Transplantation of the nanobioelectronics

Seo Jong-Mo, M.D., Ph.D.

Electrical Engineering, Seoul National University
Ophthalmology, Seoul National University Hospital

Unmet Need

- Discrepancy between the requirement/demand and support
- High MEMS Technology vs. Low Medical Technology

- High Tech.
  - Uncertainty: unstable in developing stage
  - Fast-changing: “Seize the chance”
  - Getting smaller and more efficient
- Medical Tech.
  - Patient oriented
  - Responsibility and liability

- The failure comes from
  - Inconvenience to user: doctors usually do not understand high-tech terminology
  - Inconvenience to patient: patients are impatient
  - Other chores
    - stability
    - durability
    - reproducibility
    - biocompatibility

Healthcare

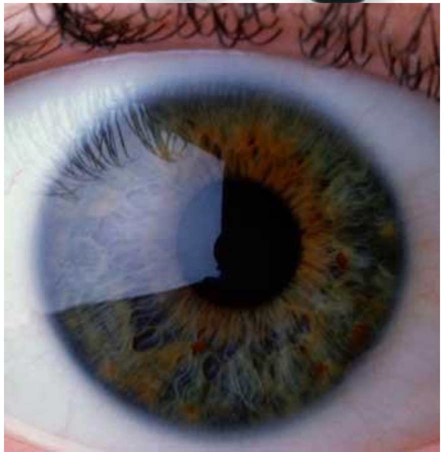
- “Medicine”
  - Restore healthy condition
  - Health: soundness of body or mind, freedom from disease or ailment
  - “Disease”
  - Diagnosis > Treatment > Rehabilitation
  - Patient – Doctor
  - Medical contract > high value

Healthcare

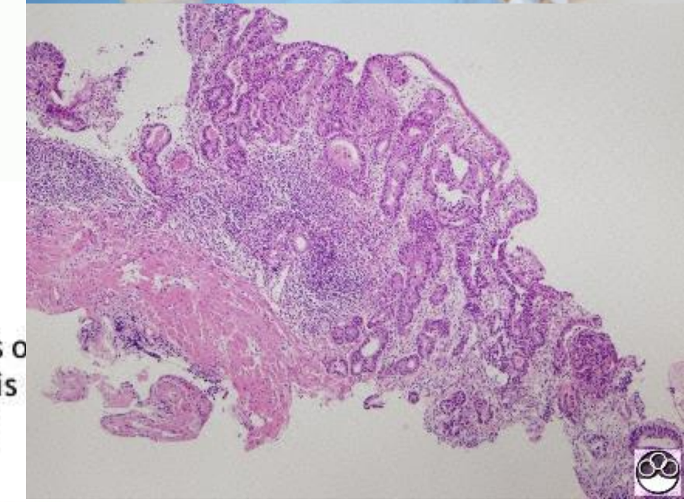
- "Health promotion"
  - Enhance healthy condition
  - "Well-being"
  - Health evaluation > Lifestyle modification
  - Normal people - ?
  - Personal willing
    > low value

efe
Electro-medical fusion engineering

Measurement

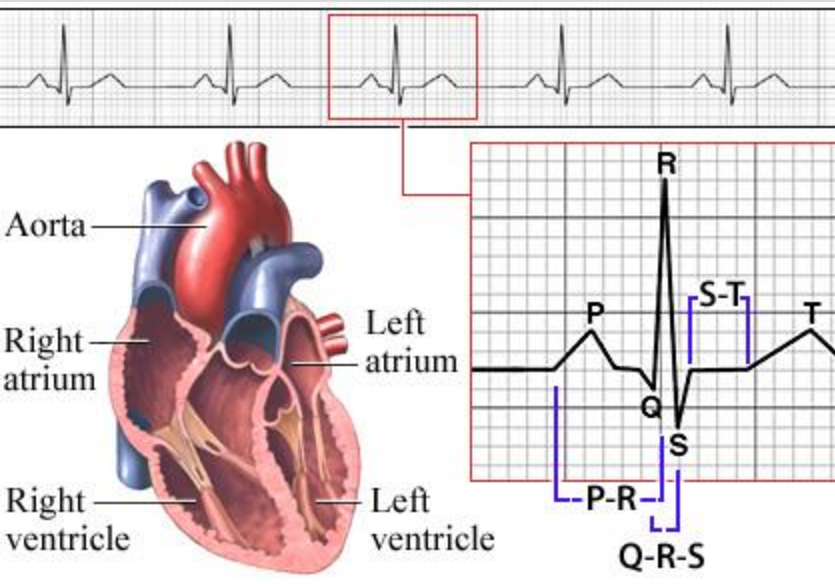


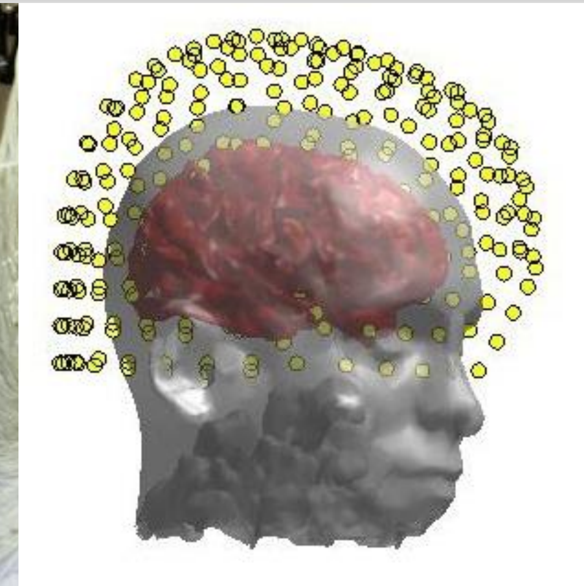
Measurement

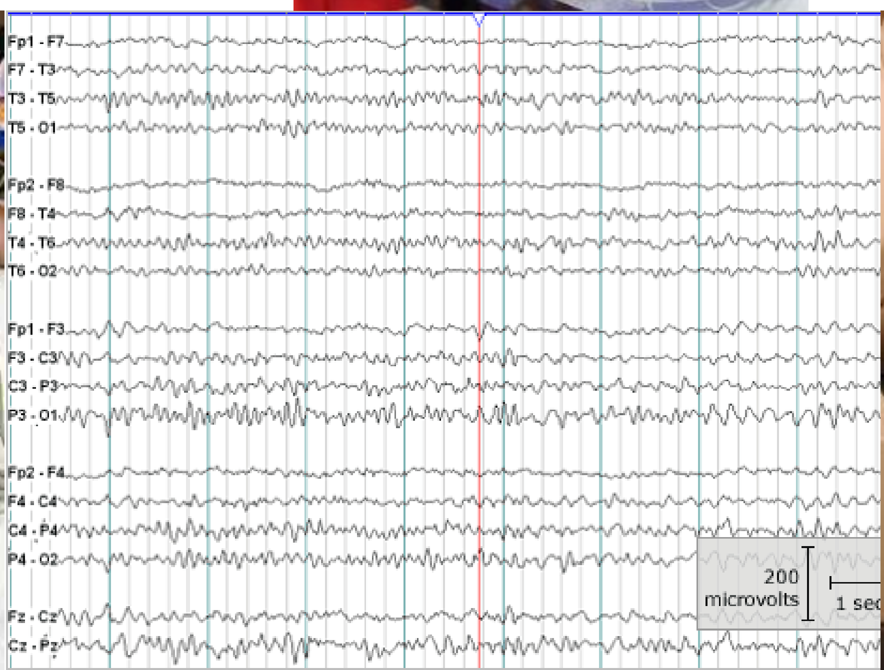


efe
Electro-medical fusion engineering

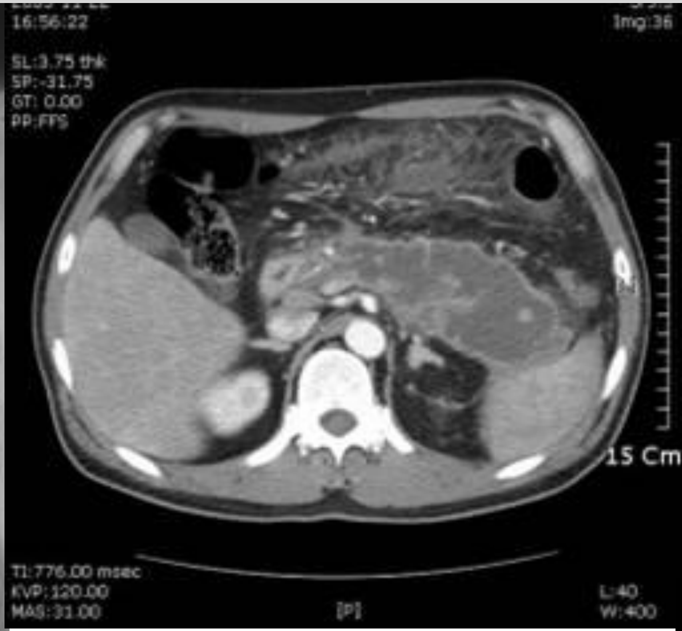
Measurement

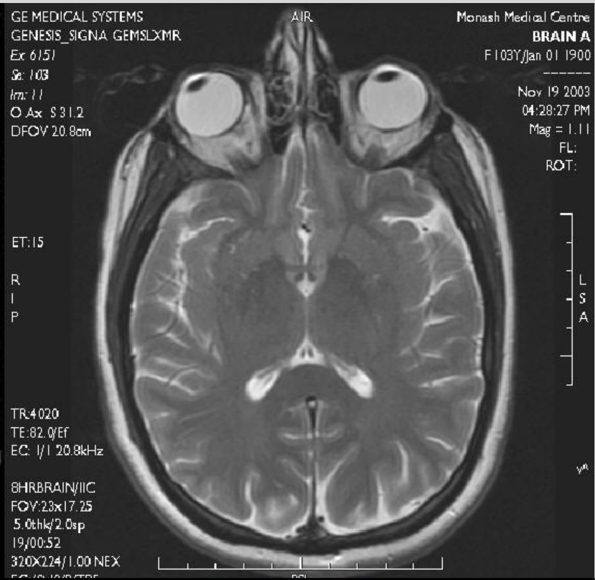


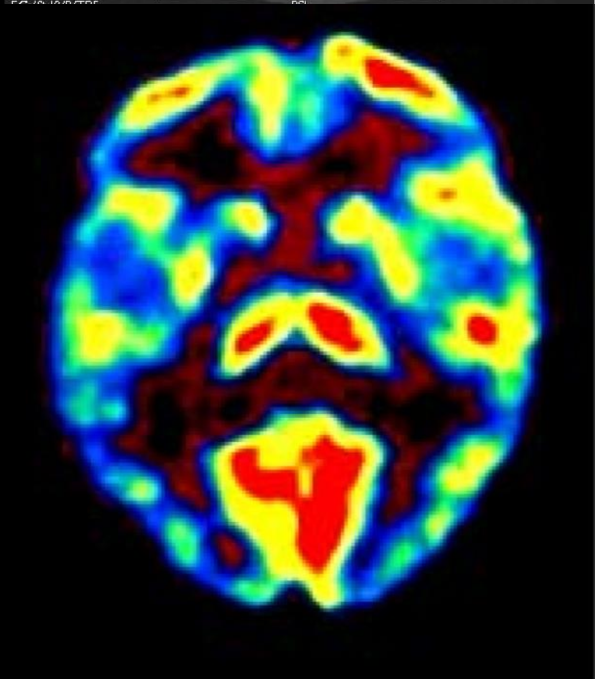




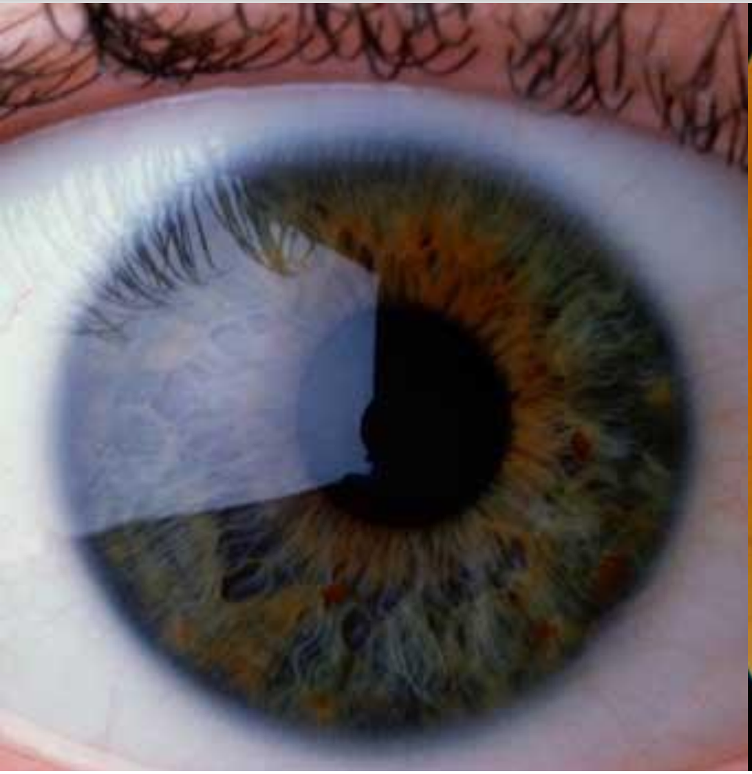
Measurement



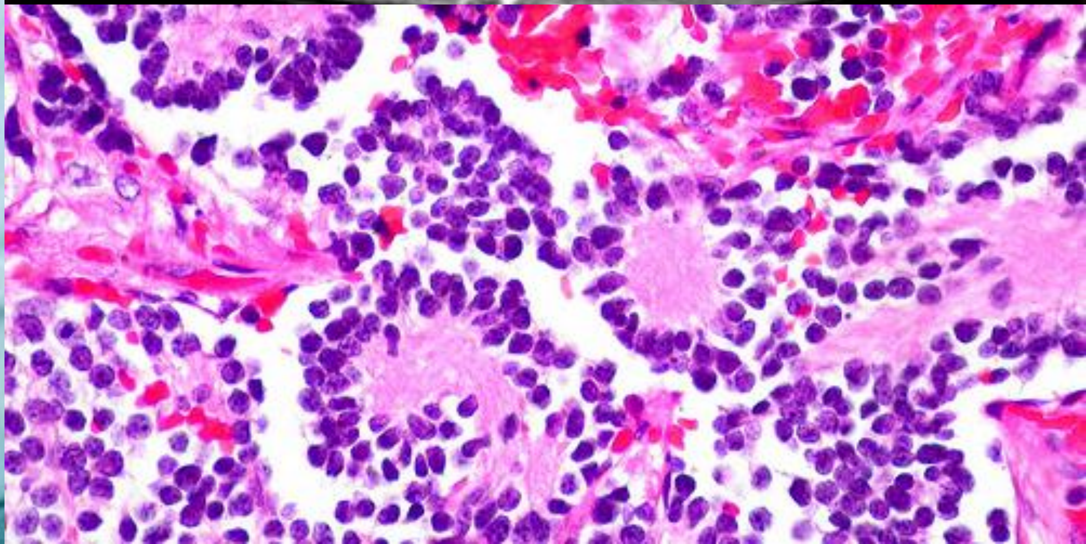




Measurement



Measurement



Diagnosis and health evaluation

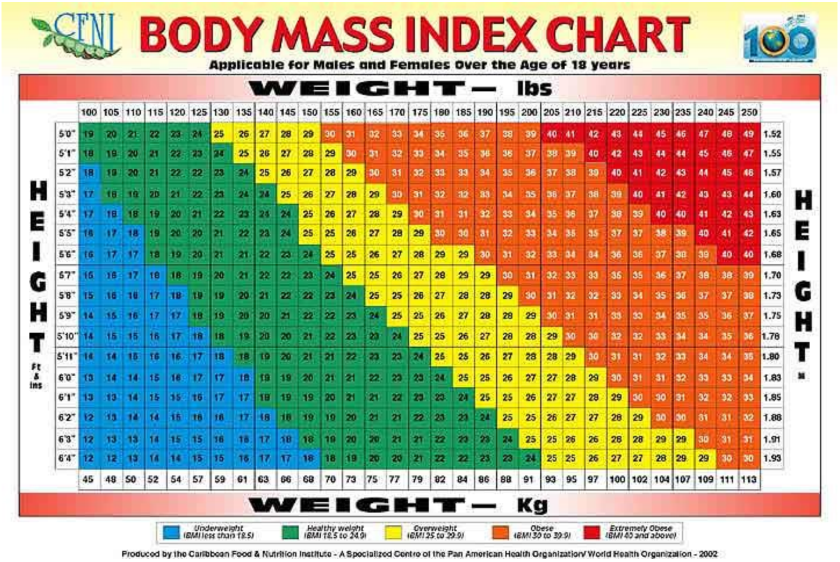
- Diagnosis
  - the process of determining by examination the nature and circumstances of a diseased condition or the decision reached from such an examination.
  - Specific: requires critical decision point
  - Starting point of the evidence-based medicine
  - Criteria for the treatment

