BB101 Selected Slides

Some Branches of BME…

- **Biomechanics**
  - application of classical mechanics to biological or medical problems
  - study of movement of biologic solids, fluids and viscoelastic materials, muscle forces
  - design of artificial limbs
- **Biomaterials:**
  - study of both living tissue and artificial synthetic biomaterials (polymers, metals, ceramics, composites) used to replace part of a living system or to function in intimate contact with living tissue (implants)
  - biomaterials:
    - nontoxic,
    - non-carcinogenic
    - chemically inert
    - stable
    - mechanically strong

…Some Branches of BME…

- **Biomedical sensors**
  - physical measurements, biopotential electrodes, electrochemical sensors, optical sensors, bioanalytic sensors
- **Bioelectric phenomena:**
  - origin in nerve and muscle cells
  - generation in nerves, brain, heart, skeletal muscles
  - analysis,
  - modelling,
  - recording and
  - diagnosis

…Some Branches of BME…

- **Biomedical signal processing and analysis**
  - collection and analysis of data from patients
  - bioelectric, physical, chemical signals
  - online (embedded) and off-line processing and analysis
- **Medical imaging and image processing:**
  - provision of graphic display of anatomic detail and physiological functions of the body
  - medical imaging methods and devices
    - physical phenomena + detectors + electronic data processing+ graphic display = image
    - x-ray, gamma photons, MRI, Ultrasound

…Some Branches of BME…

- **Medical instruments and devices:**
  - design of medical instruments and devices to monitor and measure biological functions
  - application of electronics and measurement techniques to develop devices used in diagnosis and treatment of disease
    - biopotential amplifiers
    - patient monitors
    - electrosurgical devices
- **Biotechnology**
  - technology at cellular level

…Some Branches of BME…

- **Cell and tissue engineering:**
  - utilization of anatomy, biochemistry and mechanics of cellular and subcellular structures to understand disease processes and to be able to intervene at very specific sites.
  - design, construction, modification, growth and maintenance of living tissue (bioartificial tissue and alteration of cell growth and function)
- **Rehabilitation engineering:**
  - application of science and technology to improve the quality of life for individuals with physical and cognitive impairments (handicaps)

…Some Branches of BME…

- **Prostheses and artificial organs**
  - design and development of devices for replacement of damaged body parts
    - artificial heart,
    - circulatory assist devices,
    - cardiac valve prostheses,
    - artificial lung and blood-gas exchange devices,
    - artificial kidney, pancreas

…Some Branches of BME

- **Physiologic modelling, simulation and control**
  - use of computer simulation to help understand physiological relationships and organ function, to predict the behavior of a system of interests (human body, particular organs or organ systems and medical devices)
  - developing of theoretical (computational, analytical, conceptual etc) models
- **Medical informatics:**
  - hospital information systems, computer-based patient records, computer networks in hospitals, artificial knowledge-based medical decision making
- **Bioinformatics**
  - The application of information technology to problem areas in healthcare systems, as well as genomics, proteomics, and mathematical modelling.

Artificial Hearts

- An **artificial heart** is a prosthetic device that is implanted into the body to replace the biological heart.
- It is different from a heart bypass machine, which is an external device (a CardioPulmanory Bypass - CPB).
- A CPB is only suitable for a few hours use, while artificial hearts have so far been used for periods of well over a year.

