CHAPTER 9

Effects of Implant on the Body: Biocompatibility

9.1 LOCAL EFFECTS

9.1.1 Definitions

Healing

Process of restoration of injured tissue.

Healing by First Intention (also referred to as primary and direct healing):

Restoration of continuity of injured tissue without the intervention of granulation tissue Examples are the healing of a scalpel incision in soft tissue or the healing in the very narrow gap (perhaps 2 cell diameters , 20 m) between the fragments of a fractured bone that have been re-approximated.

Healing by Second Intention:

Healing involving granulation tissue filling the gap (defect) in the injured tissue.

Inflammation (Dorland's dictionary definition and Pathologic Basis of Disease)

A localized response elicited by injury or destruction of vascularized tissues, which serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue. It is characterized in the acute form by the classical signs of pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (functiolaesa). It is caused by injurious agents: biological agents (bacteria), physical agents (heat and mechanical trauma), chemical agents (small toxic molecules and immunogenic macromolecules). The role of inflammation is to contain the injury and facilitate healing. Unresolved inflammation can be harmful.

Repair

The end result of healing is scar.

Regeneration

The end result of healing is tissue similar to the original tissue.

Clot

A semi-solid mass of blood platelets and blood cells in a fibrin matrix.

Coagulation

The process of clot formation.

Hematoma

A localized blood clot in a tissue or organ due to a ruptured blood vessel.

Thrombus

An aggregation of platelets and fibrin with entrapment of cellular elements within a blood vessel; frequently causing vascular obstruction.

Hemorrhage

Bleeding.

Hemostasis

Arrest of bleeding.

9.1 LOCAL EFFECTS: PROCESSES OF HEALING

9.1.2 Processes of Healing

Injurious Agents

Biological Agents
- Microbial infection

Chemical Agents

Physical Agents
- Thermal
- Electrical
- Mechanical
  - Trauma
  - Surgery
  - Implant movement

Features of Healing

End Result

Similar to original tissue	Regeneration
Scar	Repair

Size of Wound

No/minimal tissue destruction	Resolution
Small wound (e.g., incision)	Healing by first intention (primary or direct healing)
Large	Healing by second intention (healing with granulation tissue)

Vascularity

Vascular	Inflammation precedes repair or regeneration
Nonvascular	No inflammation No healing (cornea, meniscus, articular cartilage), regeneration (epidermis), or repair (?)

Time

Early (e.g., due to surgery)	Acute inflammation
Late (e.g., due to persistence of "injury" associated with presence of an implant)	Chronic inflammation

Predominant Cell Types

Acute	PMN, Leukocytes, Macrophage, Endothelial, Fibroblast
Chronic	Macrophage, MFBGC, Fibroblast

Repair vs. Regeneration

9.1.3 Acute Vs. Chronic Inflammation

9.1.3.1 Acute Inflammation

Comprises cellular processes, soluble mediators, and vascular changes occurring immediately following injury to vascular tissue and is of relatively short duration (from a few minutes to a few days). The classical clinical signs are: heat, redness, swelling, and pain. In many cases function of the tissue is compromised.

9.1.3.2 Chronic Inflammation

Cell types and activities associated with a persistent injury or permanent implant, that could continue for months or years.

9.1.3.2.1 Synovium

The chronic inflammatory tissue bordering an implant often has the cell composition (macrophages and fibroblasts) and arrangement (cells in mono- or multiple-layer) consistent with synovium, The tissue that lines joints and encapsulates fluid-filled sacs (bursae).

9.1.3.2.2 Granuloma

A focal accumulation of epithelioid cells (macrophages altered in appearance to resemble epithelial cells) and multinucleated giant cells. This term is also applied to collections of lymphocytes surrounded by fibrous tissue.

9.1.3.3 Scar and Contraction

9.1.4 Phagocytosis (Small Particle Disease)

9.1.4.1 Primary* Phagocytic Cells (Fig. 9.3)

Polymorphonuclear neutrophils (PMN)
Macrophages (Figs. 9.4 and 9.5)
Multinucleated foreign body giant cells (Figs. 9.3 and 9.5)
*Other cells such as fibroblasts may be phagocytic under special circumstances

9.1.4.2 Stages of Phagocytosis

a) Contact
b) Binding
   - membrane receptor binding
c) Formation of Phagosome
   - infolding of the cell membrane engulfing the particle
   - membrane-bound compartment containing the particle
d) Formation of Phagolysosome
   - fusion of lysosome (membrane-bound packet of enzyme and other degradative agents) with the phagosome

9.1.4.3 Degradative and Inflammatory Regulators Released by the Macrophage During Phagocytosis

Degradative Agents
- Lysosomal enzymes
- Oxygen–derived free radicals

Regulators
- Eicosanoids
  - prostaglandins
  - leukotrienes
- Cytokines
  - tumor necrosis factor
  - interleukins

