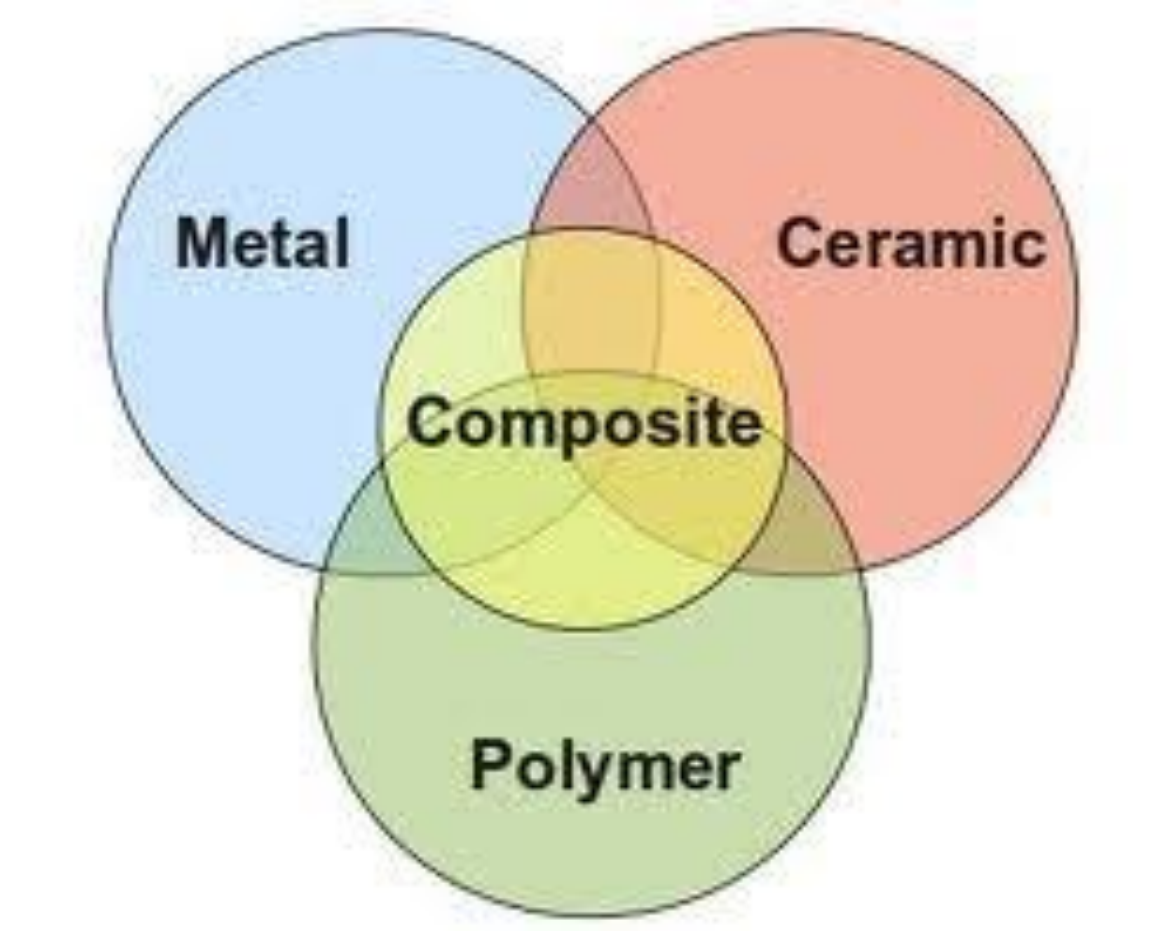
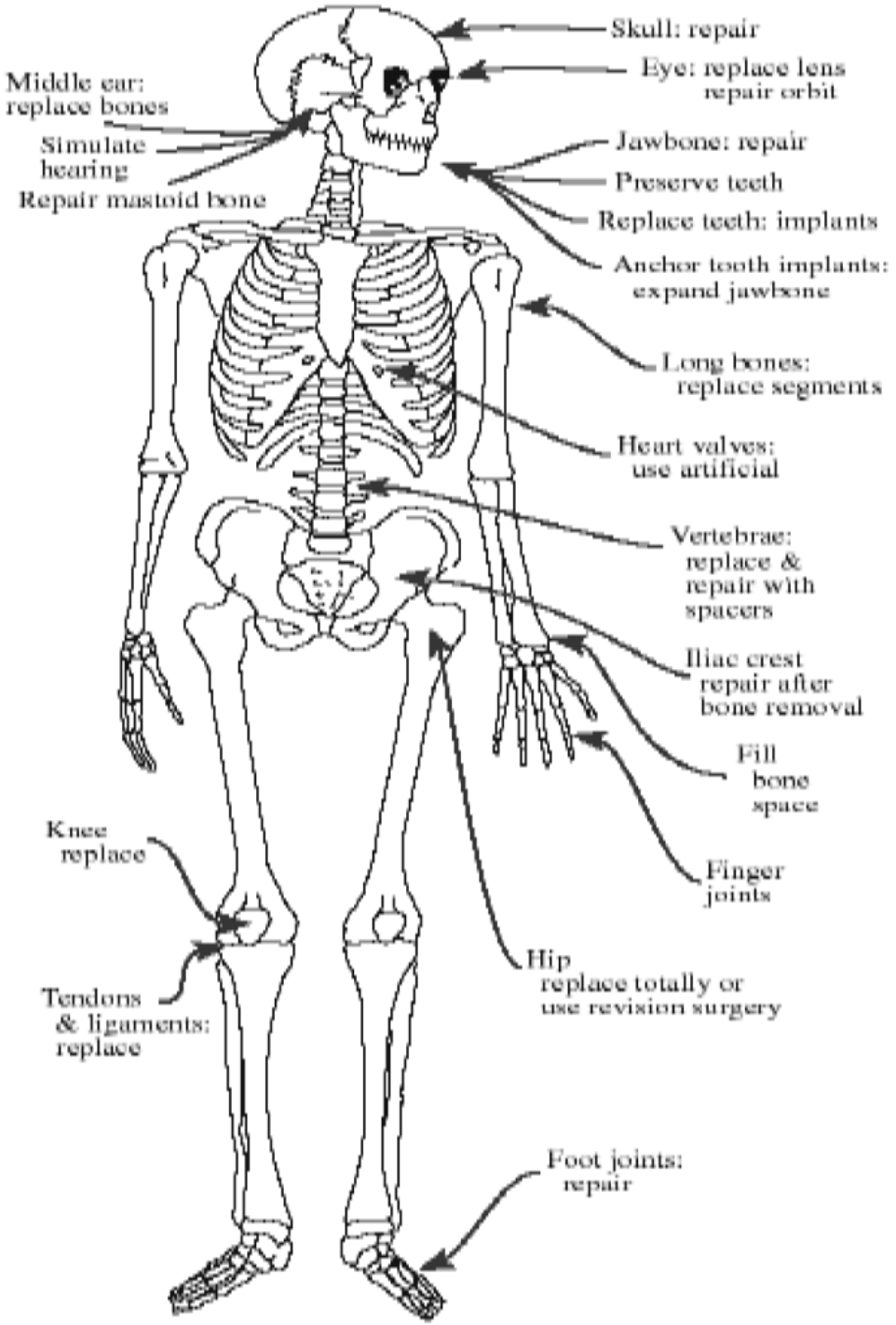

In The Name Of
GOD

آشنایی با زیست سازگاری

تهیه و تنظیم : مریم جهانی کیا
کارشناس ارشد مهندسی پزشکی
اداره کل تجهیزات پزشکی

انواع بیومتریال ها




Skull: repair
Eye: replace lens
repair orbit
Middle ear:
replace bones
Simulate
hearing
Repair mastoid bone
Jawbone: repair
Preserve teeth
Replace teeth: implants
Anchor tooth implants:
expand jawbone
Long bones:
replace segments
Heart valves:
use artificial
Vertebrae:
replace &
repair with
spacers
Iliac crest
repair after
bone removal
Fill
bone
space
Finger
joints
Knee
replace
Hip
replace totally or
use revision surgery
Tendons
& ligaments:
replace
Foot joints:
repair

- **Bioinert Biomaterials (بیومواد زیست خنثی)**

stainless steel, titanium, alumina, partially stabilized zirconia, and ultra high molecular weight polyethylene)

- **Bioactive Biomaterials (بیومواد بیو اکتیو)**

synthetic hydroxyapatite[$Ca_{10}(PO_4)_6(OH)_2$], glass ceramic)

- **Bioresorbable Biomaterials (مواد قابل جذب)**

tricalcium phosphate [$Ca_3(PO_4)_2$] and polylacticpolyglycolic acid copolymers**)**

مزایا و معایب بایو سرامیک ها

مزایا :

زیست سازگار

مقاومت در برابر سایش

وزن کم

معایب:

