# INTRODUCTION

Foreign bodies are defined as any exogenous object that has been introduced into the tissues or cavities of the body and is not rapidly absorbed. Solid materials may enter the body as a result of the implantation of medical devices, as a result of accidents (recreational, automobile, occupational and hunting) or as a result of war-time or crime-related injuries (bullets and shrapnel fragments). A biomaterial may be defined in this context as any material used in a medical device that is intended to interact with living systems. Foreign bodies may induce a wide range of local tissue reactions, in particular inflammation, giant cell formation and fibrosis.

## 1. Scope of the monograph

The exposure of interest in this monograph is the presence within the body of a solid metallic or non-metallic object as a result either of surgery or of involuntary penetration (as, for example, through a war wound).

Excluded from evaluation are exposures to:

- occupational handling of materials designed for implantation
- radiation emitted by any implanted object
- any device designed to lie on the surface of the body, either on the skin or within a cavity lined by endothelium (for, example, contact lenses and intra-uterine contraceptive devices)
- intra-ocular implants
- cochlear implants
- certain materials, including suture materials derived from animal tissues, foreign bodies of vegetable origin, and glasses
- allografts and xenografts of bone or other connective tissue

In this general introduction, some key concepts in our current understanding of host–material interactions are presented. These include consideration of the degradation of materials within the body, general mechanisms of chemical and solid state carcinogenesis, and a discussion of the pathology of sarcomas. This is followed by a short description of some characteristics of epidemiology as they relate to the study of cancers associated with implanted devices.

Subsequent chapters describe human exposure data, evidence from case reports and analytical studies for carcinogenicity in humans and in companion animals, evidence of carcinogenicity of implanted materials from animal experiments, and further

background material on mechanisms of degradation and carcinogenicity. Finally, a summary of evidence and an overall evaluation of current evidence are provided.

Some of the substances that constitute, or may be released from, foreign bodies have been evaluated previously within the *IARC Monographs*. These are listed in Table 1.

**Table 1. Substances found in (or potentially originating from) foreign bodies that have been evaluated for carcinogenicity previously in the *IARC Monographs* programme**

| Material | Use | Evaluation of evidence | | Classi-fication | Year/ Volume |
|---|---|---|---|---|---|
| | | Human | Animal | | |
| *para*-Aramid fibrils | D | I | I | 3 | 1997/68 |
| Beryllium | D | S | S | 1 | 1993/58 |
| Beryllium oxide | D | S | S | 1 | 1993/58 |
| Beryllium salts | D | S | S | 1 | 1993/58 |
| Chromium | M + D | I | I | 3 | 1990/49 |
| Chromium trioxide | M + D | S | L | 1 | 1990/49 |
| Chromium[VI] salts | M + D | S | S | 1 | 1990/49 |
| Cobalt | M + D | I | S | 2B | 1991/52 |
| Cobalt-chromium-molybdenum alloy | M + D | I | L | 2B | 1991/52 |
| Cobalt(II) oxide | M + D | I | S | 2B | 1991/52 |
| Cobalt salts | M + D | I | L | 2B | 1991/52 |
| 2,4-Diaminotoluene | M | ND | S | 2B | 1987/S7 |
| Ethylene oxide | M | L | S | 1 | 1994/60 |
| Lead and inorganic lead compounds | Bullets | I | S[a] | 2B[a] | 1987/S7 |
| Mercury | D | I | I | 3 | 1993/58 |
| Nickel (metallic) | M + D | I | S | 2B | 1990/49 |
| Nickel compounds | M + D | S | S + L + I | 1 | 1990/49 |
| Nylon 6 | M | ND | I | 3 | 1987/S7 |
| Polyethylene | M | ND | I | 3 | 1987/S7 |
| Poly(methyl methacrylate) | M + D | ND | I | 3 | 1987/S7 |
| Polypropylene | M | ND | I | 3 | 1987/S7 |
| Polytetrafluoroethylene | M + D | ND | I | 3 | 1987/S7 |
| Polyvinylpyrrolidone | M | ND | L | 3 | 1999/71 |
| Silica, amorphous | M + D | I | I | 3 | 1997/68 |
| Silica, crystalline[b] | M + D | | S | | 1997/68 |
| Titanium dioxide | M + D | I | L | 3 | 1989/47 |
| Toluene diisocyanates | M | I | S | 2B | 1999/71 |

M, medical; D, dental

[a] Lead compounds; elemental lead has not been tested adequately.

[b] Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is *carcinogenic to humans (Group 1)*. This evaluation is not relevant to implants and other foreign bodies.

Elsewhere in this introduction, statements regarding the carcinogenicity of other specific chemicals and materials should not be construed as evaluations by this Working Group and are included only to illustrate mechanistic concepts.

The approach adopted in this volume is to consider sequentially metallic, non-metallic and mixed materials, which have different profiles of biological activity. This introduction brings together a number of diverse, multidisciplinary issues that are important in evaluating the carcinogenic risks associated with implanted biomaterials and other foreign bodies. These issues are:

- Host–biomaterial interactions
- General mechanisms of solid-state carcinogenesis
- Pathology of sarcomas, reactive and pseudoneoplastic conditions
- General issues in human epidemiological research on implants and cancer

## 2. Host–biomaterial interactions as related to carcinogenesis

There is no doubt that the implantation of biomaterials or products related to biomaterials into tissues can be associated with the formation of tumours under certain conditions. In considering the significance, relevance and mechanistic implications of this phenomenon, a wide variety of factors must be taken into account. These factors relate to the nature of the materials themselves, to the nature of the host and to the relationship between the material and the host.

With respect to the materials themselves, disregarding host variations, the following variables are known or might be considered to have some influence on the process of carcinogenicity related to a biomaterial or foreign body: (*a*) intrinsic chemistry; (*b*) surface chemistry; (*c*) chemical nature of any released soluble components; (*d*) chemical or crystallographic nature of any released particulate components; (*e*) physical nature of any released particulate components; (*f*) size; (*g*) shape; (*h*) hardness of the surface; (*i*) surface energy; (*j*) surface topography; (*k*) elastic moduli of the material or the flexibility of the component; (*l*) electrical or magnetic properties; (*m*) radioactivity; and (*n*) sterilization procedures.

With respect to the host and disregarding material variations, general factors that should be taken into account are the site of implantation and the latent period for tumour formation. In animals, some factors that may influence the carcinogenic outcome are the species under study, the strain or breed, age, sex and size. When evaluating the possible human carcinogenic responses to implanted materials, consideration must be given to host factors such as known risk factors for cancer, such as age, sex, occupation, lifestyle and genetic factors, as well as pharmacological status, prior or coexistent disease and the indication for clinical intervention.

With regard to interactions within the host–material system, factors which should be considered include the extent and technique of surgery, subsequent complications and the duration of contact between the biomaterial and the host.

A review of the published data concerning solid-state carcinogenicity in animals and humans allows an assessment of the relative importance of each of these factors.

## 2.1 Variables of the material or object

### 2.1.1 *Intrinsic chemistry*

There is some difficulty over the identification of variations in susceptibility to solid-state carcinogenicity on the basis of intrinsic material chemistry (chemical composition), since many publications fail to identify accurately the precise materials that were used in an experimental study or were the subject of clinical observations. There are published reports in which tumours in experimental animals have been associated with the following materials, among many others:

- Aluminium oxide ceramic subcutaneously implanted in rats (Griss *et al*., 1977)
- Stainless steel implanted intramuscularly in rats (Stinson, 1964; Gaechter *et al*., 1977; Memoli *et al*., 1986)
- Tantalum metal implanted subcutaneously in rats (Oppenheimer *et al*., 1956)
- Silver and platinum metal implanted in rats (Nothdurft, 1955, 1956)
- Polyethylene implanted subcutaneously in rats and Syrian hamsters (e.g., Oppenheimer *et al*., 1952, 1955, 1961; Bering & Handler, 1957; Bates & Klein, 1966)
- Poly(methyl methacrylate) implanted intraperitoneally in mice and rats (e.g., Laskin *et al*., 1954; Stinson, 1964)
- Polydimethylsiloxanes implanted subcutaneously in rats (e.g., Oppenheimer *et al*., 1955; Maekawa *et al*., 1984)
- Glass fragments implanted subcutaneously in mice (Tomatis, 1963).

This list is not exhaustive, a longer compilation being available in Section 4 of this Monograph, but it is clear that all types of material, including pure noble metals, base metal alloys, ceramics and ceramic compounds, glasses, thermoplastics, thermosetting resins and elastomers, have been implicated. It has to be argued, therefore, that solid-state carcinogenicity is not primarily a function of inherent material chemistry. Although there is variation in carcinogenic response from one material to another, there is no evidence that the material chemistry *per se* is the key determinant.

