Some important aspects that can lead to poor implant/host interactions and complications related to biomaterial implantation.

What are 3 serious complications that can occur as a result of presence of biomaterials in the body?	1. Hypersensitivity 2. Infection 3. Tumorigenesis
This term is also known as an allergic reaction. It is an undesired immune response mediated by the adaptive immune response. It is typically defined as unusual, excessive, or uncontrolled.	Hypersensitivity
This type of complication associated with implants typically displays at least one of the following characteristics: Presence of biomaterial, Bacterial colonization of tissue, Resistance to host defence mechanisms and antibiotic treatment, presence of multiple bacteria species, absence of integration of biomaterial with the host, presence of cell damage.	Infection
This type of complication associated with implants typically presents as the formation of a mass of uncontrolled proliferating cells.	Tumorigenesis

Why has the definiton of biocompatibly materials been changed from inert material to include material with minimal interaction with their environment.	It is unlikely to find a material that is totally inert, but the physiological response to any biomaterial is kept within acceptable bounds.

(Exam Relevant)

The **foreign body reaction** is composed of macrophages and ”foreign body giant cells” and represents the end-stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis, or biomaterial.

The events leading up to the foreign body reaction include protein adsorption, monocyte/macrophage adhesion, macrophage fusion to form foreign body giant cells, consequences of the foreign body response on biomaterials, and cross-talk (cell-cell signaling) between macrophages/foreign body giant cells and inflammatory/wound healing cells.

Biomaterial surface properties play an important role in modulating the foreign body reaction in the first two to four weeks following implantation of a medical device, even though the foreign body reaction at the tissue/material interface is present for the *in vivo* lifetime of the medical device.

An understanding of the foreign body reaction is important as the foreign body reaction may impact the biocompatibility (safety) of the medical device, prosthesis, or implanted biomaterial and may significantly impact short- and long-term tissue responses with tissue-engineered constructs containing proteins, cells, and other biological components for use in tissue engineering and regenerative medicine.

Our perspective in this course has been on the inflammatory and wound healing response to implanted materials, devices, and tissue-engineered constructs. The incorporation of biological components of allogeneic or xenogeneic origin as well as stem cells into tissue-engineered or regenerative approaches opens up a myriad of other challenges.

An understanding of how the immune system interacts with implanted cells and how biomaterials or tissue-engineered constructs influences these interactions may prove pivotal to the safety, biocompatibility, and function of the device or system under consideration.

Useful information related to foreign body response (Q&A format)

What are five elements of the foreign body reaction?	1. Multinucleated foreign body giant cells 2. Macrophages 3. Fibroblasts 4. Capillaries 5. Multinucleated foreign body giant cellsform upon coalescence of macrophages.
What are three inflammatory stimuli that lead to chronic inflammation?	1. Chemical and Physical properties of biomaterial 2. Motion in the implant site 3. Confined to the implant site
What are two types of cells that merge to become foreign body giant cells?	1. Macrophages 2. Monocytes
What is a foreign body reaction to a flat and smooth biomaterial surface?	A layer of macrophages one or two cells in thickness.

What is a foreign body reaction to a relatively rough biomaterial surface.	Composed of multiple layers of macrophages and foreign body giant cells at the surface.
What is a foreign body reaction to rough surfaces?	Composed of macrophages and foreign body giant cells with varying degrees of granulation tissue.
What is the end stage of the healing process usually extending four or more weeks after biomaterial implantation?	Fibrous Encapsulation
What does the presence of **neutrophils** during the fibrous encapsulation stage of healing suggest?	Persisiting Inflammatory Challenge
What does the presence of **macrophages** likely suggest during fibrous encapsulation?	Production of small particles by corrosion, depolymerization, dissolution or wear.
What does the presence of **lymphocytes** likely suggest during fibrous encapsulation?	Specific Immune Response
What are three factors that determine the wall thickness of a fibrous capsule?	1. Chemical Activity Rate of the material. 2. Motion between implant and tissue 3. Shape of implant (Thicker over sharp edges)

What are the three possible outcomes for an implant?	1. Resorption (implant is resorbed and only native tissues remain) 2. Integration (implant and host reach a stable cooperative relationship that both native tissues and the implant provide some function) 3. Encapsulation (the implant is stably isolated from the remainder of the body)
What are the 7 steps that follow implantation which ultimately end in **scar formation** or **capsule development**?	1. Injury 2. Hemostasis 3. Inflammation 4. Acute Inflammation 5. Proliferation 6. Remodelling 7. Scar Tissue or Fibrous Capsule Development
What are the 7 steps that follow implantation which	1. Injury

ultimately end in **Foreign Body Giant Cell Formation**?	2. Hemostasis 3. Inflammation 4. Acute Inflammation 5. Chronic Inflammation 6. Proliferation 7. Foreign Body Giant Cell Formation
Describe **neutrophil** activity levels during host response to implant?	They are the first cells to arrive on the site. Peak hours after injury (During acute stage) and decline in number after that.
Describe Macrophage activity levels during host response to implant?	Second type of cell on site. Begin to appear hours after injury during the acute stage and gradually grow and peak during the granulation tissue stage
Describe Foreign Body Giant Cell activity levels during host response to implant?	Third cell type to appear. Start to appear days after injury during the chronic

	phase and peak during the granulation tissue stage
Describe fibroblasts activity levels during host response to implant?	Fourth cells type to appear. Start to appear between days and weeks after injury and peak during the granulation tissue stage.

