Biocompatibility of Implantable Medical Devices

Lecture 13

Summary

- Biological response to implants
- Methods to reduce adverse effects
- Regulations governing medical devices
- Testing of implantable devices

Sequence of Response

1. Injury
2. Blood/Material Interactions
3. Provisional Matrix Formation
4. Acute/Chronic Inflammation
5. Granulation Tissue Formation
6. Foreign Body Reaction
7. Fibrosis/Fibrous Capsule Development

Injury

- Implantation of the device is likely to damage blood vessels in the vicinity
- Initially damaged blood vessels constrict (haemostasis) and clots can form
- Secondly the walls of surrounding blood vessels can dilate and become porous
- This lets out exudate containing inflammatory cells and factors.

Blood/Material Interactions

- Platelets and proteins like fibrin and fibronectin interact to form clots
- These can coat the surface of the device as well as preventing further blood loss
- Platelets release growth factors and other chemicals that attract inflammatory and immune cells to the injury

Provisional Matrix Formation

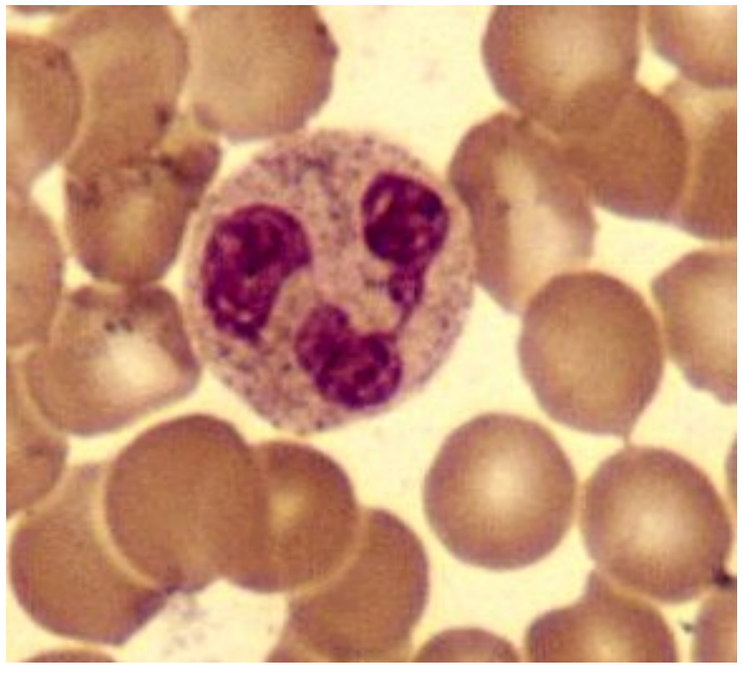
- Proteins released due to injury to vascularised tissue form the matrix
- In a normal injury this forms the basis for the healing process
- For an implant this means almost immediate protein biofouling
- This can be a problem for a sensor

Acute Inflammation

- Inflammation is named for the redness, swelling, and temperature change
- This is caused by the flooding of the injury site with blood and exudate
- This also allows antibodies and immune cells to get to the site of the injury
- The first to arrive are neutrophils