### 2.1.2 *Surface chemistry*

All considerations of the biocompatibility of materials should address the basic question of whether the surface chemistry is any different from the bulk chemistry and whether the composition and properties of the outermost layer of atoms or molecules are more relevant to carcinogenesis than those of the interior of the sample. For example, it is known that different surface molecular structures on methacrylate polymers can cause differences in cell shape and proliferation of normal and malignant human cells in culture in the absence of toxicity (Kulesh & Greene, 1986). Such findings confirm that surface chemistry can modulate cell behaviour in this respect. However, even though it would seem that different surface chemistries may have

different biological effects, the fact that material surfaces involving all three primary valence bonds (ionic, metallic and covalent) are tumorigenic suggests that surface chemistry is not the key determinant.

### 2.1.3 *Chemical nature of any released soluble components*

Chemical carcinogenesis is far better understood than solid-state carcinogenesis and some of the components of implantable biomaterials are known or suspected human or animal carcinogens. It is also clear that with virtually all biomaterials in current clinical use, there is some degree of interaction with the host tissue such that some reaction product (possibly a corrosion product, a product of polymer biodegradation or an additive released from a plastic formulation) will gain access to the tissues. It is therefore possible that solid-state carcinogenesis associated with biomaterials is related to the release of some soluble carcinogenic products, perhaps at infinitesimally low rates but over a protracted period of time.

Chromium and nickel, toluene diisocyanates and toluene diamines, that are known or suspected carcinogens, can be released from one or more biomaterials.

However, the evidence again suggests that mobilization of chemical carcinogens cannot be the cause of many cases of solid-state carcinogenesis and cannot, therefore, be a key determinant. For example, aluminium oxide ceramic is one of the most inert of all materials, being an oxide ceramic that is highly resistant to reduction to any soluble form. Polytetrafluoroethylene is the most stable of all polymers and cannot release any components under physiological conditions. Similarly, poly(methyl methacrylate) appears incapable of biodegradation under physiological conditions, although it may release residual monomers. Nevertheless, all three have been shown to produce tumours in rodents (e.g., Oppenheimer *et al*., 1955; Stinson, 1960).

### 2.1.4 *Chemical or crystallographic nature of any released particulate components*

The same arguments could be made with respect to the chemistry or crystallography of solid particles released from any biomaterial. Microscopically visible corrosion products that are released from some metallic biomaterials induce chronic inflammatory reactions that are seen around them. For example, the chromium-rich deposits seen around some grossly corroded stainless steel products induce chronic inflammation, with the presence of macrophages, giant cells and even plasma cells. The crystalline form of particulate matter is important; for example, inhalation of crystalline silica is associated with lung cancer in certain occupational exposures, while inhalation of amorphous silica is not (IARC, 1997a). Both forms of silica are used as fillers in biomaterials. Nevertheless, there does not appear to be any consistent relationship between solid-state carcinogenicity and any known chemical or crystallographic feature of particulates released from materials.

2.1.5 *Physical nature of any released particulate components*

A major clinical concern is the possibility of the release of particulate matter arising from surface abrasion of biomaterials, this being especially important with the generation of particulate wear debris in orthopaedic joint prostheses. Differences in physico-chemical characteristics of wear debris influence degradation and the identity and rate of release of chemical species from the material. Once again, it might be assumed that the presence of very large numbers of particles, whose release from devices has been estimated to be in the order of hundreds of thousands per day (Doorne *et al*., 1998), could contribute to solid-state carcinogenesis. It is very difficult to determine from the experimental evidence whether this is, in fact, the case, since it is not possible to reproduce exactly the clinical conditions in an experimental model. However, small particles of polymer are in general less likely to induce tumours than large particles (see e.g., Oppenheimer *et al*., 1961).

2.1.6 *Size and shape*

Certain physical features of implants can influence the characteristics of the host response to them. In experimental animals, the shape of the implant influences the development of the fibrous capsule that forms around the implant. Established physical parameters that influence solid-state tumorigenicity in rats and mice are listed in Table 2. Recent studies with a silicone elastomer and cellulose acetate samples with different degrees of permeability and porosity, subcutaneously implanted in rats (James *et al*., 1997), showed variations in acute inflammatory and chronic fibrotic responses, cellularity, proliferation and apoptotic cell death within the fibrous capsules. These differences were correlated with differences in carcinogenicity. Thus, physical attributes of

**Table 2. Some physical properties of non-metallic foreign bodies that affect tumour incidence in rats and mice**

| Increase in tumorigenicity | Decrease in tumorigenicity |
|---|---|
| Large size | Small size |
| Geometry | Geometry |
| Discs | Fine shreds |
| Concave buttons | Perforated sheets |
| Continuous sheets | |
| Smooth surface | Rough surface |
| Pore size (filters) | Pore size (filters) |
| < 0.02 μm (cells do not invade) | > 0.65 μm (cells invade) |

Modified from Oppenheimer *et al*. (1955), Goldhaber (1962), Bischoff & Bryson (1964), Paulini *et al*. (1975) and Moizhess & Vasiliev (1989)

the material samples are clearly important with respect to the development of tumours in rats.

### 2.1.7 *Surface energy and surface topography*

Both surface energy and the topography are able to influence cell behaviour, in the former case by virtue of the energetics of cell attachment and spreading and in the latter case by control of cell shape through direct physical interaction between cell membranes and surface features. With respect to surface energy, the fact that high-energy surfaces of metals and the low-energy surfaces of some polymers (including highly hydrophilic surfaces of polyvinylpyrrolidone and cellulosic polymers) can be tumorigenic suggests that this is not an important factor in solid-state carcinogenicity. With respect to surface topography, although macroporosity has some effect, there does not appear to be any evidence that general topographical features of solid surfaces play any part in this process.

### 2.1.8 *Hardness of the material, its elastic moduli or the flexibility of the component*

The fact that a medical device might be carcinogenic after implantation suggests that it is causing some unnatural process to take place in the adjacent tissue. One of the more obvious stimuli to a tissue associated with the presence of a foreign material is the physical or mechanical disturbance to the physiological system. If a hard, rigid, synthetic material is placed in an intramuscular site, the immediate consequence will be perturbation of the stress fields within the tissue. This could result in an increased stimulus to fibrosis through the mechanical stimulation of fibroblasts. The presence of an elastomer such as silicone within a muscle invokes less chronic inflammatory response than the presence of a rigid material, such as an aluminium oxide ceramic. There is no evidence, however, that these differences in rigidity and hardness are reflected at all in tumour formation.

### 2.1.9 *Electrical or magnetic properties of the material*

It has been speculated that some physical parameters such as the electrical or magnetic characteristics of materials are important variables that control the host response. Since some of these properties differ significantly from one material to another, and since physiological processes are known to be influenced by bioelectrical phenomena, such suggestions are quite plausible. Specific suggestions have, for example, been concerned with the possible influence of dielectric constants on biocompatibility. It does not appear that any systematic study has been performed on the relationship, if any, between carcinogenesis and these properties. Nevertheless, materials which are excellent conductors of electricity and materials which are insulators produce similar tumours under otherwise similar conditions, as do ferromagnetic and paramagnetic materials, and materials with high and with low dielectric constants.

2.1.10 *Radioactivity*

Some medical devices involve components that are radioactive. In some cases, the radioactivity is intentional as the implant is intended to deliver localized radiotherapy. In other cases, the radioactivity is associated with the presence of small amounts of impurities or additives, as with yttria-stabilized zirconia used in some joint replacement prostheses. Concern has been expressed about the possibility that these implanted sources of radioactivity could be carcinogenic, but there is no evidence of this.

2.1.11 *Sterilization procedures*

All implanted devices used in human patients have to be sterilized. Most experimental procedures with animals are performed under sterile conditions and it is assumed that most studies of the biocompatibility, including carcinogenicity, of materials involve sterilized samples. There is a theoretical possibility, therefore, that sterilization processes themselves are risk factors. One problem in examining this possibility is that not all studies specify the sterilization conditions. Additionally, there are widely different techniques for sterilization, including dry heat, steam, γ-radiation (see IARC, 2000), electron beam radiation and exposure to ethylene oxide (see IARC, 1994a). If all samples producing tumours had been sterilized by ethylene oxide, carcinogenesis initiated by residues of this gas or any product derived from it would certainly be a logical explanation. However, since tumours have clearly arisen from implants sterilized by several other techniques, it is very difficult to believe that this sterilization method could be a significant factor.

## 2.2 Host variables

2.2.1 *Species and strain*

Tumours have been associated with implanted devices or materials in the following species: humans, dogs, cats, rabbits, guinea-pigs, rats, Syrian hamsters and mice. There is no reason to suppose that this list represents all the species in which tumours could occur; humans, and to a much lesser extent dogs and cats, receive medical devices therapeutically and the other animals are the main experimental species in which materials are implanted for study. By far the largest incidence of solid-state tumours has been associated with rats, with a large number also seen with mice. This may reflect the fact that these rodents are most usually used for carcinogenicity studies, but also it could reflect significant species specificity. It is also possible that there is strain specificity, but this is even harder to define. Tumours have been seen in at least ten different strains of rats, but this factor has not been systematically investigated.

