Chapter 1

Introduction and Objectives of the Thesis

Abstract

In the general introduction the classification for medical applied biomaterials with the focus on vascular grafts and surgical sutures is discussed. The complex process of infection in particular post-operative infections, neuronal infections and medical device-associated infections are highlighted. Biofilm formation on the surface of biomaterials and the associated increase of antibiotic and host immune resistance is a challenge for patients and physicians. Graft explantation and the pre-, peri and postoperative administration of antibiotics and antiseptics is the common procedure for implant infection therapy. The utilization of devices as drug delivery systems is described. Furthermore biocompatible and haemocompatible requirements for devices are specified. Various new approaches for the prevention and on demand therapy of implant infections are presented in Chapter 1.

Keywords: Biomaterials, vascular grafts, surgical sutures, biofilm, infection

1 Introduction

In 1986 the European Society for Biomaterials, realizing that terms in this very interdisciplinary field of science are often being confused, organized a congress with the aim of harmonizing the terminology of "Definitions in Biomaterials". According to these definitions, a **prosthesis** is a device that "replaces, in part or in whole, the function of one of the organs of the body". An **implant** is named as "any medical device made from one or more materials that is intentionally placed within the body, either totally or partially buried beneath an epithelial surface". A **biomaterial** is defined as a "non-viable material, used in a medical device, intended to interact with biological systems" (107).

Biomaterials have accompanied human life since early civilizations. While the Mayan people used nacre teeth from sea shells in 600 A.D. (76), an iron dental implant four hundred years later was found in a corps dated 200 A.D. in Europe (22). Particular sutures were manufactured and applied for thousands of years (1).

A reasonable chronological classification of modern biomaterials is the allocation into first-generation, second-generation and third-generation biomaterials. The declared goal of all developed biomaterials of the first-generation during the 1960s and 1970s was to "achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response in the host" (47). The requirements for the second-generation during the 1980s and 1990s shifted from a bioinert tissue response to "instead producing bioactive components that could elicit a controlled action and reaction in the physiological environment" (49). This new mindset to utilize the biomaterial rather than to hide it, opened up new vistas in the interaction of foreign material with the biological system of the host. The compositions of a great variety of bioactive glasses, ceramics or glass ceramics reached clinical use in the mid-1980s in orthopaedic and dental applications. Bioactive glasses (composed of Na_2O-CaO-P_2O_5.SiO_2) for instance were demonstrated to cause a sequence of 11 reaction steps in the creation of a strong bond between tissue and biomaterial surface finally resulting in a formation of new bone (46). The development of resorbable biomaterials with a defined chemical breakdown and resorption marked another progress in this second-generation of biomaterials. This innovation solves the interface problem, as the regenerating tissue replaces the foreign material and provides a basis for the application of controlled-release drug delivery systems. Biodegradable sutures consisting of a composition of polylactide and polyglycolic acid as well as resorbable screws or fracture plates became an important pillar in wound management and orthopaedic treatment (43).

However the irrevocable success of first and second generation biomaterials cannot hide the fact that the clinical application of bioinert, bioactive and resorbable biomaterials is connected with many problems. The endurance for instance of skeletal prostheses and artificial heart valves is limited to 10 to 25 years (50, 89, 109) and already small improvements of failure rates require an enormous financial and experimental effort (50). This limitation, based on the fact that synthetic materials, in contrast to living tissues, can never respond to changing physiological loads or biochemical stimuli, has directed the focus of interest toward a more biological solution for a new generation of biomaterials.

The declared aim of third-generation biomaterials is the stimulation of specific cellular responses at the molecular level. The originally separately considered approaches of bioactive materials and resorbable materials have been combined and transferred to the cellular level. The inducement of cell proliferation, differentiation or gene activation in order to stimulate tissue regeneration is the target of third-generation resorbable materials such as polymers, alloys or bioactive glasses (48). Thereby two concepts are tracked, the *tissue engineering* and *in situ tissue regeneration*. For *tissue engineering,* biomaterial surfaces are modified outside the body with cellular networks imitating naturally occurring tissue and implanted into the patient. The scaffolds are resorbed and replaced by a fully functionalized host tissue.

For *in situ tissue regeneration,* biomaterials are thought to release biological active drugs like for example growth factors to stimulate tissue regeneration inside the body.

However coming along with innovations and new ideas in the field of biomaterials, it is obvious that only an effective cooperation between the different disciplines of science and a yielding dialogue between physicians, engineers and natural scientists will not only result in fruitful concepts but also in realizable products for future implants and will help patients to regain a better quality of life.

2 Biomaterials

2.1 Vascular grafts

Biomaterials applied in the cardiovascular system, the so-called cardiovascular medical devices, play a key role in the life-saving treatment of patients. Particularly the enhancement of survival, besides an improvement of quality of life, makes them unique among all other medical devices. Cardiovascular medical devices include a broad spectrum of devices from heart valves,

pacemakers, implantable cardioverter-defibrillators, cardiac assist and replacement devices to the area of stents and vascular grafts.