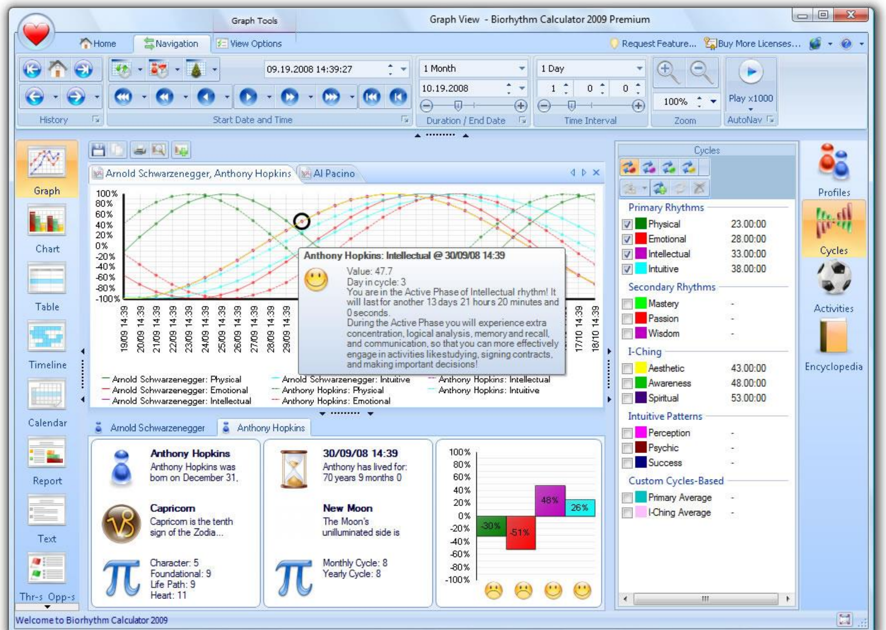
  e.g. heart beat: tachycardia, bradycardia, arrhythmia
- Symptom
  - Manifested
  - Incipient
- Sign
  - Structural; metamorphosis, dismorphysm, neoplasm
  - Functional change; mechanical, neuronal

Diagnosis and health evaluation

- Health evaluation
  - "Well-being sense" is subjective
  - Nonspecific:
    healthy vs. unhealthy
  - Proposed criteria are also subjective, even though it can be quantified

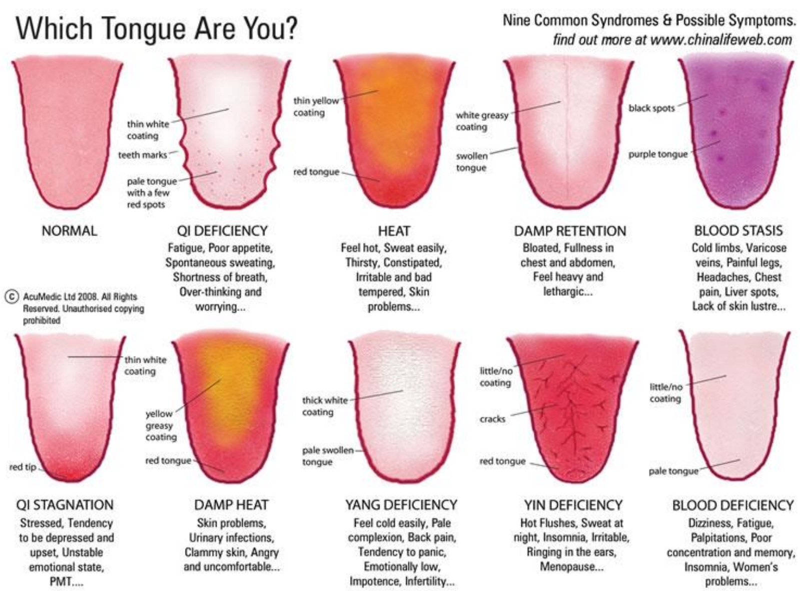
  e.g. Body-Mass Index (BMI), Bio-rhythm

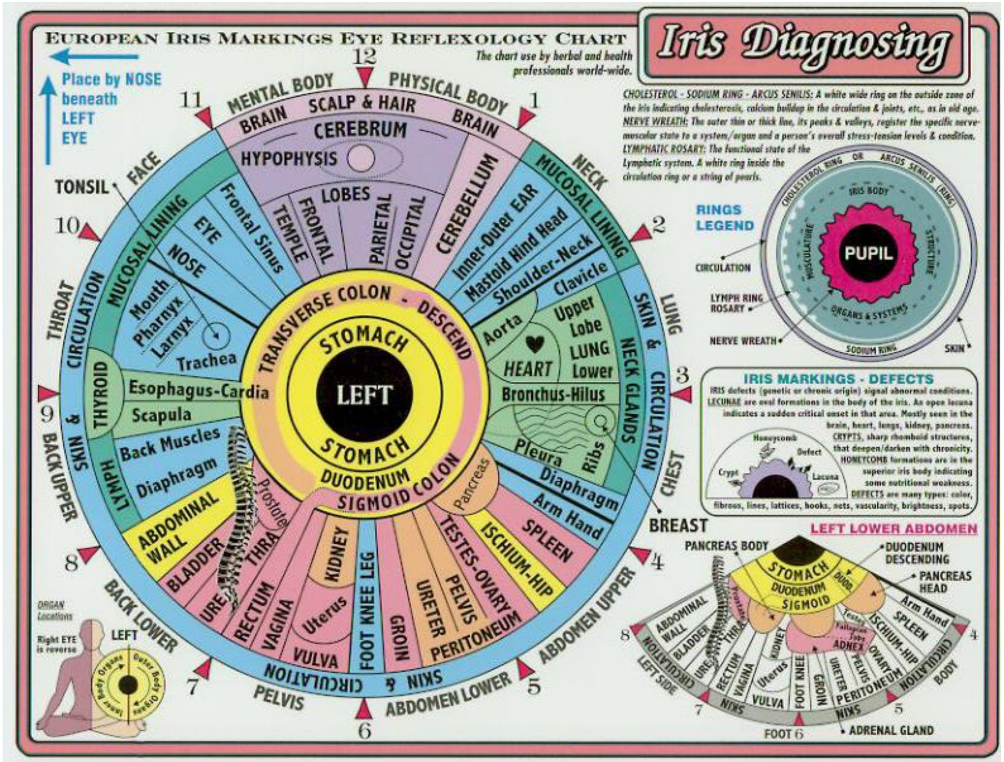


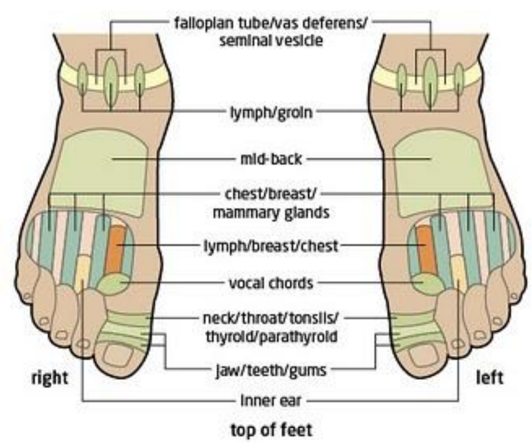


efe
Electro-medical fusion engineering

Objectiveness and Reproducibility





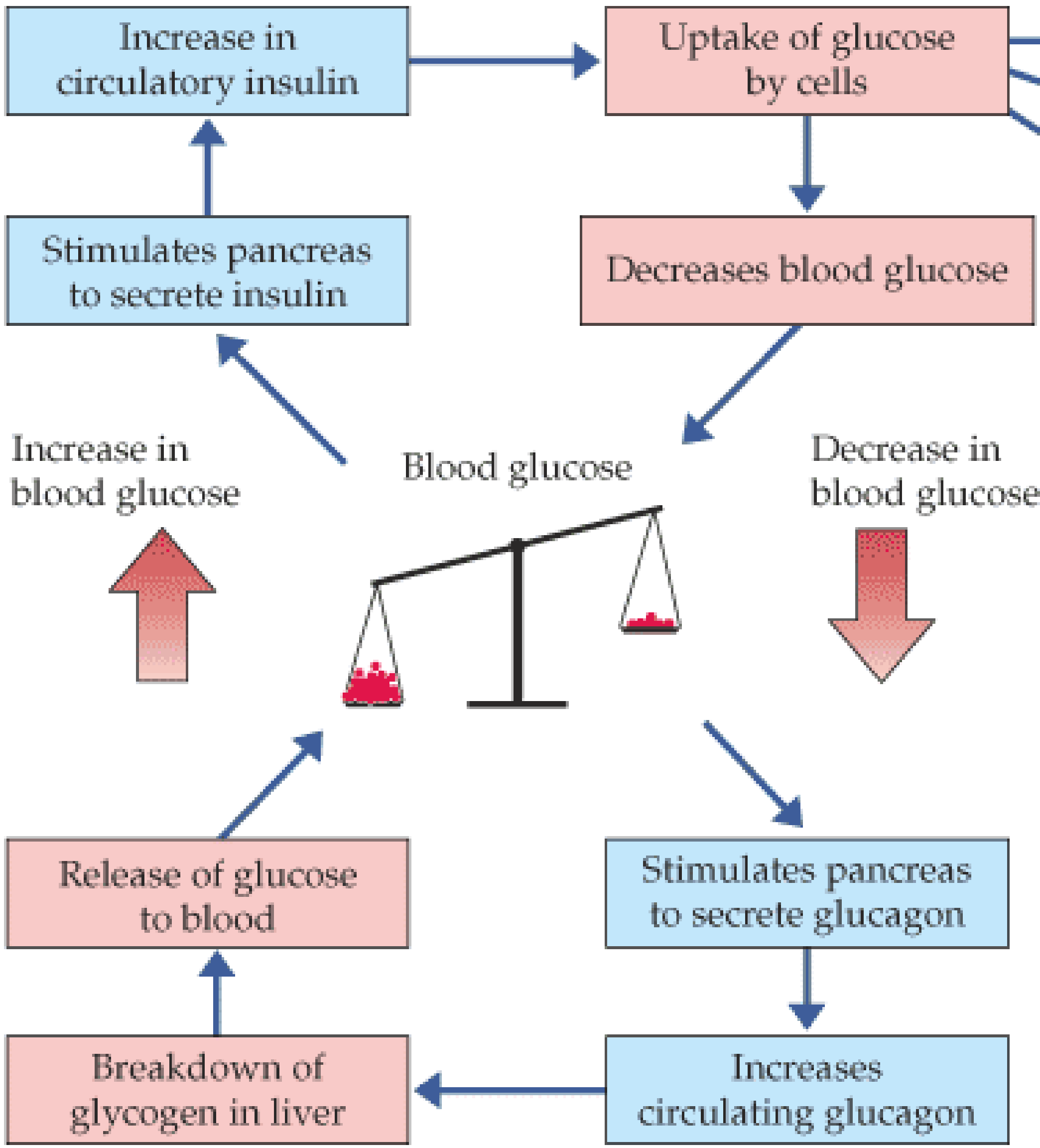


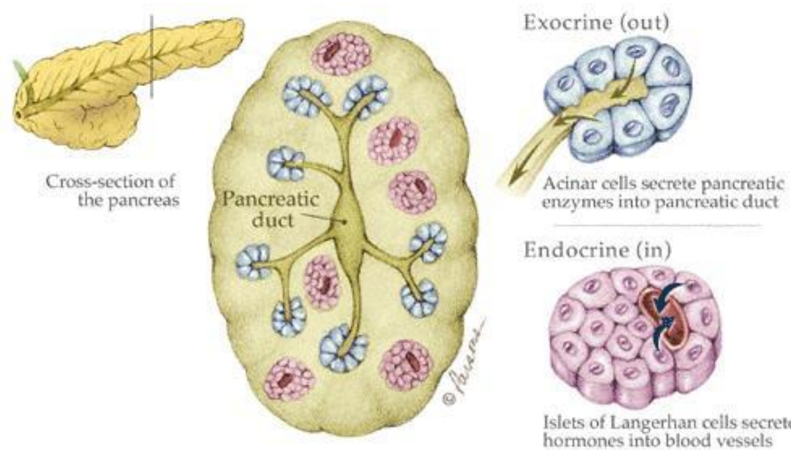
Implantable MEMS

efe Electro-medical fusion engineering

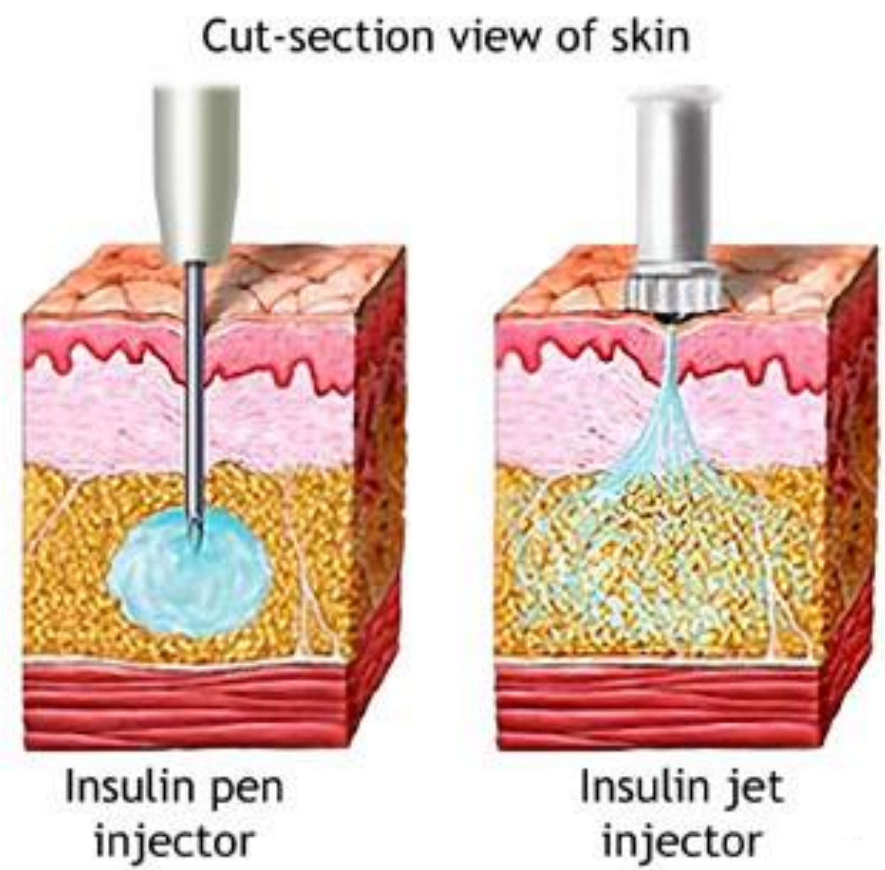
- For Diagnosis
  - Biosignal Monitoring
    - Electrophysiology:
      EKG, NCV, ECoG,…
    - Physical measurement:
      Blood Pressure in selective vessel,
      Temperature, Oxymetry,…
  - Surveillance
    - Chemical measurement:
      BUN, Glucose,…
    - Biomarker tracing:
      Disease-specific antigen,
      pathogen,…
- For Treatment
  - Drug Delivery System (DDS)
    - Slow release
      Controlled release
    - Channel-pump: Osmotic, Piezo-
      Maze
      Micro-bead
  - Functional Stimulation
    - Central Nervous System (CNS) /
      Peripheral Nervous System (PNS)
      stimulator:
      Deep brain stimulation (DBS)
      Sacral Plexus Stimulator –
      Percutaneous nerve Stimulation
      (PNS)
      Implantable Cardioverter
    - Artificial Sensory Organ:
      Artificial Cochlea
      Artificial retina

Diabetes Mellitus





Insulin

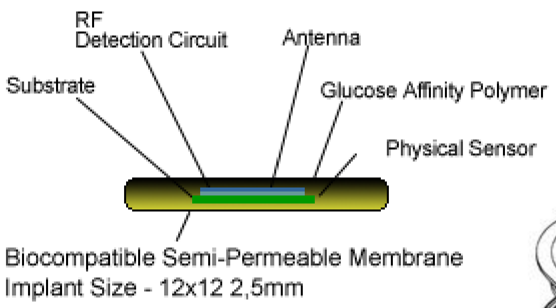


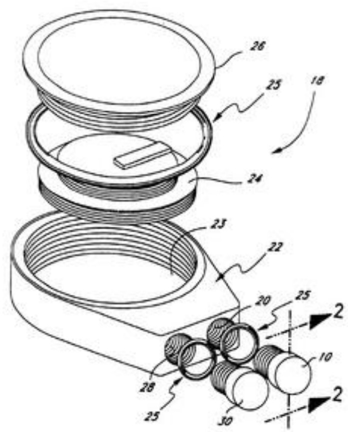
Cut-section view of skin
Insulin pen injector
Insulin jet injector

A blood sample is taken
Blood is put on monitor to check glucose levels
If glucose levels are too high insulin is administered, if glucose levels are too low carbohydrates are ingested
One way to administer insulin is
A.D.A.M.
Catheter
Fat
Insulin
Skin
Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner
Insulin pump

