is the *thromboresistance* of the luminal surface[12].

Apart from a lack of thromboresistance the other general problems that synthetic arterial grafts still have are (1) compliance mismatch, (2) lack of flexibility, (3) graft infections, and (4) insufficient durability[1].

8.4. Healing of Synthetic Vascular Grafts:

Vascular grafts generally heal by overgrowth of smooth muscle cells and endothelial cells from the adjacent artery; there is no demonstrable contribution to graft endothelium from circulating cells[12]. Successful synthetic grafts have interstitial spaces or pores that allow incorporation of the outer wall and organization of the *inner lining* or *luminal surface*. The pores of the graft are penetrated by *perivascular fibrous tissue* after one month. During this process the fibroblasts form a dense, stiff capsule around the graft. The incorporation anchors the graft to the surrounding tissue, reducing kinking and preventing fluid accumulation around the graft. Fibroblasts and capillaries then can migrate through the wall to organize the inner lining by replacing thrombus in the luminal surface with a more thromboresistant fibrocollagen matrix, the *pseudointima*[2,12].

This tissue incorporation of the synthetic vascular prosthesis is proportional to its degree of porosity. Porosity is measured by the size of the pores, which can be varied by manufacturing techniques. An optimal size for the pores is still undetermined. Grafts with large pores are better incorporated. Large pores, however, reduce the strength of the graft, predispose it to aneurysm formation, and can cause unmanageable bleeding immediately following implantation of the graft. One possibility to solve the bleeding problem is the already mentioned technique of preclotting. An attempt to combine the superior healing characteristics of a graft with large pores with the benefits of a material that is impervious to blood is impregnating the prosthesis with a biodegradable polymer[14]. Among other materials *cross-linked bovine collagen* is being studied for this purpose. After implantation the collagen is absorbed and the porous substrate with its advantageous healing characteristics remains[15]. One potential disadvantage of this concept is that the bovine collagen may activate the complement system and evoke the production of inflammatory mediators[16].

A further disadvantage of large pores is observed in grafts used to replace medium size vessels with slow flow and high outflow resistance. In that case a large pore size can lead to excessive pseudointima formation, which reduces the lumen of the graft, predisposing it to thrombosis. In the infrarenal abdominal aorta, however, porous grafts can be used because the high flow rate keeps the pseudointima thin, reducing the tendency to thrombose. Pores that are too small on the other hand will not allow proper incorporation and organization of the graft. Thus, ideal pore size may vary with the sites in which the synthetic graft is to be implanted[2].

8.5. Compliance:

Compliance is a measurement of the *elasticity* of vessels. It is defined as the percentage of radial change per unit of pressure and is a measure of the ability of an arterial conduit wall to expand with each contraction of the heart during systole. Prosthetic and biological grafts, with the exception of autogenous veins, are not as compliant as normal arteries. More importantly, the fibrous capsule that forms around the graft once it is placed in the body, limits expansion of the graft. Therefore, while the growth of surrounding fibroblasts incorporates the graft to the surrounding tissue and anchors it to it, the same process makes the graft noncompliant and stiff[2].

A stiff graft placed as a bypass in the arterial system results in a *compliance mismatch* between the graft and host artery. This does not cause systemic effects but may create profound local hemodynamic effects at the proximal and distal anastomotic sites. Compliance mismatch causes turbulence and stagnation at the anastomosis, predispoing the graft to thrombosis. With a stiff graft, there is increased blood flow velocity at the distal connection that damages endothelial cells and is a possible mechanism for the development of *intimal hyperplasia* (i.e. an abnormal increase in the number of cells on the inner arterial surface). Aneurysms occurring directly at the connection site between artery and graft are called *anastomotic aneurysms*. They mostly occur from sutures pulling out of the artery and may also be a result of compliance mismatch. With each heartbeat, the arterial wall expands but the noncompliant graft does not. The resulting tension on the arterial suture line eventually predisposes to a late anastomotic aneurysm[2)].

The thickness and thus the stiffness of the fibrous capsule can be influenced by the pore size of the graft. Furthermore the composition of the capsule, for example the ratio of collagen type I to collagen type III, also depends on the pore size and crucially influences the capsule's elastic properties. Very successful experiments were done with *replamineform* vascular prostheses. These grafts are fabricated by reproducing the uniform microporous configuration of different calcium carbonate templates, permitting control of the pore size. The optimal pore size (regarding elastic properties of the graft/capsule system) varies for different graft materials[12)].