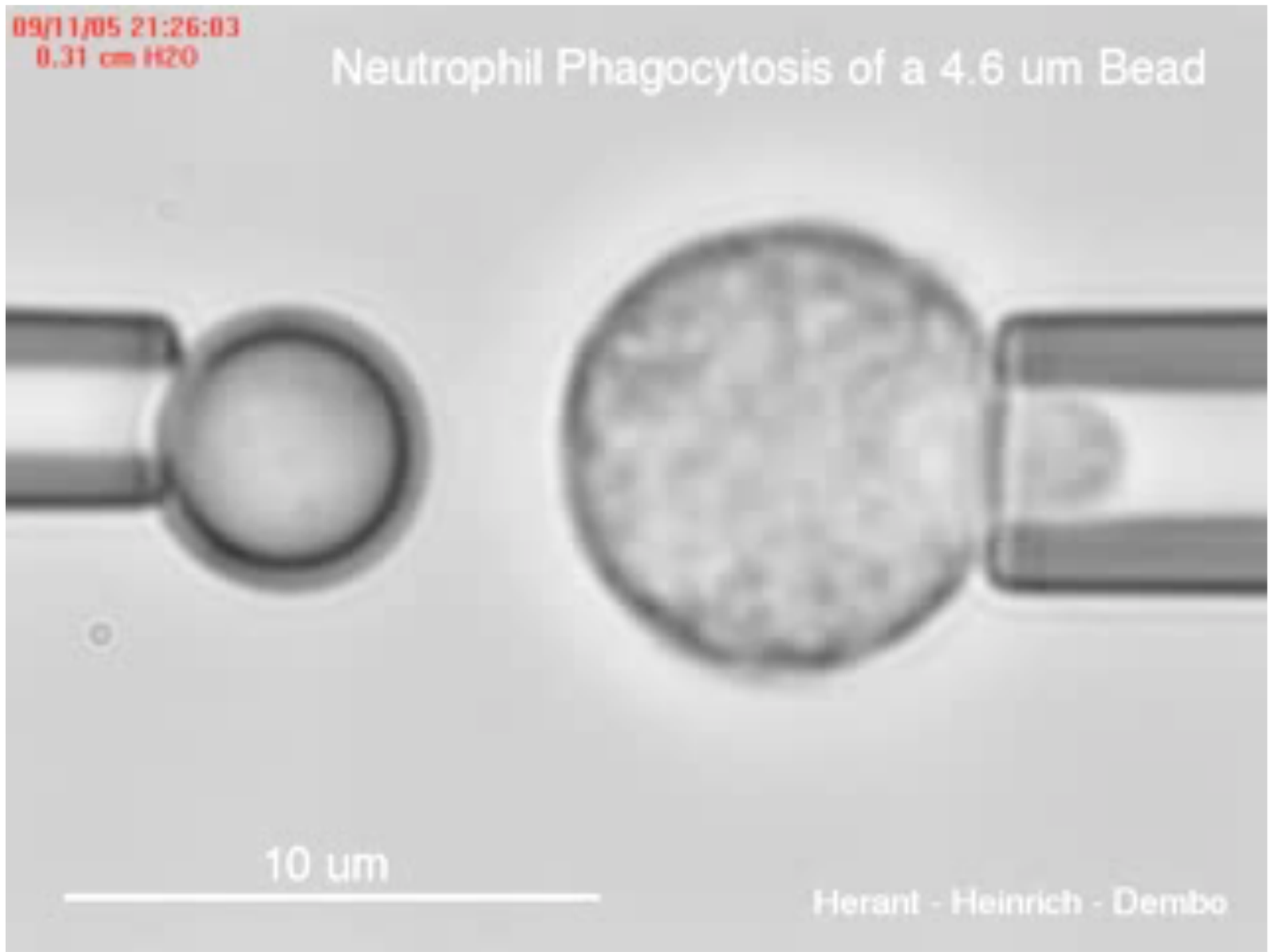
Neutrophils

- Polymorphonuclear leukocytes/neutrophils - most abundant type of white blood cell
- Phagocytes are designed to detect and consume bacteria
- They also release products to attract and stimulate other immune cells to the injury



Phagocytosis

- Neutrophils engulf attackers
- Granules inside contain anti-bacterial agents
- Oxidation generates toxins



Neutrophil Chemotaxis

- Invading bacteria are "tagged" with anti-bodies
- Chemicals attract phagocytes
- Chemotaxis is movement up a chemical gradient