2.2.2 *Age, sex and size of the animal*

Carcinogenicity studies of implanted materials always involve long-term exposure and usually extend for the lifetime of the animal. There is some evidence that the latent period of solid-state tumour formation in rats decreases with the age of implantation.

Paulini *et al*. (1975) found that rats which developed sarcomas after implantation of polyester-polyurethane sponge did so at an average age of 20.6 months (range 12.5–24.5 months), irrespective of whether the material was implanted in the first or the fifteenth month of life. In most cases, however, the incidence of tumour formation as a function of age cannot be assessed from the experimental evidence. Tumours associated with biomaterials have been reported in both male and female animals, and no consistent sex bias has been determined.

With respect to size, differences within a particular rodent species are not sufficient to allow any conclusions to be reached. Large dogs, however, may be more susceptible than small dogs to sarcoma development following implantation (Stevenson, 1991).

### 2.2.3 *Site of implantation*

Tumours have been found at the site of materials implanted via a number of different routes. The published literature suggests that experimental animals are susceptible to implantation site tumorigenesis following subcutaneous, intramuscular, intraperitoneal, intrapulmonary, intra-articular, intravascular and possibly other routes of administration of foreign bodies.

The vast majority of experiments have been performed with subcutaneous and intramuscular implantation. There have been no controlled studies to determine whether either of these types of site is more at risk than the other or whether the incidence of tumours at such sites represents anything other than the fact that they are more commonly employed.

### 2.2.4 *Known risk factors for human cancer*

Any variable in the host that can be responsible for differences in inflammatory and regenerative processes may affect susceptibility to solid-state carcinogenesis. However, the very low number of confirmed cases of implant-related tumours in humans makes analysis very difficult.

### 2.2.5 *Pharmacological status of a human host*

Similarly, it might be expected that any drug regimen, especially one that is prolonged or repeated, and or that involves anti-inflammatory or immunosuppressive components, could have some influence on susceptibility to tumours, but again the very small patient population precludes such analysis.

### 2.2.6 *Indication for clinical intervention and prior or coexistent disease*

Again, due to the paucity of data, no analysis of these factors can be made.

### 2.2.7 *Latent period for tumour formation*

The latency of tumours arising as a result of carcinogenic exposures is, in part, a function of the longevity of the species. It is therefore logical to assume that the latent period will vary from host species to host species, so that differences in incidence at

any one time period could be due to these variations. In rats the latent period is typically 15–30 weeks. Observations of tumours in clinical patients would suggest that the latent period is quite long (see Tables 33–36, Section 2D), although there are significant variations. The latent period for osteosarcomas associated with orthopaedic devices in dogs is in the range of six years (see Table 37, Section 3.1.1), which would be consistent with the period quoted above for rats and the 20 or so years in humans, on the basis of life expectancy.

### 2.3 Host–material system

Joint replacements in humans frequently entail lengthy and complex surgery that may be complicated by subsequent infection, or loosening or other failure of the prosthesis. These complications may predispose these patients to the development of subsequent tumours; however, the small number of patients that have developed joint replacement-associated tumours precludes analysis of these factors.

Immediately after biomaterials and foreign bodies are implanted, host proteins are adsorbed onto the surface. As described earlier, the physicochemical properties of the material surface influence the extent of adsorption. Host cells subsequently adhere to the modified material surface. The interaction between host cells and the implant varies depending on the anatomical site and the target cell. For example, albumin and fibrinogen are adsorbed from blood while fibronectin and vitronectin are adsorbed from the extracellular matrix. In general, host cell–material interactions may cause haemolysis, cytotoxicity, apoptosis, proliferation, altered gene expression, release of inflammatory mediators and cytokines, encapsulation by fibrosis and mutagenicity and carcinogenicity (Fubini *et al*., 1998). The mechanisms leading to mutagenicity and carcinogenicity will be discussed in more detail.

In contrast to exogenous chemicals, the dose of solid material implanted into the host that produces any cellular response is difficult to quantify. This difficulty arises because metal ions and other chemical species may be mobilized from the surface of the implant, but the composition of these mobilized constituents may not reflect the composition of the bulk material. Medical implants are often complex in structure and composition. The biologically active compounds that can be or are released from a medical device depend on the original composition of the device. These compounds may arise from modification of the biomaterial by the biological environment.

For an evaluation of the biological response to a biomaterial, especially in relation to mutagenicity and carcinogenicity, it is necessary to know: the exact composition of the biomaterial or extract(s); the composition and rates of release of leachable materials into the biological environment; the potential for degradation, which may lead to the formation of compounds with different mutagenic properties or leachability; the influence of the physical environment of the biomaterial; and the surface properties. Much of the information available for assessment is inadequate in these respects, and the methods used are often not validated. It is not possible to predict whether a biomaterial is mutagenic solely on the basis of its original composition.

Since foreign bodies and metal implants usually persist in the host for long periods of time, there is the potential for prolonged mobilization and release of metal ions and soluble chemical species from solid materials. Of particular concern is the mobilization of ions such as iron, both from the implant and from endogenous stores, because these transition elements can catalyse the generation of free radicals by Fenton reactions. Local generation of reactive oxygen and nitrogen species can be amplified by a persistent or chronic host inflammatory response (Fubini *et al*., 1998).

Mobilized metal ions and chemical species and particulate wear debris may produce local and or systemic effects. Soluble metal ions and chemical breakdown or degradation products from polymers may be transported in plasma or blood cells and distributed to distant sites. These mobilized components may bind directly to distant target cells or host macromolecules (including proteins or DNA) or be metabolized to more toxic, reactive intermediates. Alternatively, these solubilized materials may be converted to more polar metabolites and excreted in the bile or urine. Binding of soluble ions and chemical species mobilized from the surface of solid materials to cellular molecules, especially DNA, may be involved in initiation of cancer. Binding to host proteins may also initiate local or systemic immune responses.

Particulate materials and wear debris released from the surface of biomaterials are usually phagocytosed by macrophages. Macrophages may store poorly soluble, non-degradable particulates within phagolysosomes for long periods of time. In response to large particulates or fibrous materials, macrophages may fuse to form multinucleated, foreign body giant cells. Macrophages are motile cells and may transport particulates to the lymphatics where they are subsequently stored in local lymph nodes. Systemic transport and storage of particulates within macrophages residing at distant sites such as the liver, spleen and bone-marrow have also been reported, e.g., in silicosis (Silicosis and Silicate Disease Committee, 1988).

## 3. General mechanisms of solid-state carcinogenesis

All carcinogens, regardless of their physical or chemical state, can be classified according to their mechanism of action (Table 3). In general, carcinogens are classified as genotoxic (positive in bacterial mutagenesis assays and mammalian assays for the induction of micronuclei or cytogenetic alterations) or non-genotoxic agents which usually induce cell proliferation (mitogenic or cytotoxic agents and hormones). Some carcinogens induce molecular alterations by epigenetic mechanisms (binding to heterochromatin or altered patterns of DNA methylation) or by interference with DNA repair mechanisms (Butterworth *et al*., 1992). DNA damage in target cell populations may also be induced indirectly by reactive oxygen or nitrogen species released from neutrophils or macrophages at sites of persistent or chronic inflammation. Cytokines and growth factors released from activated macrophages can contribute to target cell proliferation.

**Table 3. Classification of carcinogens by mechanism of action[a]**

| Carcinogen | Biological activity |
|---|---|
| Genotoxic | DNA adducts leading to gene mutation |
| | Clastogenic |
| | Aneuploidogenic |
| Nongenotoxic | |
| Mitogenic | Stimulation of cell proliferation |
| Cytotoxic | Causes necrosis or apoptosis |
| | Compensatory or regenerative hyperplasia |

[a] Modified from Butterworth *et al*. (1992)

Although the mechanisms of solid-state carcinogenesis induced by implanted materials remain little studied and poorly understood, there is a considerable literature on the mechanisms which operate following the inhalation of asbestos, crystalline silica and poorly soluble particulates (reviewed in the Appendix). Asbestos and asbestiform fibres (IARC, 1977, 1987a) and crystalline silica (IARC, 1997a) have been classified as carcinogenic to humans. The relevance of these observations to solid-state carcinogenesis in implants of other materials remains uncertain, but a self-amplification mechanism of persistent inflammation, generation of oxidants and release of chemokines and cytokines, as has been proposed in relation to fibre carcinogenesis (Fubini, 1996) offers a unifying hypothesis for solid-state carcinogenesis in general.