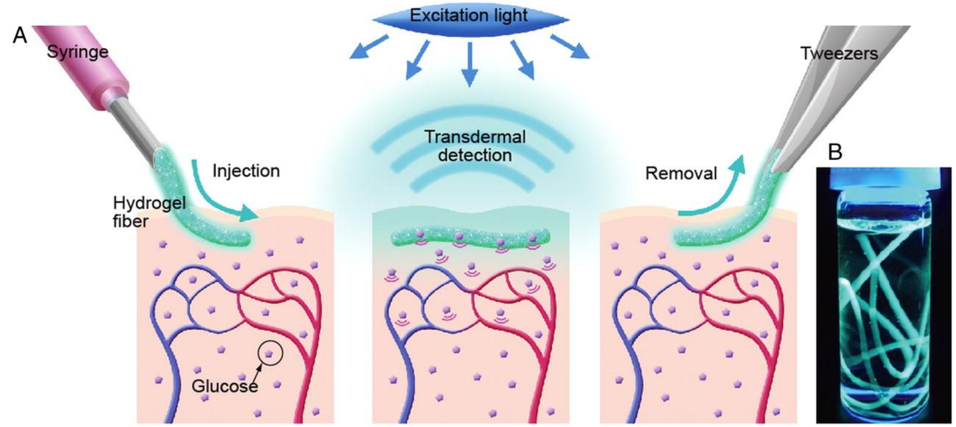
Biosignal Monitoring

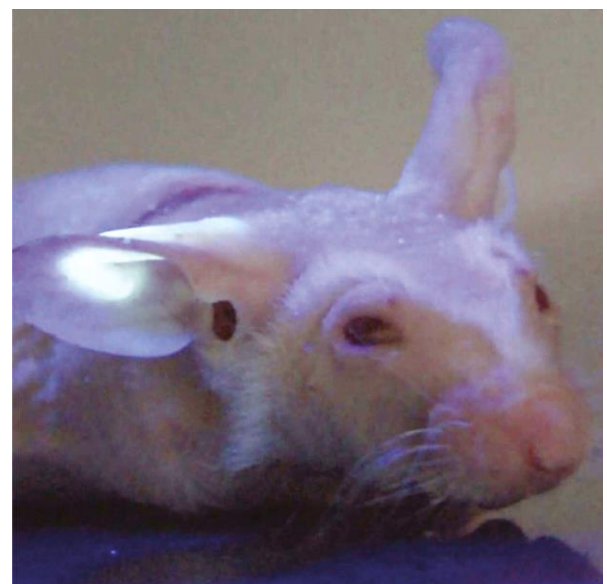
- Implantable glucose sensor and insulin pump





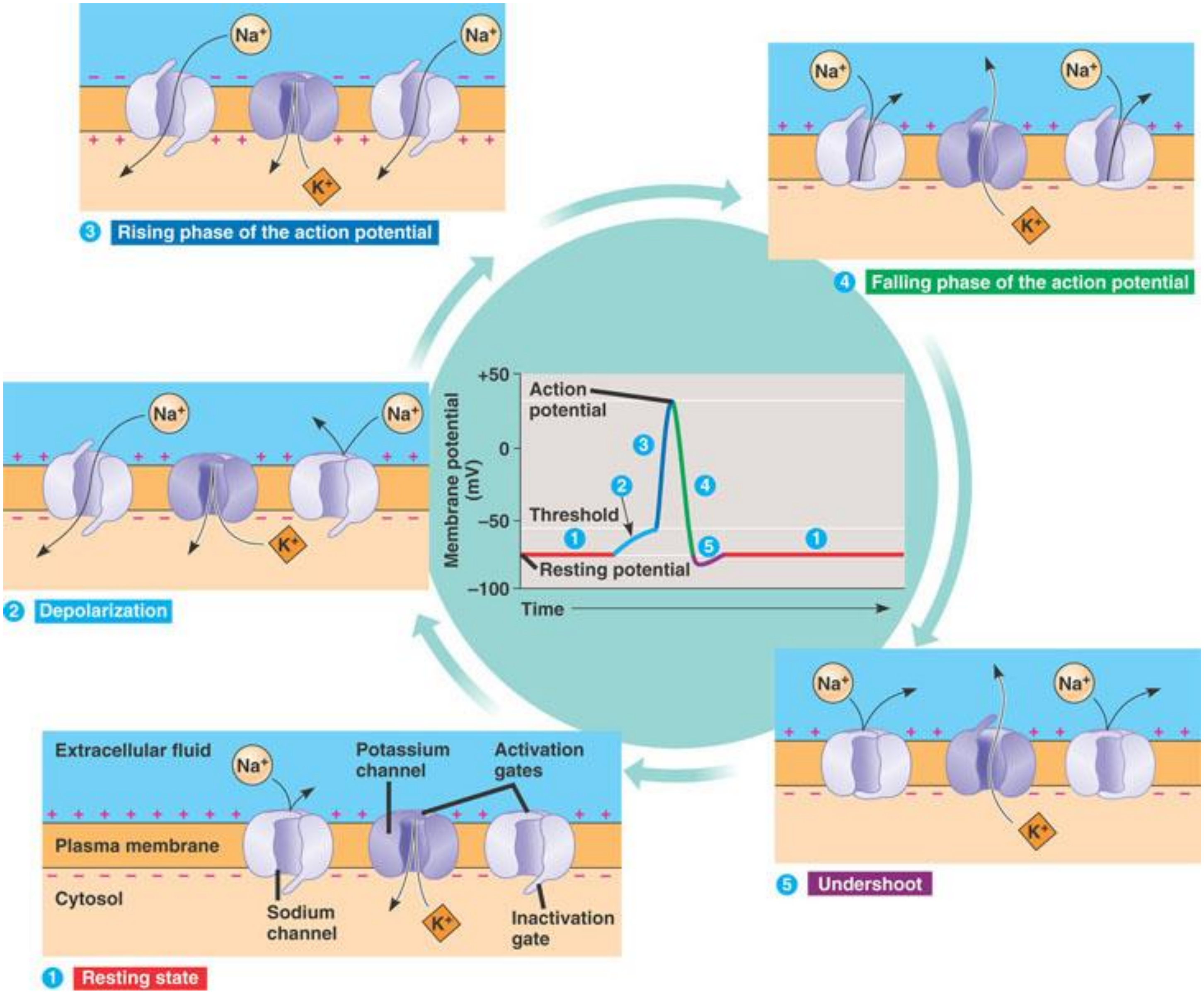
- Mouse with a glowing glucose sensor implanted in its right ear.



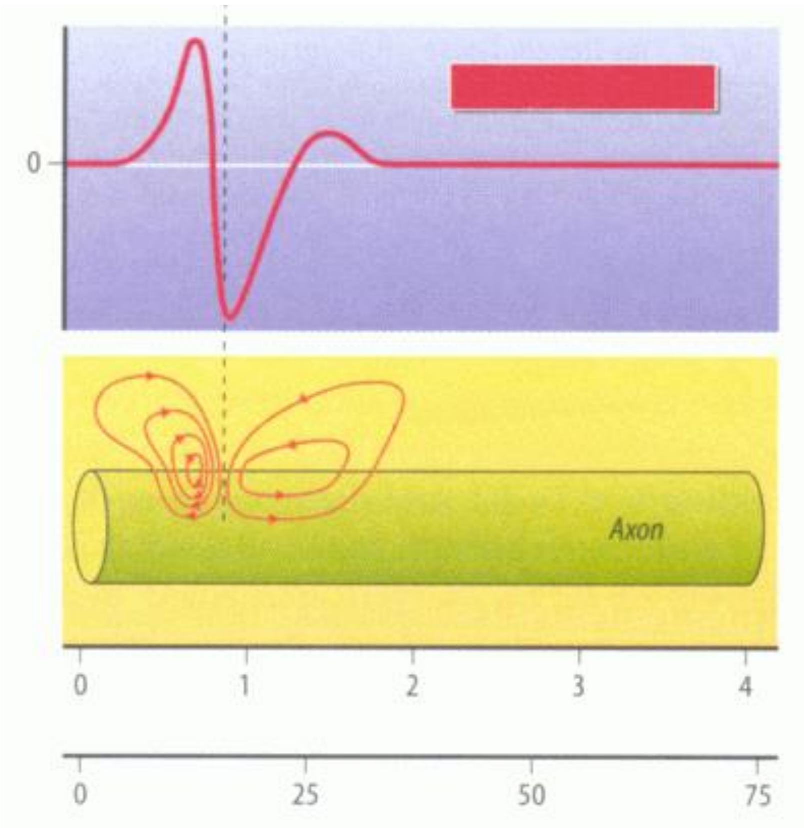


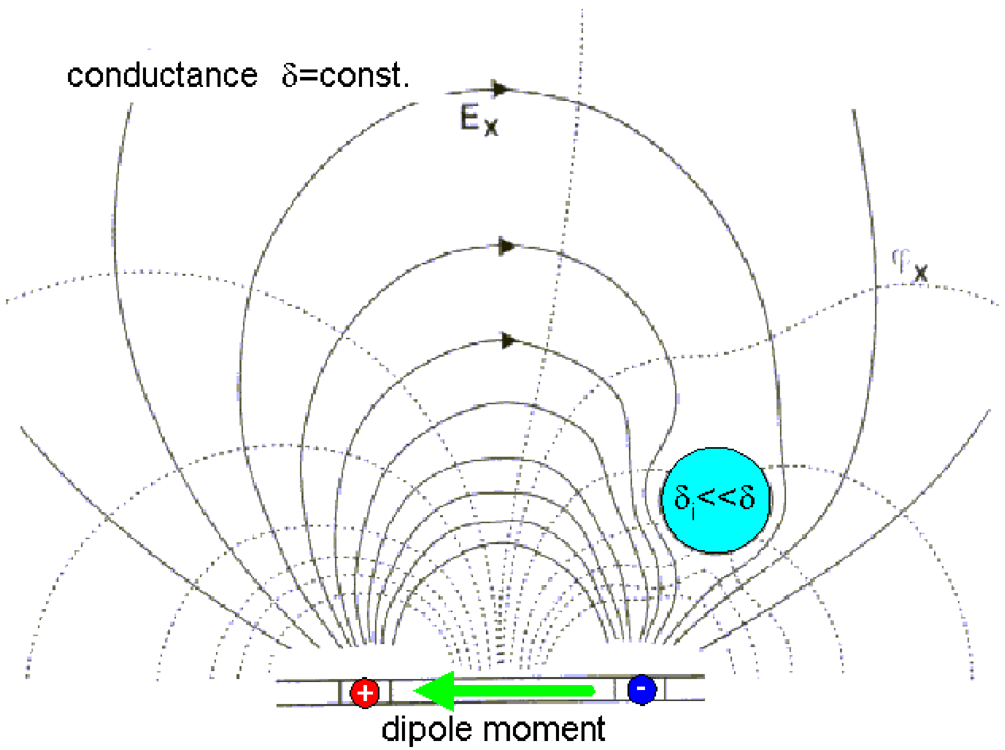
Heo et al. PNAS 2011;108:13359-13360

Action potential

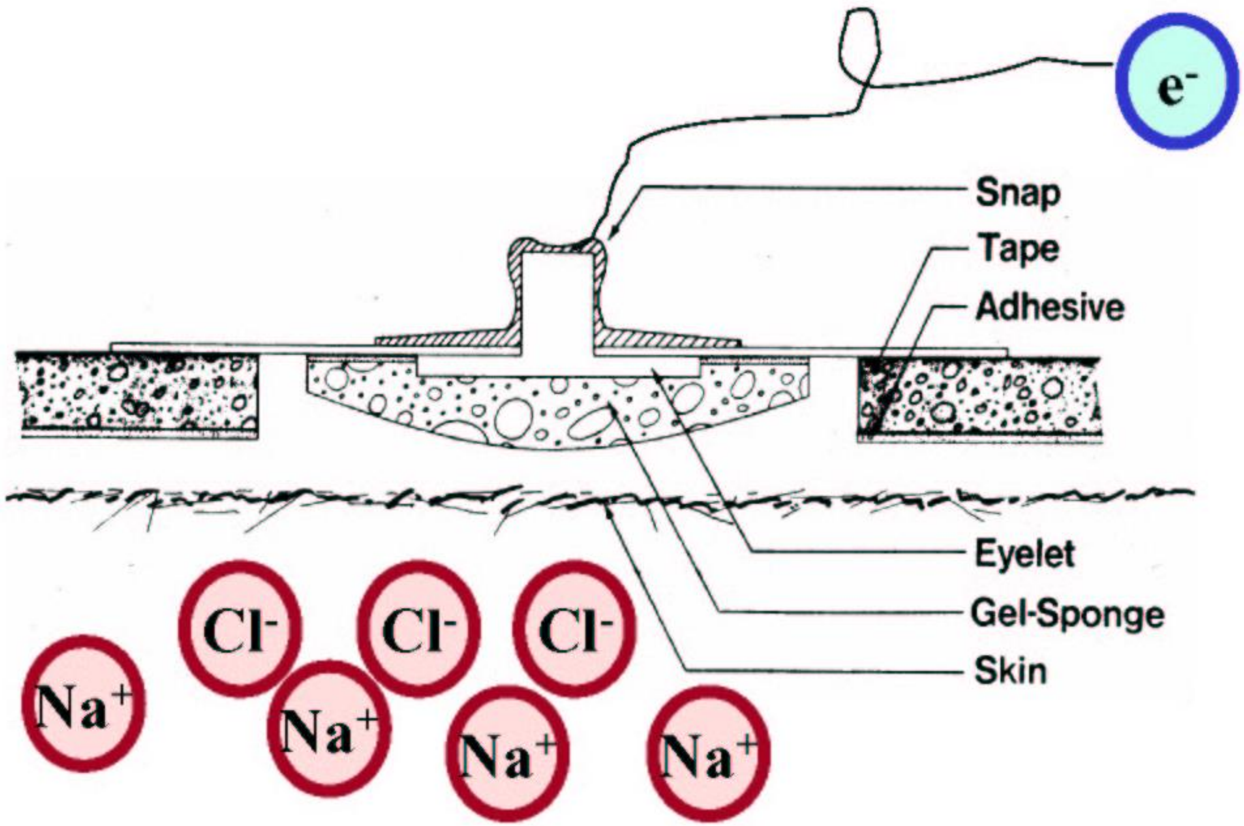


Membrane current



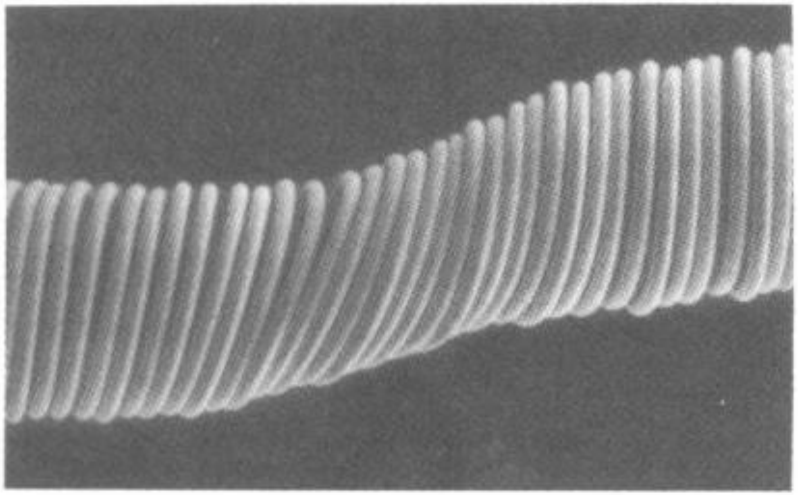


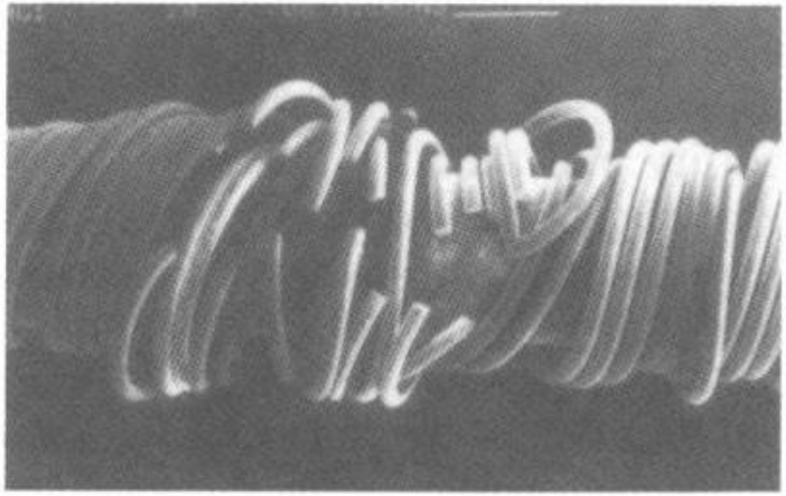
- **Electrode as a sensor : ion to free electron conversion**



Good Leads

- Good conductor
- Mechanically strong and reliable
  - Must withstand effects of movement of body
- Material cannot:
  - Dissolve in tissue
  - Irritate the tissue
  - Undergo electrolytic reaction due to stimulation
  - React biologically
- Good electrical insulation