8.6. Flexibility:

Flexibility is the ability of a graft to maintain its contour and to bend without partially occluding as it crosses joints. Although grafts are initially flexible, upon formation of the fibrous capsule the graft flexibility is lost to varying degrees. The loss of flexibility can be partially decreased by *crimping* the graft, using elasticized yarn, or by externally supported rings. A disadvantage of the crimping is that it gives the graft a certain tendency to become *calcified*[1,2)].

8.7. Thromboresistance of the Inner Graft Surface:

To date, thrombosis has been observed in every type of graft. In the early postoperative period it may be due to technical error, while late thrombosis is usually due to extension of the disease or increased vascular resistance distally. In addition blood-wall interactions can cause varying degrees of thrombogenic activity. The specific hemocompatibility of a given material can be evaluated according to its potential to inhibit thrombosis, either by controlling platelet activation and coagulation factors, by including the lysis of a thrombus which may be constituted or not, or by generating a neointima with antithrombogenic physiological properties[17].

In fact, creating an antithrombogenic surface is a new concept in hemocompatible biomaterials, and a lot of research has been done in this direction in the last few years. On the material surface, it is possible to position different polymers having specific properties. The resulting surface may be electrically neutral or not, crystalline or amorphous, or it can be exposing microdomains with different characteristics. Moreover, the surface can be biologically activated by the association of anticoagulant molecules or by adding “heparin-like” sites of which the structure chemically mimics the anticoagulant active heparin molecule. A recent field of study is the idea of designing surfaces with a preferential affinity for specific plasma proteins that might have an antithrombogenic effect[17,18].

One component of thrombogenicity that is often overlooked is the *blood-gas interface*. Gas nuclei (air) in the graft material are thrombogenic, and they are usually present under normal circumstances. The removal of these gas nuclei has been called *denucleation.* Several techniques, including immersion in ethanol, acetone, and vacuum, have been employed do denucleate biomaterials. In one particular technique the graft is first being subjected to a vacuum and afterwards to a saline solution at elevated pressures. It has generally been found that this procedure increases the patency of grafts[19,20].

8.8. Endothelium on the Inner Graft Surface:

An endothelial lining on the inner graft surface would be the optimal condition in terms of thrombogenicity, being equal to the usual inner surface of biological arteries. Furthermore, an endothelium on the graft surface could improve its resistance against infection. Regrettably, in contrast to animal models, the usual mechanisms of graft endothelialization are partially ineffective in humans. Therefore a real *neointima*,

consisting of endothelial cells, only forms within approximately 1 cm from an anastomotic suture line. The rest of the graft is covered by a *pseudointima,* a blood-contacting surface not covered by endothelium, but lined by other cellular and molecular elements derived from blood or the arterial wall[13,21].

One approach to address this problem is a *seeding* of endothelial cells on the inner surface of the graft prior to implantation. So far experimental results show that this does not lead to a stable neointimal coverage over longer time, but clinical results show an improved hemocompatibility and long-term patency of seeded grafts nevertheless[21,22]. A different method is based on the coating of the graft with a uniform, naturally produced *subendothelial extracellular matrix*. This substrate provides a most suitable biolayer for endothelial cell adhesion, growth, and differentiation. This approach has so far not been tested clinically[23].

8.9. Graft Infections:

Infection of an arterial graft is an infrequent complication. An estimate for the incidence of infection associated with vascular surgery is 2 to 3%. However, the limb- and life-threatening nature of this serious problem has induced an extensive research effort investigating the role of graft design and the biological behavior of grafts affecting infections. Arterial graft infection occurs almost exclusively in prosthetic grafts. Autogenous tissues rarely develop infection. The presence of endothelial cells and the rapid revascularization of autogenous tissue by the vasa vasorum after implantation are protective. The synthetic prostheses are foreign bodies deprived of blood supply and without endothelial cells lining the luminal surface and therefore have no mechanism to combat local infections. These grafts may be infected by local contamination at the time of operative procedure or by a bacteremia at any time following implantation[2,24].

Reduction of arterial graft infection from local contamination by soaking the graft in antibiotics just prior to its implantation has, in general, not succeeded, because the antibiotics are rapidly removed by the bloodstream once the graft is inserted. More elaborate methods of bonding antibiotics to the graft have some promise. Quinolone antibiotics for example can be bound to PET grafts based on principles of textile chemistry, using a thermofixation procedure. Surfaces of PET grafts treated in this way have been shown to demonstrate antibiotic activity for longer than two weeks after

implantation, whereas PET grafts soaked with the same amount of antibiotics lost their activity within 48 hours[25].

