CHAPTER 2

Host reactions to Biomaterials and Their Evaluation
Immunologic toxicity to surface medical devices and external communicating devices (dialyzers, laparoscopes, etc.) may represent mechanisms of sensitization and hypersensitive reactions similar to those of orally exposed biomaterials.

Hypersensitivity reactions to implants in clinically inobservable locations are difficult to recognize unless they have dermal or systemic expressions.

In addition, such reactions may be part of local toxic and/or mechanically induced inflammatory reactions using similar mediators for tissue response.

For lack of more distinct descriptions, such reactions have been referred to as “deep tissue” reactions of type IV hypersensitivity.

A vast battery of in vitro and in vivo experimental studies have been performed to study potential adverse effects of biomaterial devices such as artificial joints, heart valves, and breast prostheses.

Aseptic loosening of metallic hip prostheses have been associated with “biologic” causes in addition to biomechanical factors and wear debris.
However, it is currently unclear whether metal sensitivity is a contributing factor to implant failure. In fact, it is argued that the loosening process enhances the immunological sensitization, indicating that the cause/effect relation may be reversed.

What is clear is that local and general eczematous reactions have been observed following the insertion of metallic implants in patients subsequently shown to be allergic to cobalt, chromium, and nickel.

Many case reports also describe the immediate healing of dermal reactions associated with metal implants.

Metal allergy has also been discussed as a possible contributing factor in the development of in-stent coronary restenosis, although there is little evidence for this effect.

However, established metal allergy in a patient does not as a rule seem be accompanied by clinical reactions to implant alloys containing the metal.
• Inhomogeniety or mixture of alloys appear to determine the efflux of potentially hypersensitive metal ions, and hence increase the possibility of eliciting hypersensitive reactions.

• Methyl methacrylate bone cement is another potential allergenic factor in orthopedic surgery parallel with reactions in dentistry and cosmetics, and immune-mediated disease and silicone based implants has been a matter of discussion for some time. However, a scientifically valid cause and effect relationship between immune based disease and silicone based implants has not been established.

• An extensive literature reflects clinical surveys and research activities related to natural latex used as barrier material by the health professions.
  – It is accepted that residual latex proteins and chemicals associated with the production process may cause immediate and delayed reactions in patients and health personnel.
• The FDA testing guidance referred to above also lists other interactions of medical devices, extracts of medical devices, or adjuvants with the immune system such as impairment of the normal immunologic protective mechanisms (immunosuppression), and long-term immunological activity (immunostimulation) that may lead to harmful autoimmune responses.

• The autoimmune reaction is explained by the biomaterials-associated agent acting as an adjuvant that is stimulating to antibody/complement-based tissue damage by cross reactions with human protein.

• Chronic inflammatory, immune-related granuloma may take part in the development of autoimmune reactions.
• Biocompatibility issues related to medical devices form a multidimensional crossroad of technology and biology.

• One dimension is the various classes of biomaterials, such as plastics and other polymers, metals, ceramics, and glasses, depending on expert design to obtain maximal mechanical properties and minimal chemical dissolution.

• Another is the mode of application, ranging from skin and mucosal contact to totally submerged implants, with external communicating devices in between.

• A third dimension is the duration of contact, ranging from minutes to the expected lifetime, and the fourth, and decisive, is the biological reactions that can be expected.

• These circumstances prevent general statements on biomaterials.

• The present overview is aimed at students and limited to focus on collective mechanisms determining systemic toxicity and discuss hypersensitivity reactions documented by clinical reports.
The possibility that implant materials could cause tumors or promote tumor growth has long been a concern of surgeons and biomaterials researchers. This chapter describes general concepts in neoplasia, the association of tumors with implants in human and animals, and the pathobiology of tumor formation adjacent to biomaterials.