Information related to regulatory pathways for novel classes of biomaterials and implants

What is the standard practice for running a clinical trial for a new drug.	A double-blind study in which a placebo is randomly distributed.
Why is the standard practice for drug related clinical trials not possible to be used for implants?	It is not possible to conceal an implant (Or lack thereof) from the patient and/or the surgeon (Double blind practice is not possible).
How many phases are in a typical clinical trial.	Three
What does Phase 1 of a clinical trial usually involve?	Biomaterial being tested on a small group (60-80 people)
What does Phase 2 of a clinical trial usually involve?	Biomaterial being tested on large group (100-300 people)
What does Phase 3 of a clinical trial usually involve?	Comparison of the effectiveness of the new treatment with a standard of management (1000-3000)

Some key mechanically relevant considerations of biomaterials and their functional performance:

Provide 3 examples of bulk properties.	1. Chemical properties 2. Structural properties (mechanical properties such as stiffness, failure loads, and toughness) 3. Purity and presence of leachables
Provide 3 examples of surface properties	1. Smoothness 2. Geometry 3. Hydrophilicity / Surface Charge
Provide 4 ways that a host can physically affect an implant.	1. Abrasive, adhesive, and delamination wear 2. Fatigue and fracture 3. Stress corrosion cracking 4. General corrosion

Biologically relevant considerations of biomaterials and their functional performance:

Proved 3 ways that a host can biologically affect an implant.	1. Absorption of substances from the tissue 2. Enzymatic degredation 3. Calcification
What are 3 host factors that determine the success of an implant.	1. Age and health status of patient (cellular potency) 2. Immunological/metabolic status of host (inflammatory status) 3. Effectiveness of surgeon (mechanical effects)

(Bonus – for your benefit but will NOT be the basis of exam content)
Required experimental evidence related to regulatory approval of new implants and biomaterial formulations:

What are 7 components of biocompatibility testing that help characterize and evaluate the structure and response relationship of the biomaterial as well as the reproducability of the results?	1. Cell toxicity 2. Thrombogenecity 3. Inflammatory Response 4. Animal Tests

	5. Clinical Trials 6. FDA Regulations 7. ASTM/ISO standard
What is the main goal of level I biocompatibility testing? What are four elements that help accomplish this?	**Bulk-material** characterization tests to identify the biomaterial and confirm it meets biocompatibility specifications Elements involve tests for: 1. Surface topography 2. Cleanliness 3. Chemical structure and composition 4. Toxicity
What is the main goal of level II biocompatibility testing? What are three elements that help accomplish this?	Gathering detailed information of **specific elements of structural and functional behavior** that may relate to performance. Elements involve tests for:

	1. Surface chemistry 2. Morphology (e.g. roughness, implant surface topology, etc.) 3. Interfacial properties (host-implant tissue ingrowth and implant integration)
What is the first event in blood-surface interactions and is crucial in understanding surface-induced thrombosis?	Adsorption of plasma proteins
What are four types of In Vitro tests for estimating biocompatibility?	1. Cytotoxicity 2. Hemocompatibility 3. Mutagenicity 4. Hypersensitivity
The abilty to cause death or damage at the cellular level by direct cell lysis or by fatally altering cellular metabolism?	Cytotoxicity
Which cytotoxicity test aims to determine toxic doses and changes in cell growth or proliferation by comparing to cells cultured on a material to non treated cells over a 24 to 72 hour period?	Elution Test

Which cytotoxicity test is performed by placing the test material over a layer of agar/agarose hydrogel and covering cells for 24 hours. Components of the material diffuse through the layer to the cells and the cytotoxicity of the diffusable materials is measured.	Agar Overlay Test
What type of test is used to evaluate the effect of material on blood coagulation processes, thrombus formation, and hemolysis (Destruction of RBCs)?	Hemocompatibility Tests
What is a material called that modifies the genome of a host (Also called genotoxic).	Mutagenes
Which animal test looks for alterations in DNA or chromosomal structure or other DNA or gene damage that results in permanent inheritable changes in cell function.	Genotoxicity Test
Which genotoxicity test uses a mutant line of bacteria (Usually salmonella or E. Coli) that must be supplied with histadine to grow and are cultured in a histadine free environment. This test checks for materials that that mutate the bacteria back to a histadine independant state.	Ames Test

The leukocyte migration inhibition and lymphocyte transformational test which estimate delayed hypersensitivity reaction to implant materials and their released components are examples of what type of test?	Hypersensitivity test
What are four types of in vivo tests?	1. Short-term implantation tests 2. Long-term functional tests 3. Sensitization tests 4. Irritation tests
Which type of in vivo test involves subcutaneous, intramuscular and intraperitoneal implantation tests to evluate general tissue necrosis, fibrosis and inflammation.	Short-term implantation tests
Which type of in vivo test uses the device or compositionally identical prototypes to simulate intended end-use in an animal model and then test for functionality and histopathological evaluation.	Long-term functional test
Which in vivo test invovles guinea pigs, occluded patch	Sensitization

tests, and open epicutaneous tests?	
Which in vivo test checks for skin, ocular, and mucosal irritation?	Irritation test
What are 5 types of animal tests?	1. Nonfunctional tests 2. Function tests 3. Genotoxicity tests 4. Cancerogenity tests 5. Irritation test
What are the negative systemic effect of animal testing with regards to implantion?	Chemicals released from implant materials are distributed by blood and lymphatic system and damage organs and tissues.
What are the 4 categories of the systemic effects that result from animal testing?	1. Acute (24 hrs) 2. Sub-Acute (14-28 days) 3. Sub-Chronic (10% of animal's life span) 4. Chronic (Longer than 10% of an animal's life span)