### 3.1 Experimental implants in rodents

Isolated cases of sarcomas and carcinomas arising in association with metallic or plastic nondegradable foreign bodies and implants (Radio & McManus, 1996) have been reported at many anatomical sites (Table 4). An experimental model of foreign-body or solid-state carcinogenesis is implantation of smooth, nondegradable films subcutaneously in rats or mice (reviewed in Brand, 1982, 1987). Several physical factors are correlated with tumorigenicity, including surface area, surface continuity, size and shape, surface smoothness and erosion resistance (Moizhess & Vasiliev, 1989). Generally, powdered non-metallic materials are not tumorigenic. In various strains of mice, there are genetically determined differences in tumour latency (6–30 months) and frequency. These foreign-body tumours were classified as sarcomas and had a variety of histopathological appearances: fibromyxosarcoma, rhabdomyosarcoma, haemangiosarcoma, reticulosarcoma and osteogenic sarcoma. [The Working Group noted that, as with human sarcomas, these pathological diagnoses might be revised based on modern criteria.] The cell of origin has been postulated to be a pluripotential mesenchymal stem cell originating in the microvasculature (Johnson *et al*., 1973a,b, 1977, 1980). The sarcomas have been shown to be of clonal origin and transplantable. They usually grow

**Table 4. Foreign bodies and cancer**

| Agent | Anatomical site | Cancer |
|---|---|---|
| Shrapnel, bullets[a] (humans) | Soft tissues | Fibrosarcoma |
| | Bone | Chondrosarcoma |
| | Brain | Meningioma |
| | Lung | Bronchogenic carcinoma |
| Bone splinters[a] (humans) | Larynx | Laryngeal carcinoma |
| Experimental implants[a] (rats, mice) | Subcutaneous | Sarcomas |
| Asbestos fibres[b] (humans, rodents) | Lung | Bronchogenic carcinoma |
| | Mesothelium | Malignant mesothelioma |
| Crystalline silica[c] (humans, rats) | Lung | Bronchogenic carcinoma |
| Poorly-soluble particulates[d] (rats) | Lung | Bronchogenic carcinoma |

[a] Reviewed in Brand (1982, 1987)
[b] Reviewed in IARC (1977, 1987a)
[c] Reviewed in IARC (1997a)
[d] Reviewed in Oberdörster (1997)

rapidly and spread by local invasion; metastases are rare (Brand, 1982). The term 'pluripotential cell' is no longer used and it is currently the view that the cells of origin of mesenchymal tumours cannot be identified. Instead, the tumours are classified according to their direction of differentiation (i.e., where they are going) rather than their histogenesis (i.e., where they came from) (Gould, 1986).

The morphological sequence of tissue reactions to subcutaneous foreign bodies has been described (Brand *et al.*, 1975a). There is an initial acute inflammatory reaction with infiltration of neutrophils and monocytes at the site. Proliferating macrophages and multinucleated giant cells accumulate focally and adhere to the surface. Elongated spindle cells and collagen fibres surround the implant and new capillaries grow in. Fibroblast proliferation and collagen deposition are active until the cells become dormant at about three months. At this time, a collagenous capsule of variable density encases the implant. During this dormant phase, preneoplastic cells have been recovered from the fibrous capsule. Several months later, preneoplastic cells can also be recovered from the implant surface (Buoen *et al.*, 1975). Neoplastic cells have been hypothesized to arise from these adherent preneoplastic cells. Since these sarcomas are presumably derived from primitive vascular cells associated with capillary ingrowth, there is no direct physical interaction between the preneoplastic cells and the surface of the implant during the initial stages of tumour development. Sarcomas are also induced by intraperitoneal implants which have become surrounded by a fibrous capsule (Brand, 1982).

It is proposed that foreign bodies are nongenotoxic carcinogens that act as mitogens by stimulating proliferation of mesenchymal cells that surround the implant. Initiated cells have been postulated to arise spontaneously from microvascular precursors within this proliferating cell population (Johnson *et al*., 1973a,b, 1977, 1980). Promotion or maturation of these initiated cells was assumed to occur during the dormant phase of encapsulation by dense fibrous tissue (Brand, 1982). Some biochemical and molecular mechanisms that might be responsible for these initiation and promotion stages are discussed in Section 5 of this monograph.

Since the initial observation that cellophane films implanted subcutaneously in rats induced sarcomas (Oppenheimer *et al*., 1948), numerous plastics and polymers developed for use as medical and dental prosthetic devices have been tested for toxicity and carcinogenicity in animals (reviewed in Rigdon, 1975). In contrast to smooth nondegradable films, similar materials implanted subcutaneously or intraperitoneally in particulate or fibrous form do not induce the types of sarcoma that are typical of foreign-body tumours. Even high doses of particulates injected intraperitoneally in rats generally do not induce sarcomas or malignant mesotheliomas, although diffuse malignant mesotheliomas are readily induced by natural and man-made fibrous materials in rats (Pott *et al*., 1987). An important exception is the induction of both mesotheliomas and sarcomas in rats following intraperitoneal injection of nickel and nickel alloys containing more than 50% nickel (Pott *et al*., 1989, 1992). Direct intraperitoneal injection of particulates such as titanium dioxide induces a mild, transient inflammatory response followed by clearance of particles to mesenteric lymph nodes with no subsequent fibrotic or carcinogenic response, even after repeated weekly intraperitoneal injections in mice (Branchaud *et al*., 1993). The initial inflammatory reaction and subsequent fibrosis induced by implanted biomaterials in animals depend on the species and the anatomical site (Brand, 1982).

An acute inflammatory response of variable intensity occurs that involves oedema, leukocytes and erythrocytes, as in any inflammatory reaction. The involvement of specific cell types and the extent of fibrous encapsulation depend on the kind and physical form of material implanted (Rigdon, 1975). Implanted biomaterials become rapidly coated with host plasma proteins including albumin, immunoglobulin type G (IgG) and fibrinogen. Coating with albumin appears to down-regulate the inflammatory response, while adsorption of fibrinogen appears to trigger both coagulation and acute inflammation (Tang *et al*., 1993, 1996). Persistent inflammation at the surface of biomaterials with localized generation of oxidants not only accelerates autoxidation (Radio & McManus, 1996), but may also induce mutations indirectly in proliferating mesenchymal cells surrounding the implant. Deposition of haemosiderin following haemolysis of extravasated erythrocytes may provide a local source of iron that catalyses generation of hydroxyl radicals from oxidants released by inflammatory cells. So far, there is no evidence for or against this mechanism in rodents or humans, although there is not a good correlation between the intensity or persistence of the acute

inflammatory response and the subsequent development of foreign-body tumours (Rigdon, 1975).

The rare cases of human sarcomas arising in association with metallic foreign bodies embedded in soft tissues or bone or in association with prosthetic devices could arise by a mechanism similar to that described for foreign-body tumorigenesis in mice and rats; however, using the same techniques developed in the mouse model, no pre-neoplastic cells were identified in 50 patients who had received a variety of surgical implants (Brand, 1982). Carcinomas may develop in response to exogenous foreign bodies such as fragments of bullets or splinters of bone. In these cases, prolonged physical damage to epithelial surfaces followed by regeneration of epithelial cells may provide the stimulus for persistent cell proliferation.

## 4. Pathology of sarcomas, reactive and pseudoneoplastic conditions

### 4.1 Introduction

Both epithelial and connective tissue can undergo reactive and pseudoneoplastic proliferation in response to a variety of stimuli. The majority of reactions to foreign materials, and most diagnostic difficulties, concern the connective tissues.

The connective tissues comprise the mesodermally derived connective tissues of the trunk and extremities, i.e., bone, cartilage, muscle, fat, fibrous tissue and blood vessels, and include, by convention, peripheral nerves which are of neuroectodermal origin. Tumours of soft tissue and bone can be benign, malignant (sarcomas which metastasize) or of intermediate type (liable to recur locally but only rarely to metastasize). The commonest anatomical locations of soft-tissue sarcomas are the limbs and limb girdles, the retroperitoneum, the chest and abdominal walls and the mediastinum. Sarcomas of the head and neck form a further clinically significant subgroup, and similar tumours can occasionally arise in connective tissue elements of solid or hollow viscera. Osteosarcomas and chondrosarcomas, although most frequently of skeletal origin, also arise in extra-skeletal tissues.

### 4.2 Incidence and etiology

Benign mesenchymal tumours outnumber malignant tumours in hospital series (Enzinger & Weiss, 1995). Malignant tumours of the connective and soft tissues arise at all ages, some 5–10% of cases occurring before the age of 15 years. Age-standardized incidence rates range from 1–3 per 100 000 population per year in most areas covered by cancer registration (Parkin *et al*., 1997).

The cause or causes are in most cases unknown, although some of the underlying molecular events in the genesis of sarcomas are being elucidated. Associations have been reported with hereditary conditions, therapeutic or accidental irradiation, exposure to certain chemicals and immunological defects. Trauma can draw clinical

attention to a pre-existing malignancy, but more commonly causes pseudoneoplastic reactions. However, sarcomas have been reported to arise in burn scars and in relation to metallic and plastic surgical implants.

Soft-tissue tumours can arise in a variety of genetic diseases or hereditary syndromes. Peripheral neurofibromatosis (NF1; also known as Von Recklinghausen's neurofibromatosis), an autosomal dominant condition with variable penetrance, is complicated by malignant peripheral nerve sheath tumours and occasionally other sarcomas. Central neurofibromatosis (NF2) is associated with bilateral acoustic neuromas. In some benign nerve sheath tumours, there is loss of part of chromosome 22 (Emory *et al*., 1995), and a possible mechanism of neoplasia is loss of the tumour-suppressor gene *NF2* which is localized to 22q11.2-q12. Some malignant peripheral nerve sheath tumours are associated with loss of 17p, including the locus of the tumour-suppressor gene *p53* (Menon *et al*., 1990).