**GENERAL CONCEPTS**

- **Neoplasia**, which literally means “new growth,” is the process of excessive and uncontrolled cell proliferation. The new growth is called a neoplasm or tumor (i.e., a swelling, since most neoplasms are expansile, solid masses of abnormal tissue).
- Tumors are either benign (when their pathologic characteristics and clinical behavior are relatively innocent) or malignant (harmful, often deadly).
- **Malignant tumors** are collectively referred to as cancers (derived from the Latin word for crab, to emphasize their obstinate ability to adhere to adjacent structures and spread in many directions simultaneously).
• The characteristics of benign and malignant tumors are summarized in Ch.4.7: Table 1.
• Benign tumors do not penetrate (invade) adjacent tissues, nor do they spread to distant sites.
• They remain localized and surgical excision can be curative in many cases.
• In contrast, malignant tumors have a propensity to invade contiguous tissues.
• Moreover, owing to their ability to gain entrance into blood and lymph vessels, cells from a malignant neoplasm can be transported to distant sites, where subpopulations of malignant cells take up residence, grow, and again invade as satellite tumors (called metastases).
• The primary descriptor of any tumor is its cell or tissue of origin. Benign tumors are identified by the suffix “oma,” which is preceded by reference to the cell or tissue of origin (e.g., adenoma—from an endocrine gland; chondroma—from cartilage).
The malignant counterparts of benign tumors carry similar names, except that the suffix “carcinoma” is applied to cancers derived from epithelium (e.g., squamous or adeno-carcinoma, from protective and glandular epithelia, respectively) and “sarcoma” (e.g., osteo-or chondro-sarcoma, producing bone and cartilage, respective) to those of mesenchymal origin.

Malignant neoplasms of the hematopoietic system, in which the cancerous cells circulate in blood, are called leukemias; solid tumors of lymphoid tissue area called lymphomas.
The major classes of malignant tumors are illustrated in Ch.4.7: Fig. 1. Cancer cells express varying degrees of resemblance to the normal precursor cells from which they derive. Thus, neoplastic growth entails both abnormal cellular proliferation and modification of the structural and functional characteristics of the cell types involved. Malignant cells are generally less differentiated than normal cells. The structural similarity of cancer cells to those of the tissue of origin enables specific diagnosis (source organ and cell type); moreover, the degree of resemblance usually predicts prognosis of the patient (i.e., expected outcome based on biologic behavior of the cancer). Therefore, poorly differentiated tumors generally are more aggressive (i.e., display more malignant behavior) than those that are better differentiated. The degree to which a tumor mimics a normal cell or tissue type is called its grade of differentiation. The extent of spread and other effects on the patient determine its stage.
Neoplastic growth is unregulated. Neoplastic cell proliferation is therefore unrelated to the physiological requirements of the tissue and is unaffected by removal of the stimulus which initially caused it.

These characteristics differentiate neoplasms from
- (1) normal proliferations of cells during fatal development or postnatal growth,
- (2) normal wound healing following an injury, and
- (3) hyperplastic growth that adapts to a physiological need, but that ceases when the stimulus is removed.

All tumors, benign and malignant, have two basic components:
- (1) proliferating neoplastic cells that constitute their parenchyma, and
- (2) supportive stroma made up of connective tissue and blood vessels.

Although the parenchyma of neoplasms is characteristic of the specific cells of origin, the growth and evolution of neoplasms are critically dependent on the nonspecific stroma, usually composed of blood vessels, connective tissue, and inflammatory cells.
Neoplasms occurring at the site of implanted medical devices are unusual, despite the large numbers of implants used clinically over an extended period of time.

Nevertheless, cases of both human and veterinary implant-related tumors have been reported at 1987. In that, more than 50 cases of tumors associated with foreign material have been reported, of which approximately half were adjacent to therapeutic implants.

The remainder include tumors related to bullets, shrapnel, other metal fragments, sutures, bone wax, and surgical sponge.

Implant-related tumors have been reported both short and long term following implantation. More than 25% of tumors associated with foreign bodies have developed within 15 years, and more than 50% within 25 years.

The vast majority of malignant neoplasms associated with clinical fracture fixation devices, total joint replacements, mechanical heart valves, and vascular grafts and experimental foreign bodies in both animals and humans are sarcomas.
They comprise various histologic subtypes, including fibrosarcoma, osteosarcoma (osteogenic sarcoma), chondrosarcoma, and angiosarcoma, and are characterized by rapid and locally infiltrative growth.

Carcinomas, reported far less frequently, have usually been restricted to situations where an implant has been placed in the lumen of an epithelium-lined organ.

Illustrative reported cases are noted in Ch.4.7: Table 2. Lymphomas have been reported in association with the capsules surrounding breast. A tumor forming adjacent to a clinical vascular graft is illustrated in Ch.4.7: Fig. 2.

A non-implant-related primary tumor (gastric cancer) with a metastasis to a total knee replacement has also been reported.

Whether there is a causal role for implanted medical devices in local or distant malignancy remains controversial.

In an individual case, caution is necessary in implicating the implant in the formation of a neoplasm; demonstration of a tumor occurring adjacent to an implant does not necessarily prove that the implant caused the tumor.
Large-scale epidemiological studies and reviews of available data have concluded that there is no evidence in humans for tumorigenecity of non-metallic and metallic surgical implants.

Indeed, the risk in populations must be low, as exemplified by recent cohorts of patients with both total hip replacement and breast implants who show no detectable increases in tumors at the implant site.