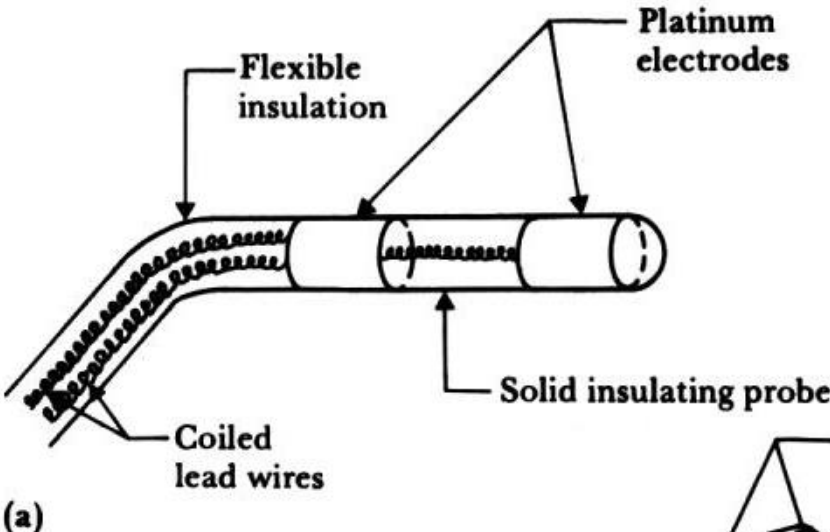


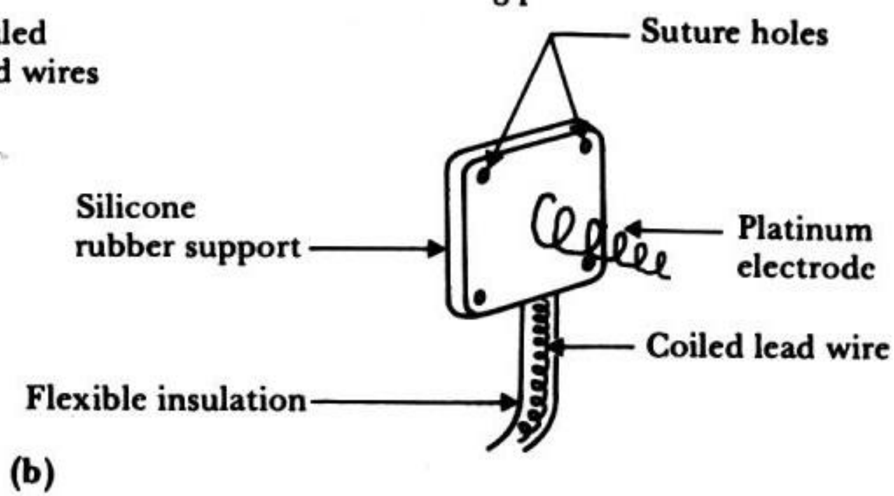


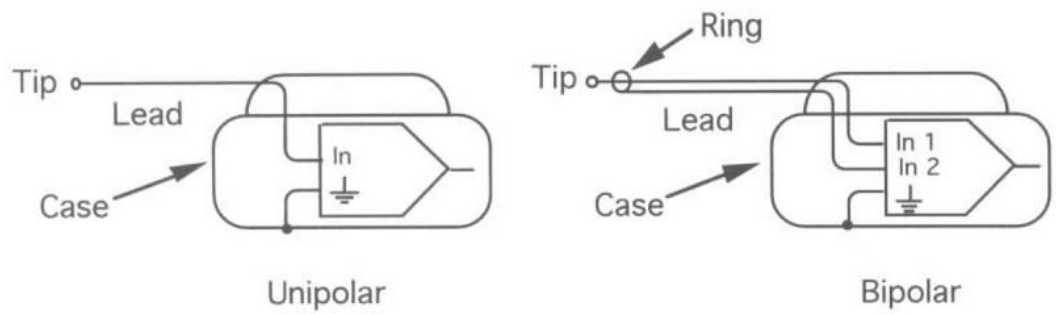
Unipolar vs. Bipolar Electrodes

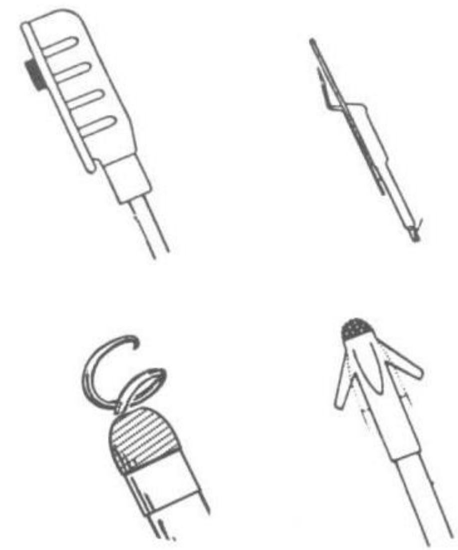
- Unipolar:
  - Single electrode
  - Negative-going pulses are conducted
  - A large indifferent electrode is located elsewhere in the body to complete the circuit
- Bipolar:
  - Two electrodes
  - Stimuli are applied across these electrodes

Pacemaker Electrodes









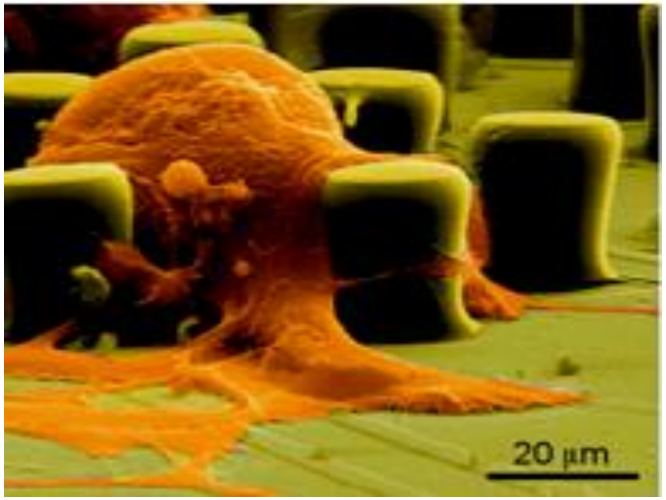
Packaging

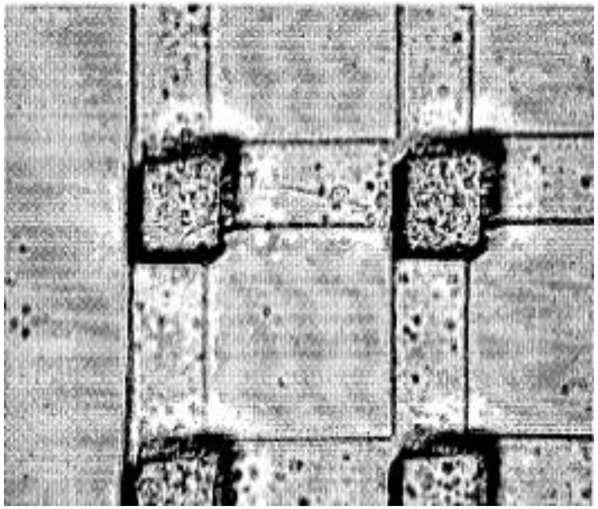
- Housing for the components must be compatible and well tolerated by the body
- Needs to provide protection to circuit components to ensure reliable operation
- Size and weight must be considered
- Common designs consist of hermetically sealed titanium or stainless steel

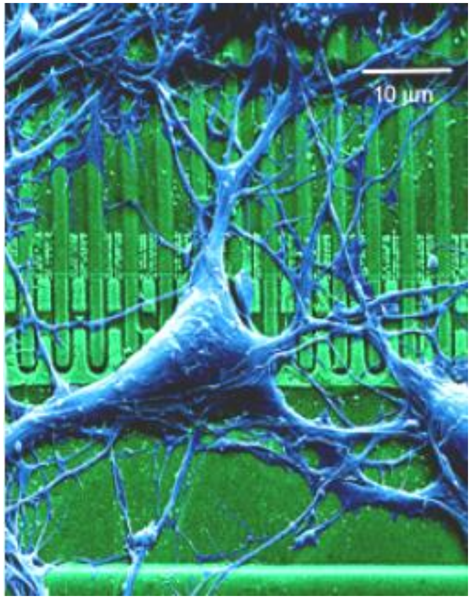
Interfacing with the Nervous System

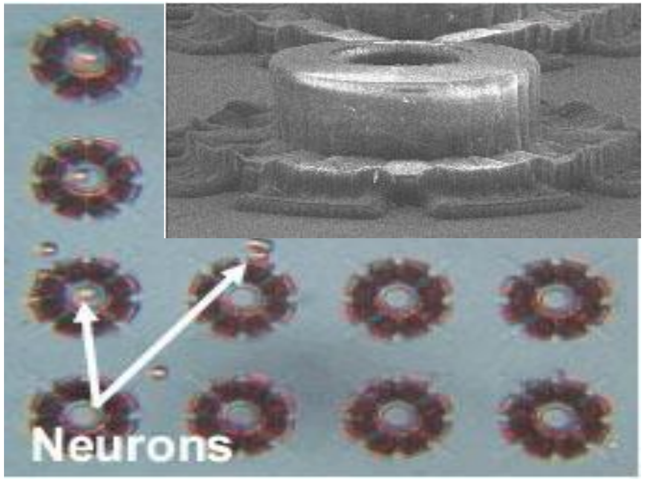
- Interfacing with Neurons
  - Microelectrodes
  - Electrical, neurochemical
  - Microdrive mechanisms
- Interfacing with Brain Tissue Slices
  - Microelectrode arrays
  - Electrical/optical recording
- Recording and Stimulating Whole Brain
  - Microelectrode arrays
  - Electrical and chemical recording; Stimulation
  - VLSI circuitry, Wireless telemetry
- Applications of interfacing microelectrodes to neurons
  - studying the effect of different chemicals/ neurotrophic factors
  - study of axon growth and regeneration
- Applications of interfacing microelectrodes to brain
  - large scale neurophysiological studies of mechanisms, diseases
  - emerging fields like brain computer interface

Interfacing with neurons

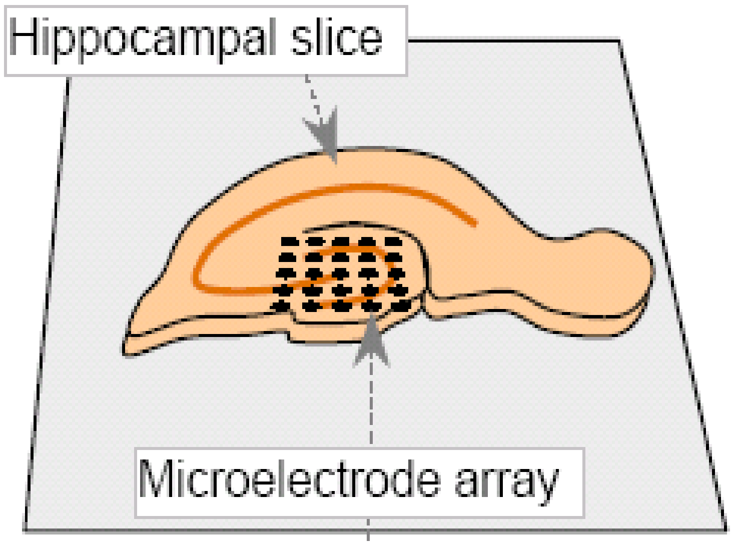


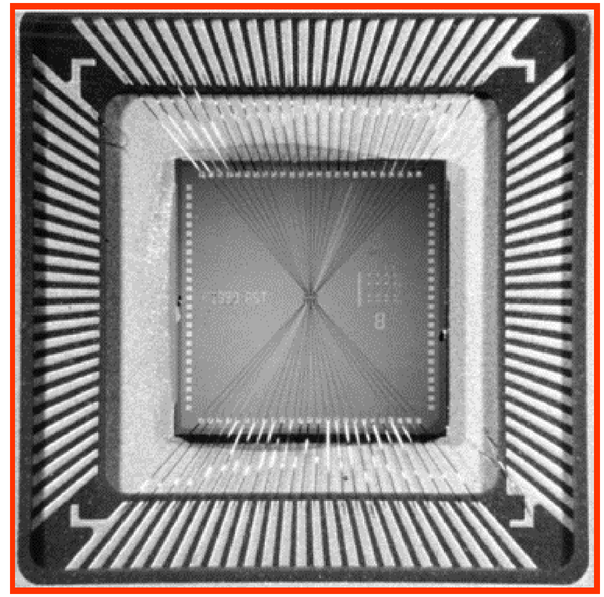


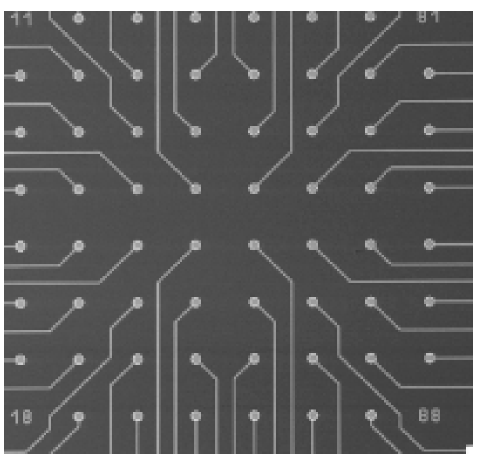


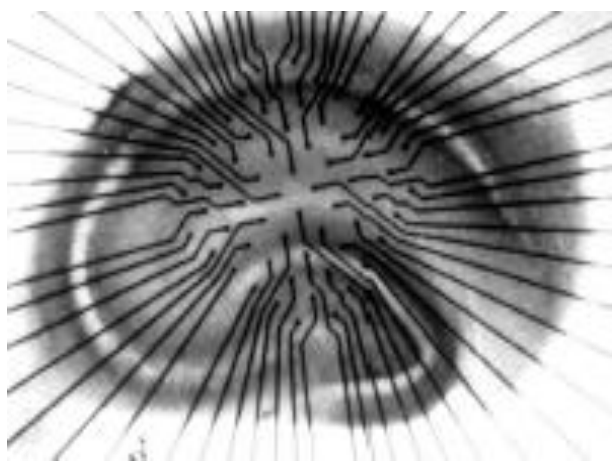


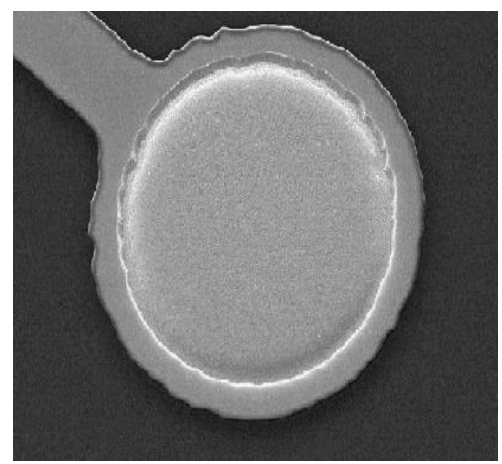
Interfacing with In Vitro Brain Slices



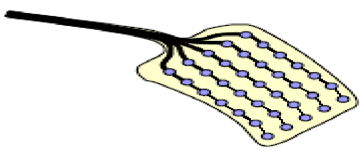




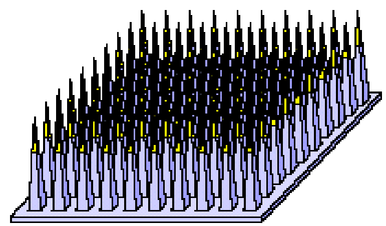




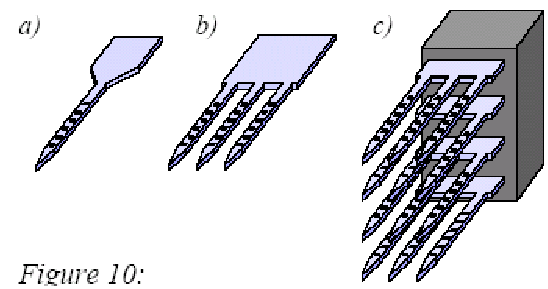
Neural Microelectrodes



Flat array of micro electrode for in-vivo application

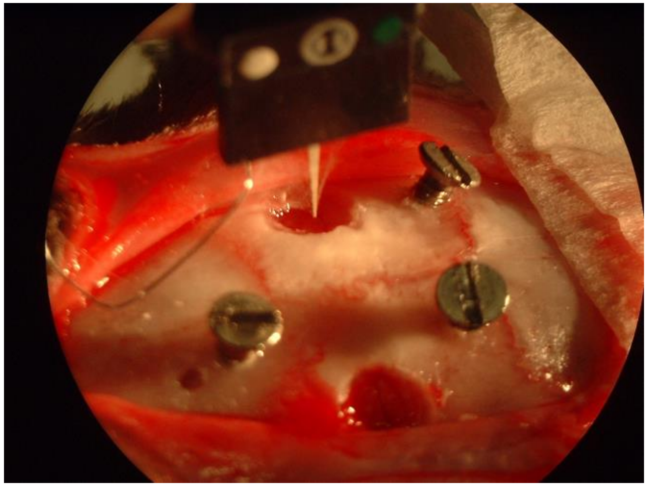


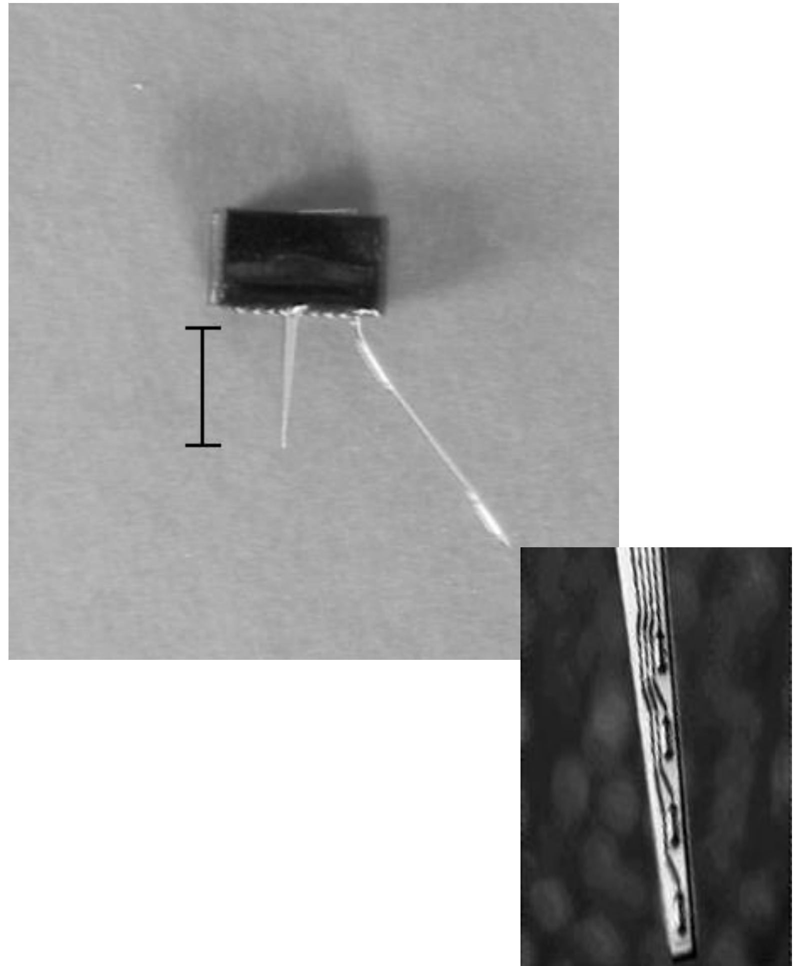
Pyramidal shaped microelectrode for in-vivo application

