Biocompatibility of Materials in Medical Devices

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Advanced Article

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Medical devices are used for a variety of functions in humans. This review elaborates on the types of tests used to evaluate biocompatibility of the interactions between man-made medical devices and host tissues and organs. The outcome of the response depends on the site of implantation, the species of the host, the genetic makeup of the host, the sterility of the implant, and the effect the device has on biological processes. Biological processes involved in host tissue responses to implantable medical devices reflect activation of a series of cascades that require blood proteins or other components found in the blood.

Two types of regulatory approvals for medical devices exist in the United States, 510(k) notification and premarket approval (PMA). The specific tests required prior to regulatory approval vary with the type of device and application; however, some general testing is usually recommended. Normally, animal testing is conducted to demonstrate that a medical device is safe, and when implanted in humans the device will reduce, alleviate, or eliminate the possibility of adverse medical reactions or conditions. The American Society for Testing and Materials (ASTM) as well as the International Organization for Standardization (ISO) publishes standards for testing medical devices. The recommended tests include culture cytotoxicity, skin irritation, short-term intramuscular implantation, short-term subcutaneous implantation, blood coagulation, long-term implantation, mucous membrane irritation, systemic injection, sensitization assays, and mutagenicity testing.

Introduction—What Are Medical Devices?

Medical devices are used for a variety of functions from promoting the healing of small wounds using adhesive bandages to maintaining the flow of blood through arteries narrowed by atherosclerosis using metallic vascular stents. The purpose of this article is not to give an overview of the many devices used in medicine to promote wellness and homeostasis but to elaborate on the types of tests used to evaluate the interactions between man-made devices and host tissues and organs. These man-made devices are called medical devices in the United States and are regulated for interstate distribution by the Federal Food and Drug Administration (FDA). In many cases, medical devices consist of assemblies of polymers, metals, ceramics, and composites that are used in diagnostic procedures and as implants in animals and in humans. In the United States, extensive biocompatibility testing occurs before the devices are marketed to the general public. Prior to 1976, no federal regulations existed to oversee the sale and uses of medical devices in the United States. In 1976, the U.S. Congress enacted the Medical Device Amendments to the Federal, Food, Drug, and Cosmetic Act of 1938, which called for the establishment of three classes of medical devices (**Table 1a**). Class 1 devices are those that present little or no risk to the user, whereas Class 2 and 3 devices present some risk and a high degree of risk to the user, respectively. These devices are regulated by requiring limited animal testing (Class 2) and extensive animal and human testing (Class 3). The European Union has a system of device classification similar to the United States as recognized by the Medical Device Directive (**Table 1b**).

The term biocompatible is used widely to infer that an implant is safe for use in the general population. Although this term is used broadly, it may be a misnomer because only materials that are found in living tissues are truly biocompatible. Below, we examine what methods are used to evaluate the biocompatibility of materials used in medical devices.

Biocompatibility—What Is Does it Mean?

The word biocompatibility is a relative term that means that the materials used in a medical device do not elicit a reaction that either 1) makes the device not perform its intended use or 2) causes reactions that affect the functioning and health of

Table 1a Classifications of medical devices marketed in the united states

Class	Type of device	FDA filing required
I	Crutches, bedpans, depressors, adhesive bandages, hospital beds	PMN/510K
II	Hearing aids, blood pumps, catheters contact lens, electrodes	510(k)
III	Cardiac pacemakers, intrauterine devices, intraocular lens, heart valves, orthopedic devices	PMA

PMN, premarket notification.

Table 1b Classifications of medical devices of the european union

Class	Type of device	Regulatory requirements
I	Stethoscopes, hospital beds, wheelchairs	Technical file, other assurances
IIa	Hearing aids, electrographs, ultrasound assessment equipment	Technical file, conformity
IIb	Surgical lasers, infusion pumps, ventilators Intensive care monitoring equipment	Technical file, type examination
III	Balloon catheters, heart valves	Audit of quality assurance, examination of design

the host. All materials used in devices will elicit a response from the host; it could be an immediate response, one that is prolonged, or even a delayed reaction that occurs sometime after contact with the device. The outcome of the response depends on the site of implantation, the species of the host, the genetic makeup of the host, and the sterility of the implant. All implants have a significantly greater rate of infection when compared with the background rate associated with the surgical procedure performed in the absence of the device. At the very least, an implant should not interfere with biological processes that are required for normal homeostasis of the host.

Biological Systems—Which Ones Are Important for Normal Homeostasis and Survival?

Devices in contact with the external tissues such as skin typically are considered separately from a biocompatibility perspective from devices implanted internally. Implantable devices affect biological processes that involve blood; therefore, the testing of these devices is somewhat more complicated. Many skin contact devices are used short term, and therefore biocompatibility testing is limited. However, for permanent internal implants, the required testing can be as long as several years and require analysis of the effects of the device on cells and tissues as well as on healing responses that occur at the interface between the tissue and the device. For this reason, it is important to understand which biological systems may be affected when permanent implants are to be used.