A clinical and experimental study even suggested that the evidence of breast carcinoma may be decreased in women with breast implants.

However, one study suggested a small increase in the number of lung and vulvar cancers in patients with breast implants. Importantly, the presence of an implant does not impair the diagnosis of breast cancer.

Moreover, neoplasms are common in both humans and animals and can occur naturally at the sites at which biomaterials are implanted.

Most clinical veterinary cases have been observed in dogs, a species with a relatively high natural frequency of osteosarcoma and other tumors at sites where orthopedic devices are implanted.
Moreover, spontaneous human musculoskeletal tumors are not unusual.
However, since sarcomas arising in the aorta and other large arteries are rare, the association of primary vascular malignancies with clinical polymeric grafts may be stronger than that with orthopedic devices.
Clinically benign but exuberant foreign-body reactions may simulate neoplasms. For example, fibrohistiocytic lesions resembling malignant tumors may occur as a reaction to silica, previously injected as a soft-tissue sclerosing agent.
Moreover, regional lymphadenopathy (i.e., enlargement of lymph nodes) may result from an exuberant foreign-body reaction to material that has migrated from a prosthesis.
This has been documented in cases of silicone emanating from both finger joints and breast prostheses, as well as in association with conventional metallic, ceramic, and polymeric replacements of the temporomandibular joint and large joints.
A mass lesion caused by foreign-body granuloma in a lymph node can masquerade as a neoplasm on physical examination (sometimes called a pseudotumor). Potentially, it could evolve into a lymphoma owing to chronic stimulation of the immune system.
Considerable progress has made over the past several decades in the understanding of the molecular basis of cancer.

Four principles are fundamental and well accepted:

1. Neoplasia is associated with and often results from nonlethal genetic damage (or mutation), either inherited or acquired by the action of environmental agents such as physical effects (e.g., radiation, fibers or foreign bodies), chemicals or viruses.

2. The principal targets of the genetic damage are cellular regulatory genes (normally present and necessary for physiologic cell function, inducing cellular replication, growth and repair of damaged DNA).

3. The tumor mass evolves from the clonal expansion of a single progenitor cell that has incurred the genetic damage.

4. Tumorigenesis is a multistep process, generally owing to accumulation of successive genetic lesions.

PATHOBIOLOGY OF FOREIGN BODY TUMORIGENESIS
After a tumor has been initiated, the most important factors in its growth are the kinetics (i.e., balance of replication or loss) of cell number change and its blood supply.

The formation of new vessels (angiogenesis) is essential for enlargement of tumors and for their access to the vasculature and, hence, metastasis.

The pathogenesis of implant-induced tumors is not well understood, yet most experimental data indicate that physical effects rather than the chemical characteristics of the foreign body are the principal determinants of tumorigenicity.

Tumors are induced experimentally by a wide array of materials of diverse composition, including those that could be considered essentially nonreactive, such as certain glasses, gold or platinum, and other relatively pure metals and polymers.

Indeed, one surgeon performed a much-maligned experiment in which dimes inserted in rats yielded a rate of 60% sarcomas in 16 months (prompting the suggestion that dimes and probably all metallic coins were carcinogenic and should be discontinued!).
• Solid materials implanted in a configuration with high surface area are most tumorigenic.
• Materials lose their tumorigenicity when implanted in pulverized, finely shredded or woven form, or when surface continuity is interrupted by multiple perforations.
• This trend is often called the Oppenheimer effect.
• Thus, foreign-body neoplasia is generally considered to be a transformation process mediated by the physical state of implants, it is largely independent of the composition of the materials, unless specific carcinogens are present.
• Solid-state tumorigenesis depends on the development of a fibrous capsule around the implant.
• Tumorigenicity corresponds directly to the extent and maturity of tissue encapsulation of a foreign body and inversely with the degree of active cellular inflammation.
• Thus, an active, persistent inflammatory response inhibits tumor formation in experimental systems.
Host (especially genetic) factors also affect the propensity to form tumors as a response to foreign bodies.

Humans are less susceptible to foreign-body tumorigenesis than are rodents, the usual experimental model. In rodent systems, tumor frequency and latency depend on species, strain, sex, and age.

Concern has recently been raised over the possibility that foreign-body neoplasia can be induced by the release of wear debris or needlelike elements from composites in a mechanism that is analogous to that of asbestos-related mesothelioma.

However, animal experiments suggest only particles with very high length-to-diameter ratios (>100) produce this effect.