- استحکام کششی کم
- ساختن دشوار
- چقرمگی کم
- مقاومت کم

تاثیر فرایند های مختلف تولید بر زیست سازگاری

Production

Raw materials

Aggregates
Release agent
Pigments
Plasticizer
…

Component

Processing

Auxiliary agent
Contamination
Coating
Surface treatment
Shaping
Cleaning

Medical device

Processing and Packaging

Packaging material
Labeling
Glue

Packaging

Process conditions

Sterilization

Transport

Transport-
and
Storage conditions

Storage

Ageing

Transport

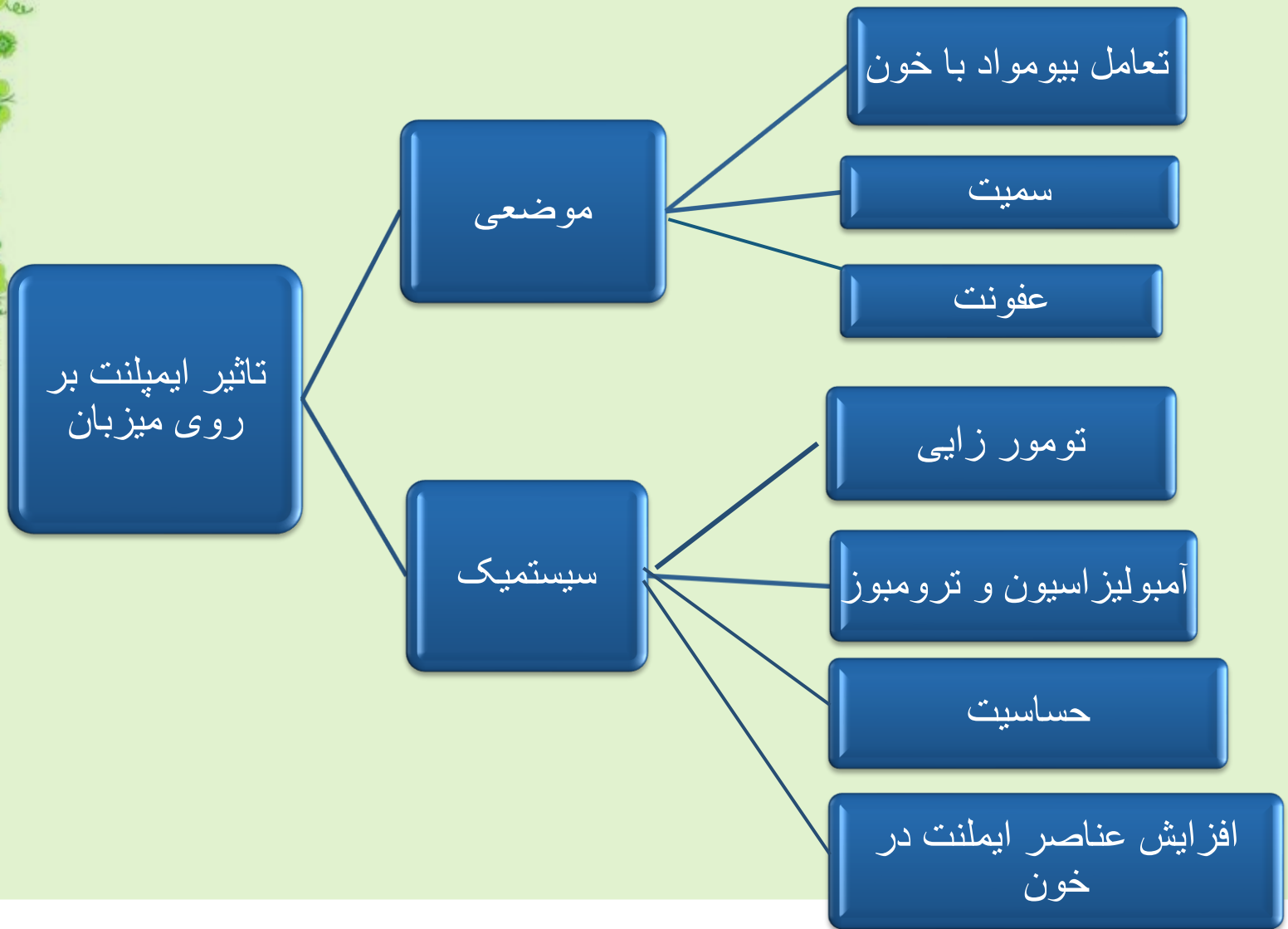
Storage

Host Reaction to Biomaterials

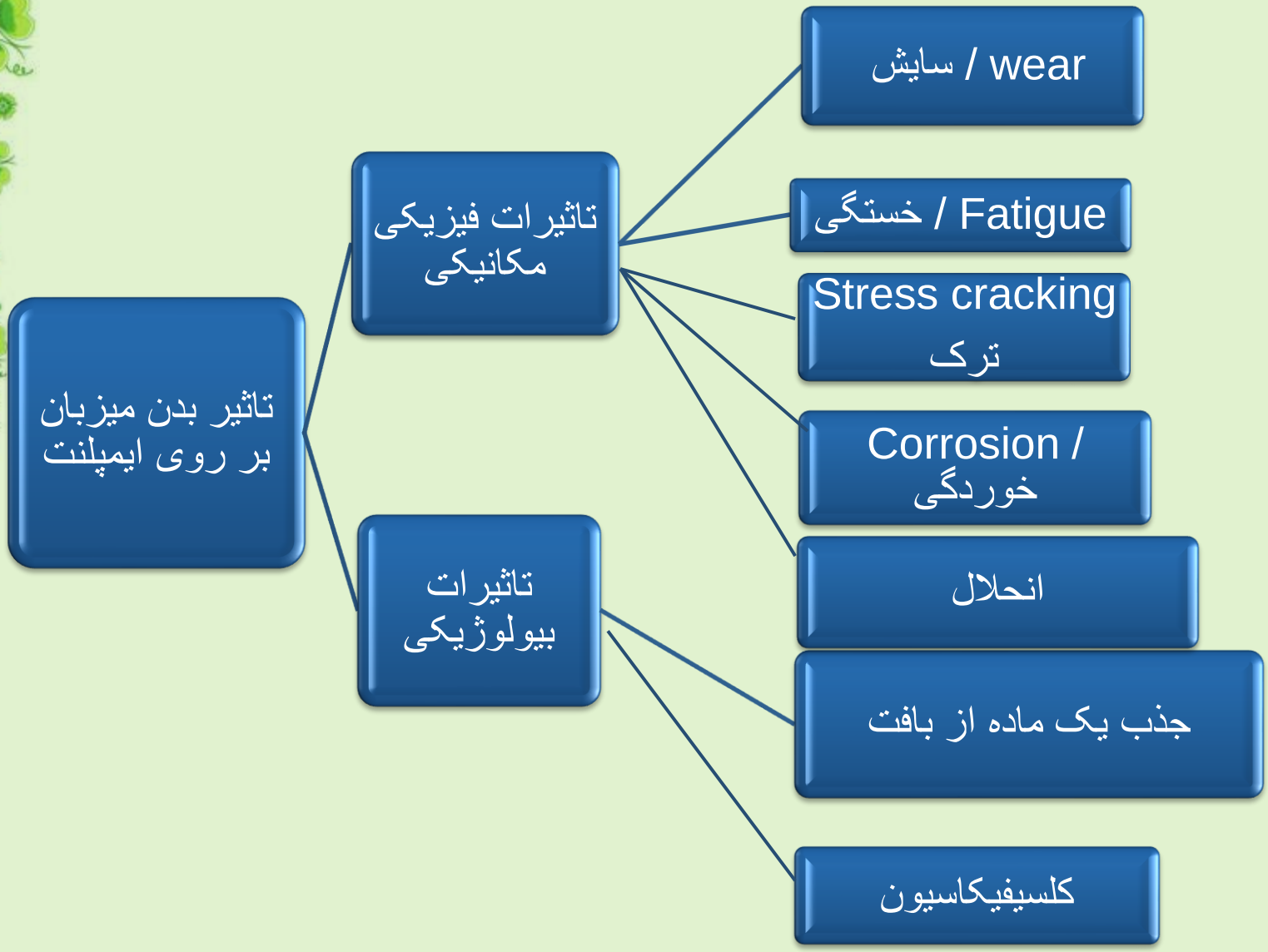
همه ایمپلنت ها تا حدودی با محیط بافتی که در آن قرار می گیرند، تعامل دارند.

این شامل هر دو اثر ایمپلنت بر روی بافت میزبان و اثرات میزبان بر روی ایمپلنت است

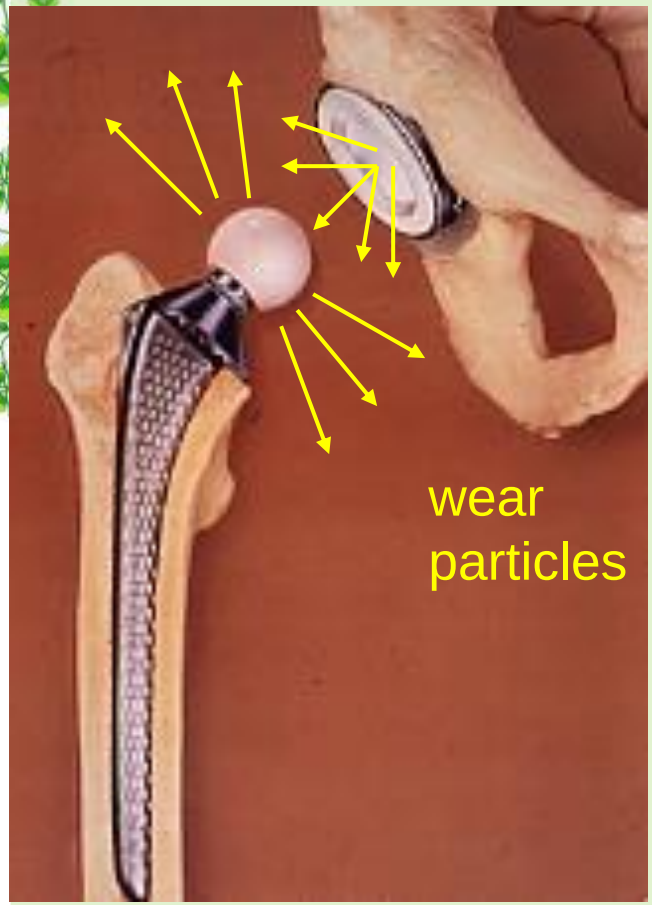
واکنش میزبان به بیومواد



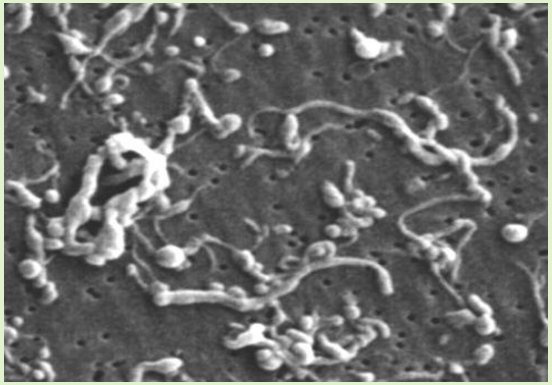
واکنش میزبان به بیومواد

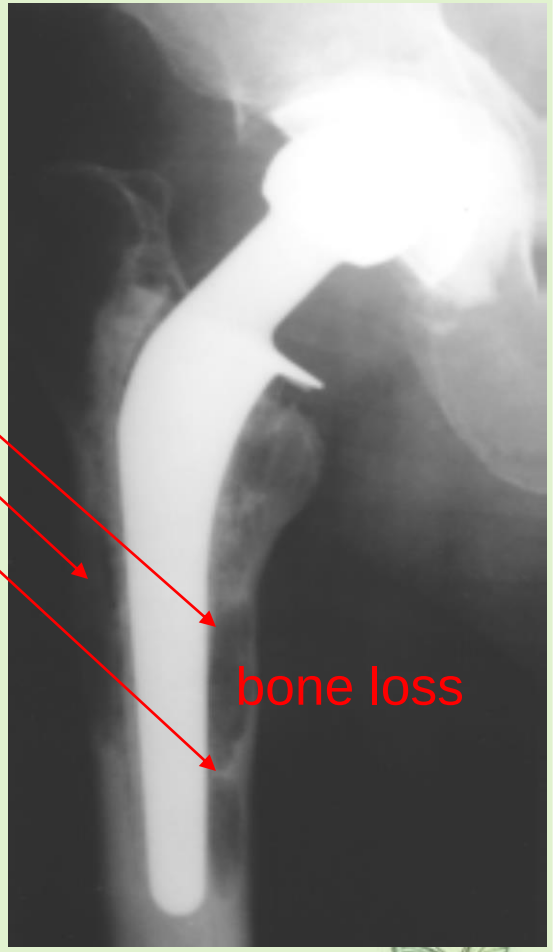


Wear-Mediated Osteolysis

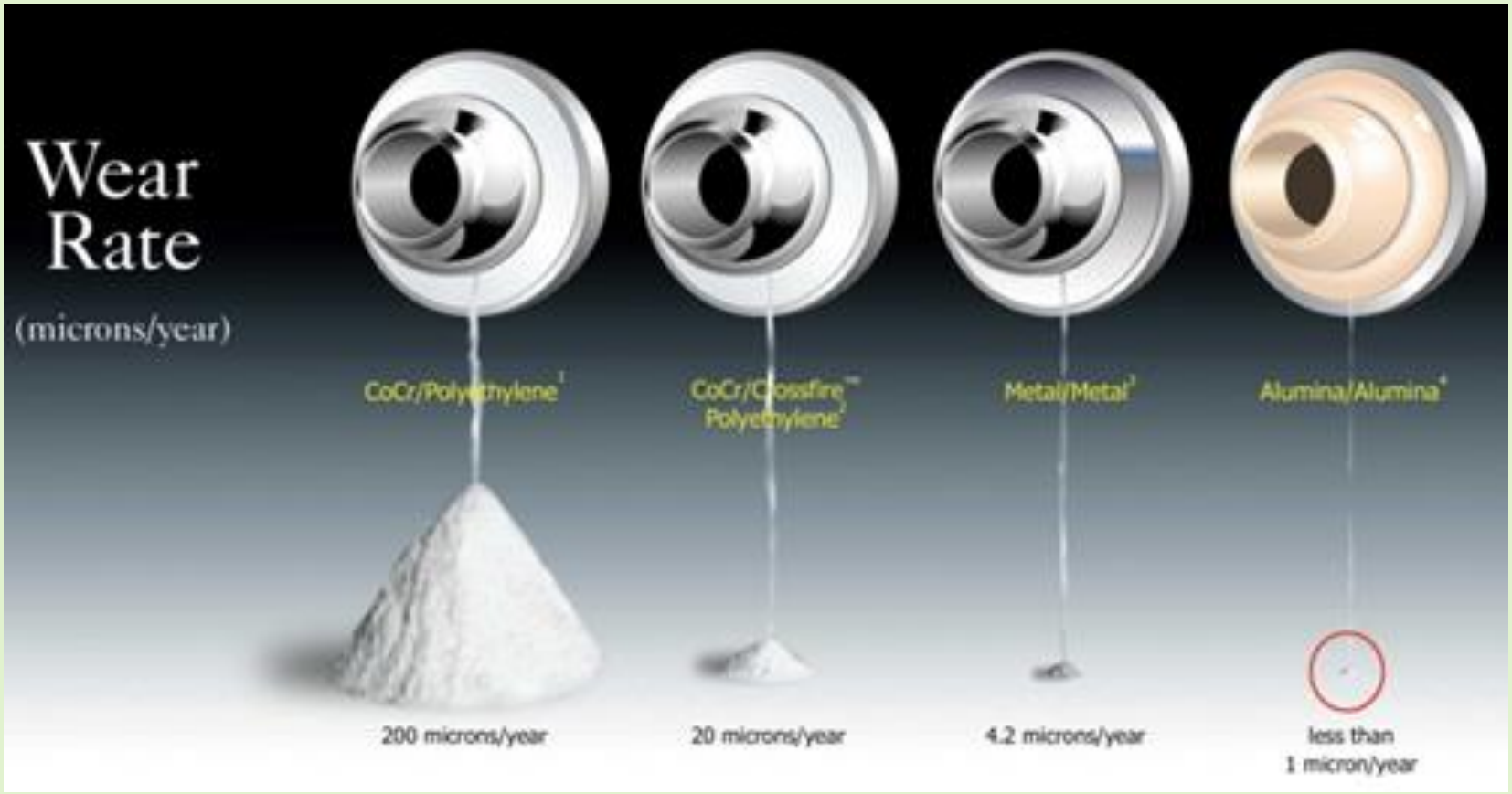


Wear particles from the replacement head and liner cause inflammation that can lead to pain, bone loss, and ultimately revision surgery