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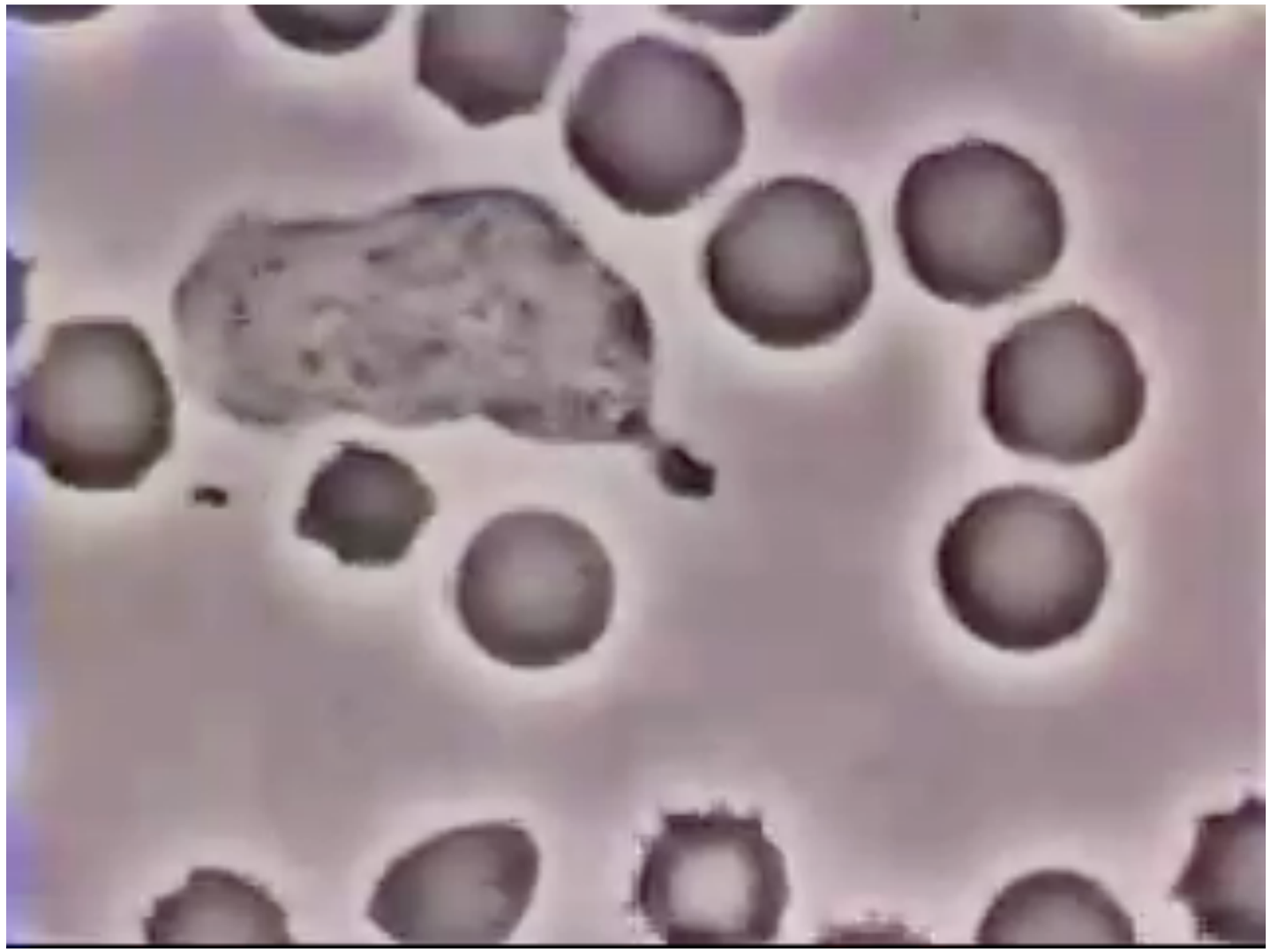
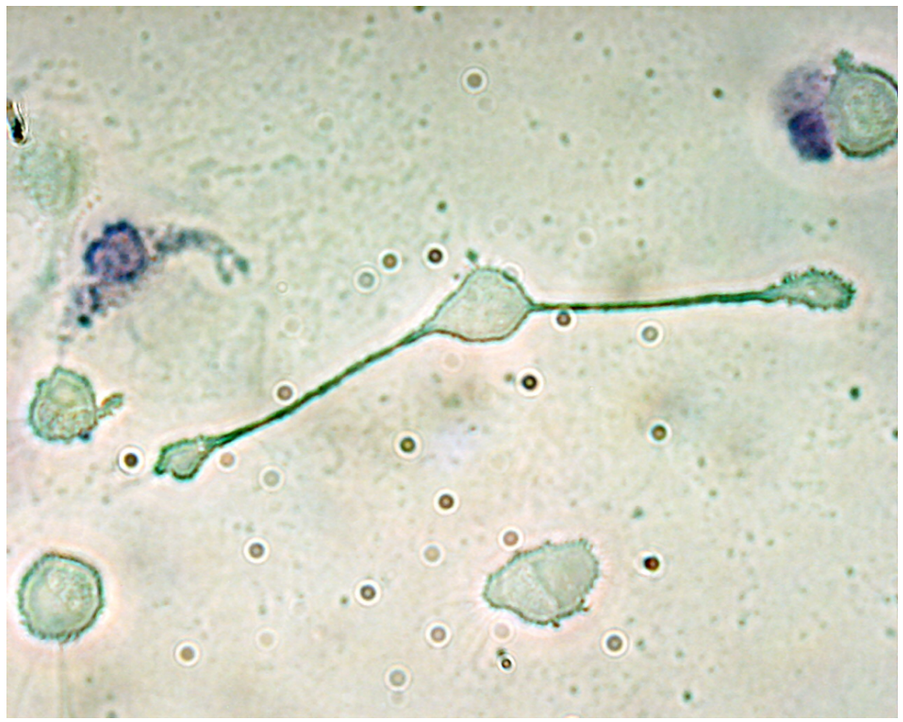


Macrophages

- Monocytes are attracted to the wound site within a few hours/days of injury
- Growth factors present encourage them to mature into macrophages
- Much larger than neutrophils
- They consume pathogens and damaged tissue