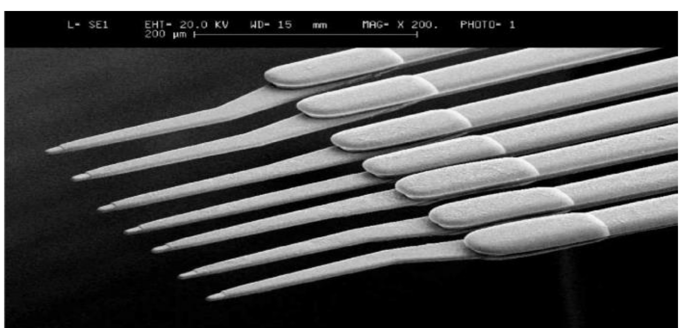


Simple, triple and multiple shank electrode for in-vivo application

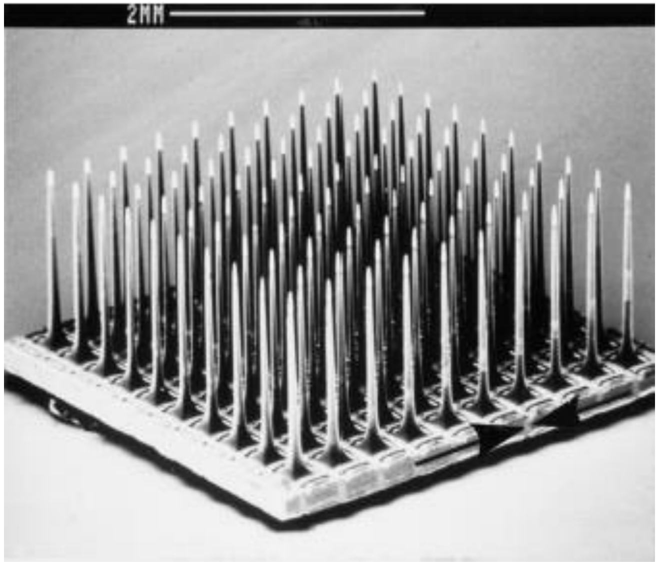
Interfacing with brain

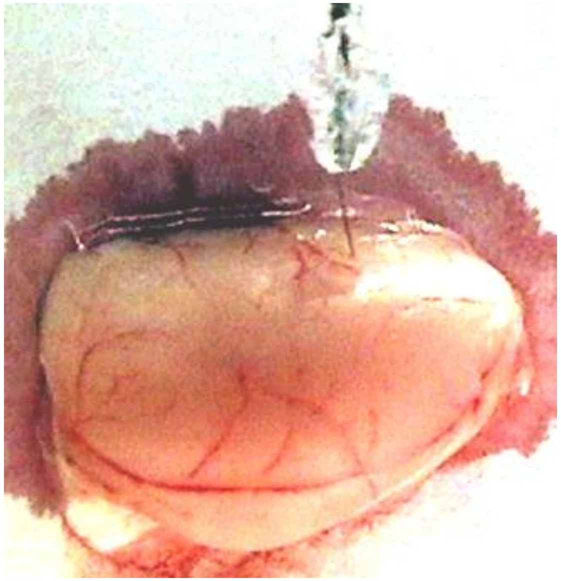


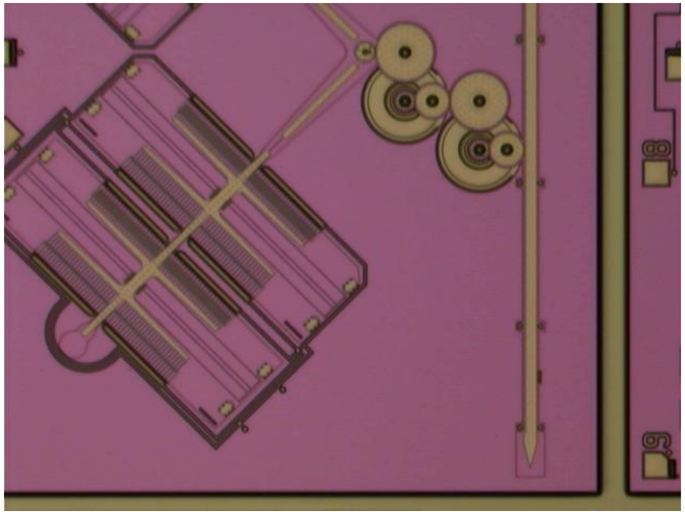


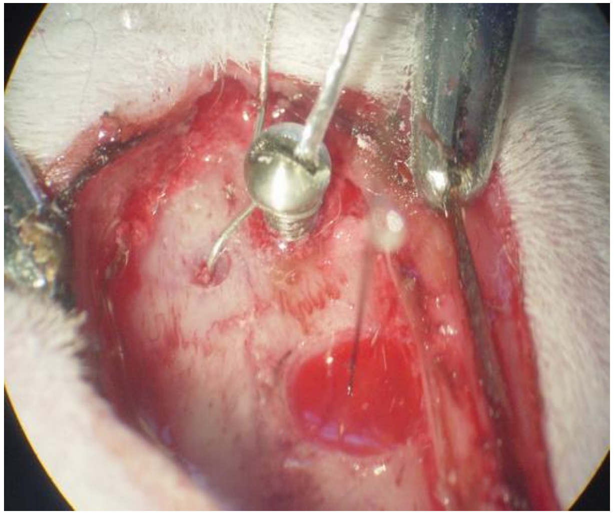


Cortical Microelectrodes

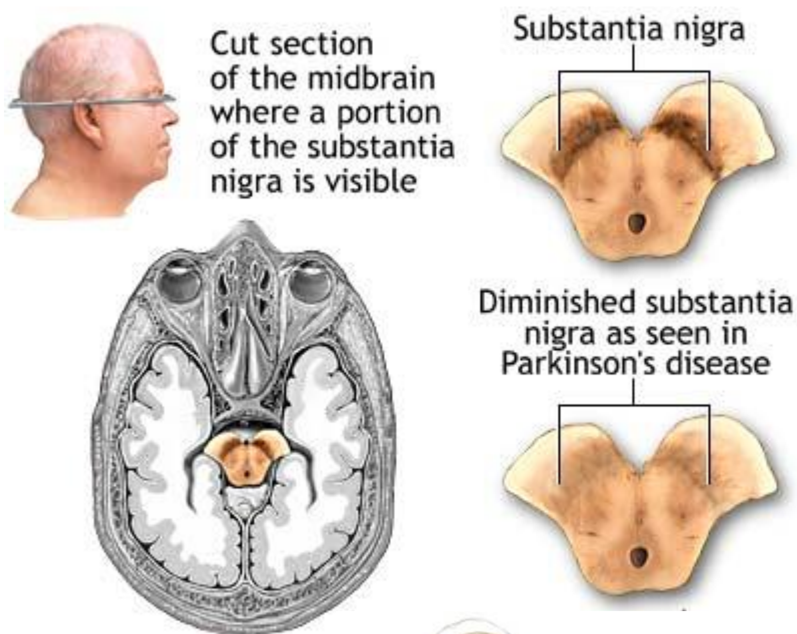


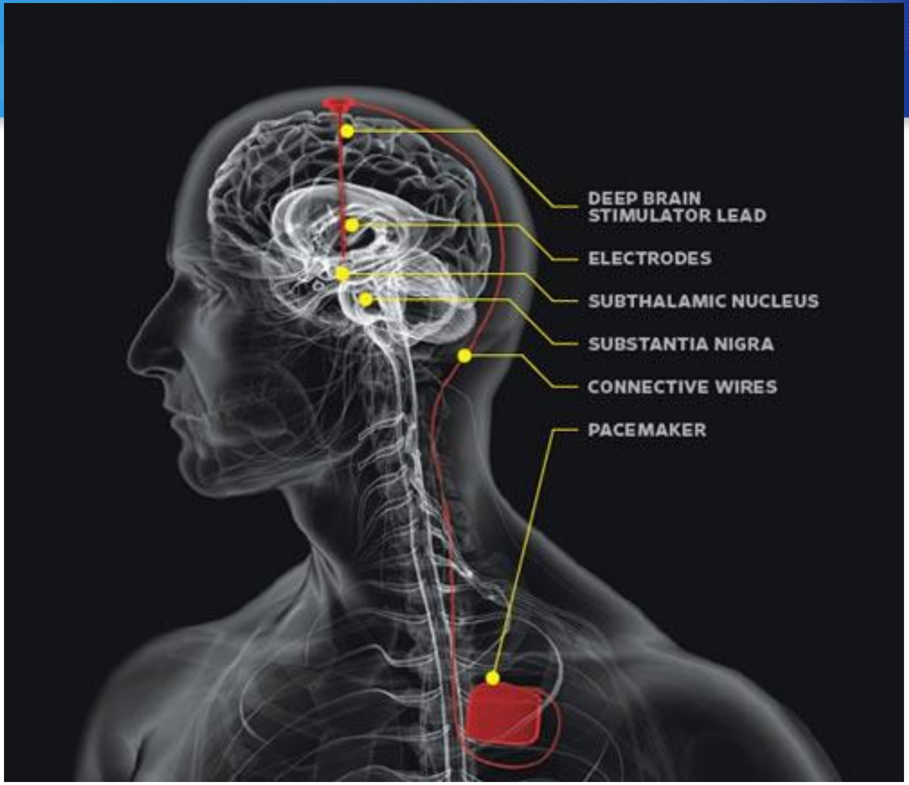


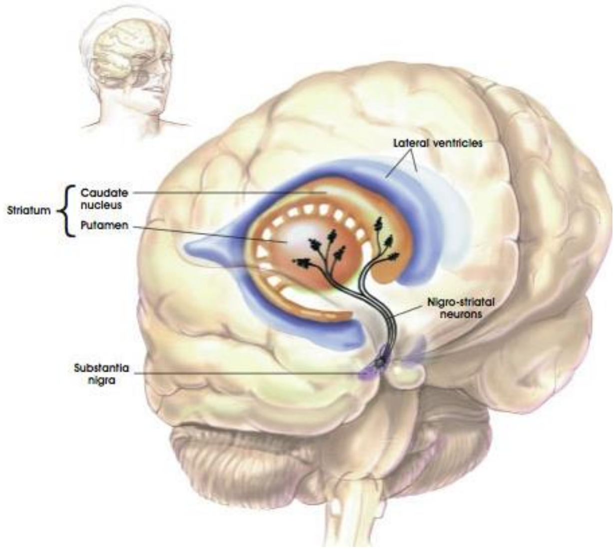


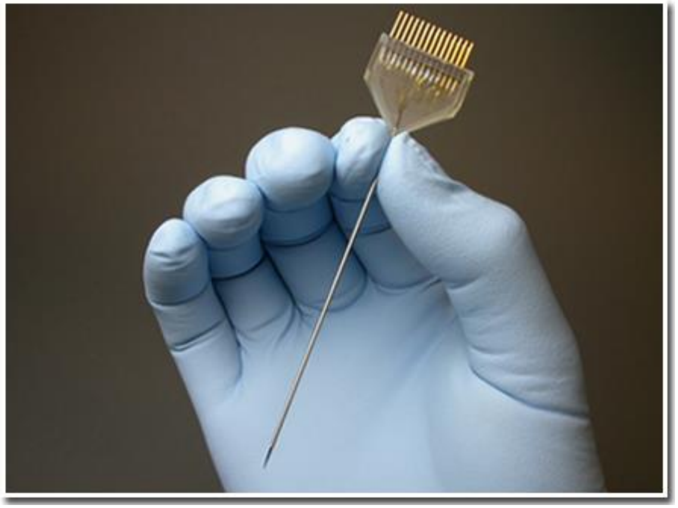


Parkinsonism

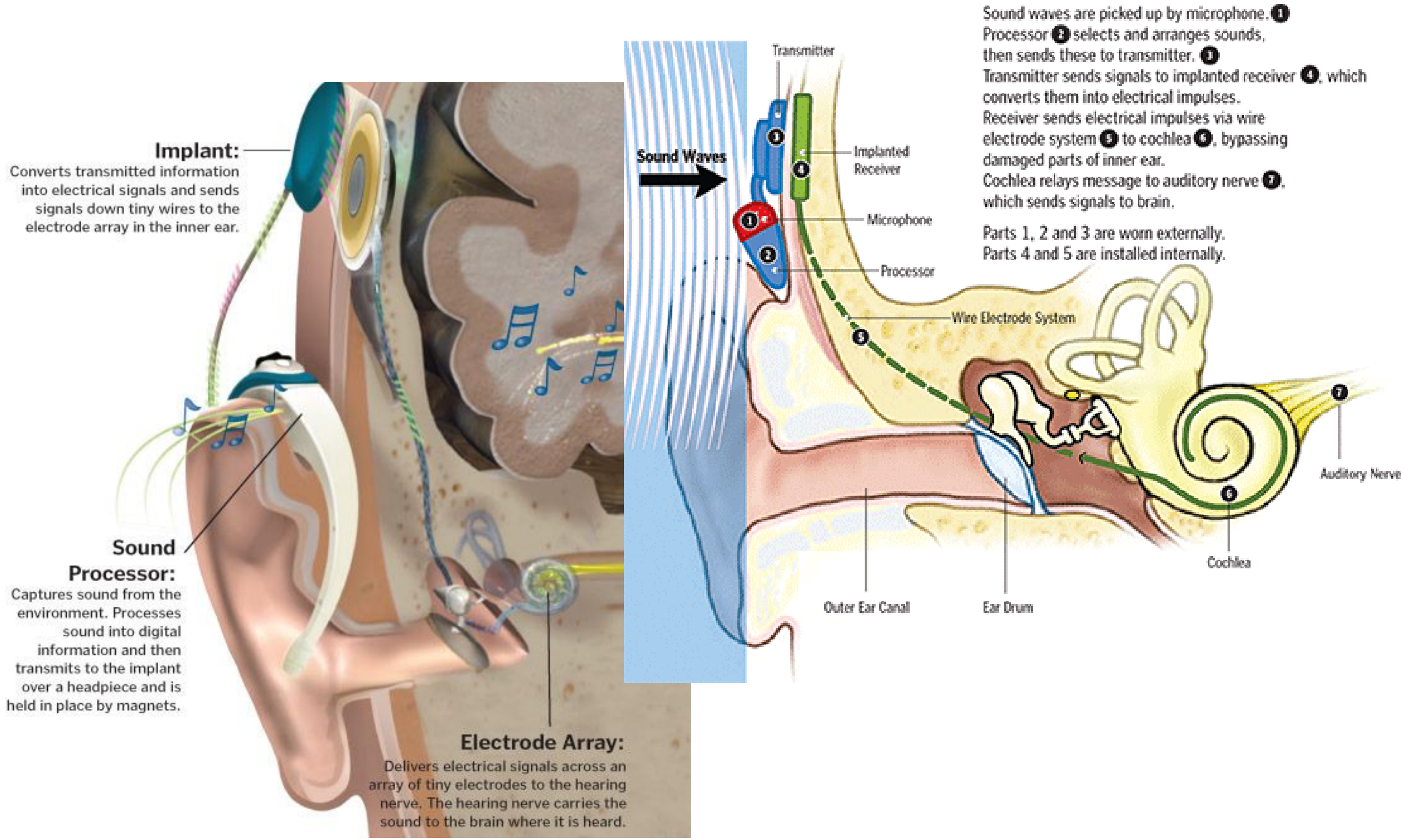




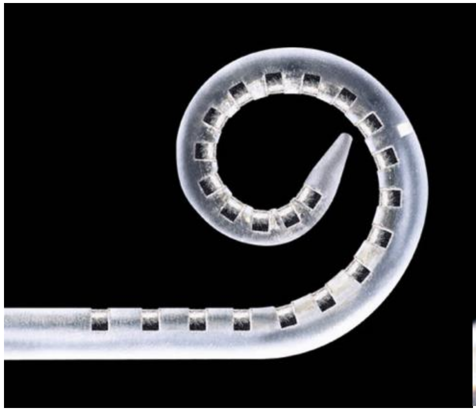


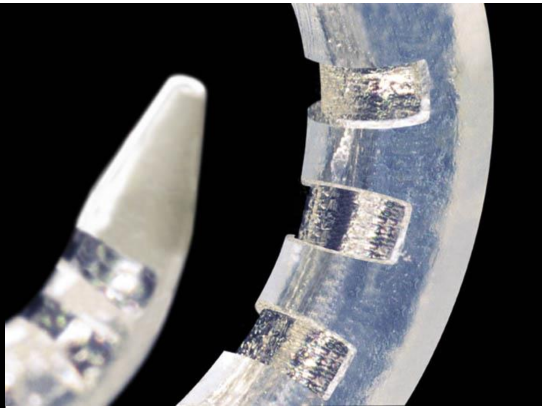


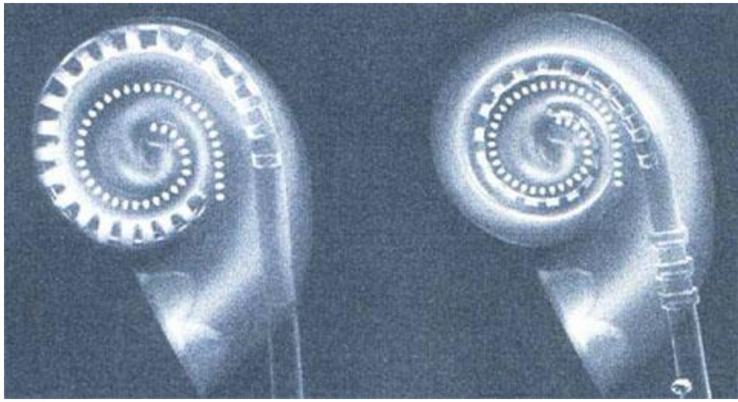
Artificial Cochlea



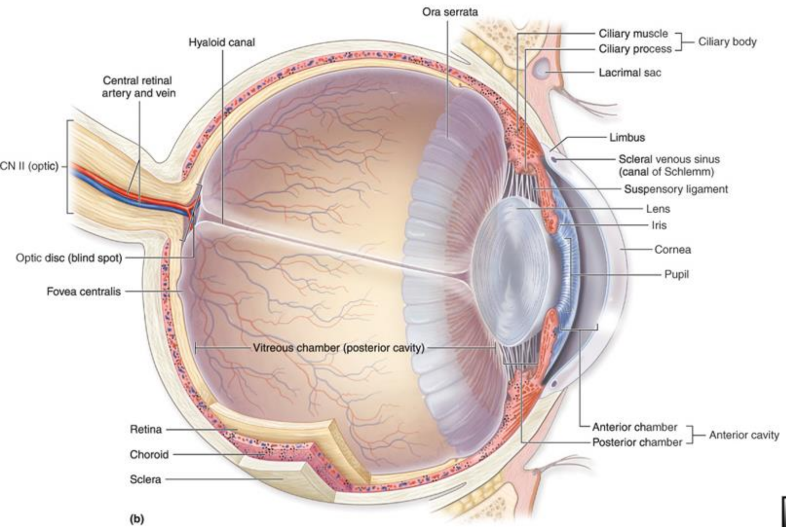
Cochlear Ltd, Australia

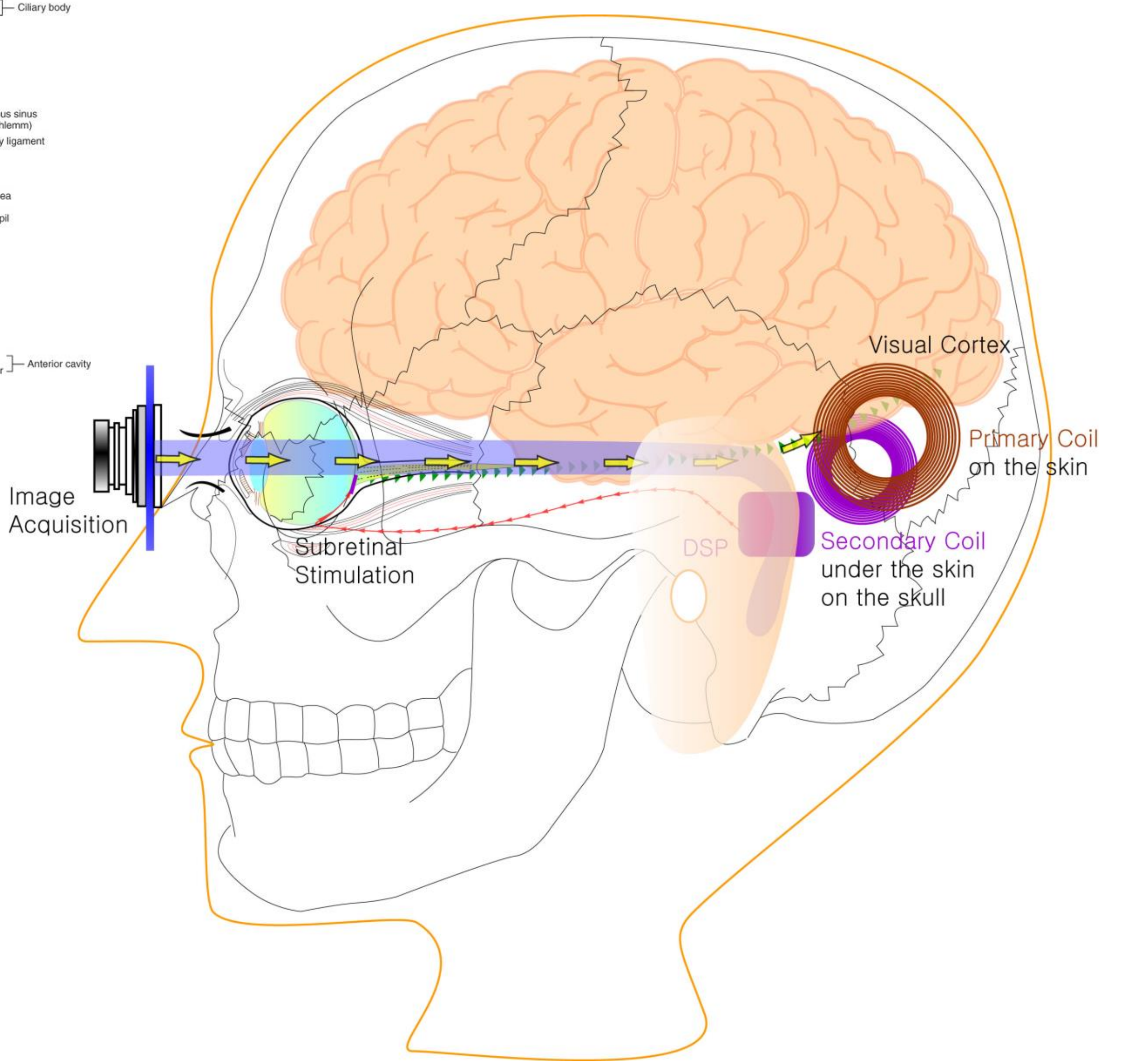