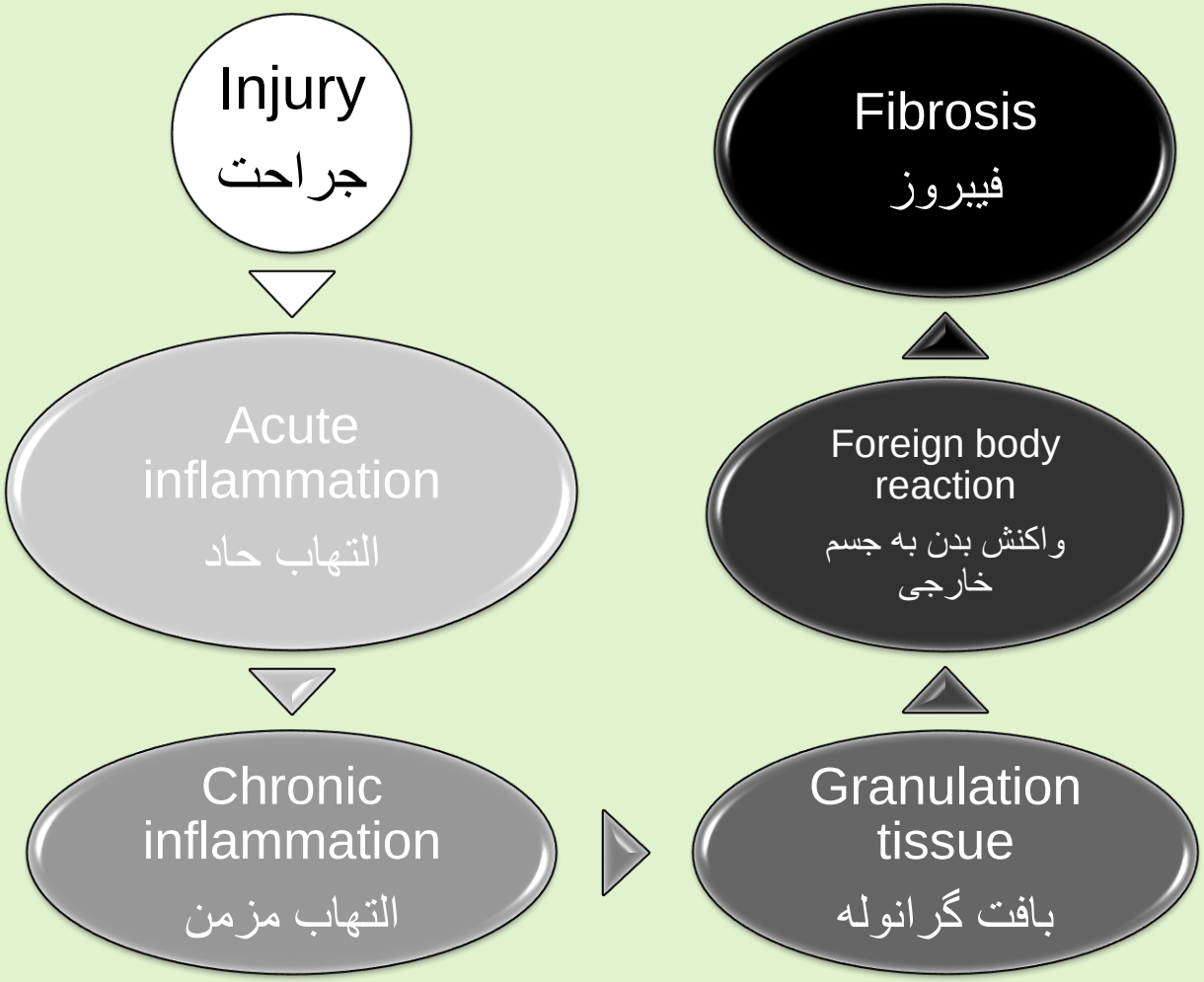
Archibeck, MJ; Jacobs, JJ; Roebuck, KA; Glant, TT. *Journal of Bone & Joint Surgery,* 2000


Wear Rate
(microns/year)
CoCr/Polyethylene[1]
CoCr/Crossfire™ Polyethylene[2]
Metal/Metal[3]
Alumina/Alumina[4]
200 microns/year
20 microns/year
4.2 microns/year
less than 1 micron/year

Host Reaction to Biomaterials

Sequence of Local Events Following Implantation

توالی فرآیند ها بعد از کاشت ایمپلنت



واکنش میزبان به بیومواد

جراحت - Injury

- بلافاصله پس از آسیب، تغییراتی در جریان عروقی و نفوذپذیری ایجاد می شود. مایعات، پروتئین ها و سلول های خونی از سیستم عروقی به بافت آسیب دیده فرار می کنند

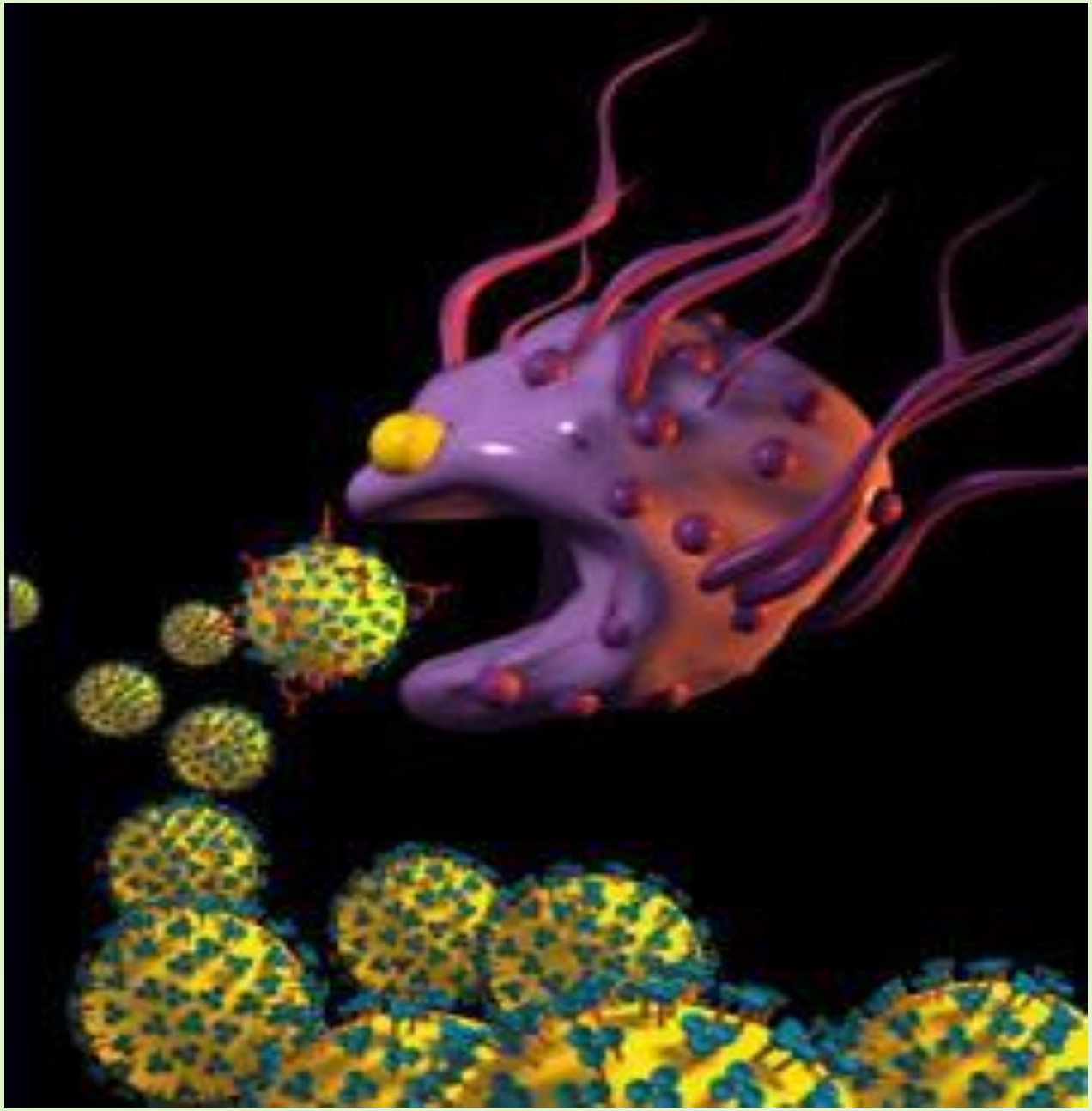
- نوع سلول های حاضر در محیط به زمان طی شده از ابتدای جراحت بستگی دارد.

Neutrophil (24-48 hr) ⟶ Monocyte ⟶ Macrophage

- Size
- Shape
- Physical / chemical properties

- Variation in Intensity
- Duration of the inflammatory
Or wound healing process

Biocompatibility of a biomaterial



واکنش میزبان به بیومواد

التهای حاد و مزمن - Acute & chronic inflammation

مدت زمان کوتاه – بسته به وسعت آسیب، از دقیقه تا چند روز طول می کشد.

مشخصه اصلی: ترشح مایعات و پروتئین های پلاسما و مهاجرت لکوسیت ها.
اگرچه بیومواد به طور کلی توسط نوتروفیل ها یا ماکروفاژها فاگوسیتوز نمی شوند، زیرا اندازه آنها نابرابری است (سطح آنها از نظر اندازه بزرگتر از سلول است)، ممکن است اتفاقات خاصی رخ دهد.

التهاب مزمن از نظر بافت شناسی کمتر از التهاب حاد یکنواخت است

واکنش میزبان به بیومواد

بافت گرانوله - Granulation tissue

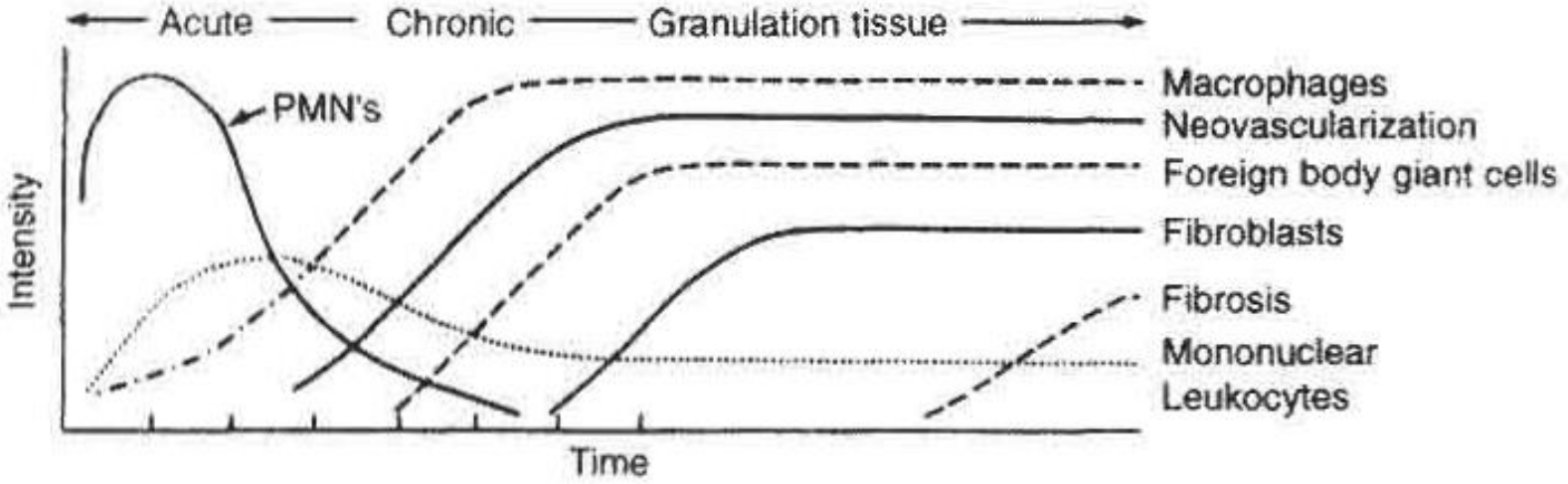
ظاهری صورتی و دانه ای نرم بر روی سطح و بهبود زخم ها.

شامل رگ‌های خونی کوچک و فیبروبلاست‌ها می‌شود.

بسته به میزان آسیب، ۳ تا ۵ روز پس از کاشت بیومتریال مشاهده می شود.

واکنش میزبان به بیومواد

Granulation tissue



The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign body reaction to implanted biomaterials.

واکنش میزبان به بیومواد

Foreign body reaction - واکنش به جسم خارجی

سطح بیومواد

سطوح صاف و صاف (پروتزهای پروتز سینه)
لایه ای از ماکروفاژها به ضخامت یک تا دو سلول

سطوح نسبتا ناهموار (پروتزهای عروقی(ePTFE ، ماکروفاژها و سلول های غول پیکر خارجی

.

A. Surface properties
B. Form & topography
C. Surface / Volume

Foreign body reaction & ratio of macrophages

اگرچه این سلول‌های غول پیکر خارجی ممکن است در طول عمر ایمپلنت باقی بمانند، اما مشخص نیست که فعال می‌مانند، اجزای لیزوزومی خود را آزاد می‌کنند یا خاموش می‌شوند.