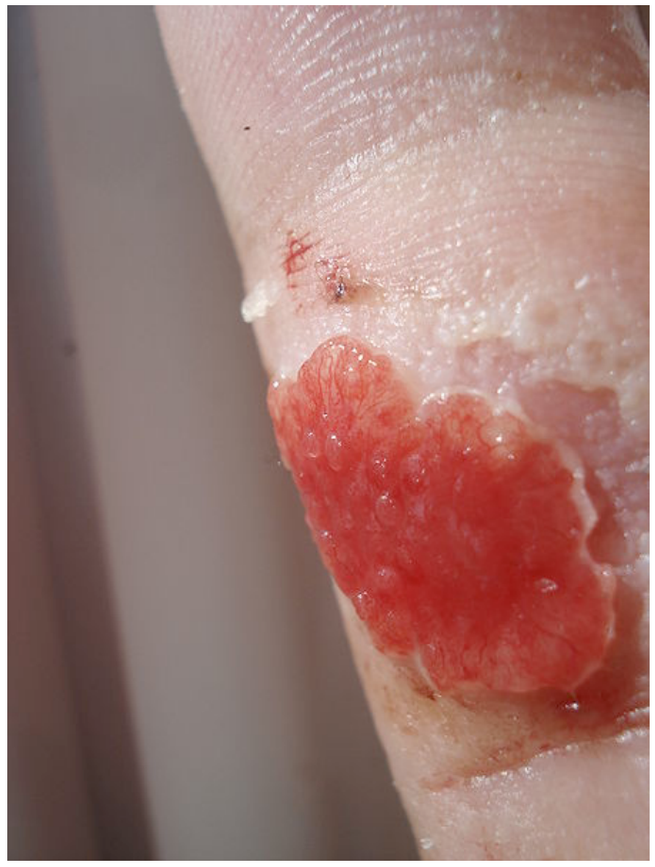


Chronic Inflammation

- Inflammation should be a short term process or healthy tissue can be damaged
- Foreign bodies like medical implants can lead to unwanted chronic inflammation
- Chemical and physical properties of an implant are important considerations
- Movement of the implant can affect healing

Granulation Tissue

- Fibroblasts and endothelial cells proliferate at the implant site within a day or so
- Together with immune cells they form granulation tissue, with red and granular appearance
- This consists of a fibrous tissue matrix and new blood vessels

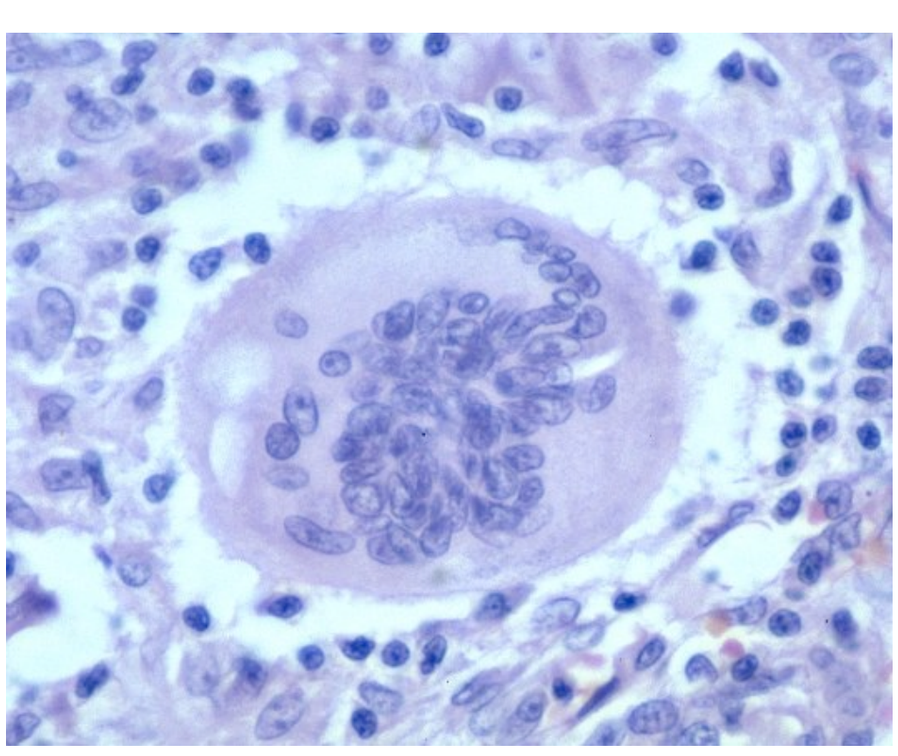


Angiogenesis

- Fibroblasts and other cells in the granulation tissue require oxygenation
- Vascular endothelial cells at implant site form capillaries to supply blood
- This process is known as angiogenesis or neo-vascularisation

Foreign Body Reaction

- Phagocytes will not be able to engulf a typical implant due to size disparity
- Macrophages activated at the implant surface will produce corrosive enzymes
- They can also coalesce to form multi-nucleated foreign body giant cells