9.1.4.4 Mechanisms of Release of Products from the Macrophage

Cell death
Regurgitation
Perforation/Cell Wounding
Reverse endocytosis

9.1.4.5 Chemotactic Stimuli for Monocytes

Chemotactic peptides (bacteria)
Leukotriene B_4
Lymphokines (cytokines from lymphocytes)
Growth factors (*e.g.*, PDGF, TGF-)
Collagen and fibronectin (fragments)
Fragments of complement molecules (*viz.*, C5a)

9.1.4.6 Macrophage Properties

Tissue Injury	Fibrosis
Oxygen metabolites	Cytokines
Proteases	– IL-1, TNF
Eicosanoids	– FGF, PDGF
Cytokines	– TGF-
	– angiogenesis factor

9.1.4.7 Increased Activities Associated with "Activated" Macrophages

Bacteriocidal activity
Tumoricidal activity
Chemotaxix
Endocytosis
Secretion of biologically active products

9.1.4.8 Life Spans of Phagocytes

PMNs: days
Macrophages: monocytes circulate in the periheral blood 24-72 hours;
macrtophages survive in tissue from months to years
Multinucleated Foreign Body Giant Cells: survive in tissue from months to ?

9.2.1 Migration of Molecules (Soluble) and Particles (Insoluble); Lymphatic System

Local and regional lymphadenopathy caused by wear particles released from joint replacement prostheses is becoming increasingly recognized as a possible complication of arthroplasty. Particles generated by mechanical wear of prostheses can leave the site of the implant via the lymphatics and become engulfed by macrophages within local and regional lymph nodes. Accumulation of cells containing particles causes enlargement of the lymph node and the characteristic histologic appearance of sinus histiocytosis[6]. Distension and prominence of the lymphatic sinuses is due to the presence of large numbers of a) histiocytes derived from the cells that line the sinuses or b) macrophages derived from circulating monocytes. Multinucleated giant cells, resulting from the fusion of macrophages or histiocytes, might also be found in the dilated sinuses.

Accumulation of polyethylene, polymethylmethacrylate, and metal particles in lymph nodes draining joints replaced with prostheses has been found in animal[13,24] and human studies[2,3,8,12], a few of which have reported lymphadenopathy in operative patients[6,15,20]. Total joint prostheses produce particulate debris through adhesive, abrasive, and fatigue (delamination) wear processes occurring 1) at the articulating interface between metal and polyethylene, 2) at the junctions of the modular portions of a modular total joint prosthesis, 3) at the interface between component and cement, or 4) at the interface between implant and bone . Polyethylene, polymethylmethacrylate, and metal particles are all capable of stimulating resorption of periprosthetic bone[1,4,9,10,16,18,19,21,25,26]. The adverse consequences of periprosthetic bone loss have focused a great deal of attention on the problems caused by wear particles locally at the implant-bone interface. Much less attention has been focused on the pathologic response to these particles at distant sites in the body.

The tissue response to wear particles is that of a foreign body reaction, with varying amounts of macrophages and foreign body giant cells[8,24,28]. Synovial macrophages readily engulf particles released into the joint space. When the production of particulate debris exceeds the phagocytic capacity of synovial macrophages, excess particles a) migrate into periprosthetic tissue where they are ultimately phagocytosed by macrophages, that release agents that stimulate bone resorption[19], or b) enter lymphatic vessels[25]. There is evidence that macrophages laden with partcles can also gain entry to the lymphatics[7]. Macrophages present within lymph nodes endocytose free particles traveling within the lymphatic system. A steady influx of wear debris causes these macrophages to accumulate within the sinus of the lymph node[3]. Over several years macrophages containing particles may become so abundant that they cause dilatation of nodal sinuses and node enlargement. The accumulation of histiocytes or macrophages within lymph node sinuses is described pathologically as sinus histiocytosis. The histopathologic response to polyethylene particles in lymph nodes and periprosthetic tissue is comparable. At both sites, macrophages containing polyethylene have abundant, granular, eosinophilic cytoplasm, with small central nuclei. Polyethylene particles smaller than three micrometers are seen within individual cells, while larger particles are surrounded by foreign body giant cells[22].

Systemic Migration of Particles Derived from Implants

There are numerous reports in the literature of migration of particles, released from implants, to lymph nodes and many organs. The spread particles of silicone elastomer and liquid droplets (namely, from breast implants) is well documented (see for review Travis, *et al.*[25]). The translocation of these particles has been found to be due to a) migration through soft tissues, b) entry into the lymphatic system, and c) direct entry into the vascular system[22]. Silicone particles have been found to migrate from breast implants through soft tissue to sites as distant as the groin[5]. The finding of silicone lymphadenopathy in axillary lymph nodes is common in patients with breast implants[23]. The hematogenous dissemination of silicone to viscera has also been reported as a result of soft tissue injection of the material[22]. In the orthopedic literature, silicone lymphadenopathy has become a common finding in patients receiving finger joint prostheses made of silicone elastomer[6,7].