Biological processes involved in host-tissue responses to implantable medical devices reflect the activation of a series of cascades that require blood proteins or other components found in blood. Biological systems activated by implants include blood clotting, platelet aggregation, complement activation, kinin formation, fibrinolysis, phagocytosis, immune responses, and wound healing (1) (**Table 2**). Wound healing involves several biological processes, including blood clotting, inflammation, dilation of neighboring blood vessels, accumulation of blood cells and fluid at the point of contact, and finally deposition of fibrous tissue around an implant. Vasodilation of blood vessels and accumulation of interstitial fluid around an implant can occur through activation of the kinin and complement pathways (1). Phagocytosis of dead tissue occurs by attraction and migration of inflammatory cells to the site of injury near an implant. The inflammatory cells attracted include neutrophils and monocytes that are present to digest dead tissue and implant materials. Once phagocytosis occurs, it may lead to digestion of implant remnants and formation of fibrous scar tissue around the implant. If a large blood clot surrounds an implant, then fibrinolysis must proceed to remove the clotted blood before the healing process can be completed (1).

Blood proteins are involved in the lysis of foreign cells via the complement pathway (1). This mechanism involves activation of complement proteins in the presence of an antibody–antigen complex attached to the surface of a foreign cell. Components of the complement pathway are sometimes compromised by activation and/or adsorption onto the surface of a medical device. This action leads to complement component depletion that causes the patient to be at risk for bacterial infection and makes evaluation of complement depletion an important aspect of the

Table 2 Biological systems affected by medical devices (1)

System	Function	Device effect
Blood clotting	Maintains blood fluidity	Clot formation-occlusion
Complement	Prevents bacterial invasion	Depletes complement
Fibrinolysis	Degrades blood clots	Degrades tissue grafts
Immune responses	Limits infection	Prolongs inflammation
Kinin formation	Causes vasodilation	Prolongs inflammation
Platelet aggregation	Limits bleeding	Shortens platelet life
Phagocytosis	Limits infection	Prolongs Inflammation
Wound healing	Repairs tissue defects	Promotes fibrous scar Tissue

design of cardiovascular devices. Activated complement components also prolong inflammation by generating C3a and C5a, which are agents that cause vasodilation. Complement activation is associated with and contributes to whole-body inflammation, which is observed as a complication to cardiopulmonary bypass. Complement activation is responsible for hyperacute rejection of animal tissue grafts (2) and is important in reactions to implants (3–5).

Most foreign surfaces cause blood to clot as a result of direct contact with a foreign surface. This clotting occurs via the intrinsic clotting cascade or from injury to tissue that develops during implantation as result of activation of Hageman factor and factor IX, which are two proteins found in blood (**Table 2**). Platelets, which are enucleated cells, are also found in blood; they release factors that contribute to formation of blood clots. Devices used in the cardiovascular system normally are designed to limit their propensity to clot blood. In the case of cardiovascular devices, excessive blood clotting will cause the device to occlude; in these applications, blood clotting is minimized. Because foreign materials typically cause blood clots, they are only used to replace large and medium-sized vessels. Host vessels are used to replace the function of small-diameter vessels. Several tests are used to measure blood clotting and platelet aggregation caused by contact with a medical device (6–8).

In addition to activating blood clotting (9), activated Hageman factor activates prekallikrein of the kinin system, which leads to bradykinin that causes vascular vasodilation. Activation of Hageman factor and blood clotting also leads to the conversion of plasminogen to plasmin which initiates the degradation of fibrin formed during clotting by a process termed fibrinolysis (1).

Phagocytic cells including neutrophils and macrophages, coat medical devices either from direct blood contact or via inflammation and extravascular movement of these cells into the tissue fluids that surround a device. In either situation, first neutrophils and then monocytes arrive in the area around the device and attempt to degrade the implant. If the implant is biodegradable, then these cells remain until the device is totally removed. If the device is nondegradable, then the number of cells surrounding an implant will depend on the how reactive the implant is. For example, although Dacron vascular grafts are permanent devices, monocytes can be observed surrounding the implant for months and years. In some patients, continued reactivity can cause peri-implant fluid accumulation, which if left uncorrected can require implant removal. In other cases where contact of tissue with the implant causes a prolonged inflammatory response, other white blood cells including eosinophils, B cells, and T cells can be observed in the vicinity of the device. These cells are an indication of either an allergic reaction or the formation of antibodies that stimulate prolonged inflammation. Measurement of inflammatory cells surrounding an implant is usually accomplished by direct histological evaluation (10–12).