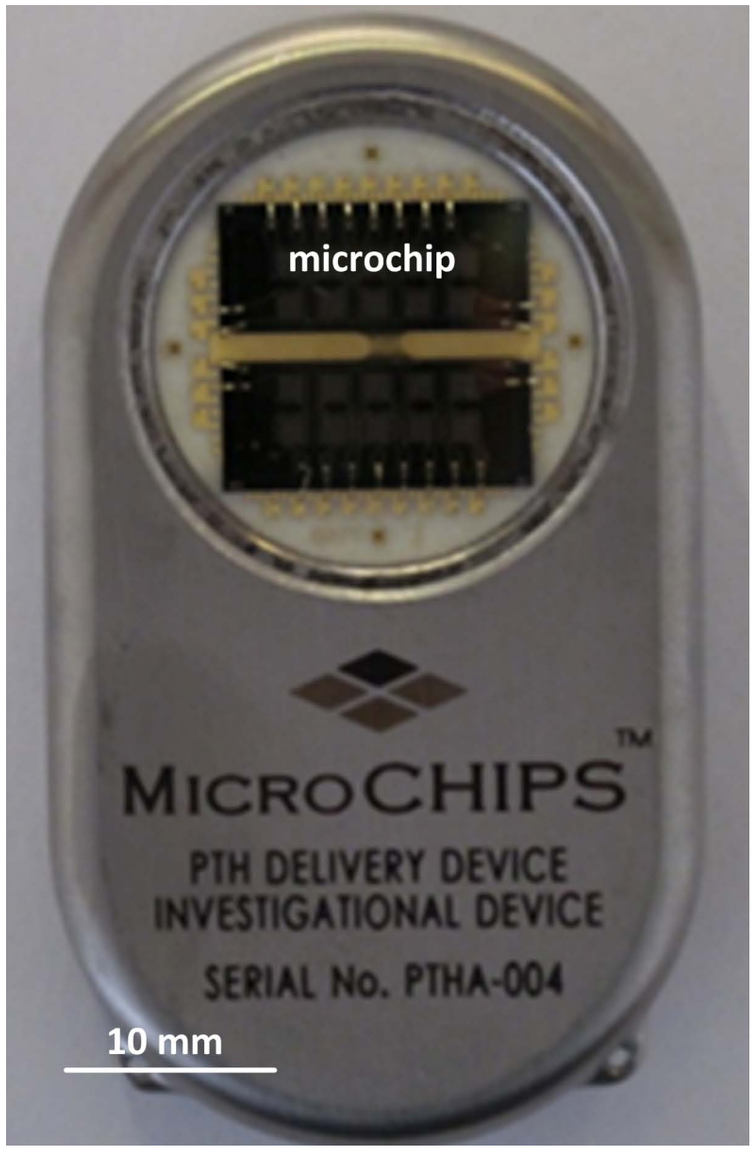
Fibrosis/Fibrous Tissue Formation

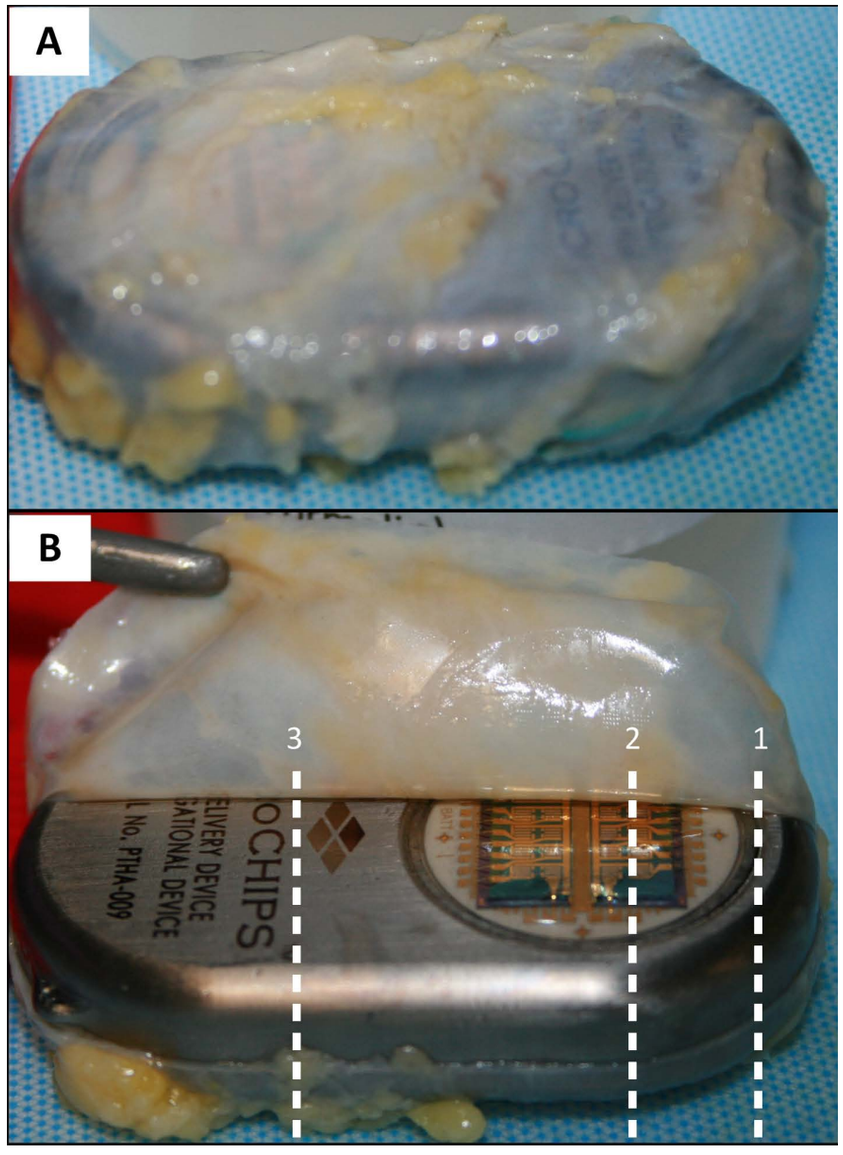
- Macrophages and FBGC may exist at the device surface for the lifetime of implant
- Beyond this the fibroblasts will gradually begin to produce a collagen matrix
- This fibrous tissue can eventually encapsulate the implant and seal it away
- This may not happen with porous materials