Fibromatosis or desmoid tumour (a non-metastasizing but locally aggressive lesion) is found in about 10% of patients with the autosomal dominant condition of familial adenomatous polyposis (FAP), in whom it often arises in the mesentery. Gardner's syndrome additionally includes other benign soft-tissue, cutaneous and bone tumours (Enzinger & Weiss, 1995). The FAP locus at 5q21-22 contains the *APC* gene, mutations of which are implicated in FAP and in the genesis of colon cancer. In fibromatoses, a variety of abnormalities have been described including trisomy 7, 8 and 20 (in deep fibromatoses) and, in those associated with FAP, loss of heterozygosity due to deletion of 5q (Dei Tos & Dal Cin, 1997).

Li–Fraumeni syndrome is an autosomal dominant trait in which patients with germline *p53* mutations have a familial predisposition to cancers (Strong *et al*., 1992). These include childhood soft-tissue sarcomas, breast and other malignancies.

Among patients who survive familial retinoblastoma, 10–20% develop sarcomas including osteosarcoma in the first decade, then other types later in life. This is related to loss of the *Rb* tumour-suppressor gene which is located at 13q14 (Stratton *et al*., 1989).

Therapeutic irradiation (see IARC, 2000) (for example, in treatment of lymphomas, Hodgkin's disease or breast or gynaecological cancers) is followed, in a very small proportion (0.1%) of cases, by development within the irradiated field of sarcomas in soft tissue or bone (Laskin *et al*., 1988; Wiklund *et al*., 1991; Mark *et al*., 1994; Pitcher *et al*., 1994). Such sarcomas, which arise after a long interval (exceeding three years and frequently much longer), are, with rare exceptions, of high-grade malignancy. Reported subtypes include malignant fibrous histiocytoma, osteosarcoma, chondrosarcoma, leiomyosarcoma, angiosarcoma (which is sometimes low-grade, notably in the breast (Parham & Fisher, 1997)) and synovial sarcoma (van de Rijn *et al*., 1997).

Exposure to herbicides containing 2,3,7,8-tetrachlorodibenzo-*para*-dioxin has been associated with human sarcomas (IARC, 1997b), and occupational exposure to vinyl chloride has been implicated in the etiology of angiosarcoma of the liver as well as other neoplasms (IARC, 1979a; Evans *et al*., 1983; IARC, 1987b).

Sarcomas can develop in immunosuppressed hosts. These include Kaposi's sarcoma linked to human immunodeficiency virus (HIV) infection (IARC, 1996) and acquired immune deficiency syndrome (AIDS), which is associated with infection with Kaposi's sarcoma herpesvirus (KSHV), a recently discovered herpesvirus previously designated HHV8 (Cesarman & Knowles, 1997; IARC, 1997c). Recently, smooth muscle tumours have been reported in immune-disordered children and adults (including transplant recipients and AIDS patients). In some of these, the Epstein–Barr virus (EBV) (IARC, 1997c) genome was demonstrated (Lee *et al.*, 1995; McClain *et al.*, 1995).

### 4.3 Classification

In contrast to carcinomas, it is not clear from which cells sarcomas arise since they have no in-situ phase. With a few exceptions, soft-tissue malignancies arise *de novo* and only rarely from pre-existing benign soft-tissue tumours, although the latter are numerically much more frequent. The most familiar example of this phenomenon is the malignant peripheral nerve sheath tumour arising in a neurofibroma, particularly in the setting of NF1.

Sarcomas are, therefore, classified by their apparent direction of differentiation, i.e., according to the cell or tissue type which they most resemble (Table 5). Thus, liposarcomas display fatty differentiation, leiomyosarcomas form smooth muscle, rhabdomyosarcomas form skeletal muscle and so on. Most sarcomas display one line of differentiation, although this sometimes changes when the tumour recurs. Because neoplasms can resemble embryonic tissues at different developmental stages, as well as adult tissues, and because of the wide variety of cell types and tissues derived from mesenchyme, there is a large number of sarcoma subtypes. The second edition of the

**Table 5. Classification of sarcomas according to type of differentiation**

| Mesenchymal differentiation (adult or embryonic) | Other differentiation (consistent pattern) | No specific differentiation (variable pattern) |
|---|---|---|
| Liposarcoma (adipose tissue) | Synovial sarcoma (epithelial) | MFH (fibroblastic) |
| Leiomyosarcoma (smooth muscle) | Epithelioid sarcoma (epithelial) | Storiform-pleomorphic |
| Rhabdomyosarcoma (striated muscle) | Clear-cell sarcoma (melanocytic/neural) | Myxoid |
| Angiosarcoma (endothelial cell) | Ewing's sarcoma/pPNET (neural) | Giant cell |
| MPNST (Schwann cell) | Alveolar soft part sarcoma (nature uncertain) | Xanthomatous |
| Osteosarcoma (bone) | | Sarcoma (NOS) |
| Chondrosarcoma (cartilage) | | |
| Fibrosarcoma (fibroblastic) | | |

MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; pPNET, peripheral primitive neuroectodermal tumour; NOS, not otherwise specified
The terminology used for soft-tissue sarcomas is that of WHO (Weiss, 1994)

WHO classification of soft-tissue tumours (Weiss, 1994) lists nearly 100 intermediate or malignant entities.

Cellular differentiation is apparent at a variety of levels. Morphologically, an initial assessment will include cell shape, and the presence of any obvious tissue type—for example, formation of neoplastic fat, muscle, bone, cartilage or blood vessels. In many cases, precise categorization requires further investigation by immunohistochemistry, electron microscopy or genetic techniques. Immunohistochemistry is of particular use in differential diagnosis of spindle- and round-cell sarcomas, and electron microscopy in the diagnosis of tumours with no or multiple immunohistochemical markers (Erlandson, 1994). Cytogenetic and molecular genetic techniques can reveal aberrations in a number of sarcomas and are valuable for diagnosing childhood-type small round-cell tumours and some myxoid tumours. Of special interest is the consistent presence in some sarcoma subtypes of specific chromosomal translocations, for many of which the relevant fusion genes have been identified (Cooper, 1996; Fisher, 1999) (Table 6). It is not known how these events arise, but they allow more precise classification and diagnosis and clarify the interrelationship of morphological subtypes. For example, it has been shown that round-cell liposarcoma is the poorly differentiated variant of myxoid liposarcoma (Weiss, 1996); that Ewing's sarcoma of both soft tissue

**Table 6. Chromosomal translocations in malignant soft-tissue tumours**

| Tumour type | Usual and variant translocations | Fusion genes |
|---|---|---|
| Synovial sarcoma | t(x;18)(p11.2;q11.2) | *SSX1* or *SSX2*, *SYT* |
| MRC liposarcoma | t(12;16)(q13;p11) | *CHOP*, *TLS* |
| | t(12;22)(q13;q11-q12) | *CHOP*, *EWS* |
| Ewing's sarcoma/pPNET | t(11:22)(q24;q12) | *FL11*, *EWS* |
| | t(21:22)(q22;q12) | *ERG*, *EWS* |
| | t(7;22)(p22;q12) | *ETV1*, *EWS* |
| | t(2;22)(q33;q12) | *FEV*, *EWS* |
| | t(17;22)(q12;q12) | *E1AF*, *EWS* |
| Desmoplastic SRCT | t(11;22)(p13;q12) | *WT1*, *EWS* |
| Alveolar rhabdomyosarcoma | t(2:13)(q35;q14) | *PAX3*, *FKHR* |
| | t(1;13)(q36;q14) | *PAX7*, *FKHR* |
| Myxoid chondrosarcoma (extra-osseous) | t(9;22)(q21-31;q12.2) | *CHN*, *EWS* |
| Clear-cell sarcoma | t(12;22)(q13;q12) | *ATF1*, *EWS* |
| DFSP/GCF | t(17;22)(q22;q13) | *COLIA*, *PDGFB1* |
| CIFS | t(12;15)(p13;q25) | *ETV6*, *NTRK3* |

MRC, myxoid/round cell; pPNET, peripheral primitive neuroectodermal tumour; SRCT, small round-cell tumour; DFSP, dermatofibrosarcoma protuberans; GCF, giant-cell fibroblastoma; CIFS, congenital-infantile fibrosarcoma

From Fisher (1999)

and bone, peripheral primitive neuroectodermal tumours (pPNET) and thoraco-pulmonary small round-cell tumours (Askin tumour) all have the same underlying genetic abnormality; and that clear-cell sarcoma of soft parts and malignant melanoma are separate conditions, as are soft-tissue and osseous variants of myxoid chondrosarcoma (Brody *et al*., 1997a).