Even so, the antibiotic does not remain on the surface indefinitely, whereas the grafts are still susceptible to infection months or even years after implantation. It was demonstrated in experimental animals that the susceptibility to infection from bacteremic contamination is a function of the completeness of the pseudointima. Grafts have different rates of healing, and large areas of incompletely formed pseudointima can exist 6 months to one year after implantation. These areas are potential sites of graft contamination. Therefore grafts should form a stable pseudointima a the earliest possible time following implantation. The best solution to graft infection from bacteremia would be a synthetic graft with an endothelial lined luminal surface[2].

8.10. Durability:

Vascular prostheses suffer from two basic long-term failure modes. The first is occlusion, which may be due to thrombosis or to some type of intimal hyperplasia. The second type of long-term failure mode is structural failure of the prosthesis itself or of the suture line. The term *durability* describes the ability of a graft to maintain its physical structure after implantation in the human body. Prosthetic grafts must withstand two threats to structural integrity[2]:

1) *Biodegradability* due to body reaction.
2) *Mechanical fatigue* of the graft wall from exposure to arterial pressure.

Dilatation and rupture has especially been a problem of the lighter PET grafts. PTFE is a very inert material. No evidence of degradative changes in the material has been observed, even more than 20 years after implantation. It is still, however, susceptible to mechanical fatigue, especially in the thin-walled ePTFE form. PET is not as inert as PTFE and can be susceptible to chemical attack and hydrolysis[1].

Apart from the material itself damage done to the graft before or during the implantation is very important for the long-term durability. Damage can be done either during the processing of the graft or during surgery. Flaws that are produced in that way can seriously endanger the stability of the graft[1].

Chapter 9: Prospective Arterial Grafts

9.1. Polyurethane:

Over the past decade there has been increasing interest in the development of small diameter arterial prostheses. Much of the research effort has concentrated on the development of *elastomeric* polymers, since they offer a good opportunity to match the elastic properties of biological arteries. *Polyurethane* (*PU*) elastomers have been the focus of many researchers. They are synthesized from an *aliphatic diol*, the *"soft segment"*, and a *methylene diphenyl-diisocyanate* and chain extender to form the *"hard segment"*. They can be easily modified by changing the concentrations of the hard and soft segments. Over the last 20 years they have been prepared as solid materials and as micoroporous structures with either open or closed pores. PU elastomers have high mechanical compliance, superior suture pullout strength and little tendency to dilate. Compared with other polymers used for cardiovascular implants, PUs have demonstrated during in vitro investigations that they possess highly attractive chemical and mechanical properties for use as vascular prostheses. Their in vivo patency rates, however, have varied and are therefore less certain[26,27,28,29)].

9.2. Silicone Rubber:

A second elastomer that seems to be very promising for small vessel replacement is *silicone rubber*. Replamineform silicone rubber prostheses can be fabricated to exactly match the compliance of the artery they are anatomosed to. Tests have shown that they also remain equal in compliance to the artery after implantation as they are encapsulated only by a thin fibrous membrane. Silicone rubber furthermore exhibits excellent suture retention in addition to some other desirable physical characteristics[12,30)].

9.3. Composite Materials:

The mechanoelastic properties of arteries are actually *anisotropic*. A new concept to match these anisotropic properties is the use of *composite materials*. A new family of synthetic composite materials for biomedical prostheses is based on the technique of *filament-winding*. A basic feature of this technique is its ability to produce a two-phase structure of continuous fiber-reinforced polymeric matrix, shaped like a mandrel. This

structure offers a number of advantages over common synthetic soft prostheses, for example better control of the mechanical properties and closer match with anisotropic properties of native tissues, as well as more degrees of design freedom with respect to pore size, biodegradability, and biocompatibility[31].

Chapter 10: Conclusion

At the moment none of the materials that are in clinical use as arterial prostheses matches the requirements for an ideal arterial graft. The momentarily best solution for replacement of small to medium-sized vessels is the autogenous greater saphenous vein. This graft has the problem of rapid aging, which can lead to occlusion of the prosthesis. It would furthermore be nice if this solution could be replaced by a synthetic material, since the autogenous graft has to be harvested from the patient himself, necessitating the surgical removal of a healthy vein.

So far the best materials for replacement of large to medium-sized arteries are PTFE and PET. The most serious problems that grafts made from these materials still have is a lack of thromboresistance and a compliance mismatch to the artery they are anastomosed to, which prevents their use for replacement of smaller arteries. Further problems that occasionally occur are infections and structural failure of the graft.