Reconstructive vascular surgery dates back to the nineteenth century when the first animal experiments were carried out testing different sewing techniques and vascular replacements using aluminium, silver, glass or Lucite® tubes (9, 62). These experiments paved the way for the first surgical intervention in a human being in 1897 by the american surgeon John B. Murphy who redissected a traumatized femoralis segment and reconstructed the vessel via a special sewing technique (9).

In contemporary vascular surgery, the application of autogenous, allogenous, xenogenous or alloplastic vascular replacements is standard practice. The accidental observation of a pseudointima formation around a silk suture gave the impulse to develop vascular grafts out of alloplastic material (104). The requirement of biological indifference and porosity led to the invention of a pool of different biocompatible alloplastic grafts consisting of materials like Nylon®, Orlon®, Ivalon®, Marlex®, Teflon® and Dacron® (24, 106).

Teflon® (Polytetrafluoroethylene) and Dacron® (Polyethylenterephtalate) showed the most suitable and superior properties (42) and represent the gold standard of synthetic vascular grafts nowadays. Variations of the texture (knitted or woven) and unilateral or bilateral velour trimming, as well as crimping and the invention of expanded PTFE (ePTFE), improved the physiological characteristics of alloplastic grafts (27). While Dacron® prostheses are more commonly used for “larger vessel applications”, Teflon® grafts are preferred to bypass “smaller vessels” (up to 4 mm diameter) leaving the decision of size to the surgeon`s discretion (76). Before application, porous alloplastic Dacron® grafts are impregnated with connective tissue proteins or preclotted with the patient`s blood in order to reduce blood loss, aid clotting and stimulate tissue ingrowth.

After implantation the inner surface of a vascular graft becomes covered with a so-called pseudointima developed from the interaction of plasma proteins, in particular fibrinogen, and thrombocytes aggregating into a platelet-fibrin layer. A neointima is formed when endothelial cells cover this layer (Figure 1). This desirable as nonthrombogenic formation of a neointima is unfortunately limited to a small area adjacent to the anastomosis, nevertheless efforts are being made in the area of tissue engineering to find solutions (72).

From the outside, the surrounding connective tissue encapsulates the vascular graft within normal tissue and develops a foreign-body reaction. The exterior surface is mantled with giant cells covered by a mixture of collagen, fibroblasts, extracellular and cellular tissue elements as well as blood vessels (76).

The great advantages of alloplastic vascular grafts such as short operation times, availability of each required size and large numbers as well as facile operation techniques, are overshadowed by several unsatisfying observations. The short-term and long-term patency is dependant on the size of interposition, the graft diameter and the flow resistance in such a way that an increase in interposition size and a decrease of vessel diameter, associated with an increase in resistance to flow, leads to a decrease in both the short-term and long-term patency rates. Five to ten years patency rates of 90 % for grafts used for aortofemoral bypass are reduced to 50 % for small vascular grafts (< 8 mm diameter) (17). The common most frequently occurring complications of vascular grafts are thrombosis, thromboembolism, periprosthetic fluid collection, pseudoaneurysm, intima hyperplasia, structural degeneration and infection. The problem of infection of PTFE grafts will be elaborated in chapter 3.2.

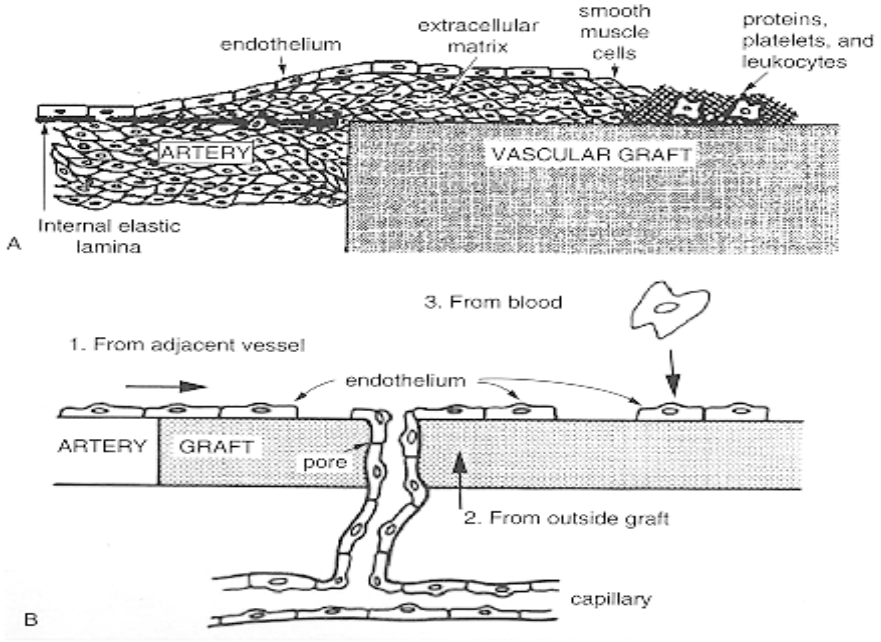

Figure 1. Vascular graft healing. A) Pannus formation, smooth muscle cells migrate from the media to the intima of the adjacent artery and proliferate on the graft surface. B) Possible sources of endothelium on the blood-contacting surface of the vascular graft (76).