A number of soft-tissue sarcomas do not resemble any normal mesenchymal element and many of these have been found to display non-mesenchymal differentiation (see Table 5). Thus synovial sarcoma (Fisher, 1986) and epithelioid sarcoma (Fisher, 1988) show epithelial differentiation, Ewing's sarcoma and pPNETs are primitive neural tumours and clear-cell sarcomas of tendons and aponeuroses have melanocytic features (Chung & Enzinger, 1983).

Malignant tumours composed of neoplastic fibroblasts have a particularly wide variety of manifestations. The lower grades include fibrosarcomas classified according to the accompanying stromal changes—myxoid (Angervall *et al*., 1977), fibromyxoid (Evans, 1993) or inflammatory (Meis & Enzinger, 1991). The higher-grade or pleomorphic sarcomas have been classified as malignant fibrous histiocytomas (Weiss & Enzinger, 1978), and until recently the commonest adult soft-tissue sarcoma was malignant fibrous histiocytoma of the storiform pleomorphic type (Fisher *et al*., 1992). The application of modern pathological techniques has, however, enabled many of these to be identified as poorly differentiated examples of various specific types of sarcoma (Fletcher, 1992; Fisher, 1996). It is also clear that some carcinomas, melanomas and even lymphomas can assume malignant fibrous histiocytoma-like patterns in solid organs and in soft tissues (Fletcher, 1992). The residual group of pleomorphic sarcomas, in which no differentiation is detected, show fibroblastic features, and should perhaps be called pleomorphic fibrosarcoma but the term malignant fibrous histiocytoma is well established and useful in diagnostic and clinical practice.

In contrast to the sarcoma types listed in Table 5, malignant fibrous histiocytomas do not show consistent genetic abnormalities, although they display a number of non-specific aberrations.

### 4.4 Behaviour, grading and staging

Sarcomas grow and infiltrate locally, and many eventually metastasize. They spread commonly to the lungs and bone, and in some cases to lymph nodes. Their behaviour can be predicted to some extent by histological subtypes; some types are known to metastasize early, while others are indolent.

For the remainder, which form the majority of soft-tissue sarcomas, the behaviour is variable. One of the principal factors in assessing prognosis and determining management is the histological grade. Grading is an attempt to predict behaviour from microscopic features and usually relates to the degree of differentiation or resemblance to normal tissue. For carcinomas, where the degree of differentiation is readily assessed, grading is relatively straightforward, but the task is more difficult for sarcomas, which

include many different types of tumour. Some resemble adult tissue, e.g., smooth muscle or fatty tumours, yet may have a poor prognosis even when well differentiated. Others recapitulate normal embryonic tissue but can have either a good or bad prognosis: although rhabdomyosarcoma is high-grade, myxoid liposarcoma is not. Additionally, many soft-tissue sarcomas do not resemble any normal tissue, so that their differentiation cannot be determined. Grading systems need to take these factors into account as well as the fact that some sarcomas always have a slow course and low metastatic potential and others are always aggressive.

Several grading systems are in clinical use (Coindre, 1993) as none has been universally accepted. As well as diagnostic category, factors commonly used are pleomorphism, mitotic index and necrosis. In some systems, these are assigned scores which are summed to give the final grade. Most systems have three grades, which relate to differences in survival.

Molecular genetic findings might relate to prognosis. For example, in alveolar rhabdomyosarcoma those tumours with t(1;13)(q36;q14) have a more favourable outcome than those with t(2:13)(q35–37;q14) (Kelly *et al*., 1997) and, in synovial sarcoma, a significantly longer metastasis-free survival period has been associated with patients whose localized tumour involved the *SSX2* gene rather than the *SSX1* gene (Kawai *et al*., 1998).

Some lesions, notably fibromatosis, are technically benign but can be relentlessly locally recurrent and infiltrative and thereby cause significant morbidity and mortality.

### 4.5 Pseudosarcomas and reactive conditions

#### 4.5.1 *Reactions to injury*

##### (*a*) *Early reactions to injuries*

Tissue destruction is followed by the formation of granulation tissue, with ingrowth of inflammatory cells, endothelial cells and myofibroblasts. The latter display features of both smooth muscle cells and fibroblasts (Schürch, 1997) and have contractile and collagen synthetic functions; they play a major role in wound healing and resultant fibrosis or development of scar tissue which represents the late stage of reaction to trauma.

Diagnosis of malignancy can be difficult, both from benign neoplasms of similar differentiation and from a large group of tumours and tumour-like lesions, sometimes called pseudosarcomas. These can be mistaken for malignancies (particularly spindle-cell sarcomas), both clinically because of their rapid growth and microscopically by the presence of atypical cells and frequent mitoses. Any of the diagnostic categories can be involved, but the commonest are proliferations of fibroblasts or myofibroblasts. These include cutaneous fibrous histiocytomas, the keloids, fasciitis, and the majority of reactions to injury or to foreign substances.

Assessment of such lesions begins with consideration of clinical factors. Among these are the size and duration of the tumour (for example, a sarcoma is generally larger with a longer history, while fasciitis is smaller and of more rapid onset), and its location,

including anatomical plane—cutaneous, subcutaneous or deep. Most pseudosarcomas and benign tumours, but only rarely sarcomas (predominantly myxofibrosarcoma, epithelioid sarcoma, malignant peripheral nerve sheath tumour and leiomyosarcoma), occur in the superficial soft tissues. Conversely, a mass located beneath the deep fascia, within or between muscles, is more likely to be a sarcoma. The plane in which the tumour is situated can also be determined by imaging (computerized tomography or nuclear magnetic resonance), which can additionally suggest the composition of the lesion.

*Fasciitis*

Soft-tissue myofibroblastic reactions include the various types of fasciitis, a term which includes a number of possibly unrelated conditions of which the type example is nodular fasciitis. Proliferative myositis, occurring within skeletal muscle, is closely similar and inflammatory pseudotumours in some visceral locations, including larynx, bladder and spermatic cord, also resemble nodular fasciitis conditions.

Nodular fasciitis (Meister *et al*., 1978; Bernstein & Lattes, 1982; Montgomery & Meis, 1991) is a reactive condition characterized by its extremely rapid growth (more so than the usual sarcoma). There is sometimes a history of recent trauma. Nodular fasciitis occurs in relation to the superficial fascia, mainly on the upper limb and trunk in young adults, although cases arise elsewhere including head and neck. The lesion achieves its small size of 2–3 cm in a matter of days or weeks; only rarely are lesions larger or of longer duration (three to 12 months). This lesion has been reported in the dermis (Lai & Lam, 1993; Price *et al*., 1993), and intravascular fasciitis (Patchefsky & Enzinger, 1981) and cranial fasciitis (Lauer & Enzinger, 1980) are well documented variants.

Most early cases display a zonation effect or maturation from the centre (hypocellular or hyalinized) to the periphery (hypercellular with inflammatory cells and blood vessels). In between, a loose myxoid area is populated by non-pleomorphic myofibroblasts loosely arranged in a ‘tissue culture’-like manner in a variably myxoid stroma, with lymphocytes and red blood cells. Older lesions have a variety of patterns with storiform foci, interdigitating bundles and myxoid, hyalinized (especially in older lesions) or cystic areas, even in the same lesion. Most examples contain one or two mitoses per 10 high power fields (× 400); a lesion with large numbers of mitoses or abnormal forms should be viewed with caution and may represent a malignant process. Ultrastructurally, the cells are myofibroblasts and fibroblasts, in keeping with which immunohistochemistry demonstrates smooth muscle and muscle-specific actins (but not desmin or CD34).

Because of its rapid growth and mitotic activity, nodular fasciitis is often confused by both clinicians and pathologists with a sarcoma, particularly myxofibrosarcoma or leiomyosarcoma. It is, however, essentially a reactive and non-recurrent lesion.

*Proliferative fasciitis and myositis*

These two benign lesions, which occur at older ages than nodular fasciitis, are characterized by a fasciitis-like background containing clusters of ganglion-cell-like modified fibroblasts which have basophilic cytoplasm and a large nucleus with prominent nucleolus. The same changes may occur either in superficial soft tissues (proliferative fasciitis; Chung & Enzinger, 1975) or in skeletal muscle (proliferative myositis; Enzinger & Dulcey, 1967). Architecturally, proliferative fasciitis resembles nodular fasciitis, whereas proliferative myositis is characterized by a chequerboard infiltration of the connective tissue, separating muscle fibres. In both conditions, rounded basophilic ganglion-like cells form nodular aggregates within areas having the more traditional features of nodular fasciitis. The ganglion-like cells are considered to be modified fibroblasts (Meis & Enzinger, 1992).

Proliferative fasciitis (Enzinger & Dulcey, 1967) and myositis can be confused with malignancies, including carcinoma, melanoma or large-cell lymphoma in adults, and rhabdomyosarcoma or ganglioneuroblastoma in children. These are usually readily separable by the clinical picture and by immunohistochemistry.