Impact on Implanted Devices

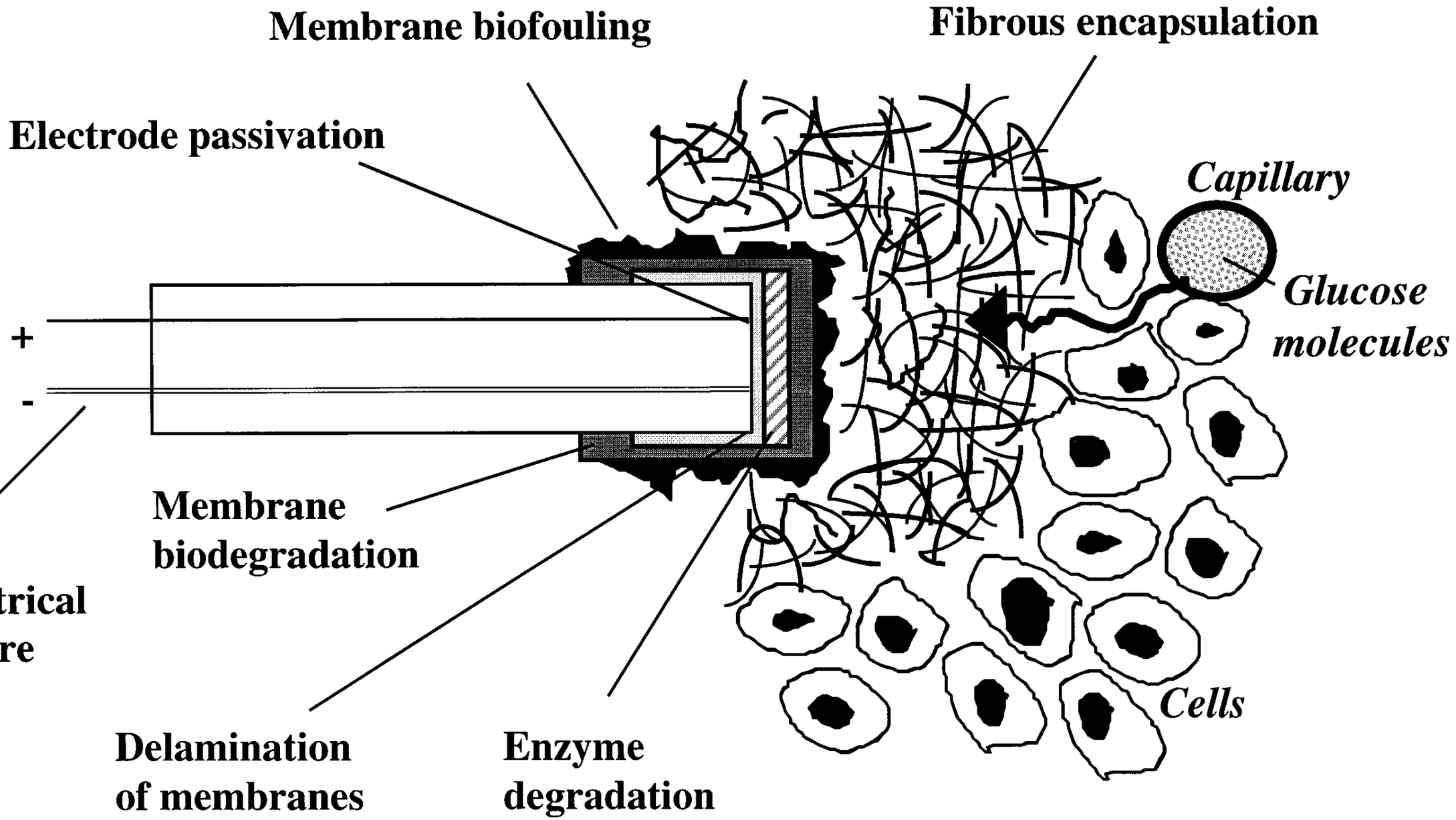
- Protein biofouling can lead to immediate reduction in sensor sensitivity
- Macrophages and FBGCs can release factors that degrade the implant
- Fibrous capsule formation can cut off a sensor from the environment
- Neo-vascularisation during granulation tissue stage could increase sensitivity

Implanted Drug Delivery System





Impact on Biosensor



Engineering Tissue Response to Implants

- Different approaches and techniques are required to control different effects
- Protein biofouling is the first adverse effect on an implanted sensor device
- Proteins adsorb more onto hydrophobic surfaces so use hydrophilic materials?
- Poly(ethylene) glycol (PEG) is a possibility