Categorization of medical devices

Medical devices can be categorized to facilitate the selection of appropriate tests

The categorization is based on
- Nature of body contact
- Duration of body contact

Categorization of medical devices
Surface contact

Skin
– Devices that only contact intact skin surfaces
– Examples: Electrodes, tapes, compression bandages, various monitor probes, external orthopedic braces

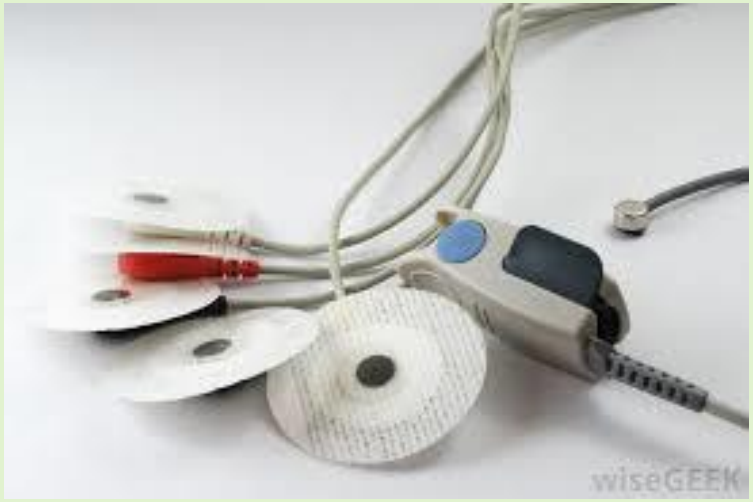
• **Mucous membranes**
– Devices that contact intact mucous membranes
– Examples: Feeding tubes, endoscopes, endotracheal tubes, oral swabs, intrauterine devices

• **Breached or compromised surfaces**
– Devices that contact breached or otherwise compromised body surfaces
– Examples: Dressings / bandages, for wounds, ulcers, burns…

Categorization of medical devices

Surface contact

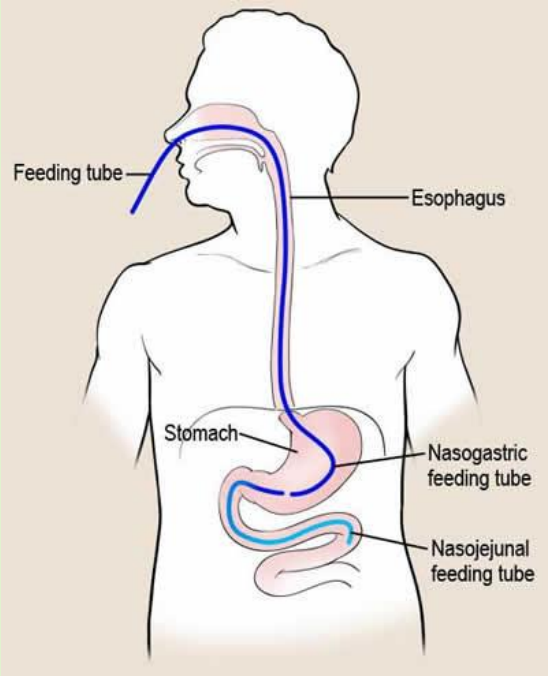
Skin

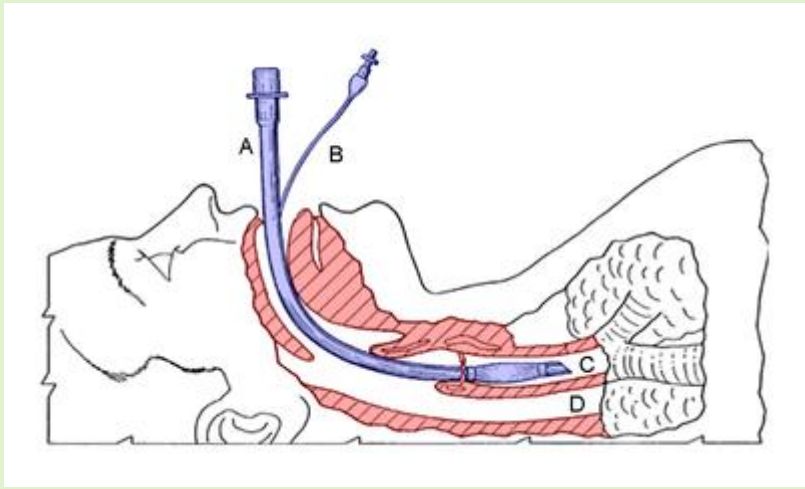


Categorization of medical devices

Surface contact

Mocous membrane





Categorization of medical devices

Surface contact

Breached or compromised surfaces

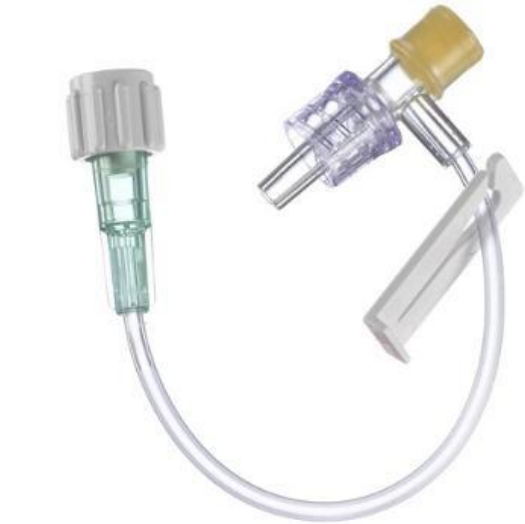
Categorization of medical devices
External communicating

Blood path, indirect
– Devices that contact the blood path at one point and serve as a conduit for entry into the vascular system
– Examples: IV sets, extension sets, transfer sets, etc.

• **Tissue/bone/dentin**
– Devices that contact tissue, bone or pulp/dentin systems
– Examples: Arthroscopes, drains, dental cements, dental alloys, skin staples/sutures (Not internal staples or suture)

• **Circulating blood**
– Devices that contact circulating blood
– Examples: Extracorporeal tubing, filters, oxygenators, etc. dialyzers, tubing, intravascular catheters

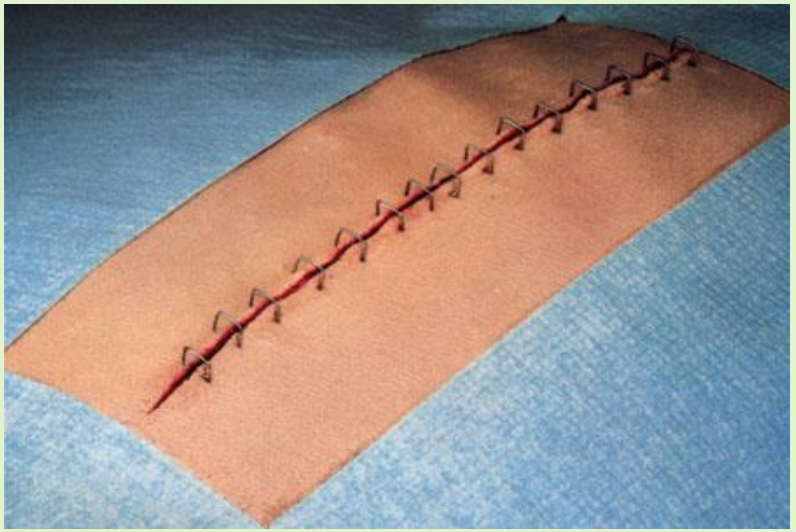
Categorization of medical devices
External communicating devices
Blood path , indirect

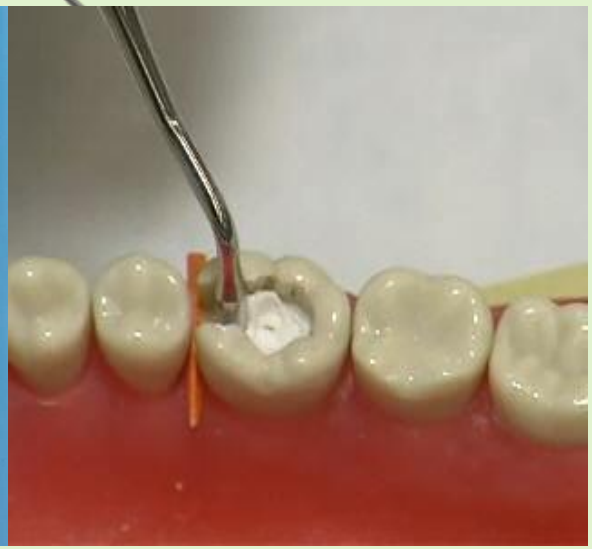


Categorization of medical devices

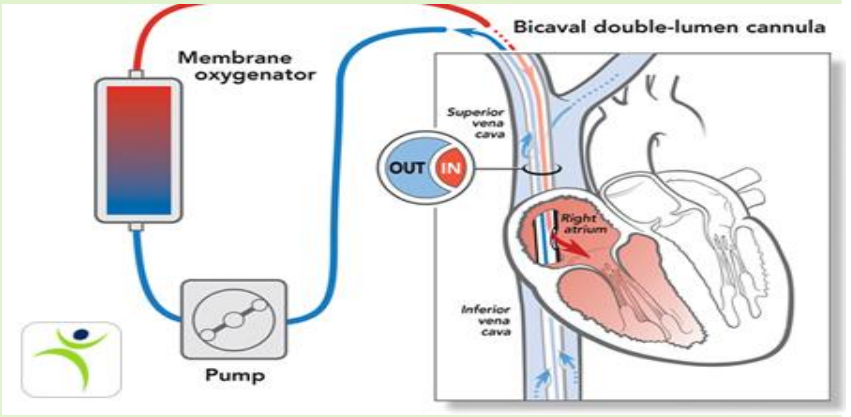
External communicating devices

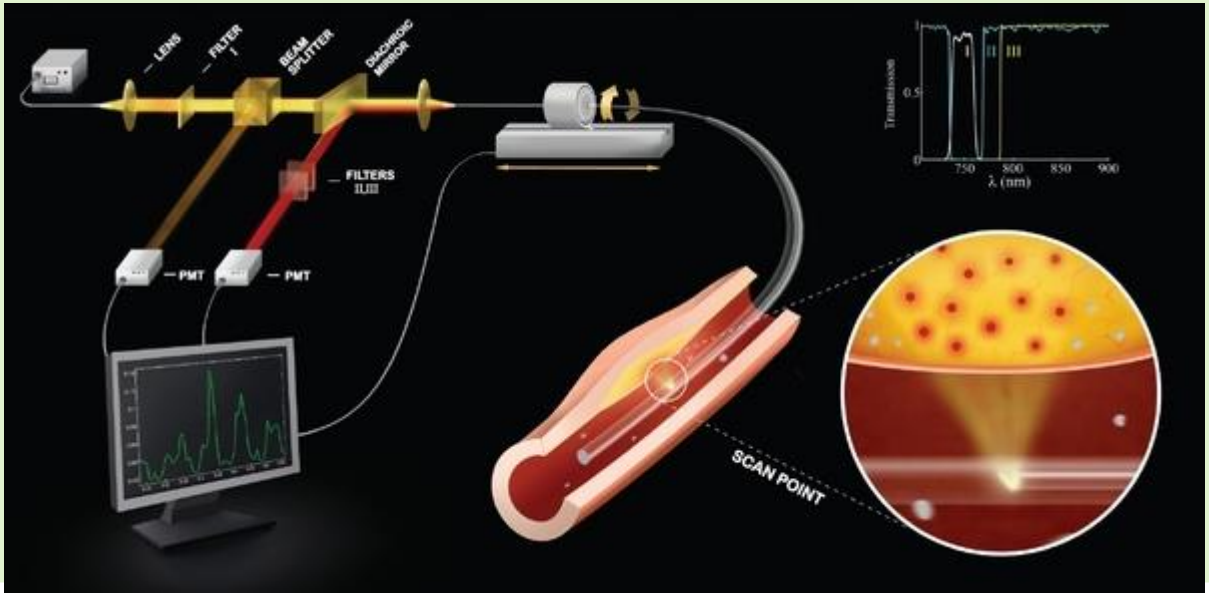
Tissue / Bone / Dentin





Categorization of medical devices
External communicating devices
Circulating Blood





Categorization of medical devices
Implantable

Tissue/bone

– Devices principally contacting bone or tissue and tissue fluid

– Examples:

• Orthopedic pins, plates, joints, cements, etc.