Reports documenting dissemination of particles in the lymphatic system from total joint prostheses are mounting, suggesting that this phenomenon may be more common than previously thought (Table 1). There are several animal studies documenting lymphatic spread of polyethylene particles to regional nodes[13,24]. Bos *et al.* recently provided evidence from human autopsies that polyethylene, polymethylmethacrylate, and metal particles released from stable total hip replacements spread to inguinal, parailiac, and paraaortic lymph nodes as early as 1.5 years following implantationof the prosthesis[3]. Sinus histiocytosis in association with wear particles of polyethylene has been an incidental finding in lymph nodes biopsied at revision arthroplasty[14], and the staging of prostate[2,6] and breast cancer[15]. Adenopathy related to an implant is not limited to total hip and knee replacement prostheses. O'Connell recently reported a case of axillary histiocytic lymphadenopathy in association with polyethylene wear particles from a total shoulder replacement[15].

Kinetics of Particle Migration from Joints and Bone

The kinetics of migration of particles from joints and osseous sites have been the subject of several investigations. Noble, *et al.*,[14] investigated the leakage of particles labeled with a radioisotope from intra-articular injection sites in the rabbit knee; particles included human serum albumin, carbonized microspheres, gold colloid, and ferric hydroxide, with sizes ranging from thirty nanometers to tens of micrometers. Approximately 1 per cent of the injected dose of ferric hydroxide ("inert") particles, less than one micrometer in diameter, migrated from the joint twenty four hours after injection. The kinetics of migration (leakage rate) of particles from the joint space was related to particle size; there was an order-of-magnitude difference in the leakage rates (2.2 to 0.1 per cent after twenty four hours) for particles ranging from less than 0.1 to 15.0 millimeters.

In other studies a canine model was used to investigate the spread of cell-sized radioactive microspheres from the distal femur into the lymphatic system, venous drainage, and local tissue[17]. In this model microspheres, fifteen micrometers in diameter, were injected into the medullary canal of the femur. Particles entered directly into the venous system (within fifteen seconds of injection) and were effectively filtered by the lungs, thus preventing dissemination in the arterial system. No migration of particles from the femur into the lymphatic system was found after four days. However, similar microspheres injected into soft tissue in the distal femur were found in the iliac lymph nodes in two of nine animals after this time period. In neither of these animals were particles found in the lungs. A subsequent study[11] demonstrated that particles as large as 100 micrometers, injected into the canal of the distal femur, migrated to the lungs within fifteen minutes of injection. These results suggest that under certain conditions particles generated by wear might directly enter the venous system. The majority of these particles would be filtered in the lung, preventing hematogenous spread. Collectively the investigations indicate that a marked number of particles can be disseminated to various sites in the body within hours after their generation.

Clinical Implications

Lymphadenopathy secondary to the accumulation of wear particles in sinus macrophages may cause confusion regarding the appropriate diagnosis, especially in cases where malignancy is suspected. Shinto, *et al.*, recently reported a case of a nineteen year-old man who presented with right inguinal pain and a three x three centimeter palpable mass, three years after placement of a right total knee replacement following resection of an osteosarcoma[20]. The lymph node was biopsied to evaluate for suspected metastatic recurrence of osteosarcoma. Histologic examination revealed sinus histiocytosis due to metal particles released from the knee prosthesis. There was no evidence of malignancy.

The ultimate fate of particles released from total joint prostheses is unknown. A recent report suggests that metallic particles from orthopedic prostheses may pass through the lymphatics and gain a systemic distribution[12]. The clinical sequelae of polyethylene particles in lymph nodes and other organs is unknown. However, the fact that disseminated polyethylene particles cannot be removed focuses attention on investigations of the long term host response to polyethylene particles.

TABLE 1

Reports of Particle Migration

Year	Author	Prosthesis (n)	Type of Particles	Location(s)
Animal Studies				
1973	Walker[24]	THR* (NA)**	Polyethylene (PE)	lymph nodes (LN), alveolar walls
1974	Mendes[13]	THR (3)	PE	LN
Human Autopsy Studies				
1990	Bos[3]	THR (32)	PE, Metal, Polymethylmethacrylate	Regional and para-aortic LN
Human Operative Studie				
1974	Heilmann[8]	THR (2)	Polyester	Inguinal LN
1989	Gray[6]	THR (2)	PE, Metal	Inguinal and paraaortic LN
1992	Langkamer[12]	THR (2)	Metal	Paraaortic LN and spleen
1993	Bauer[2]	TKR (1)	PE,Carbon fiber	Paraaortic LN
1993	Shinto[20]	TKR (1)	Metal	LN
1993	O'Connell[15]	TSR (1)	PE	Axillary LN

* THR, total hip replacement; TKR, total knee replacement; TSR, total shoulder replacement
** n, the number of animals, was not specified.

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