Surface Modifications

- Hydrogels are polymer networks that are highly absorbent to water
- Typically they do not affect diffusion of analytes to a sensor membrane
- They can be modified with ligands to promote certain cells to adhere
- Growth factors to control angiogenesis and fibrosis could also be incorporated

Drug Delivery

- Controlled release of growth factors or other drugs from implant surfaces
- Biodegradable microspheres are one possible delivery method
- VEGF - Vascular Endothelial Growth Factor
- Dexamethasone - anti-inflammatory and anti-fibrotic drug

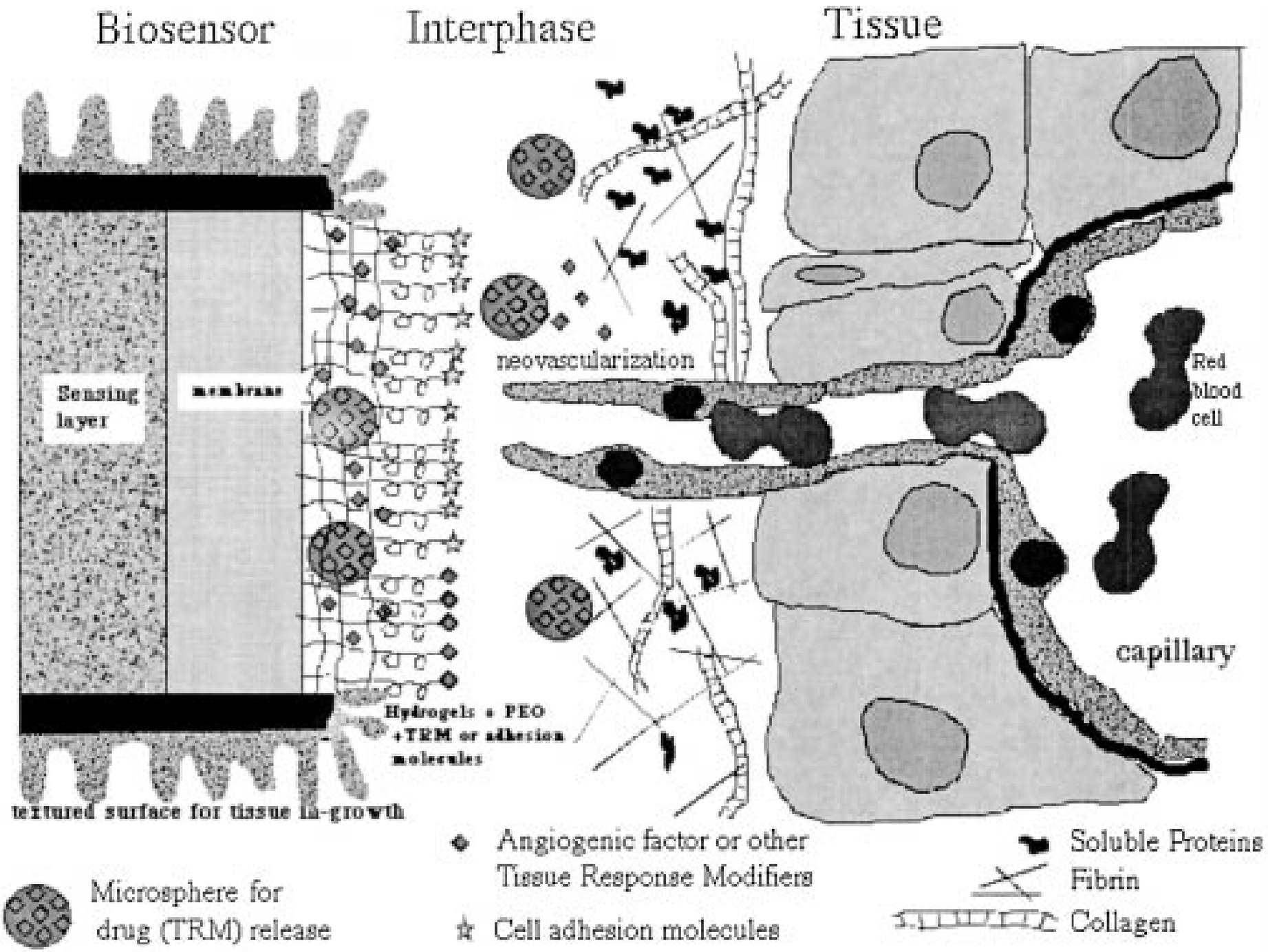
Nitric Oxide Release

- Nitric oxide (NO) is a naturally occurring compound that causes vasodilation
- It is also involved in the inflammatory process and wound healing
- It has been shown to promote angiogenesis and reduce fibrous capsule formation
- Possible interference with chemical sensors

Physical Modification

- The micro and nano-scale topography of materials influences the tissue response
- Porous surfaces can encourage tissue ingrowth but pore size is very important
- Small pores increase fibrous encapsulation
- Large pores encourage inflammatory cells
- Ideally the pores should encourage capillary development around the sensor