• Pacemakers, tendon implants, breast implants

• **Blood**

– Devices principally contacting blood

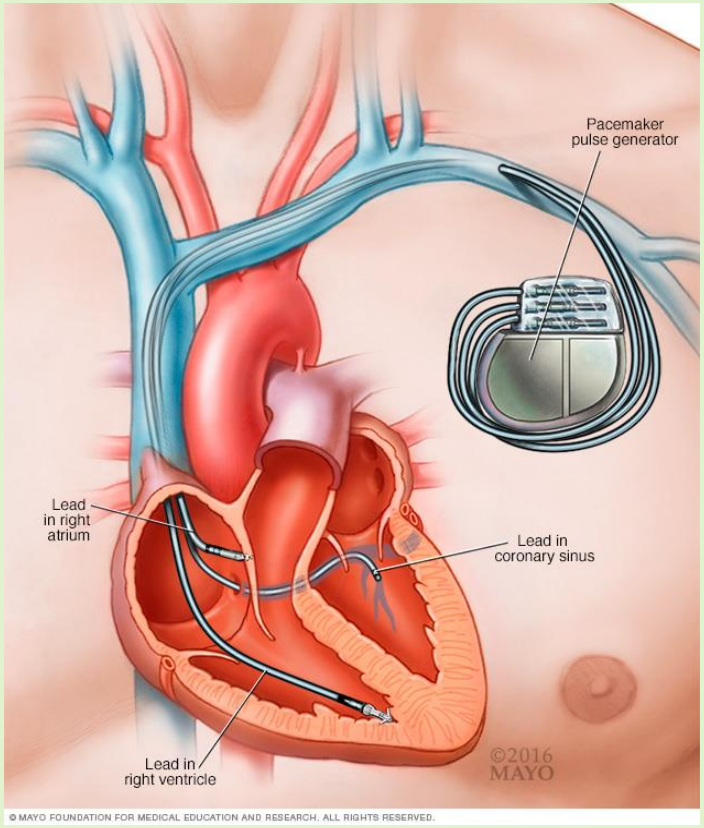
– Examples:

• Heart valves, vascular grafts, internal delivery catheters, pacemaker electrodes

Categorization of medical devices

Implantable

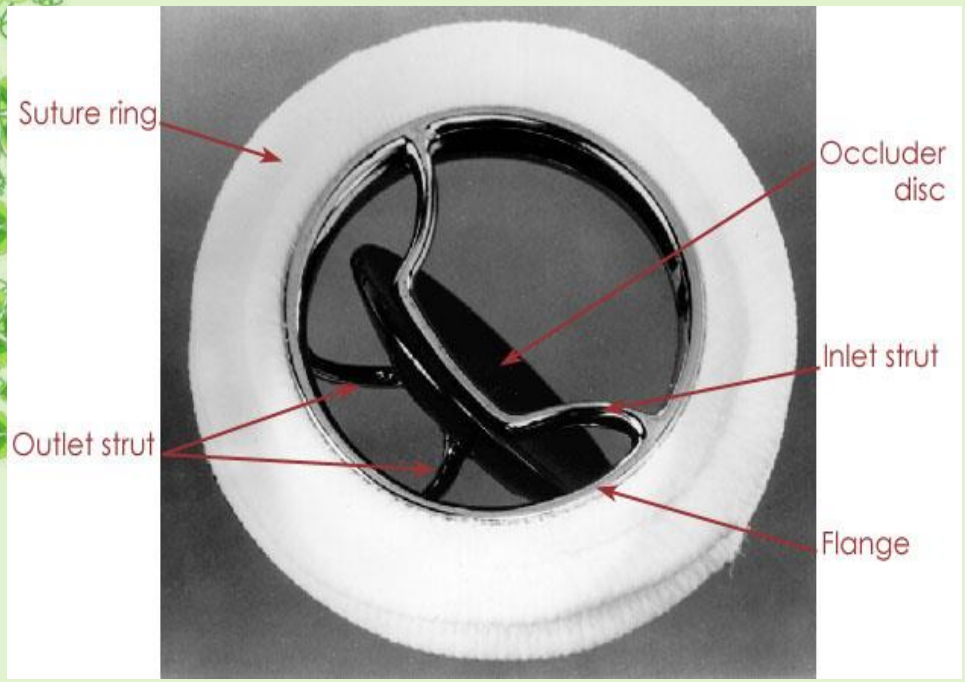
Tissue / Bone

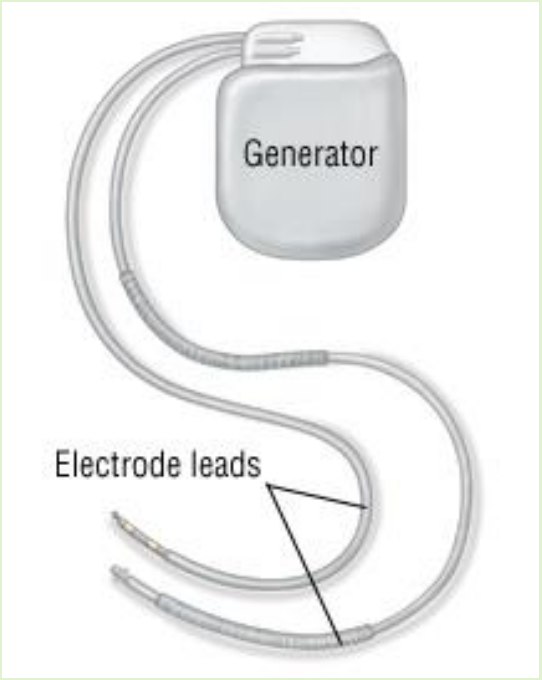


Categorization of medical devices

Implantable

Blood





Categorization of medical devices
Duration

- **Limited exposure (A):** Up to 24 h;
- **Prolonged exposure (B):** Exceed 24 h but not 30 days
- **Permanent contact (C):** Exceeds 30 days.

Contact includes single or multiple use (cumulative effects)

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device	Skin	A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

How to deal with changes ?

The materials or final product shall be

re-evaluated if any of the following occurs:

a) any change in the source or in the specification of the materials used in the manufacture of the product

- change of supplier
- change of animal origin source to vegetable derived material
- change of mol mass
- change of pore size (e.g. polymer meshes)

b) any change in the formulation, processing, primary packaging or sterilization of the product

- addition of BaSO4 (radiopacity)
- change of additives and process aids
- laser marking, chemical etching, ink jet marking
- change of PE *vs* glass vials
- ethylene oxide versus irradiation sterilization

How to deal with changes ?

c) any change in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transport

- degradation during shelf life (toxic monomers)
- improper storage
- catastrophes
- substances leaching from packaging materials

d) any change in the intended use of the product

- change of body contact

e.g. hyaluronic acid (ophthalmic *vs* intra-articular applications)
e.g. polyurethan (catheter tubings *vs* polymer heart valves)
e.g. extension for blood contact

- change of contact duration

e.g. oxygenator 6h / 14d

How to deal with changes ?

e) any evidence that the product may produce adverse effects when used in humans

- post market surveillance data

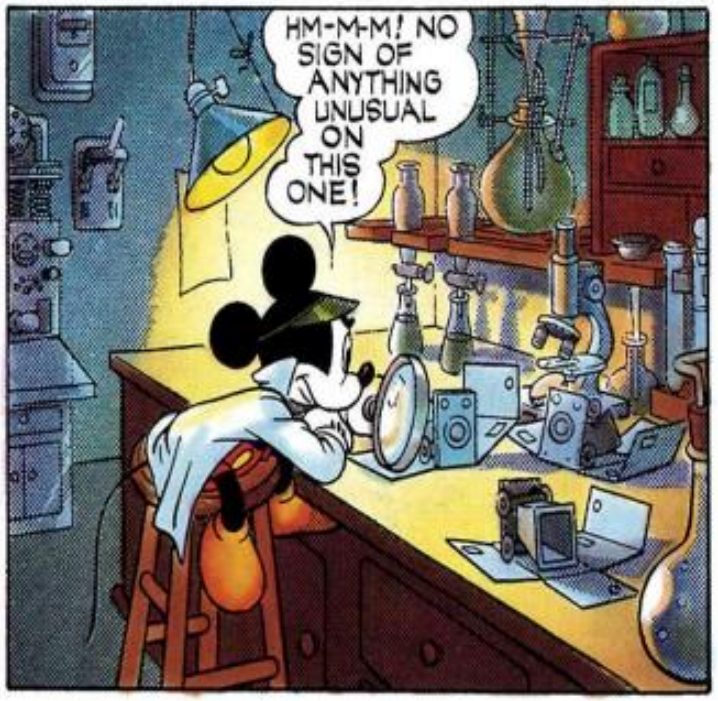
e.g. prostheses loosening

- reprocessing of single use devices

Choice of Test laboraty

PSB Singap

Good Laboratory Practices (GLP)



Accreditation (ISO/IEC 17025)

≅ competence

سمیت سلولی – Cytotoxicity

سمیت سلولی: ایجاد اثرات سمی (مرگ، تغییر در نفوذپذیری غشای سلولی، مهار آنزیمی و غیره.) در سطح سلولی

امروزه اغلب سلول‌هایی که برای کشت استفاده می‌شوند از رده‌های سلولی تثبیت‌شده خریداری شده از تامین‌کنندگان بیولوژیکی یا بانک‌های سلولی هستند.

یک ماده سمی به عنوان ماده ای تعریف می شود که یک ماده شیمیایی را به مقدار کافی برای کشتن سلول ها به طور مستقیم یا غیرمستقیم از طریق مهار مسیرهای متابولیکی کلیدی آزاد می کند.
تعداد سلول هایی که تحت تأثیر قرار می گیرند نشان دهنده دوز و قدرت ماده شیمیایی است.
اگرچه عوامل مختلفی بر سمیت یک ماده شیمیایی تأثیر می گذارد (به عنوان مثال، ترکیب، دما، سیستم آزمایش)، مهم ترین آنها دوز یا مقدار ماده شیمیایی تحویل داده شده به سلول است .

TABLE 1 Advantages and Disadvantages of Cell Culture Methods

	Direct contact	Agar diffusion	Elution
Advantages	Eliminate extraction preparation	Eliminate extraction preparation	Separate extraction from testing
	Zone of diffusion	Zone of diffusion	Dose response effect
	Target cell contact with material	Better concentration gradient of toxicant	Extend exposure time
	Mimic physiological conditions	Can test one side of a material	Choice of extract conditions
	Standardize amount of test material or test indeterminate shapes	Independent of material density	Choice of solvents
	Can extend exposure time by adding fresh media	Use filter paper disk to test liquids or extracts	
Disadvantages	Cellular trauma if material moves	Requires flat surface	Additional time and steps
	Cellular trauma with high density materials	Solubility of toxicant in agar	
	Decreased cell population with highly soluble toxicants	Risk of thermal shock when preparing agar overlay	
		Limited exposure time	
		Risk of absorbing water from agar	

Sensitization Test - حساسیت زایی

قرار گرفتن در معرض یا تماس با مقادیر بسیار اندک مواد استخراجی بالقوه از وسایل پزشکی یا بیومواد می تواند منجر به واکنش های آلرژیک یا حساسیت شود.

تست‌های حساسیت سازی پتانسیل ایجاد حساسیت تماسی با دستگاه‌های پزشکی، مواد و/یا عصاره‌های آنها را تخمین می‌زنند.

علائم حساسیت اغلب در پوست دیده می شود و آزمایشات اغلب به صورت موضعی در خوکچه هندی انجام می شود.

Sensitization Test

ISO 10993-10

- **Guinea Pig Maximization Method**
  (Magnusson / Kligman)
  20 animlal ….Positive test : 15% show reaction
- **Guinea pig Closed Patch Method (Buehler's)**

- **Local Lymph Node Assay (LLNA).**

Sensitization Test
Test method

<u>Use 3 young rabbit</u>

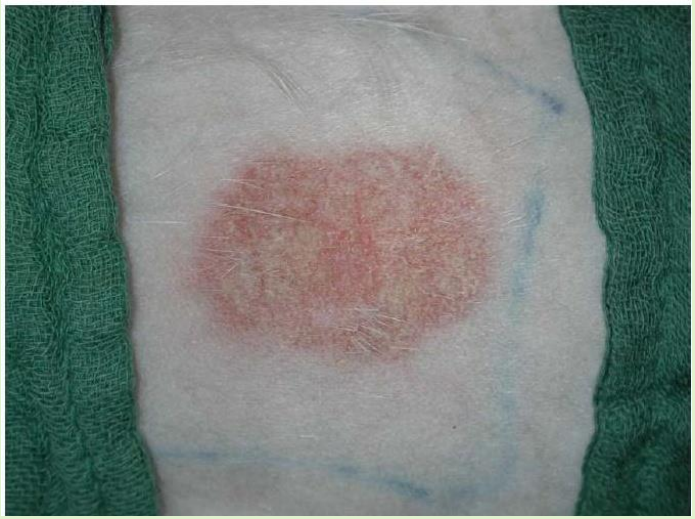
Weight > 2kg

- Powder Material : Moisture with water befor test
- Dress the site : 4hr
- Use natural or full spectrum lighting : Visualize the skin reaction

Irritation, and Intracutaneous Test
تحریک زایی

آزمایش تحریک برای تعیین اثرات تحریکی مواد و بافت های استخراج شده آن بر روی م پوست، چشم و غشاهای مخاطی مانند دهاناستفاده می شود.

خرگوش های آلبینو شایع ترین هستند



Irritation, and Intracutaneous Test

ISO 10993-10 : Tests for irritation and skin sensitization

- **Skin irritation test (Dermal irritation)**
  - Topical application for at least 4 hours
  - Erythema & oedema formation
  - Primary or cumulative (for repeated dose) irritation index
- **Intracutaneous reactivity test**
  - Selected for external communicating device and implant device
  - Intracutaneous injection (ISO 10993-10: 2010, 3 animals)
  - Erythema & oedema formation
- **Ocular irritation test**
  - Single dose (ISO 10993-10)
  - 22-day Repeated dose with histopatholgoy analysis (ISO 9394:2012)

Systemic Toxicity - سمیت سیستمیک

تست سمیت سیستمیک برای ارزیابی سمیت سیستمیک تعمیم یافته، نه سمیت اندام هدف یا سیستم اندام خاص، حتی اگر این اثرات ممکن است ناشی از جذب و توزیع سیستمیک سموم باشد، استفاده می شود.

موش‌ها یا خرگوش‌ها حیوانات منتخب معمول برای انجام این آزمایش‌ها هستند

بسته به کاربرد مورد نظر ماده زیستی، ممکن است از مصرف خوراکی، پوستی، استنشاقی، داخل وریدی، داخل صفاقی یا زیر جلدی ماده آزمایش استفاده شود.