*Ischaemic fasciitis*

This was first described as atypical decubital fibroplasia (Montgomery *et al*., 1992), and subsequently it was termed ischaemic fasciitis (Perosio & Weiss, 1993). Predominantly affected are elderly patients who are physically debilitated or immobilized. The sites include soft tissues of the shoulder, posterior chest wall, sacrum, greater trochanter, buttock, thigh and arm, with a short history of three weeks to six months. Lesions are located in the deep subcutis and occasionally extend into the muscle, but extensive epidermal ulceration is absent. Somewhat similar appearances can be found in infected surgical wounds which fail to heal.

Microscopically, there is a lobular arrangement of zones of fibrinoid and coagulative necrosis with fibrin thrombi and spindle cells in a prominent myxoid stroma rimmed by ingrowing ectatic thin-walled vessels. The spindle cells are focally atypical with large hyperchromatic nuclei, or with prominent nucleoli and basophilic cytoplasm, resembling the cells of proliferative fasciitis. Fat necrosis is seen at the periphery. Two thirds are actin-positive, and half display CD34. Desmin is negative although one case had cytokeratin. An occasional case recurs but none has metastasized. This can be misdiagnosed as epithelioid sarcoma, myxoid malignant fibrous histiocytoma, myxoid chondrosarcoma or myxoid liposarcoma.

Somewhat similar atypical fibroblastic proliferations are seen in a variety of non-neoplastic circumstances, including trauma, ischaemia and following radiation therapy, presumably as a common reaction. For the pathologist, the importance lies in not over-diagnosing a sarcoma by misinterpreting the atypia (there are no abnormal mitoses) and necrosis.

*Non-neoplastic heterotopic ossifications*

A number of possibly related reactive or benign neoplastic conditions of soft tissues are characterized by formation of osteoid or bone (Kilpatrick *et al*., 1997). Because such lesions can be very cellular in the early stages, they may be misdiagnosed as sarcomas. They occur in muscle, and also sometimes in subcutis, fascia or periosteum, and are therefore variously termed myositis ossificans, ossifying fasciitis, florid reactive periostitis and fibro-osseous pseudotumour of digits. Collectively, they can be regarded as pseudomalignant osseous tumours of soft tissue. Many but not all cases have a definite history of trauma, so that they conceivably represent an exaggerated dystrophic response to tissue damage.

The type example is myositis ossificans (Enzinger & Weiss, 1995), which affects young adults, and especially the flexor muscles of the arm and the quadriceps muscles of the thigh. It appears within a few weeks and can form a mass exceeding 6 cm in diameter. Histologically, the developed lesion displays zonation, with a central nodular fasciitis-like vascular myofibroblastic proliferation, and peripheral progressively maturing bone. The growth of myositis ossificans is usually self-limiting, and it can spontaneously regress.

The principal differential diagnosis is from extraskeletal osteosarcoma, which can readily be misdiagnosed in the early stages, when there is very cellular tissue with immature bone. This can be particularly difficult in a small core needle biopsy. However, the infiltrative growth, nuclear atypia and abnormal mitoses of osteosarcoma are absent. Fibro-osseous pseudotumour of digits is somewhat similar, but is located in the subcutis, is not zoned and has an irregular multinodular growth pattern. Cartilage was present in two of 21 cases and showed maturation to bone without atypia (Dupree & Enzinger, 1986).

Bizarre parosteal osteochondromatous proliferation (BPOP, Nora's reaction; Nora *et al*., 1983) is a lesion which is thought also to be related to trauma, but which might conceivably have an ischaemic etiology. It was described initially as involving the small tubular bones (proximal phalanges, metatarsals or metacarpals) of hands and feet, but a subsequent larger series (Meneses *et al*., 1993) identified nearly half of the cases in long bones. Typically, a mass protrudes from the cortex of a bone into the adjacent soft tissue. Histologically, there is a cap of aggressive cytologically bizarre cartilage showing irregular ossification, with spindle cells in the inter-trabecular spaces of the bone.

BPOP requires distinction not only from other non-neoplastic soft-tissue lesions with bone formation such as the pseudomalignant osseous tumours of soft parts mentioned above (which generally lack atypia), but also from parosteal osteosarcoma. BPOP is smaller, has a lobular architecture, more slender, short and irregular bony trabeculae and differs in location and radiological features from the osteosarcoma, and it does not invade adjacent muscle.

*Inflammatory pseudotumours*

These arise in a variety of organs, including soft tissue, with or (mostly) without a history of trauma. They are composed of a variable mixture of bland-looking myofibroblastic and fibroblastic cells, chronic inflammatory cells and fibrous tissue. This is a heterogeneous group (Chan, 1996), comprising:

(1) Post-inflammatory repair reactions. A subgroup of these, histologically resembling spindle-cell sarcomas, has been described following surgical procedures or trauma, primarily in the urogenital tract, and especially in the bladder neck, prostate or vagina, and also in the buccal mucosa. They are sometimes termed post-operative spindle-cell nodules (Proppe *et al*., 1984), but similar tumours can also arise spontaneously, especially in the lower urinary tract, where they have been given a variety of descriptive terms.
(2) Benign or low-grade malignant myofibroblastic tumours (including the inflammatory myofibroblastic tumour/inflammatory fibrosarcoma spectrum) (Meis & Enzinger, 1991; Coffin *et al*., 1995).
(3) EBV-positive inflammatory follicular dendritic-cell sarcomas, especially in liver and spleen (Chan, 1997).
(4) Reactions to infectious agents. These are attributable to a variety of bacteria, including the specific situation of mycobacterial (*Mycobacterium avium-intracellulare* or *M. tuberculosis*) infection in patients with HIV (IARC, 1996) or other causes of immunosuppression.
(5) Reactive mediastinal spindle-cell tumours in anthracosis and anthrasilicosis (Argani *et al*., 1998).

(*b*) *Neoplasms associated with scar tissue*

Exuberant scar tissue in the skin with dense bands of collagen is termed a keloid, and this must be distinguished from dermal sarcomas such as dermatofibrosarcoma protuberans which it clinically resembles. In spite of the intense cellular proliferation and extracellular matrix formation, characteristic of healing wounds, the process is self-limiting. Neoplasms described include squamous-cell carcinoma after burns, basal-cell carcinoma at smallpox vaccination sites (Kaplan, 1987), and sarcomas which arise rarely in longstanding scars (Drut & Barletta, 1975; Brand, 1982; Sherlock *et al.*, 1987; Gargan *et al.*, 1988). The latter have included malignant fibrous histiocytoma (Gargan *et al*., 1988; Cocke & Tomlinson, 1993), osteosarcoma (Drut & Barletta, 1975), liposarcoma (Nishimoto *et al*., 1996) and leiomyosarcoma (Can *et al*., 1998). There are sporadic case reports of fibrosarcoma or malignant fibrous histiocytoma arising in surgical scars (Ju, 1966; Kanaar & Oort, 1969; Sherlock *et al*., 1987). However, in view of the common occurrence of scars and the rarity of malignancies arising within them, a chance association cannot be ruled out.

Fibromatosis is a clonal proliferation of uniform, bland, evenly dispersed, parallel-aligned fibroblasts and myofibroblasts which produce excessive collagen (Lucas *et al*., 1997). It is unrelated to trauma but can be histologically difficult to distinguish from

scar tissue, especially in the early stages. Fibromatosis can arise in the superficial or deep soft tissues. Examples of the former include palmar, plantar and penile fibromatoses. The latter are desmoid tumours, which typically involve large muscle groups. A common location for desmoid tumours is the anterior abdominal wall, where they can arise in association with pregnancy. Fibromatosis occasionally has an increased familial incidence and some examples in the abdomen (mesentery) are associated with familial polyposis coli in Gardner's syndrome (Rodriguez-Bigas *et al*., 1994). Desmoid tumours infiltrate locally and can recur, but do not metastasize. They need to be distinguished from scar tissue and nodular fasciitis, and from the closely similar low-grade fibromyxoid sarcoma (Evans, 1993), which has metastatic potential.

4.5.2 *Reactions to foreign material*

Foreign material invokes a variety of tissue reactions. In most instances there is inflammation, followed by encircling fibrosis with or without a foreign body giant cell reaction. In some cases, however, there are more specific morphological appearances, notably with reactions to particulates which can be phagocytosed by macrophages; these appearances can be mistaken for sarcomas. For example:

(*a*) Polyvinylpyrrolidone (PVP) (see IARC, 1999a), formerly used as a plasma expander, has continued to be inappropriately applied as a 'blood tonic' for intravenous injection. It can leak into adjacent tissues and result in the so-called PVP granuloma (Kuo *et al.*, 1997). This is a cellular pseudosarcomatous lesion with abundant extracellular material containing characteristic blue-grey vacuolated macrophages which display positive staining reactions to mucicarmine, colloidal iron and alkaline Congo red, and none with periodic acid–Schiff (PAS) stain and alcian blue. This lesion somewhat resembles myxoid liposarcoma but its cells lack the morphology of lipoblasts and it does not have the characteristic vascular pattern. Its history as well as the pathological findings are usually diagnostic (Hizawa *et al.*, 1984).