Sensor Adaptions



Regulating Implant Biocompatibility

- Medical devices are heavily regulated by
  - Food and Drug Agency (FDA - US)
  - European Medicines Agency (EMA - EU)
  - Medicines and Health Regulatory Agency (MHRA - UK)
- Standards are set by the International Standardisation Organisation (ISO)

Active Implantable Medical Devices

- European commission directive 90/385/EEC
- Revised in 2007 with directive 2007/47/EC
- Covers the placing on the market and putting into service of active implantable medical devices (AIMDs)
- Active means they use electrical energy or some other power source to operate

AIMD Directive

- Sets out which standards the active implants must follow
- This includes things like sterilisation, labelling and other supplied information
- The bulk of the standards applied concern evaluation and testing of implants
- These are set out in ISO 10993

Standard ISO 10993

- There are 18 parts to ISO 10993
- The most import for implants are:
  1. Evaluation and testing within a risk management process
  4. Selection of tests for interactions with blood
  5. Tests for in vitro cytotoxicity
  6. Tests for local effects after implantation

Standard ISO 10993

- Continued:
  9. Framework for identification and quantification of potential degradation products
  10. Tests for irritation and delayed-type hypersensitivity
  11. Tests for systemic toxicity
  12. Sample preparation and reference materials
  13. Identification and quantification of degradation products from polymeric medical devices

Standard ISO 10993

- Continued:

16. Toxicokinetic study design for degradation products and leachables
17. Establishment of allowable limits for leachable substances
18. Chemical characterization of materials

Medical Device Categorisation

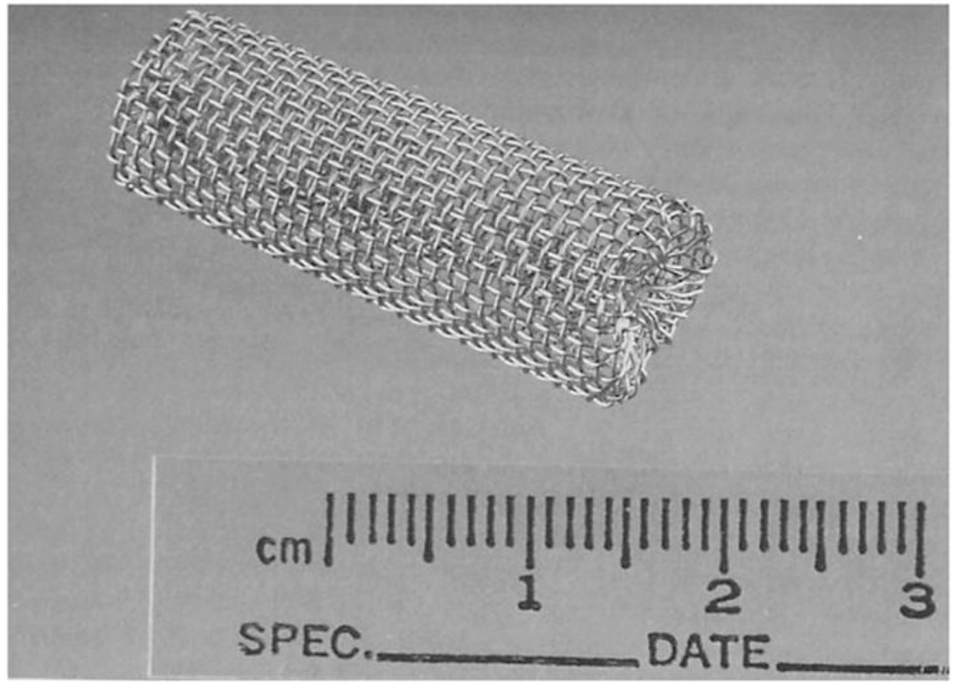
- ISO 10993-1:2009 categorises devices by level of tissue contact and contact duration
  - Surface devices - Skin, mucosal membranes or breached/compromised surfaces
  - External communicating devices - Blood path (indirect), tissue/bone/dentin or circulating blood
  - Implant devices - Tissue/Bone or blood
- Limited (<24 hours), Prolonged (1-30 days), Permanent contact (>30 days)

In-Vitro Testing

- ISO 10993-5:2009 - Tests for in vitro cytotoxicity
- Cells are cultured directly on samples of implant material
- Lysing of cells, cell rounding and/or growth inhibition indicates cytotoxicity
- Cell lines used are defined in the standard

Cage Method for In-Vivo Testing

- Material to be tested is implanted within a stainless steel wire mesh cage (rat)
- Exudate is collected from the cage and analysed for inflammatory cells
- This data is compared with empty controls or controls with "safe" materials



Post-Explantation Testing

- Implanted sensors used in in-vivo testing should be recovered
- The function of the device after explantation needs to be confirmed
- Thickness of the fibrous capsule and other histopathological testing is required

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