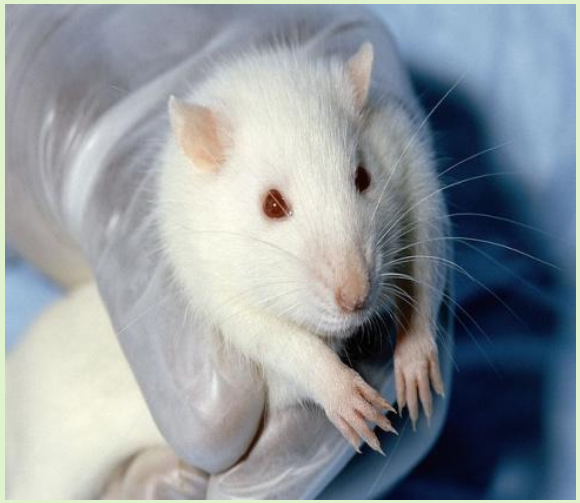
Systemic Toxicity

Systemic toxicity	adverse effects
Acute ≤ 24 h	occurring at any time after single, multiple or continuous exposures of a test sample within 24h
Subacute > 24 h and ≤ 28 d	occurring after multiple or continuous exposures between 24 h and 28 d "short-term repeated exposure systemic toxicity study" Subacute intravenous studies are generally defined as treatment durations of > 24h but < 14d.
Subchronic > 28 d and ≤ 90 d	occurring after the repeated or continuous administration of a test sample for a part of the lifespan (usually 90 d in rodents but not exceeding 10% of the lifespan of other species) Subchronic intravenous studies are generally defined as treatment durations of 14 d to 28 d.
Chronic usually 6 to 12 months	occurring after the repeated or continuous administration of a test sample for a major part of the lifespan

Systemic Toxicity

تست‌های تب زایی نیز در دسته سمیت سیستمیک قرار می‌گیرند تا واکنش‌های تب‌آور ناشی از مواد به عصاره‌های دستگاه‌ها یا مواد پزشکی را شناسایی کنند.

قابل توجه است که هیچ آزمایش واحدی نمی تواند واکنش های تب زایی را که با واسطه مواد از واکنش های ناشی از آلودگی اندوتوکسین ایجاد می شود، متمایز کند.



Systemic responses

Lungs	Alteration in air exchange and breathing patterns
Kidney	Alterations in urine excretion, pain
Joints	Pain, swelling, loss of function
Liver	Alterations in blood chemistry
Lymphoid	Swelling, alteration of blood count
GI tract	Diarrhea or constipation

The following usually give local responses but may also be involved in systemic responses.

Skin	Rashes, swelling, discoloration
Eyes	Swelling, itching, watery
Nose	Itching, running, sneezing

The following usually do not give observable signs and symptoms until damage is extreme.

Brain, skeletal system, muscles

Systemic Toxicity

Observation	Acute	Subacute	Subchronic/ Chronic
Body weight change	+	+	+
Clinical observations	+	+	+
Clinical pathology	*	*	+
Gross pathology	*	+	+
Organ weights	*	+	+
Histopathology	*	*	+

*Consideration should be given to these measurements when clinically indicated or if longer exposure testing is not anticipated.

Systemic Toxicity

ISO 10993-11: 2006 Tests for systemic toxicity

- Use 5 animals : (A) : 2 or more die
  (B) : 2 or more convulsion/prostrain
  (C) : 3 or more body weight less than 10%

- If any animal show slight sign of biological reactivity
  OR 1 animal show symptomof biological reactivity

  Repeat by 10 animal

- If all 10 animal show no meaningful biological reactivity :
  Sample meet the requirment of the test.

Carcinogenicity - سرطان زایی

- آزمایش‌های سرطان‌زایی پتانسیل تومورزایی مواد، ویا عصاره‌های آن‌ها را از تماس‌ها یا تماس‌های منفرد یا چندگانه در یک دوره از بخش عمده طول عمر حیوان آزمایشی تعیین می‌کند.

سرطان زایی - Carcinogenicity

سرطان زایی (تومورزایی) و سمیت مزمن ممکن است در یک مطالعه تجربی مورد مطالعه قرار گیرد. استفاده از کنترل های مناسب ضروری است زیرا حیوانات ممکن است به طور خود به خود تومور ایجاد کنند و مقایسه آماری بین بیومتریال/دستگاه آزمایش و کنترل ها ضروری است.

- Short term / long term

  25% implants : Development of tumor within 15 year

  50% implants : Development of tumor within 25 year

Carcinogenicity

- Determination od tumorogenicity :
  (Physical effect > chemical characteristic)

- Solid Material ↑
  Surface area ↑
  } Tumorogenicity ↑

- Materials : Any kind. Including nonreactive (glasses,gold, platinium)
  And Pure metals and polymers

TABLE 2 Tumors Associated with Implant Sites in Humans—Representative Reports

Device (adjacent material)[a]	Tumor[b]	References	Postimplantation (years)
Fracture fixation			
Intramedullary rod (V)	L	MacDonald (1981)	17
Smith-Petersen (V)	OS	Ward *et al.* (1987)	9
Total hip			
Charnley–Mueller (UHMWPE, PMMA)	MFH	Bago-Granell *et al.* (1984)	2
Mittlemeier (Al_2O_3)	STS	Ryu *et al.* (1987)	1+
Charnley-Mueller (UHMWPE)	OS	Martin *et al.* (1988)	10
Charnley–Mueller (SS, PMMA)	SS	Lamovec *et al.* (1988)	12
Total knee			
Unknown (V)	ES	Weber (1986)	4
Vascular graft			
Abdominal aortic graft (D)	MFH	Weinberg *et al.* (1980)	1+
Abdominal aortic graft (D)	AS	Fehrenbacker *et al.* (1981)	12

سمیت ژنی - Genotoxicity

- The initial in vitro assays should cover the three levels of genotoxic effects:
  - DNA destruction,
  - gene mutations, and
  - chromosomal aberrations

- **ISO 10993-3: 2003 Tests for genotoxicity, carcinogencity and reproductive toxicity**

Genotoxicity

Test Strategy (ISO 10993-3: 2003)

- **Option 1**

  - a test for gene mutations in bacteria (OECD 471); and
  - a test for gene mutations in mammalian cells (OECD 476); and
  - a test for clastogenicity in mammalian cells (OECD 473)

- **Option 2**

  - a test for gene mutations in bacteria (OECD 471); and
  - a test for gene mutations in mammalian cells (OECD 476),

  specifically a mouse lymphoma assay incorporating colony number and size determination in order to cover both endpoints

  (gene mutations and clastogenicity).

- OECD = **Organisation for Economic Co-operation and Development**

Genotoxicity

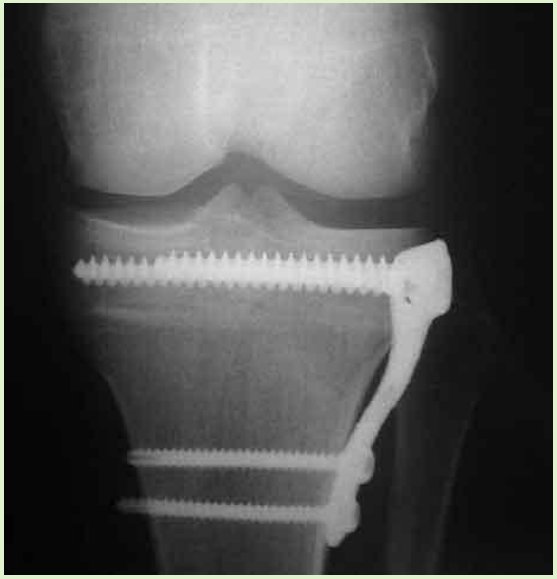
استراتژی ارزیابی : اگر هر یک از آزمایش‌های آزمایشگاهی مثبت باشد، باید آزمایش‌های جهش‌زایی in vivo انجام شود یا فرض شود که مواد جهش‌زا هستند.

ارزیابی ایمنی باید تمام شرایط مختلف مانند شدت و غلظت-وابستگی سمیت ژنتیکی، نوع حلال مورد استفاده برای استخراج و درصد مواد قابل استخراج، و ماهیت و مدت تماس بدن با دستگاه پزشکی را در نظر بگیرد.

کاشت - Implantation

آزمایش کاشت برای تعیین اثر موضعی ماده آزمایش پس از کاشت، با مقایسه پاسخ بافتی ماده آزمایش با مواد کنترل استفاده می شود.

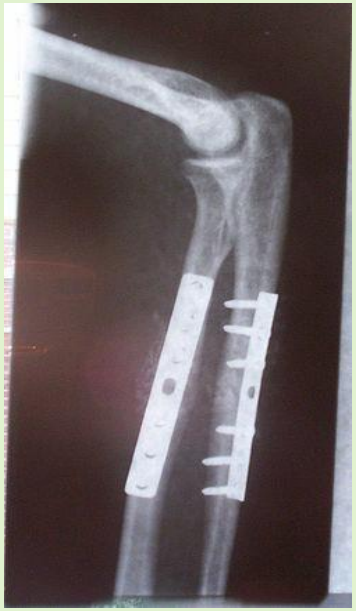
- **ISO 10993-6: Tests for local effects after implantation**

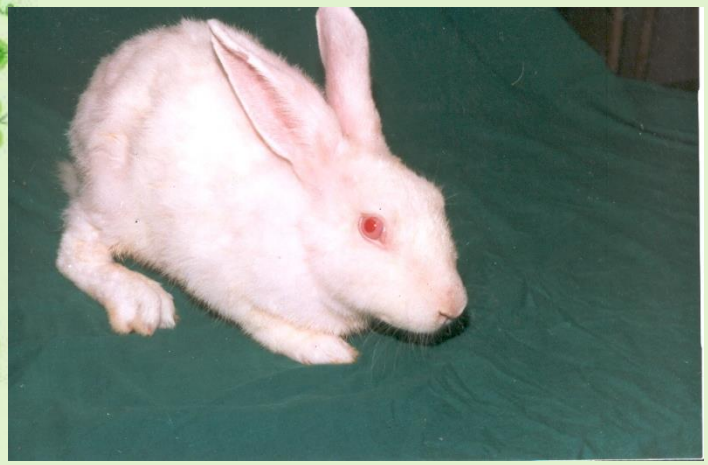


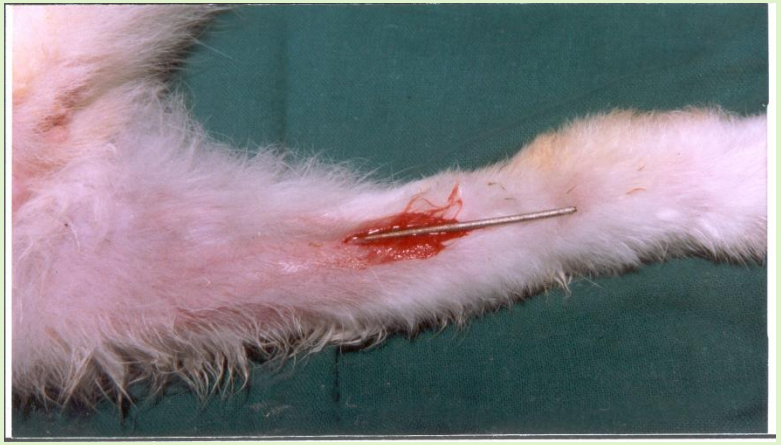
کاشت - Implantation

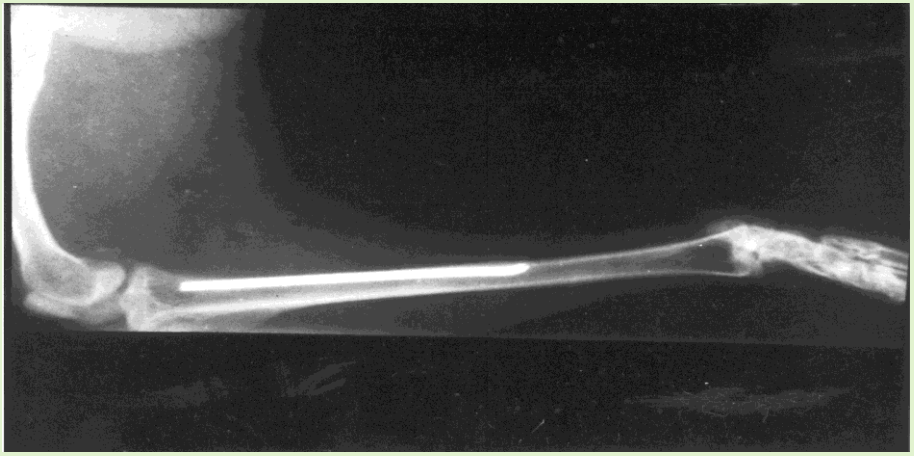
- For **short-term implantation** evaluation out to 12 weeks, mice, rats, guinea pigs, or rabbits are the usual animals utilized in these studies.

- For **longer-term testing** in subcutaneous tissue, muscle, or bone, animals such as rats, guinea pigs, rabbits, dogs, sheep, goats, pigs, and other animals with relatively long life expectancy are suitable.





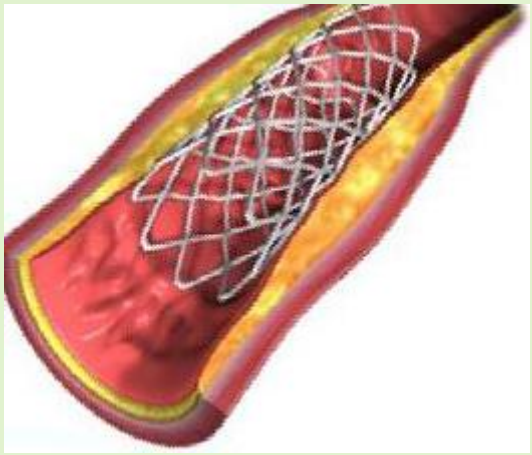




Hemocompatibility - خون سازگاری

تست‌های خون سازگاری اثرات روی خون و/یا اجزای خون را توسط مواد پزشکی در تماس با خون ارزیابی می‌کنند.