The solutions to these problems clearly lie in the field of the biomaterials. The mechanoelastic properties of the graft material for example are one of the keys to the problem of compliance mismatch. The compliance is furthermore a function of the way the graft is incorporated by the surrounding tissue, which can be controlled by the used material and its microstructure, i.e. its porosity. The important feature to solve the lack of thromboresistance is the surface of the graft material, which can be altered by means of materials science.

The answer to the question of this paper's title is therefore clearly a "yes": biomaterials are the limiting factor in the progress of arterial prostheses.

References:

1) G.W. HASTINGS (Editor): *Cardiovascular Biomaterials*; Springer Verlag; London, Berlin, New York; 1992
2) J.M. GIORDANO, H.H. TROUT,III, and R.G. DEPALMA: *The Basic Science of Vascular Surgery*; Futura Publishing Company; New York; 1988
3) C.R. LEESON, T.S. LEESON, and A.A. PAPARO: *Textbook of Histology*; Fifth Edition; W.B. Saunders Company; Philadelphia; 1985
4) A.W. HAM and D.H. CORMACK: *Histology*; Eighth Edition; J.B. Lippincott Company; Philadelphia; 1979
5) S.R. BURKE: *Human Anatomy and Physiology in Health and Disease*; Third Edition; Delmar Publishers Inc.; Albany; 1992
6) H. SHELDON: *Boyd's Introduction to the Study of Disease*; Ninth Edition; Lea & Febiger; Philadelphia; 1984
7) M.H. ROSS and E.J. REITH: *Histology - A Text and Atlas*; J.B. Lippincott Company; New York; 1985
8) L. WEISS: *The Blood Cells and Hematopoietic Tissues*; Second Edition; Elsevier; New York; 1984
9) S.A. FRIEDMAN (Editor): *Vascular Diseases - A Concise Guide to Diagnosis, Management, Pathogenesis, and Prevention*; John Wright, PSG Inc.; London; 1982
10) R.J. YOUNG and P.A. LOVELL: *Introduction to Polymers*; Second Edition; Chapman & Hall; London; 1994
11) R. GUIDOIN, N. CHAKFÉ, S. MAUREL, T. HOW, M. BATT, M. MAROIS, and C. GOSSELIN: "Expanded Polytetrafluoroethylene Arterial Prostheses in Humans: Histopathological Study of 298 Surgically Excised Grafts"; *Biomaterials*; Vol. 14; No. 9; pp. 678-693; 1993
12) R.A. WHITE: "The Effect of Porosity and Biomaterial on the Healing and Long-term Mechanical Properties of Vascular Prostheses"; *ASAIO Transactions*; Vol. 34; pp. 95-100; 1988
13) F.J. SCHOEN: "Biomaterials Science, Medical Devices, and Artificial Organs - Synergistic Interactions for the 1990's"; *ASAIO Transactions*; Vol. 37; pp. 44-48; 1991
14) D. COHN, Z. ELCHAI, B. GERSHON, M. KARCK, G. LAZAROVICI, J. SELA, M. CHANDRA, G. MAROM, and G. URETZKY: "Introducing a Selectively Biodegradable Filament Wound Arterial Prosthesis: A Short-term Implantation Study"; *Journal of Biomedical Materials Research*; Vol. 26; pp. 1185-1204; 1992
15) J.C.A. DE MOL VAN OTTERLOO, J.H. VAN BOCKEL, E.D. PONFOORT, P.J. VAN DEN AKKER, J. HERMANS, and J.L. TERPSTRA: "Randomized Study on the Effect of Collagen Impregnation of knitted Dacron® Velour Aortoiliac Prostheses on Blood Loss During Aortic Reconstruction"; *British Journal of Surgery*; Vol. 78; pp. 288-292; March 1991
16) J.C.A. DE MOL VAN OTTERLOO, J.H. VAN BOCKEL, E.D. PONFOORT, E.J.P. BROMMER, J. HERMANS, and M.R. DAHA: "The Effects of Aortic Reconstruction and Collagen Impregnation of Dacron Prostheses on the Complement System"; *Journal of Vascular Surgery*; Vol. 16; No. 5; pp. 774-783; November 1992
17) G. JANVIER, J. CAIX, L. BORDENAVE, P. REVEL, C. BAQUEY, and D. DUCASSOU: "An Ex Vivo Original Test Using Radiotracers For Evaluating Haemocompatibility of Tubular Biomaterials"; *Applied Radiation and Isotopes*; Vol. 45; No. 2; pp. 207-218; 1994