(*b*) Silicone, from prosthetic implants or cosmetic injections, can cause a variety of soft-tissue reactions, including the formation of a fibrous capsule (van Diest *et al*., 1998). Synovial metaplasia has also been reported in about 10% of cases in relation to movement of the prosthesis. Free silicone, via injection or leakage, can induce foreign body giant cells, granulomas and a histiocytic tissue reaction in which the cells, with their ingested silicone, resemble lipoblasts, suggesting a diagnosis of well differentiated liposarcoma (Weiss, 1996). Leaked silicone can also reach draining lymph nodes and a lesion resembling Kikuchi's disease (histiocytic necrotizing lymphadenitis) has been observed (Sever *et al*., 1996).

(*c*) There are a number of case reports of sarcomas arising in association with metallic (cobalt–chromium, aluminium oxide ceramic, stainless steel) surgical implants, either for fixation of a fracture or reconstruction (see Section 2C.1). However, specific diagnoses in some earlier reports are inadequately documented or might be changed if re-evaluated using current criteria and modern techniques.

(*d*) The extent of skin and soft tissue damage produced by shrapnel and bullets depends on the type of weapon and the firing distance. Military bullets are fully encased by metal and do not fragment in soft tissues. These bullets are delivered at high velocity and may pass intact through tissues, causing minimal damage. In contrast, hunting bullets expand upon contact with the target, causing extensive soft-tissue damage. Contact wounds produced by high-velocity rifles cause massive destruction, leaving residual powder soot and searing at the entrance site. When fired at greater distances, powder soot produces stippling or tatooing of the skin surface. Metallic balls released from shrapnel projectiles cause multiple soft-tissue wounds. In contrast to entrance wounds, exit wounds do not have a collar of abraded tissue. In general, bullets are not hot when fired. Searing of the skin at the site of a contact wound is caused by the flame of burning powder particles (Di Maio, 1985).

## 5. General issues in epidemiological research on implants and cancer

There has been relatively little epidemiological research on the association between implants and the occurrence of human cancer. Most of the evidence accumulated so far comes from case reports of malignancies occurring at or near the site of implant. Case reports can be used to identify potential risks but, due to their selective nature and the absence of a control group, they cannot quantify risk nor provide evidence of a cause–effect relationship. Moreover, reports of cancer formation at the site of an implant are extremely rare, in relation to the millions of individuals worldwide who have received implanted devices (Coleman, 1996). The more relevant studies for evaluating whether implants increase cancer risk are case–control and especially cohort studies.

For one form of implant, silicone breast implants, descriptive studies have been conducted to evaluate whether certain cancer incidence trends may be associated with the widespread introduction of these implants. Based on data from the United States Surveillance, Epidemiology and End Results (SEER) programme, no change in the incidence of malignant fibrosarcoma or other sarcoma of the breast was observed between 1973 and 1990 (May & Stroup 1991; Engel *et al*., 1995), the period of time when breast implants have been in use. While the ecological nature of this type of analysis requires cautious interpretation, the rarity of sarcoma (particularly sarcoma of the breast) in humans suggests that even a few additional cases would lead to a detectable change in incidence.

There are a number of methodological difficulties in investigating the potential association between implants and subsequent cancer risk. These difficulties involve design issues such as selection of study populations, latency and length of follow-up, statistical power, and accuracy of exposure classification, as well as data analysis issues such as control for confounding and multiple hypothesis testing. All of these

need to be evaluated before reported exposure–disease associations can be assessed for causality.

### 5.1 Identification and selection of study population

A primary concern in epidemiological studies of implanted devices is that patients receiving implants may have a lower baseline risk for cancer compared with the general population. This appears to be true for patients selected for hip and knee replacement, who have a better life expectancy than the general population, as they are also likely to have lower cancer morbidity and are encouraged to give up smoking (Holmberg, 1992; Visuri *et al*., 1994, 1996). Similarly, women at low baseline risk for breast cancer may preferentially seek breast augmentation, and the presence or absence of breast cancer risk factors may influence the plastic surgeon's decision whether or not to perform augmentation (Brinton *et al*., 1996; Deapen *et al*., 1997; Kern *et al*., 1997). These risk factors include family history of breast cancer, and there is some evidence that large breasts are a risk factor for breast cancer, although this was accounted for, in part, by obesity (Hsieh & Trichopoulos, 1991).

Similarly, rheumatoid arthritis is a common indication for hip or knee replacement and is believed to be associated with a higher incidence of certain types of tumour, including non-Hodgkin lymphoma and brain cancer, compared with the general population (Gridley *et al*., 1993). Therefore, studies of hip or knee replacement in relation to cancer occurrence should either exclude patients with rheumatoid arthritis altogether or at least analyse those patients with rheumatoid arthritis separately (Gillespie *et al*., 1996; Lewold *et al*., 1996; Visuri *et al*., 1996). An observed excess of cancer restricted to the rheumatoid arthritis group, particularly if it is independent of latency, would suggest an association with rheumatoid arthritis and not necessarily with the hip or knee implant itself (Lewold *et al*., 1996).

With respect to breast augmentation, an additional concern is that women may undergo more intense pre-operative screening and will be deterred from receiving an implant if breast abnormalities are detected. However, this type of detection bias would tend to produce the largest reduction in breast cancer risk during the first year or two after implantation followed by an increased risk later on, a pattern which has not been consistently observed in the epidemiological studies to date (Brinton & Brown, 1997).

It has also been hypothesized that breast implants may interfere with physical breast examination or mammographic visualization of breast tumours, leading to delays in breast cancer diagnosis and worse prognosis among women receiving implants. However, a number of epidemiological studies suggest that women with implants do not present with more advanced stages of breast cancer or experience shorter survival (Birdsell *et al*., 1993; Brinton *et al*., 1996; Deapen *et al*., 1997; Friis *et al*., 1997).

### 5.2 Latency and length of follow-up

The observation periods in follow-up studies need to be long in order to evaluate thoroughly the long-term health consequences of implants. This is particularly true given the long latency and low incidence of several of the relevant types of cancer, as well as the increasing use of joint replacements at younger ages and the increasing length of time they are in place in the body.

Moreover, it is important to examine cancer risk by time since implantation and to exclude the first year or two of follow-up. Cancers which occur within a short latency period are likely to be coincidental or to represent a surveillance bias in the implant group (Nyrén *et al*., 1995). With respect to cancer occurrence, latency is of particular concern given the immunological changes hypothesized to occur along with deterioration of the breast implant capsule over time (Brinton & Brown, 1997), or the increase over time of metallic or non-metallic materials in other types of implants associated with deterioration (Coleman, 1996).

### 5.3 Statistical power

Many of the epidemiological studies conducted to date have a rather low statistical power to detect any increased risk of rare types of cancer, especially sarcomas (Gillespie *et al*., 1988; Visuri & Koskenvuo, 1991; Malone *et al*., 1992; Gabriel *et al*., 1994; Visuri *et al*., 1996; Friis *et al*., 1997). Only as larger cohorts of implant recipients are identified, and as more time has elapsed since implants were first used, can these risks be evaluated with adequate power. Moreover, low statistical power precludes adjustment for extraneous factors which could potentially confound an association between implants and cancer risk.

### 5.4 Exposure classification

In retrospective cohort studies, errors in recorded surgical procedures can produce underascertainment of exposure and underestimates of the risk associated with implants. However, this type of bias in exposure classification is likely to be minimal if based on registry data (Nyrén *et al*., 1995). In contrast, the accuracy of implant data is often questionable in case–control studies which rely on patient reports of previous hip or knee replacement or breast implant.

### 5.5 Multiple hypothesis testing

In epidemiological studies of implants in relation to a variety of malignancies, multiple comparisons (or multiple hypothesis testing) can produce artifactual increases or decreases in risk for site-specific cancers that are a result of chance alone. The occasional statistically significant finding requires cautious interpretation, given that it is often based on small numbers of cases and may reflect the problem of multiple comparisons. As a result, conclusions regarding the association between implants and specific types of cancer must be based on the collective evidence, taking into account consistency across studies and a plausible temporal sequence.

### 5.6 Control for confounding influences

A major difficulty may be inability to control adequately for implant recipient characteristics, which may be independently related to cancer risk and which may artificially increase or decrease the observed risk estimates. This is of particular concern in studies which use external reference groups or in record-linkage studies, in which the investigator does not have the opportunity to collect additional data on known or suspected confounding variables. For example, among breast augmentation recipients, the potential confounders include higher socioeconomic status, younger age at first birth, leanness, small breasts, and better access to medical care. Similarly, women who smoke cigarettes and who have a greater number of lifetime sexual partners appear more likely to seek breast augmentation and are independently at higher risk for lung or cervical cancer (Cook *et al*., 1997; Deapen *et al*., 1997; McLaughlin *et al*., 1998). With respect to hip or knee replacement patients, potential confounders include immunosuppressive therapy, tobacco smoking, alcohol abuse, use of non-steroidal anti-inflammatory drugs and obesity.