آزمایش‌های خون سازگاری in vivo معمولاً برای شبیه‌سازی هندسه، شرایط تماس و دینامیک جریان دستگاه یا ماده در کاربرد بالینی آن طراحی می‌شوند.



Hemocompatibility

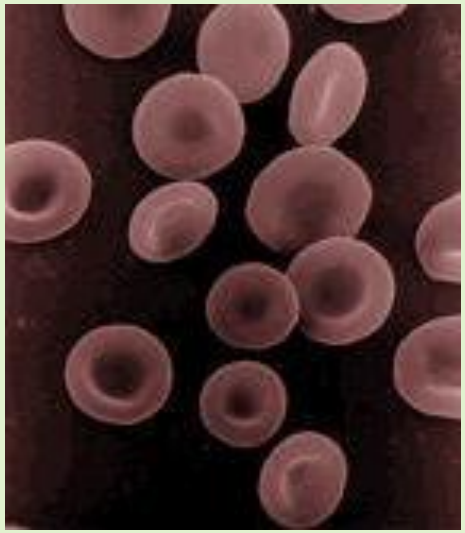
- *In vivo* testing in animals may be convenient, but species' differences in blood reactivity must be considered and these may limit the predictability of any given test in the human clinical situation.

- **ISO 10993-4: 2002**

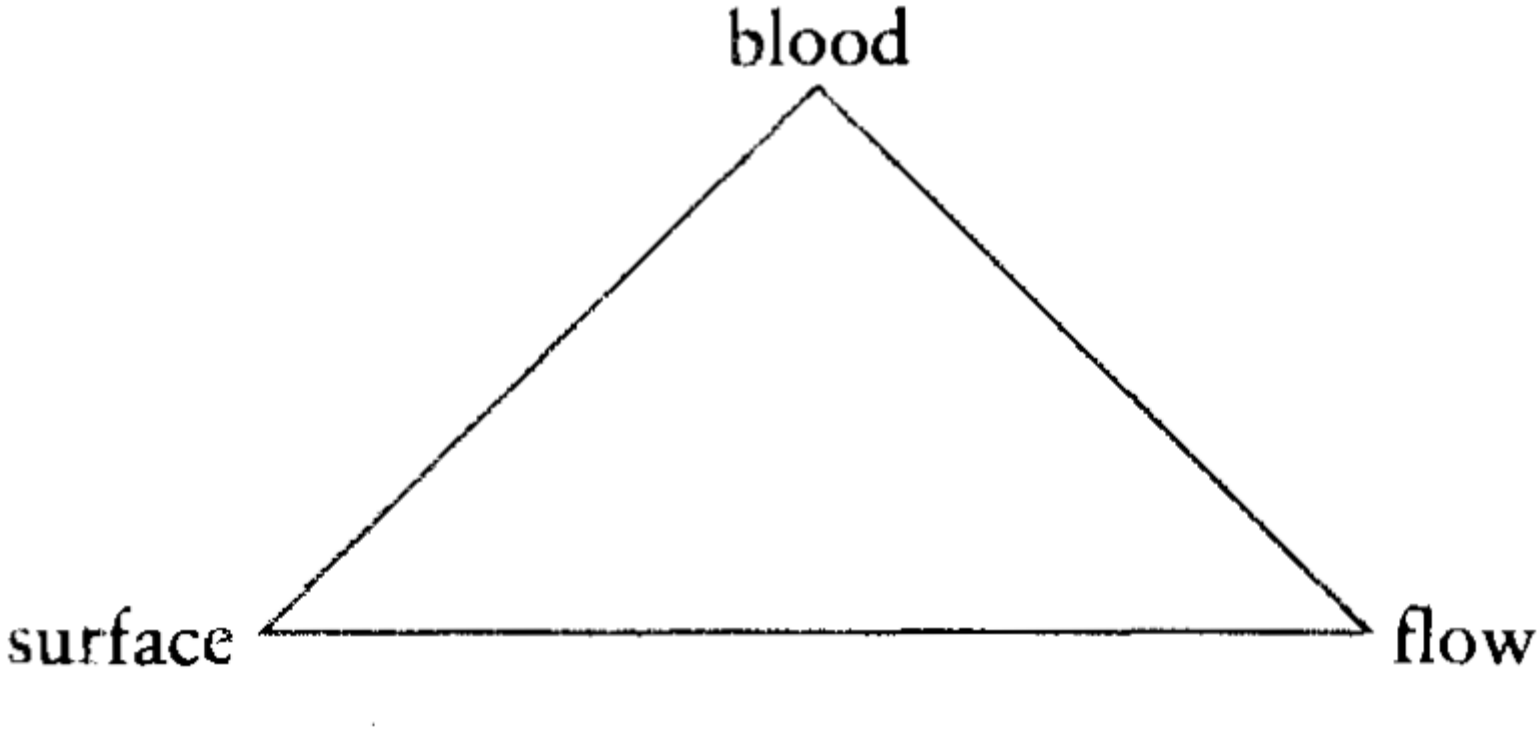
Five test categories:

- Thrombosis

- Coagulation (PT, PTT)
- Platelets (counts, aggregations)
- Haematology, including haemolysis
- Complement system (overall and particular)



Hemocompatibility



Immune Response

- Immune response evaluation is not a component of the standards currently available for in vivo tissue compatibility assessment.
- However, ASTM, IS0, and the FDA currently have working groups developing guidance documents for immune response evaluation where pertinent.
- Synthetic materials are not generally immunotoxic.
- However, immune response evaluation is necessary with modified natural tissue implants such as collagen, which has been utilized in a number of different types of implants and may elicit immunological responses.

TABLE 5 Potential Immunological Effects and Responses

- Effects
  - Hypersensitivity
    - Type I—anaphylactic
    - Type II—cytotoxic
    - Type III—immune complex
    - Type IV—cell-mediated (delayed)
  - Chronic inflammation
  - Immunosuppression
  - Immunostimulation
  - Autoimmunity
- Responses
  - Histopathological changes
  - Humoral responses
  - Host resistance
  - Clinical symptoms
  - Cellular responses
    - T cells
    - Natural killer cells
    - Macrophages
    - Granulocytes

SELECTION OF ANIMAL MODELS FOR IN VIVO TESTS

- Animal models are used to predict the clinical behavior, safety, and biocompatibility of medical devices in humans
- The selection of animal models for the in vivo assessment of tissue compatibility must consider the advantages and disadvantages of the animal model for human clinical application.
- Several examples follow, which exemplify the advantages and disadvantages of animal models in predicting clinical behavior in humans.

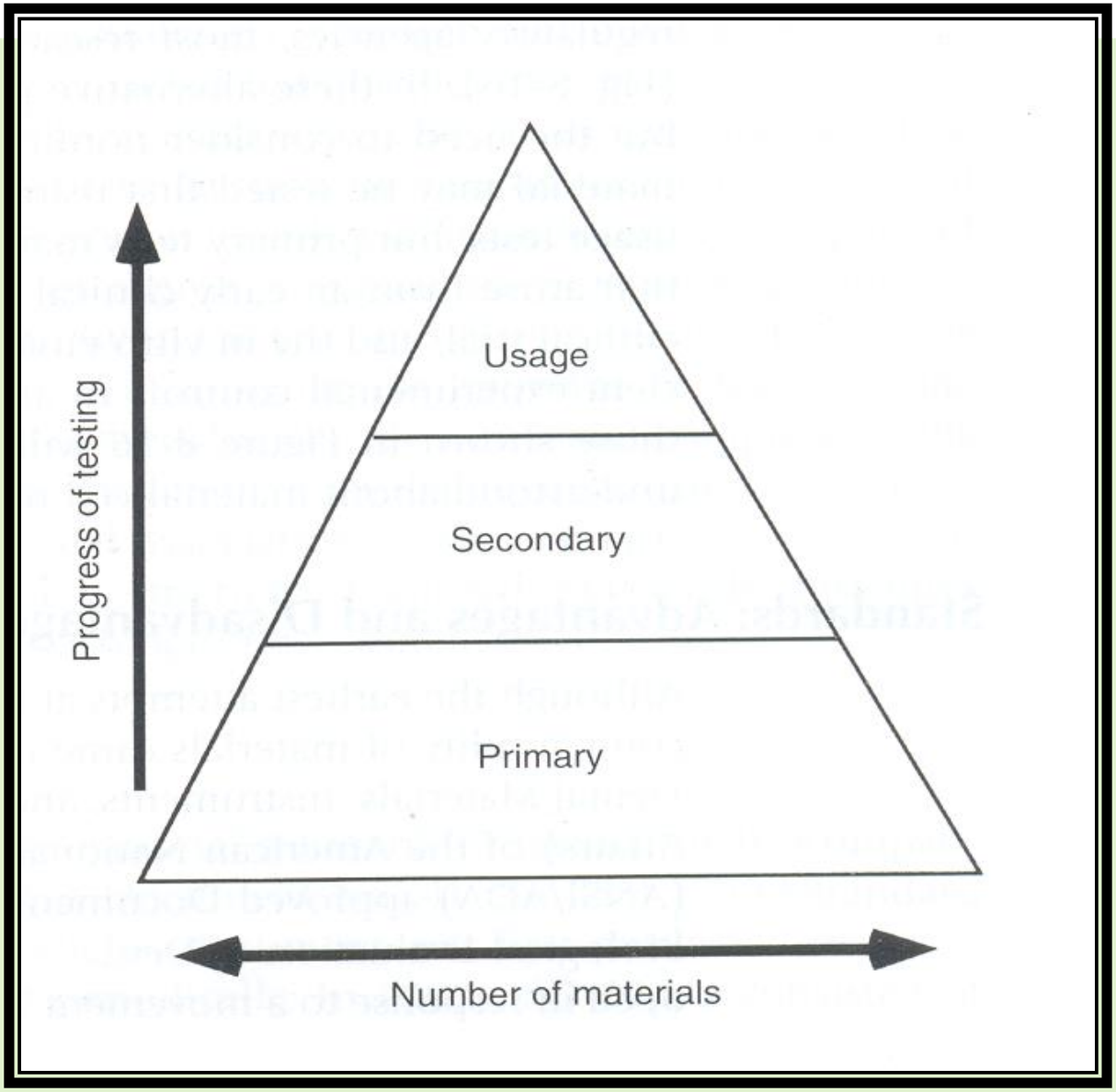
TABLE 7 Animal Models for the *In Vivo* Assessment of Medical Devices

Device Classification	Animal
Cardiovascular	
Heart valves	Sheep
Vascular grafts	Dog, pig
Stents	Pig, dog
Ventricular assist devices	Calf
Artificial hearts	Calf
Ex-vivo shunts	Baboon, dog
Orthopedic/bone	
Bone regeneration/substitutes	Rabbit, dog, pig, mouse, rat
Total joints—hips, knees	Dog, goat, nonhuman primate
Vertebral implants	Sheep, goat, baboon
Craniofacial implants	Rabbit, pig, dog, nonhuman primate
Cartilage	Rabbit, dog
Tendon and ligament substitutes	Dog, sheep
Neurological	
Peripheral nerve regeneration	Rat, cat, nonhuman primate
Electrical stimulation	Rat, cat, nonhuman primate
Ophthalmological	
Contact lens	Rabbit
Intraocular lens	Rabbit, monkey

SELECTION OF ANIMAL MODELS FOR IN VIVO TESTS

- Thus, the choice of this animal model for bioprosthetic heart valve evaluation is made on the basis of accelerated calcification in rapidly growing animals, which has its clinical correlation in young and adolescent humans.