18) D.A. PANKOWSKY, N.P. ZIATS, N.S. TOPHAM, O.D. RATNOFF, and J.M. ANDERSON: "Morphologic Characteristics of Adsorbed Human Plasma Proteins on Vascular Grafts and Biomaterials"; *Journal of Vascular Surgery*; Vol. 11; No. 4; pp. 599-606; April 1990

19) C.V. BENSEN, R.D. VANN, K.E. KOGER, and B. KLITZMAN: "Quantification of Gas Denucleation and Thrombogenicity of Vascular Grafts"; *Journal of Biomedical Materials Research*; Vol. 25; pp. 373-386; 1991

20) R.D. VANN, E.F. RITTER, M.D. PLUNKETT, C.W. WYBLE (Jr.), C.V. BENSEN, W.A. GERTH, W.J. BARWICK, and B. KLITZMAN: "Patency and Blood Flow in Gas Denucleated Arterial Prostheses"; *Journal of Biomedical Materials Research*; Vol. 27; pp. 493-498; 1993

21) G. PASQUINELLI, A. FREYRIE, P. PREDA, T. CURTI, M. D'ADDATO, and R. LASCHI: "Healing of Prosthetic Arterial Grafts"; *Scanning Microscopy*; Vol. 4; No. 2; pp. 351-362; 1990

22) J.P. MAZZUCOTELLI, J.L. ROUDIÈRE, F. BERNEX, P. BERTRAND, J. LÉANDRI, and D. LOISANCE: "A New Device for Endothelial Cell Seeding of a Small-Caliber Vascular Prosthesis"; *Artificial Organs*; Vol. 17; No. 9; pp. 787-790; 1993

23) A. SCHNEIDER, R.N. MELMED, H. SCHWALB, M. KARCK, I. VLODAVSKY, and G. URETZKY: "An Improved Method for Endothelial Cell Seeding on Polytetrafluoroethylene Small Caliber Vascular Grafts"; *Journal of Vascular Surgery*; Vol. 15; No. 4; pp. 649-656; April 1992

24) D.N. SCHWARTZ, S.D. FIHN, and R.A. MILLER: "Infection of an Arterial Prosthesis as the Presenting Manifestation of Disseminated Coccidioidomycosis: Control of Disease with Fluconazole"; *Clinical Infectious Diseases*; Vol. 16; pp. 486-488; April 1993

25) C.K. OZAKI, M.D. PHANEUF, M.J. BIDE, W.C. QUIST, J.M. ALESSI, and F.W. LOGERFO: "In Vivo Testing of an Infection-Resistant Vascular Graft Material"; *Journal of Surgical Research*; Vol. 55; No. 5; pp. 543-547; November 1993

26) R. GUIDOIN, M. SIGOT, M. KING, and M.-F. SIGOT-LUIZARD: "Biocompatibility of the Vascugraft®: Evaluation of a Novel Polyester Urethane Vascular Substitute by an Organotypic Culture Technique"; *Biomaterials*; Vol. 13; No. 5; pp. 281-288; 1992

27) Z. ZHANG, M.W. KING, R. GUIDOIN, M. THERRIEN, M. PEZOLET, A. ADNOT, P. UKPABI, and M.H. VANTAL: "Morphological, Physical and Chemical Evaluation of the Vascugraft®: Comparison of a Novel Polyurethane Device with other Microporous Structures"; *Biomaterials*; Vol. 15; No. 7; pp. 483-501; 1994

28) A. TAKAHARA, J.-I. TASHITA, T. KAJIYAMA, and M. TAKAYANAGI: "Effect of Aggregation State of Hard Segment in Segmented Poly(urethaneureas) on their Fatigue Behavior after Interaction with Blood Components"; *Journal of Biomedical Materials Research*; Vol. 19; pp. 13-34; 1985

29) H. YOSHIDA, K. YASUDA, and T. TANABE: "New Approach to Aortic Dissection: Development of an Insertable Aortic Prosthesis"; *Annals of Thoracic Surgery*; Vol. 58; pp. 806-810; 1994

30) R.L. WHALEN, R.R. CARDONA, and A. KANTROWITZ: "A New, All Silicone Rubber Small Vessel Prosthesis"; *ASAIO Journal*; Vol. 38; pp. M207-M212; 1992

31) B. GERSHON, D. COHN, and G. MAROM: "Compliance and Ultimate Strength of Composite Arterial Prostheses"; Biomaterials; Vol. 13; No. 1; pp. 38-43; 1992