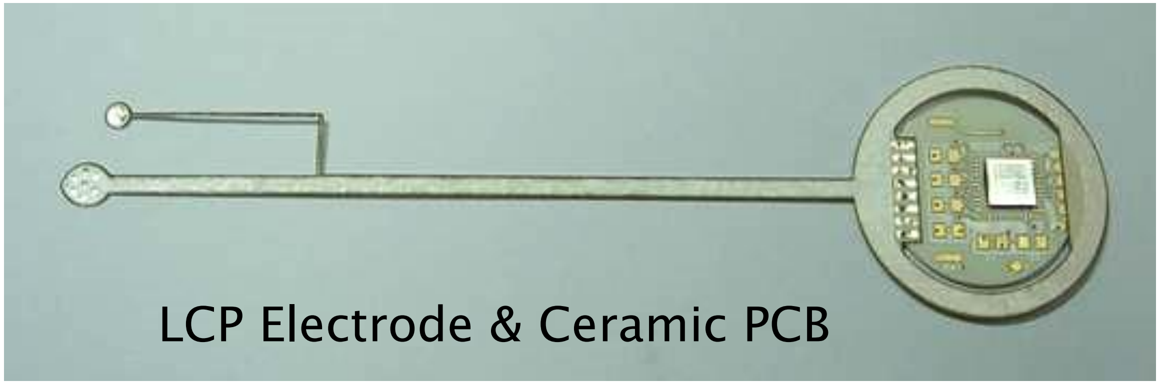


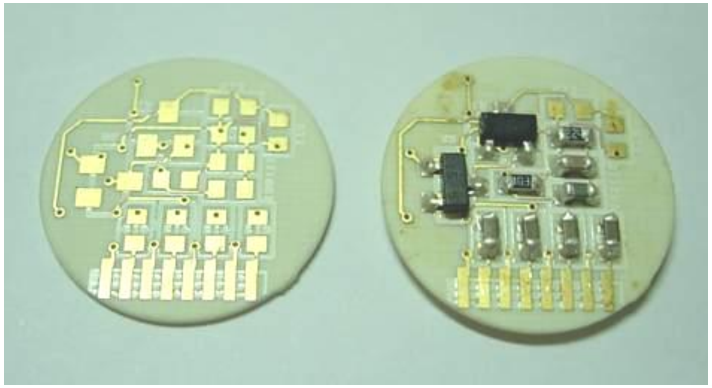
Artificial Retina

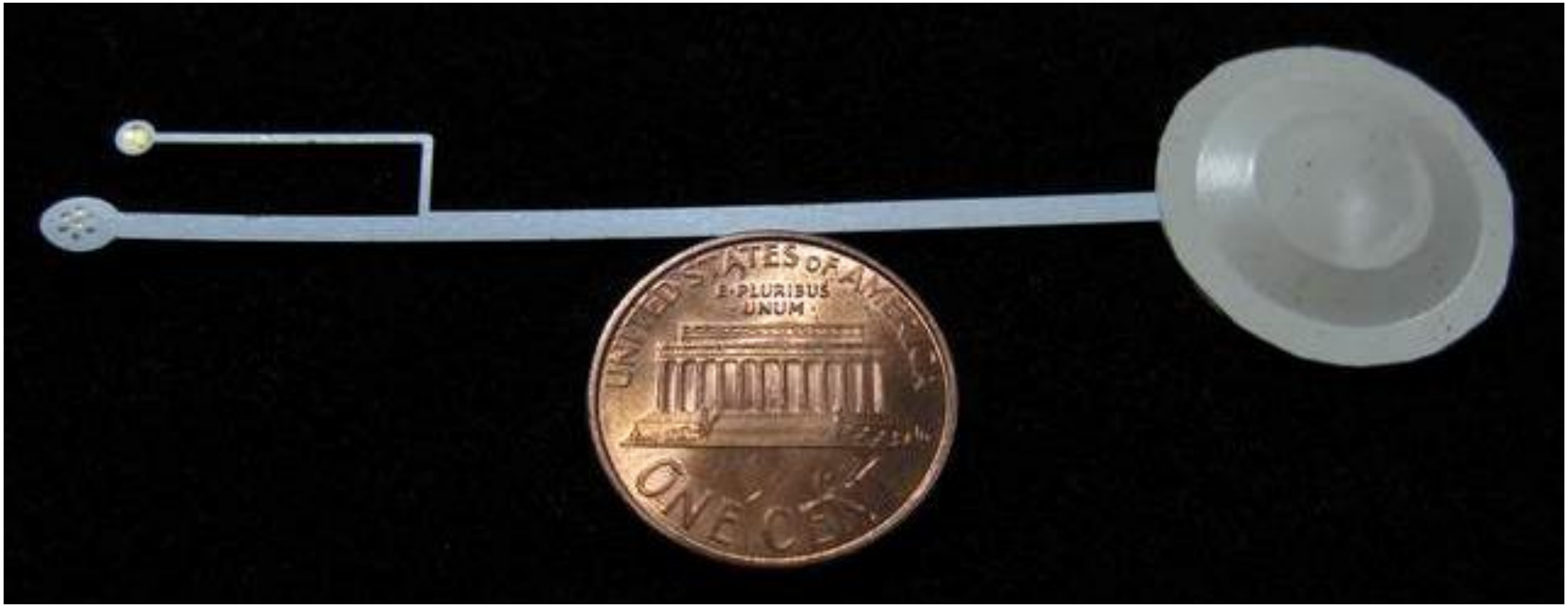




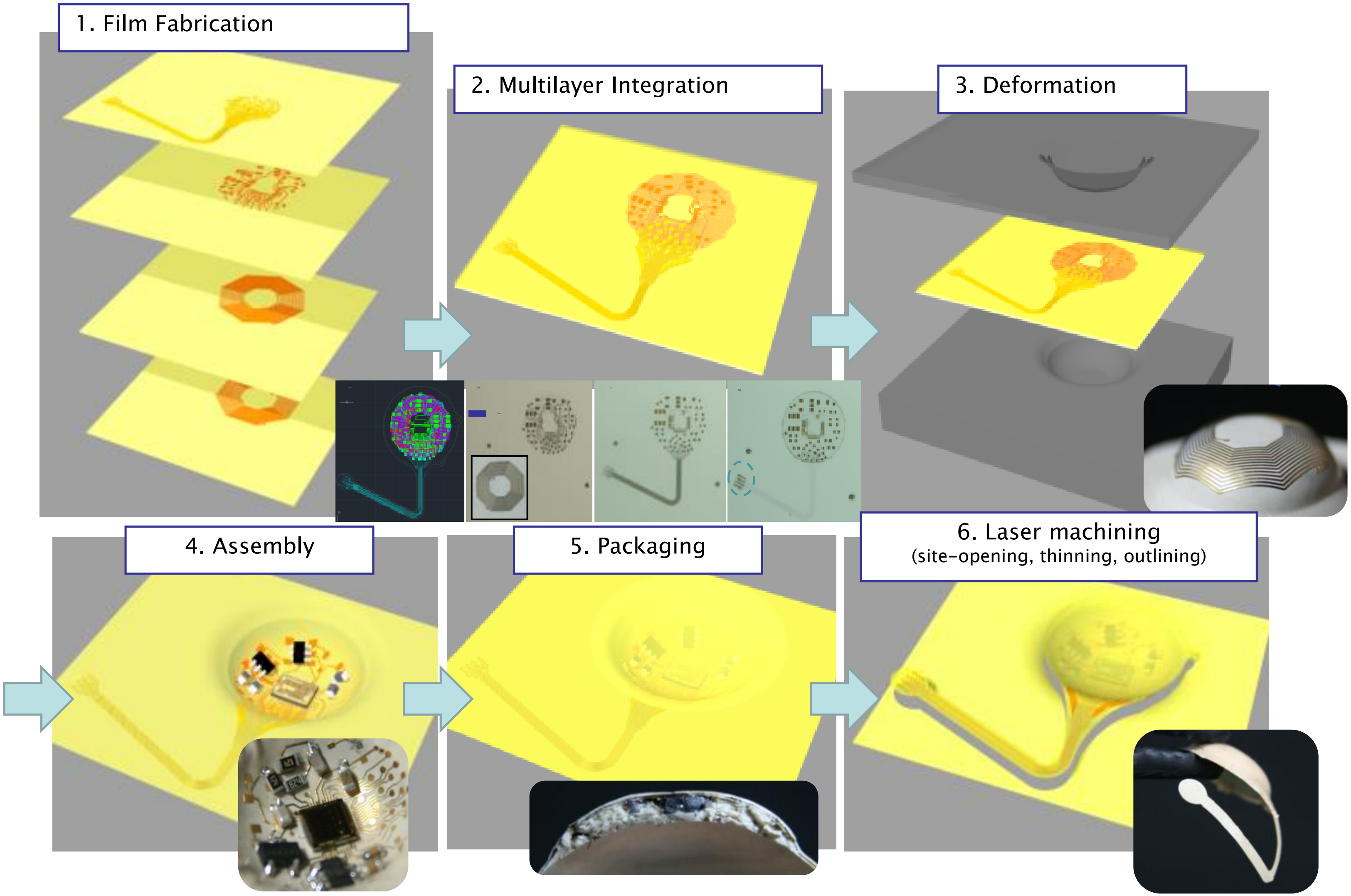
LCP-based system







Revision of the LCP package design



Liquid Crystal Polymer (LCP), an Attractive Substrate for Retinal Implant
Sensors and Materials, Vol 24, No. 4 (2012) pp. 189-203

Implantable devices

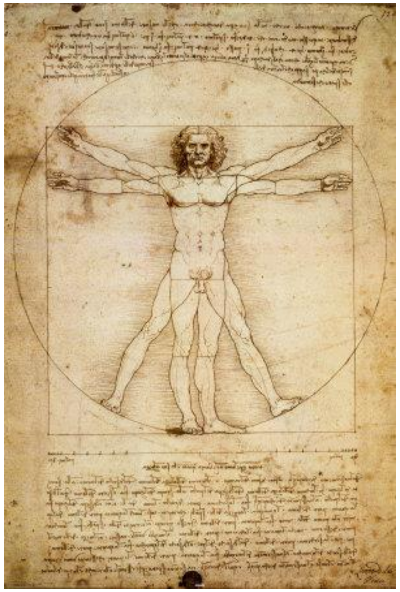
- Device surgically placed in the body and left there.
- Issues
  - Biocompatibility
  - Power source
  - Safety – leakage current etc.
  - Risks from environment EM fields – MRI, airport X-Ray
- Why ?
  - Many conditions require continuous monitoring and the action taken depends on that. Implantable devices can achieve this without loss of mobility.