- Nevertheless, normal sheep may **not** provide a sensitive assessment of the propensity of a valve to thrombosis,



Classical progression of biocompatibility tests

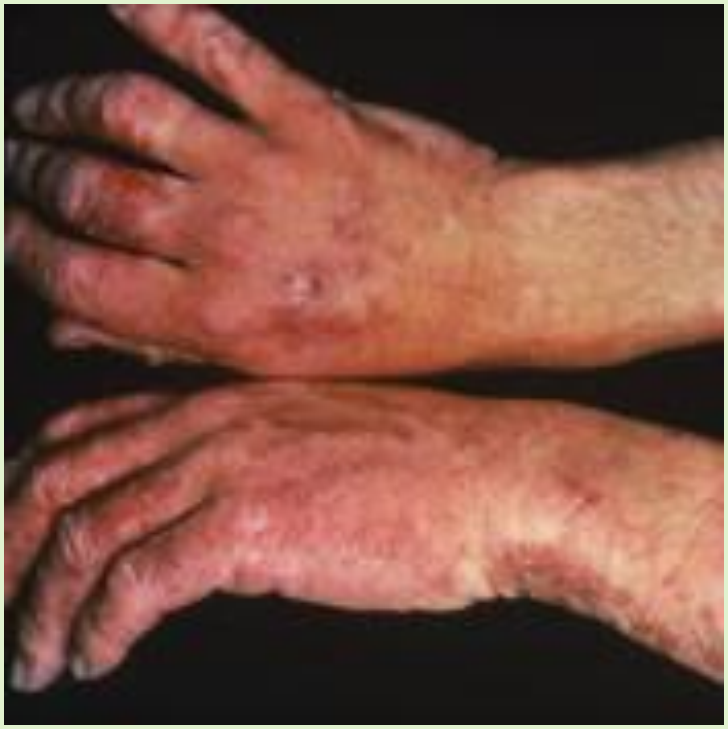
Allergy to Latex Products

- Polyether component- main causative agent

  …March,1988

- Dermatitis of hand (eczema) most common adverse reaction

- Localized rashes & swelling to wheezing & anaphylaxis



Prevention:

Use Vinyl gloves or gloves made of other synthetic polymer gloves:-

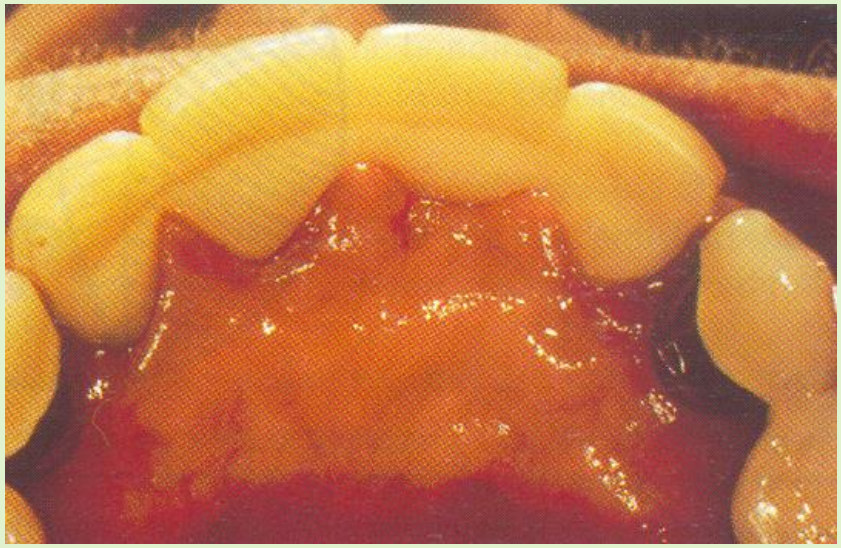
Polythene gloves.

Powder free gloves.

Nitrile gloves.

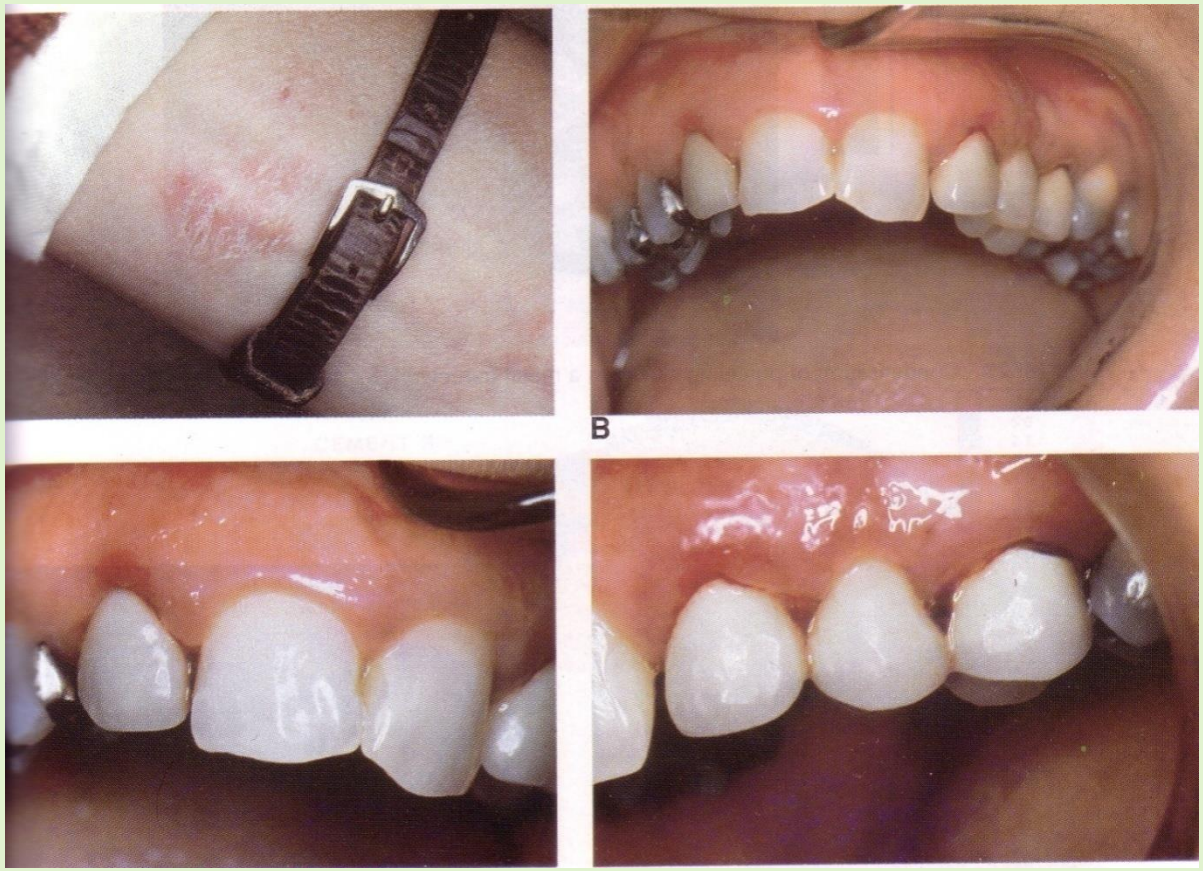
Nickel

- Most common cause of allergic dermatitis
- Female : Male :: 10 : 1
- Intraorally : little chance of allergy
- Nasal & sinus cancer among nickel refinery workers due to nickel carbonyl



Beryllium

- Component of base metal alloys
- Highest risk to dental technicians during melting & trimming of alloy
- Berylliosis : inflammatory lung disease due to inhalation of beryllium dust or fumes

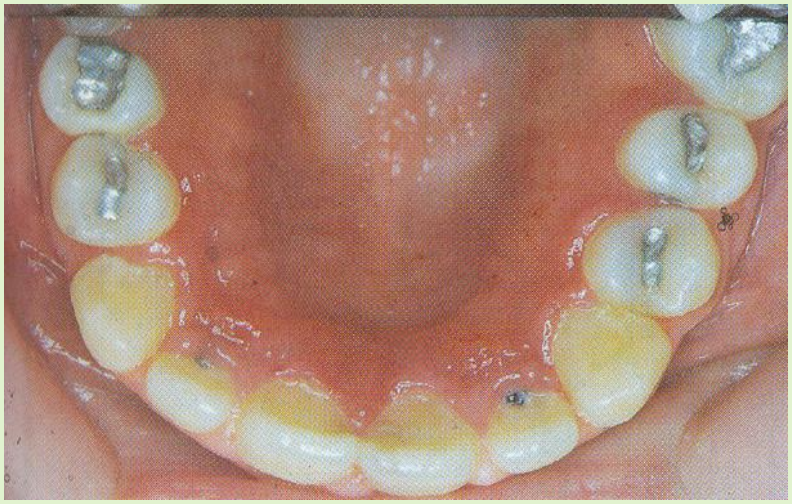

B

Gold

- Pure gold is inert
- Allergy to gold is very rare
  (1 in 1 million)

Acrylic Resin

- Cause allergic reactions (denture stomatitis) when used as denture base material or provisional fixed partial denture resin



- Highest risk for dental professionals due to frequent exposure to unpolymerized monomer

Implant Materials

- Commercially pure Titanium & its alloys are the most biocompatible restorative materials
- Bio-glass ceramics used as implant materials also exhibit good biocompatibility

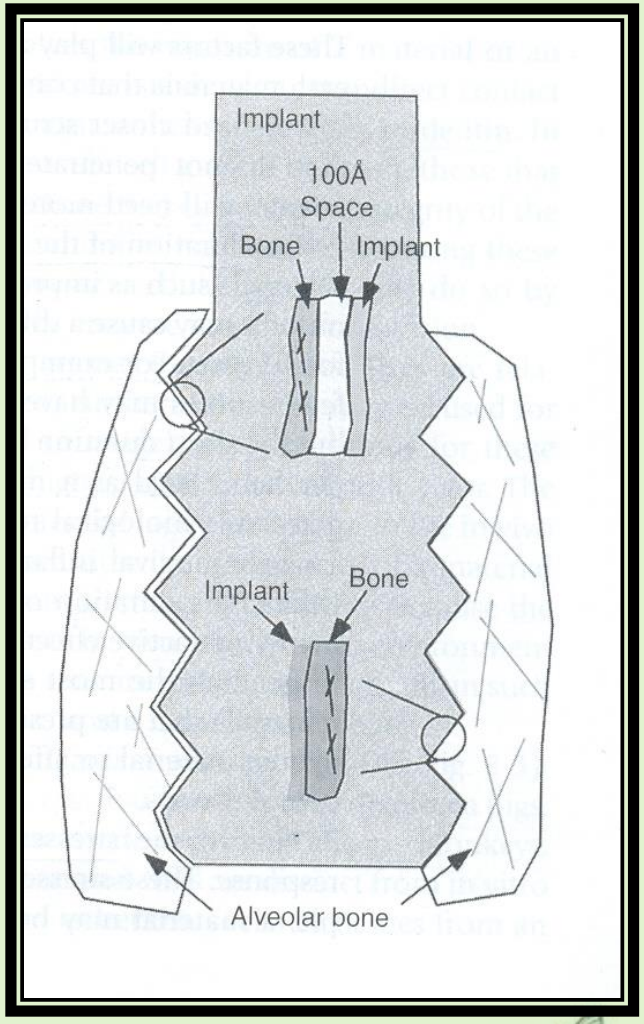
Implant Materials

- Osseointegration :- Materials have very low degradation rates, & tend to form surface oxides that promote bony approximation within 100A^{o} space

  eg. Titanium, tantalum, several forms of ceramics

- Biointegration :- Materials undergo degradation to promote bone formation without any intervening space

  eg. Bio-glass ceramics



STANDARDS

ISO 10,993, Biological Evaluation of Medical Devices, International Standards Organization, Geneva, Switzerland:

ISO 10,993-1.	Evaluation and testing
ISO 10,993-2.	Animal welfare requirements
ISO 10,993-3.	Tests for genotoxicity, carcinogenicity, and reproductive toxicity
ISO 10,993-4.	Selection of tests for interactions with blood
ISO 10,993-5.	Tests for cytotoxicity: *In vitro* methods
ISO 10,993-6.	Tests for local effects after implantation
ISO 10,993-7.	Ethylene oxide sterilization residuals
ISO 10,993-9.	Framework for the identification and quantification of potential degradation products

STANDARDS

ISO 10,993-10.	Tests for irritation and sensitization
ISO 10,993-11.	Tests for systemic toxicity
ISO 10,993-12.	Sample preparation and reference materials
ISO 10,993-13.	Identification and quantification of degradation products from polymers
ISO 10,993-14.	Identification and quantification of degradation products from ceramics
ISO 10,993-15.	Identification and quantification of degradation products from metals and alloys
ISO 10,993-16.	Toxicokinetic study design for degradation products and leachables

ASTM, American Society for Testing and Materials, Annual Book of ASTM Standards, 1999:

ASTM F-619-97	Practice for Extraction of Medical Plastics
ASTM F-720-96	Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig Maximization Test
ASTM F-748-95	Practice for Selecting Generic Biological Test Methods for Materials and Devices
ASTM F-749-98	Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit
ASTM F-981-93	Practice for Assessment of Compatibility of Biomaterials (Nonporous) for Surgical Implants with Respect to Effect of Materials on Muscle and Bone
ASTM F-1439-96	Guide for the Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials
ASTM F-763-93	Practice for Short-Term Screening of Implant Materials

US FDA Memorandum

United States Food and Drug Administration (US FDA)
Blue Book memorandum - Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing‘

¾ Additional tests may be applicable based on Table of #95-1
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm

Biocompatibility Guidelines (US)

American Society for Testing and Materials (ASTM)

- Biocompatibility Test Methods - 32 test methods, practices and guides
- Biomaterials and Biomolecules for Temps- 9 test methods and guides
- Cardiovascular standards- 5 test methods, practices and guides
- Cells and Tissue Engineered constructs for Temps- 3 methods and guides

Biocompatibility Guidelines- US

United States Pharmacopoeia (USP)

- USP rabbit pyrogen test, USP 35 (2012) <151>
- USP 35 (2012) <87> Biological reactivity test, in vitro
- USP 35 (2012) <88> Biological reactivity test, in vivo
- etc… …

Biocompatibility Guidelines- Japan

Japan

Japanese MHLW, Notice from Office Medical Device Evaluation Notice No. 36, Mar 19 2003
(updated version No. 20, Mar 01 2012)

- Selection of test items
  Notification No. 0715001 ISO 10993-1
- Selection of test procedures
  Announcement No.36 with Notification No. 99 ISO 10993-X
- Test quality (Laboratory qualification)
  Notification No. 0930001
  Japan affiliate OECD member so that MHLW (PMDA) shall recognized GLP certified under OECD