Particles with this high aspect ratio are highly unlikely to arise as wear debris from orthopedic implants. Nevertheless, cancer at foreign-body sites may be mechanistically related to that which occurs in diseases in which tissue fibrosis is a prominent characteristic, including asbestosis (i.e., lung damage caused by chronic inhalation of asbestos), lung or liver scarring, or chronic bone infections.
• However, in contrast to the mesenchymal origin of most implant-related tumors, other cancers associated with scarring are generally derived from adjacent epithelial structures (e.g., mesothelioma with asbestos).

• Chemical induction effects are also possible. With orthopedic implants, the stimulus for tumorigenesis could be metal particulates released by wear of the implant.

• Indeed, implants of chromium, nickel, cobalt, and some of their compounds, either as foils or debris, are carcinogenic in rodents, and the clearly demonstrated widespread dissemination of metal debris from implants (to lymph nodes, bone marrow, liver, and spleen, particularly in subjects with loose, worn joint prostheses) not only could cause damage to distant organs, but also could be associated with the induction of neoplasia.

• Although unequivocal cases of metal particles or elemental metals provoking the formation of malignant tumors are not available, continued vigilance and further study of the problem in animal models is warranted.
• “Nonbiodegradable” and “inert” implants have been shown to contain and/or release trace amounts of substances such as remnant monomers, catalysts, plasticizers, and antioxidants.

• Nevertheless, such substances injected in experimental animals at appropriate test sites (without implants), in quantities comparable to those found adjacent to implants, are generally not tumorigenic.

• Moreover, chemical carcinogens such as nitrosamines or those contained in tobacco smoke may potentiate scar-associated cancers.

• A chemical effect has been considered in the potential carcinogenicity of polyurethane biomaterials.

• Under certain conditions (i.e., high temperatures in the presence of strong bases), diamines called 2.4-toluene diamine (TDA) and 4, 4-methylene dianiline (MDA) can be produced from the aromatic isocyanates used in the synthesis of polyurethanes. TDA and MDA are carcinogenic in rodents.
• However, it is uncertain whether (1) TDA and MDA are formed in vivo, and (2) these compounds are indeed carcinogenic in humans, especially in the low dose rate provided by medical devices.

• Although attention has been focused on polyurethane foam-coated silicone gel-filled breast implants, one type of which contained the precursor to TDA, the risk is considered zero to negligible.

• Foreign-body tumorigenesis is characterized by a long latent period, during which the presence of the implant is required for tumor formation.

• Available data suggest the following sequence of essential developmental stages in foreign-body tumorigenesis (*Ch.4.7: Table 3*):

  • (1) cellular proliferation in conjunction with tissue inflammation associated with the foreign-body reaction (specific susceptible preneoplastic cells may be present at this stages);
  • (2) progressive formation of a well-demarcated fibrotic tissue capsule surrounding the implant;
• (3) quiescence of the tissue reaction (i.e., dormancy and phagocytic inactivity of macrophages attached to the foreign body), but direct contact of clonal preneoplastic cells with the foreign body surface;
• (4) final maturation of preneoplastic cells; and
• (5) sarcomatous proliferation.
• Support for this multistep hypothesis for foreign body tumorigenesis comes from an experimental study in which premalignant lesions were frequently found in implant capsules.
• A spectrum of lesions was observed, from proliferative lesions without atypical calls to atypical proliferation to incipient sarcoma.
• The essential hypothesis is that initial acquisition of neoplastic potential and the determination of specific tumor characteristics does not depend on direct physical or chemical interaction between susceptible cells and the foreign body, and, thus, the foreign body per se probably does not initiate the tumor.
However, although the critical initial event occurs early during the foreign-body reaction, the final step to neoplastic autonomy (presumably a genetic event) is accomplished only when preneoplastic cells attach themselves to the foreign-body surface.

Subsequently, there is proliferation of abnormal mesenchymal cells in this relatively quiescent microenvironment, a situation not permitted with the prolonged active inflammation associated with less inert implants.

Thus, the critical factors in sarcomas induced by foreign-bodies include implant configuration, fibrous capsule development and remodeling, and a period of latency long enough to allow progression to neoplasia in a susceptible host.

The major role of the foreign body itself seems to be that of stimulating the formation of a fibrous capsule conducive to neoplastic cell maturation and proliferation.

The rarity of human foreign body-associated tumors suggests that cancer-prone cells are infrequent in the foreign-body reactions to implanted human medical devices.
• Neoplasms associated with therapeutic clinical implants in humans are rare; causality is difficult to demonstrate in any individual case.
• Experimental implant related tumors are induced by a large spectrum of materials and biomaterials, configuration of the implant.
• The mechanism of experimental tumor formation, as yet incompletely understood, appears related to the implant fibrous capsule.