ISO 10993-5: Biological evaluation of medical devices

- ISO 10993-1: Evaluation and testing
- ISO 10993-2: Animal welfare requirements
- ISO 10993-3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4: Selection of tests for interactions with blood
- ISO 10993-5: Tests for in vitro cytotoxicity
- ISO 10993-6: Tests for local effects after implantation
- ISO 10993-7: Ethylene oxide sterilization residuals
- ISO 10993-8: Selection of reference materials
- ISO 10993-9: Framework for identification and quantification of potential degradation products
- ISO 10993-10: Tests for irritation and delayed-type hypersensitivity
- ISO 10993-11: Tests for systemic toxicity
- ISO 10993-12: Sample preparation and reference materials
- ISO 10993-13: Identification and quantification of degradation products from polymeric medical devices
- ISO 10993-14: Identification and quantification of degradation products from ceramics
- ISO 10993-15: Identification and quantification of degradation products from metals and alloys
- ISO 10993-16: Toxicokinetic study design for degradation products and leachables
- ISO 10993-17: Establishment of allowable limits for leachable substances
- ISO 10993-18: Chemical characterization of materials
- ISO/TS 10993-19: Physico-chemical, morphological and topographical characterization of materials
- ISO/TS 10993-20: Principles and methods for immunotoxicology testing of medical devices

Biocompatibility

- In vitro test
  - Cytotoxicity
  - Genetic toxicity
  - Sterility
  - Hemolysis
- In vivo test
  - Sensitization
  - Intradermal reaction
  - Acute systemic toxicity
  - Subacute systemic toxicity
  - Genetic toxicity
  - Transplantation
  - Pyogenicity
  - Oral mucosa stimulation

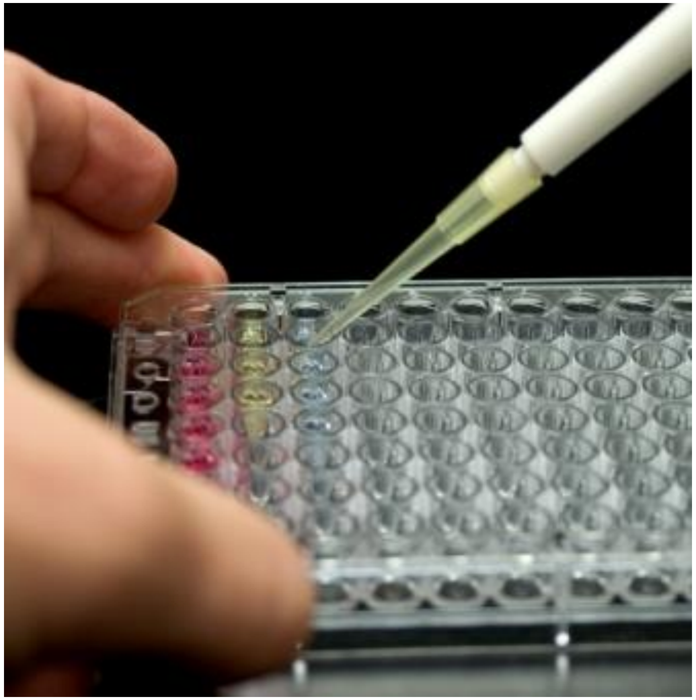


efe
Electro-medical fusion engineering

Cytotoxicity test

- By direct contact
  By elute or extract
- Test cell: NCTC clone 929

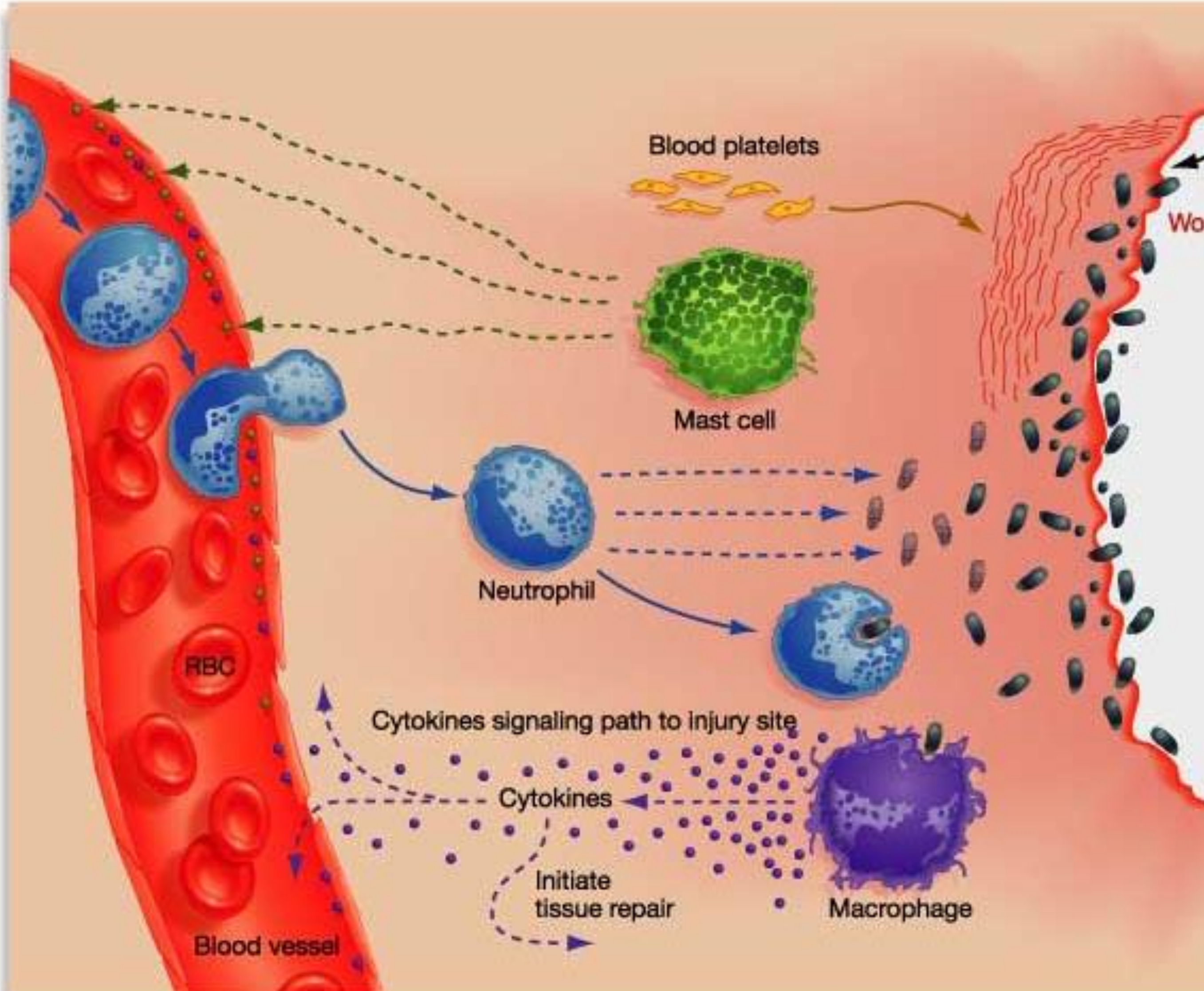
Group	Test Item	Concentration	Treated Time (hr)	Column	Row
Blank	MEM	-	24	1,12	A~H
Negative Control	Extract of HDPE	1X dilution	24	2,11	A~H
Positive Control	DMSO	10% in media	24	3~5	A~H
Treatment	Extract of Test article	1X dilution 2X dilution 4X dilution 8X dilution 16X dilution	24	6~10	A~H



Text Table 1. Reactivity Grades for Elution Test

Grade	Reactivity	Conditions of all cultures
0	None	Discrete intracytoplasmic granules; no cell lysis
1	Slight	Not more than 20% of the cells are round, loosely attached, and without intracytoplasmic granules; occasionally lysed cells are present
2	Mild	Not more than 50% of the cells are round and devoid of intracytoplasmic granules; extensive cell lysis and empty areas between cells
3	Moderate	Not more than 70% of the cell layers contain rounded cells and/or are lysed
4	Severe	Nearly complete destruction of the cell layers

Inflammation



1. Bacteria and other pathogens enter wound.

2. Platelets from blood release blood-clotting proteins at wound site.

3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases.

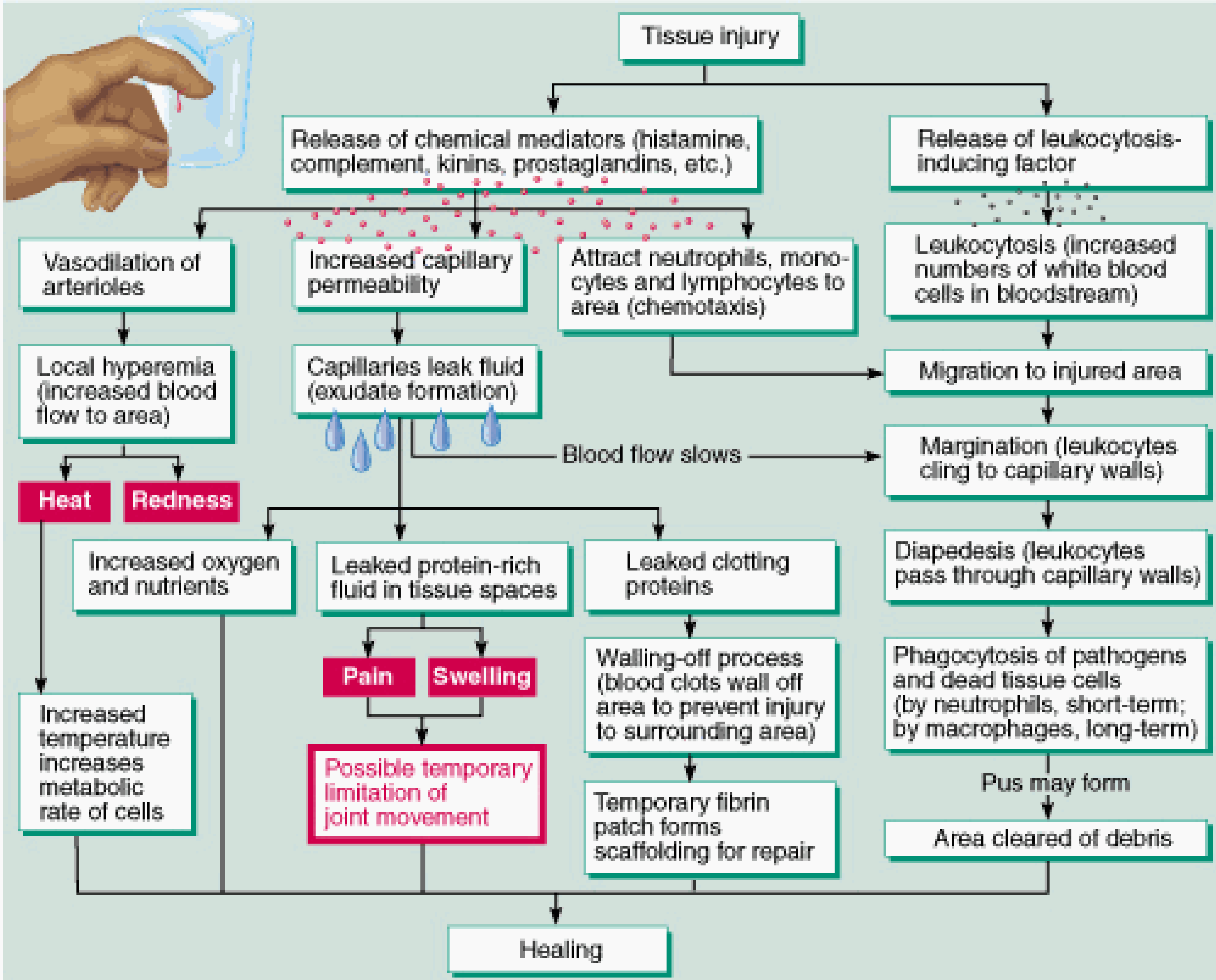
4. Neutrophils secrete factors that kill and degrade pathogens.

5. Neutrophils and macrophages remove pathogens by phagocytosis.

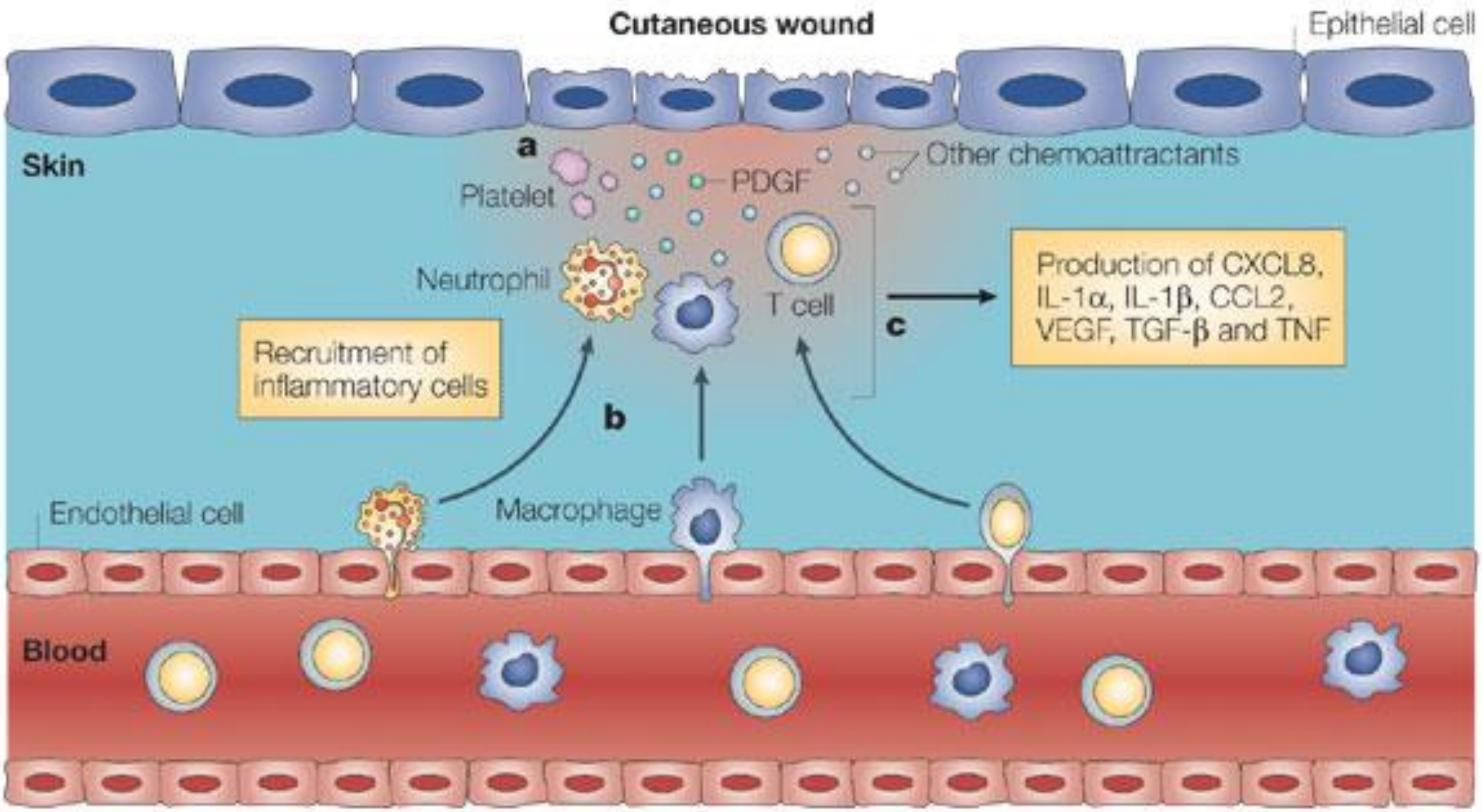
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair.

7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired.