As phagocytic cells accumulate near the implant, they elaborate hydrolytic enzymes that degrade both the implant and the surrounding tissues; fibroblasts and endothelial cells are also migrating into the area around the device and begin to lay down new extracellular matrix with capillaries and collagen fibrils (1). Thus, the wound healing process involves inflammation, removal of the implant and tissue components, as well as the deposition of new extracellular matrix. If the implant is nondegradable and nonporous, then a fibrous capsule forms around it. The thickness of the fibrous capsule depends on the degree of inflammation caused by the device. If the implant is porous, the device may biodegrade and lead to the formation of a small amount of fibrous scar tissue in the defect when the implant is removed. In some cases, however, after the implant biodegrades, an abundance of scar tissue can be deposited where the implant was previously observed. The thickness of the fibrous capsule formed around an implant is usually measured histologically.

Wear particles generated by a moving device can lead to prolonged inflammation and even implant failure in the case of hip and knee implants. Small polymeric or metallic particles, which are about 1 μm in diameter, are ingested by neutrophils and monocytes and may lead to necrosis of these cells and the release of inflammatory mediators into the wound area. Large particles are surrounded by monocytes, which form multinucleated giant cells that can in many cases be tolerated by tissues

without leading to implant failure. However, once wear particles are released from the implant, they can migrate to other tissues or even to local lymph nodes causing swelling and systemic problems. Implant wear particles are quantitatively determined from histological and electron-microscopic studies (13–15).

Types of Tests—What Types of Tests Are Used?

Two types of regulatory approvals exist for medical devices in the United States, 510(k) notification and premarket approval (PMA). The types of tests required for approval depend on the classification of the medical device. 510(k) notification involves marketing a device that is substantially equivalent to a device on the market prior to 1976. All devices introduced after 1976 that are not substantially equivalent to devices on the market before 1976 are automatically classified as Class 3 devices and require PMA (16). For a device to be considered substantially equivalent to a device on the market before 1976, it must have the same intended use, no new technological characteristics, and have the same performance as one or more devices on the market prior to 1976. In addition, all medical devices must be sterilized either by end-sterilization or by some other acceptable means that can be validated, which means that any test done in cell culture or in an animal model must be conducted on a device that has been validated to be sterile. Sterility validation is conducted on all medical devices as described in the literature (17).

The testing conducted on biomaterials intended for use in medical devices must address safety and effectiveness criteria that depend on the intended use as described above as discussed in depth the literature (18, 19). The specific tests required vary with the type of device and application; however, some general testing is usually recommended. Normally, animal testing is conducted to demonstrate that a medical device is safe, and when implanted in humans that the device will reduce, alleviate, or eliminate the possibility of adverse medical reactions or conditions (17).

According to the American Society of Testing Materials (ASTM) Medical Devices Standards (Annual Book of ASTM Standards, Section 13, Medical Devices, ASTM 1916 Race Street, Philadelphia, PA 19103; available at: *www.astm.org*), the type of generic biological test methods for materials and devices depends on the end-use application. The ASTM as well as the International Organization for Standardization (ISO) publishes standards for testing medical devices as listed in **Tables 3** and **4**. Biological reactions that are detrimental to the successful use of a material in one device application may not be applicable to the success of a material in a different end use. A list of potentially applicable biocompatibility tests that are related to the end use of a material and/or a device is given in **Table 3** as a starting point. These tests are as follows:

Cell culture cytotoxicity

This test is used to evaluate the toxicity of a material *in vitro* or an extract of a material used in a device. Several different tests have been used and have produced a spectrum of biocompatibility assessments on the same material (20–22). The tests used measure the viability of cells in contact with a material or an extract of a material. A variety of cell lines can be used; however, a modified fibroblast line is usually the gold standard. Some tests used include 1) direct cell culture, 2) agar diffusion testing, 3) filter diffusion testing, and 4) barrier testing (22).

Table 3 Biological tests used to evaluate biocompatibility based on ASTM medical device standards, section 13

Test	ASTM standard
Cell culture cytotoxicity	F748
Skin irritation	F719
Intramuscular and subcutaneous implant	F748
Blood compatibility	F748
Hemolysis	F756
Carcinogenesis	F748
Long-term implantation	F748
Mucous membrane irritation	F748
Systemic injection acute toxicity	F750
Intracutaneous injection	F749
Sensitization	F720
Mutagenicity	F748
Pyrogenicity	F748

As pointed out by Learmonth (23), although the intact implant may not be cytotoxic to cells, any material and mechanical flexural mismatch may lead to release of wear particles that can excite a cytochemical reaction that culminates in inflammation and cell cytotoxicity. The generation of wear particles and their size is of particular importance to the failure of joint implants through a process termed osteolysis (23).

Skin irritation assay

This test involves applying a patch of the material (or an extract of the material) to an area of an animal that has been shaved; in some cases the skin is abraded before the test material is applied. After 24 hours of contact, the patch is removed, and the skin is graded for redness and swelling. The grading scale can vary from 0 to 4: 0 means no redness and/or swelling and 4 means extensive redness and/or swelling. Standard test materials are used to evaluate skin irritation (24).

Short-term intramuscular implantation

This test is designed to evaluate the reaction of tissue to a device for periods of 7 to 30 days. This test can be conducted in the muscle below the skin in rabbits or rodents including mice, rats, and guinea pigs. At the conclusion of the test period, the samples are graded both visually and based on analysis of histological sections. A test described in the United States Pharmacopia (USP) is widely used. The purpose of this test is to evaluate the inflammatory potential (e.g., redness and swelling) grossly. In some cases, histological evaluation of the tissue is performed at the light and electron microscopic levels to look for phagocytic and immune cells. Some investigators use an

Table 4 Biological evaluation of medical devices based on ISO standards

Test	ISO standard
Part 1: Evaluation and testing	10993-1:2003
Part 2: Animal welfare requirements	10993-2:2006
Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	10993-3:2003
Part 4: Selection of tests for interactions with blood	10993-4:2002
Part 5: Tests for in vitro cytotoxicity	10993-5:1999
Part 6: Tests for local effects after implantation	10993-6:2007
Part 10:Tests for irritation and delayed-type hypersensitivity	10993-10:2002
Part 11:Tests for systemic toxicity	10993-11:2006

intramuscular implantation site because the blood supply and hence the inflammatory potential may be easily evaluated. In addition, the results of short-term implantation tests may not reflect material-mediated inflammatory responses that may also occur (25).

Short-term subcutaneous implantation

This test is an alternative for studying the reaction of tissue to a device for a period of days to weeks. In this test, a tissue pocket is made in the skin above the muscle layer, the device is inserted into the pocket, and the pocket is sutured or stapled closed. Normally the device is placed deep into the pocket away from the site of insertion of the device so that reactions at the suture or clip site do not affect the evaluation of biocompatibility. Although short-term implantation studies do give an analysis of the biocompatibility of a material at a local site; systemic effects can also be observed from corrosion products that develop from vascular implants that migrate to other sites (26).

Blood coagulation

Blood coagulation is normally assessed by determination of clotting times and extent of platelet aggregation initiated by the device surface in either static or dynamic systems. In a dynamic test, blood flows through the device or over a test surface made of the materials used in the device. This test is normally conducted on blood-contacting devices to ensure that the blood-coagulation and platelet-aggregation pathways are not modified. The tests are conducted *in vitro* using human or animal blood, *ex-vivo* in a flow chamber using animal blood, or *in vivo* in an animal model. It has been noted that variability in the results using standard materials is noted in *ex-vivo* tests of blood compatibility; this finding is attributed to the type of animal model used, the flow velocity, the time of exposure, and the method used to measure blood cell adhesion (27). Studies of stents used in the cardiovascular system illustrate that clot or thrombus formation is dependent on the type and design of the device (28, 29) and may be influenced by the corrosion of metallic implants (30).

Hemolysis

Hemolysis is determined by placing powder, rods, or extracts of a material in contact with human or animal plasma for about 90 minutes at 37°C (31). The amount of hemoglobin released into solution after lysis of the red cells in contact with the device is measured. When red cells undergo lysis, hemoglobin is released from the cells, and the absorbance from released hemoglobin is proportional to the amount of cell lysis. Extensive red-cell lysis is not desirable for devices that are to be implanted in the cardiovascular system. The measurement of hemolysis and its relevance is a question that should be addressed it each device application.

Carcinogenicity

Carcinogenicity testing involves long-term implantation (up to 2 years) in an animal model usually under the skin to look for tumor formation (32). This test is required for devices that employ materials that have not been extensively tested. Typically these tests are conducted in rodents, although rodents do form tumors to most solid implants (1).

Long-term implantation tests

These tests are covered by ASTM specifications F361 and F469 for muscle and bone, respectively. Implant materials are placed in the muscle as a soft-tissue model and in bone as a hard-tissue model. The implantation site is evaluated grossly and histologically for inflammation, giant cell formation, signs of implant movement, and for tissue necrosis. Although long-term implantation gives some indication of biocompatibility, it does not consider issues such as biofilm formation, infection, and encrustation associated with use of devices such as urologic implants (33). It is recommended that long-term implantation tests be conducted on a model relevant to the intended end use. In addition, the effect of wear particles is an important consideration with long-term implantation (23).

Mucous membrane irritation

Mucous membrane irritation is evaluated by placing a material in close proximity to a mucous membrane such as the oral mucosa. The test evaluates the amount of irritation and inflammation from gross and histological measurements. The hamster cheek pouch or oral mucosa is a model frequently used for this test (34).

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