4 Cardinal signs

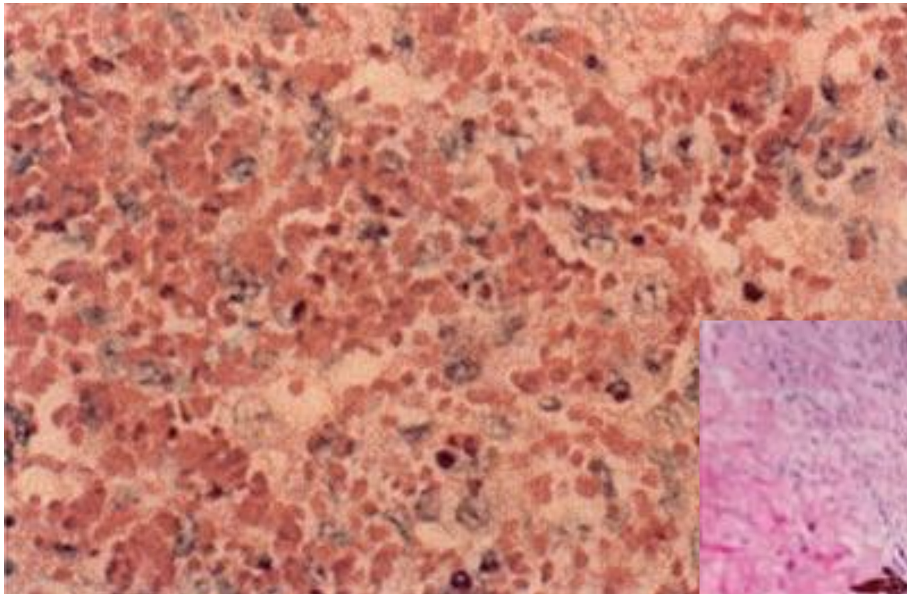


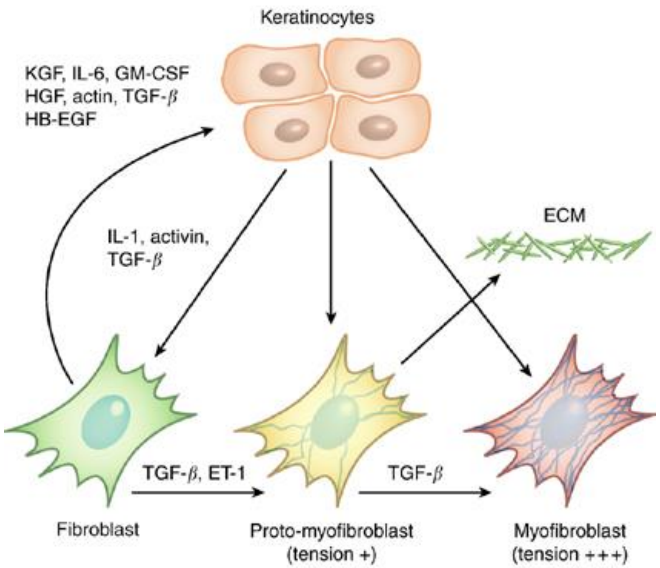
Inflammatory phase

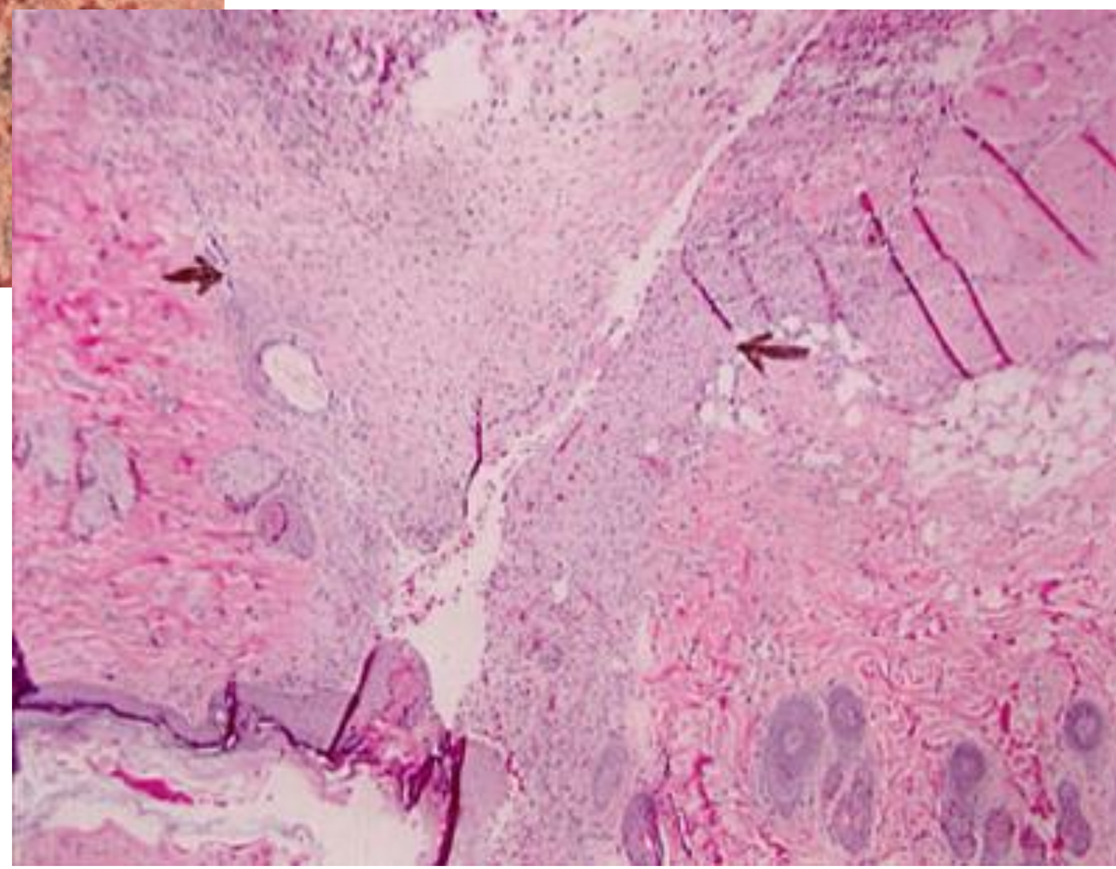


Nature Reviews | Immunology

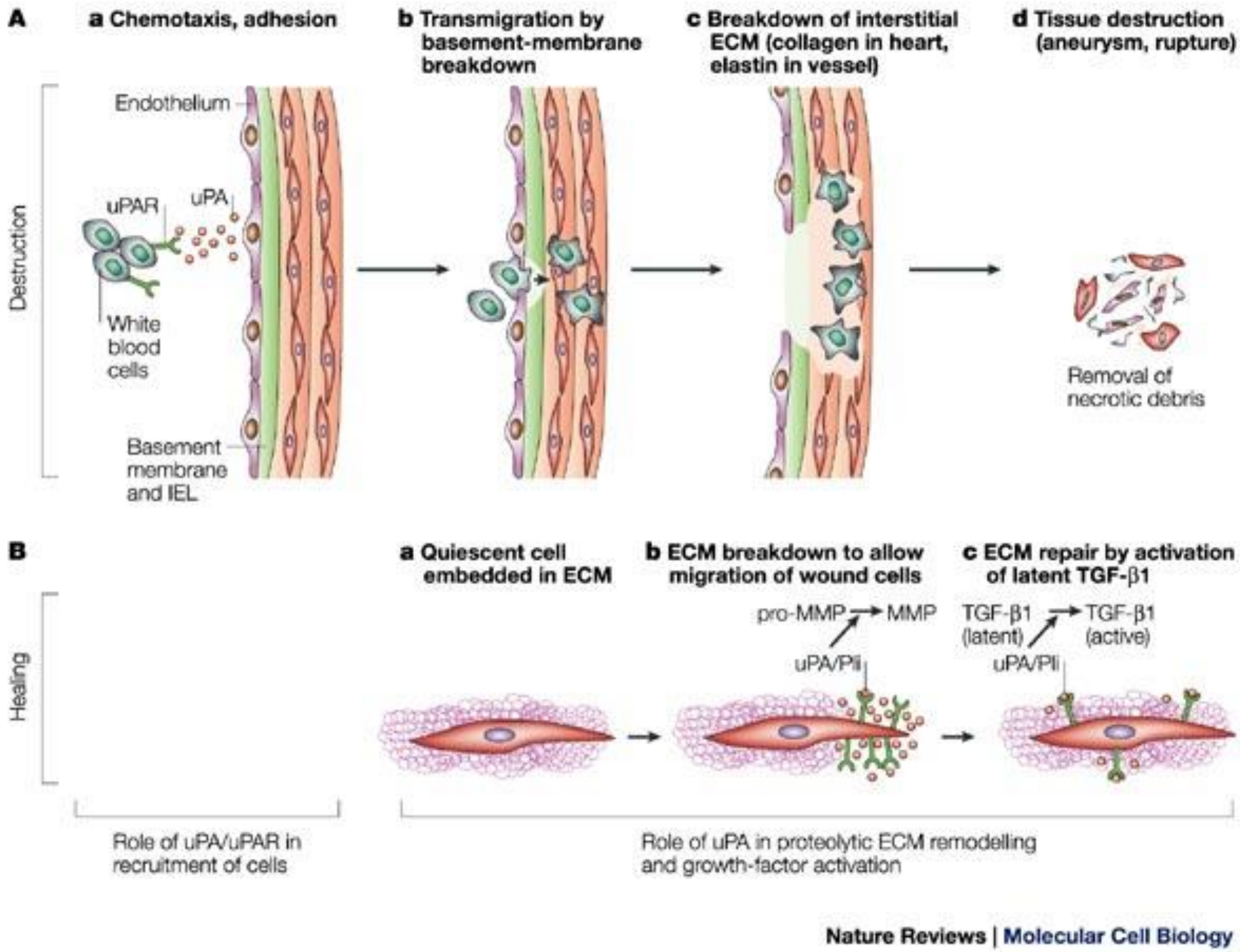
Proliferative phase



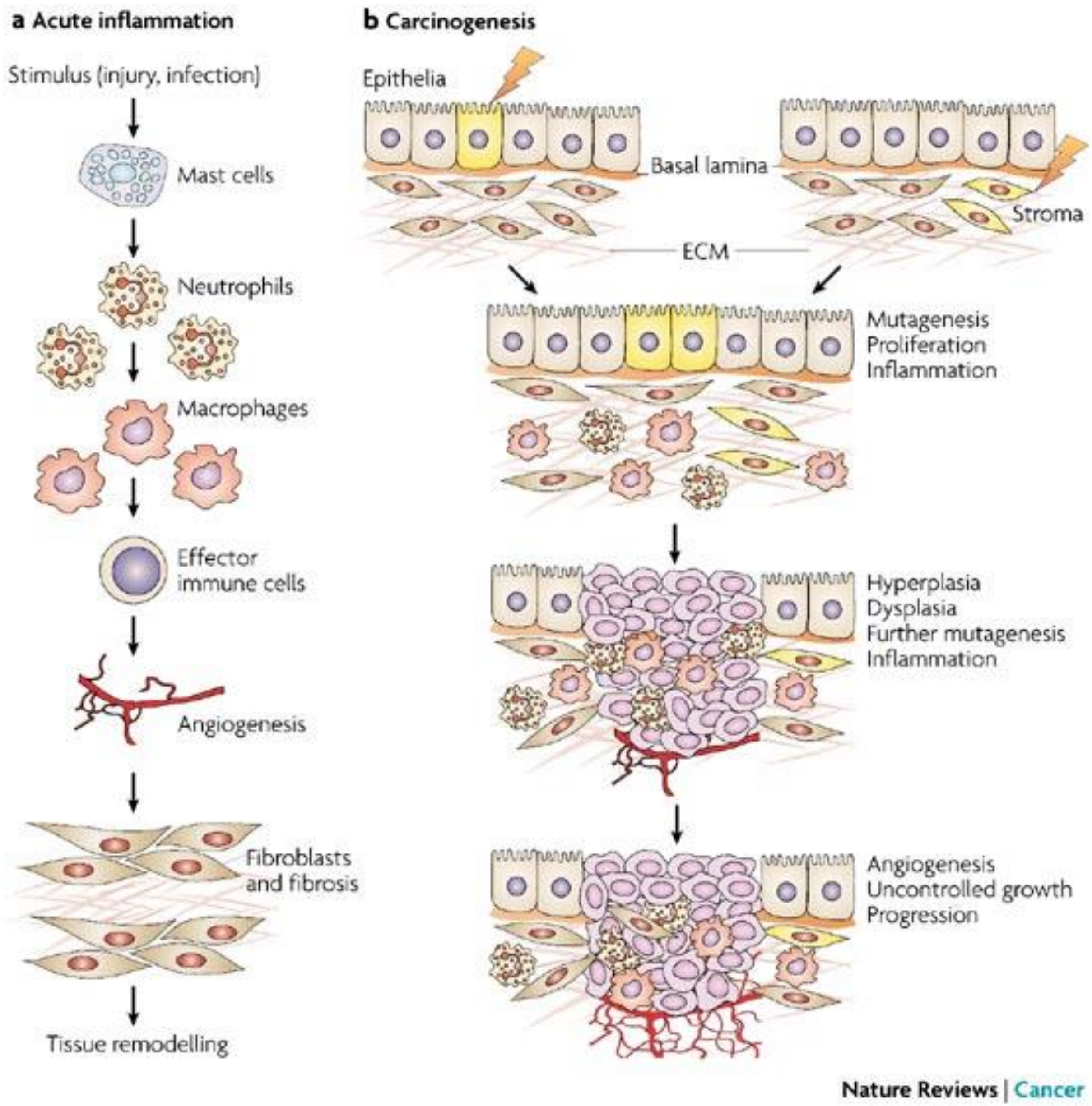




Remodeling phase



Carcinogenesis



Mobile device

- Pros
  - Small, lightweight
  - Multi-function: camera, accelerometer, gyroscope, GPS
  - Intuitive
  - Wireless network
- Cons
  - Battery lifetime
  - Nonspecific
  - Resolution, size
  - Speed
  - Contamination

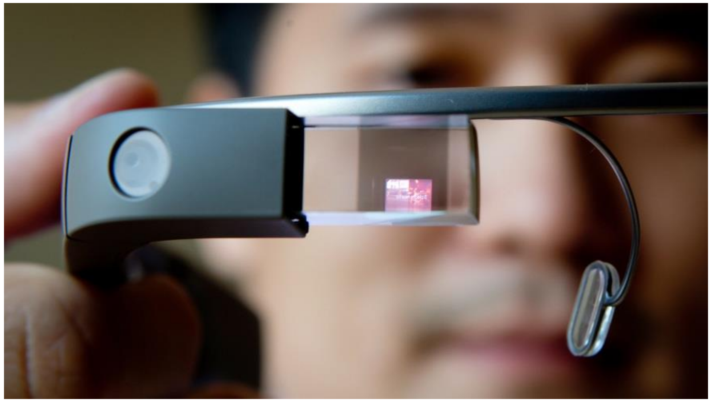
Blood Sugar Test

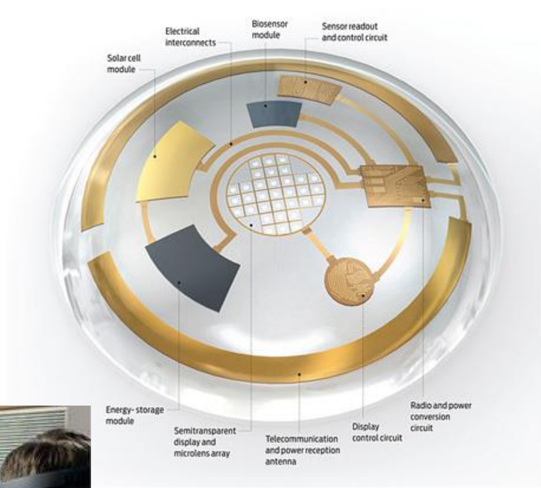
- Pros
  - Instant, convenient
  - Record and tracking
  - Networking
- Cons
  - Contamination, invasive
  - Test strip

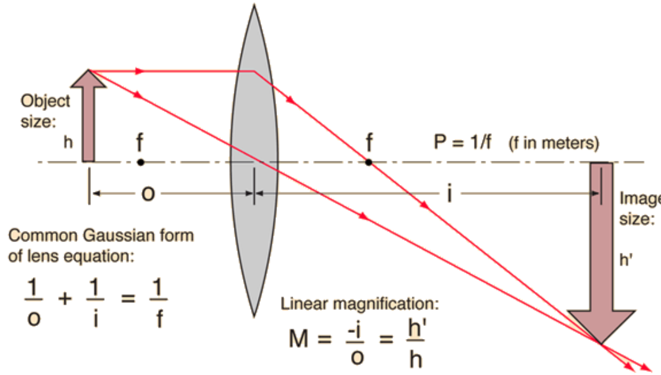
Blood Sugar Test

Accommodation: Focusing for Close Vision

- Lens bulging > pupil constriction and convergence
- Forceful convergence > lens bulging and pupil constriction
- Bright light > pupil constriction > lens bulging and convergence

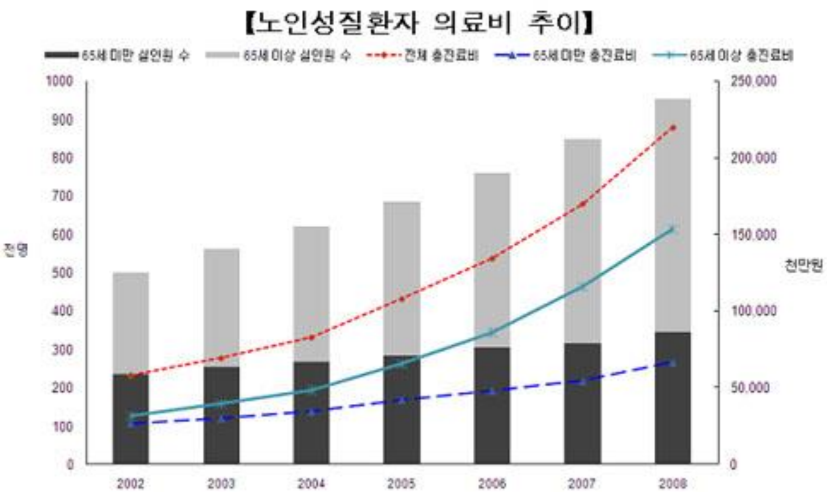




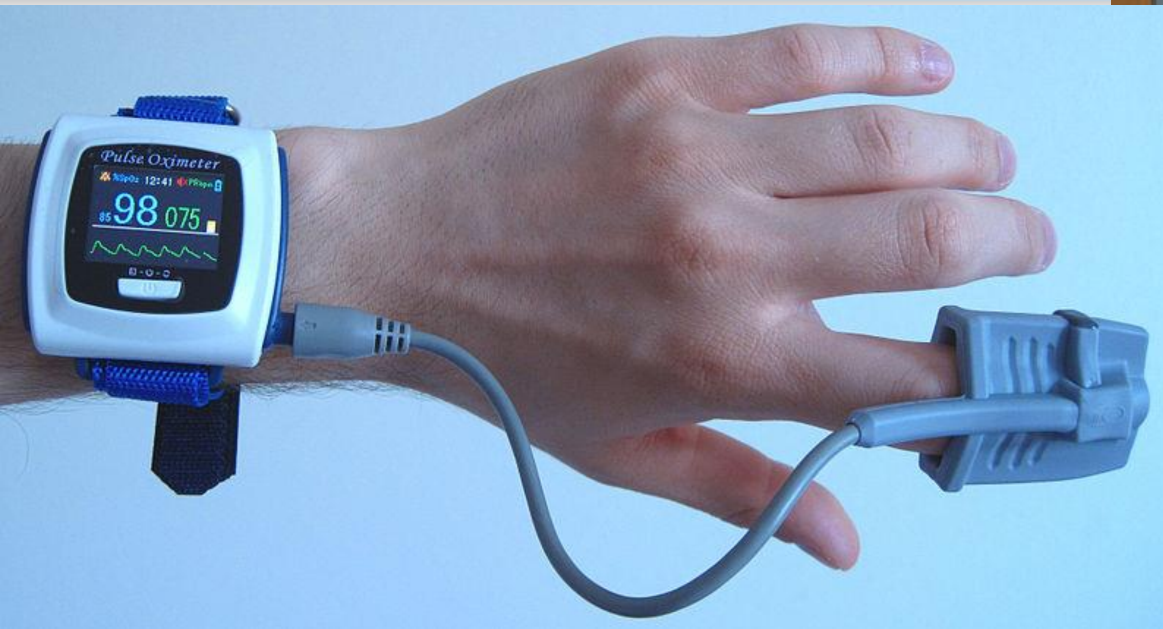


Head mount display – virtual reality

Aging society



Thank you


Pulse Oximeter
12:41
98 075


Pause
569 steps
0.25mi 20kcal


CYON
당뇨폰
다이어트폰
뷰티폰
한방폰
스트레스폰


FUEL