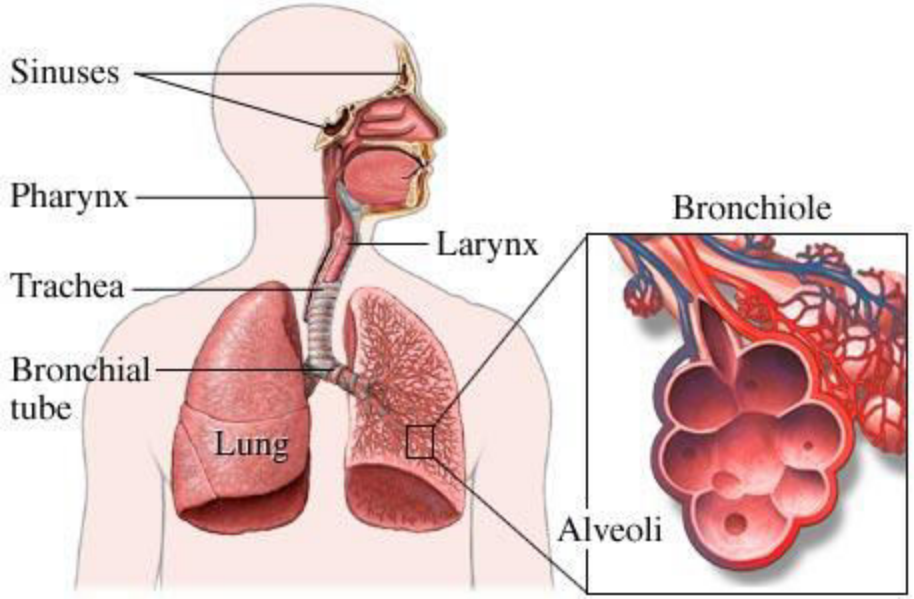
Artificial Hearts

- Heart is basically a pump, but with a lot of subtleties.
- Lower the need for transplants
- Foreign-body rejection a problem
- Right is Abiocor

CardioPulmonary Bypass (CPB)

- Temporarily takes over the function of the heart and lungs during surgery, maintaining the circulation of blood and the oxygen content of the body. Referred to as a *Heart-Lung Machine*
- Oxygenator was first described by Robert Hooke in the 17th Century – removes carbon dioxide, injects oxygen to/from blood

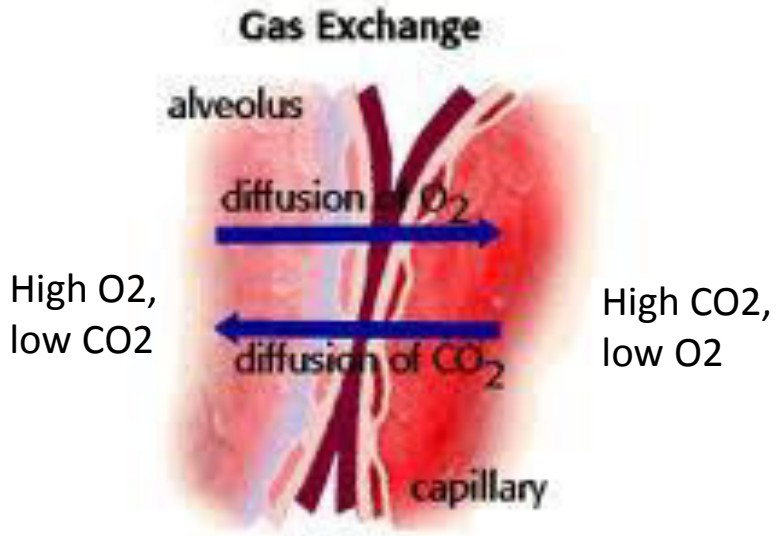
Physiology of Oxygen Transport – Respiratory system



Oxygen enters body through nose/mouth

Travels down airway into alveoli

Gas exchange occurs between alveoli and capillaries driven by pressure gradient



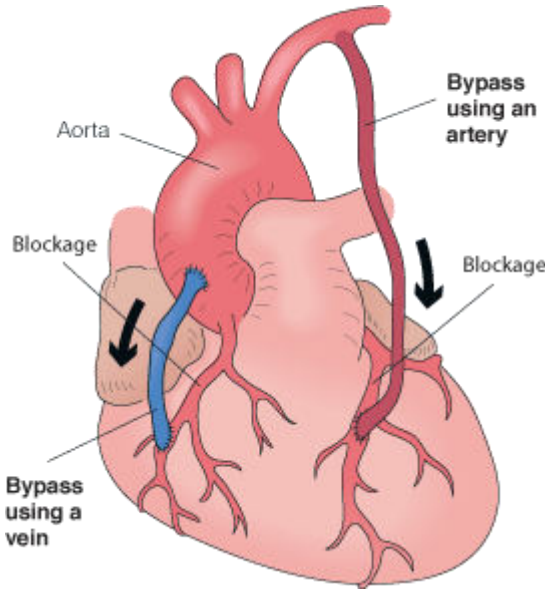
Composition of air by volume:

78% nitrogen, **21% oxygen**, 0.03% CO_2

Heart bypass surgery

Surgery wherein blood flow bypasses the heart and lungs, since operating on an active heart is difficult to accomplish

Coronary artery bypass surgery/graft (CAPG) entails grafting vessels from elsewhere in the body to reroute blood flow around blocked regions in the coronary arteries



For the past half century, has utilized artificial pumping and oxygenating, which is accomplished by the heart-lung device

Pancreas

- The pancreas is below the stomach and above the duodenum. It releases endocrine hormones (insulin, amylin and glucagon) into the portal vein, where it flows directly to the liver.

- Diabetes is the inability of the beta cells of the pancreas to produce sufficient insulin.

Artificial Pancreas

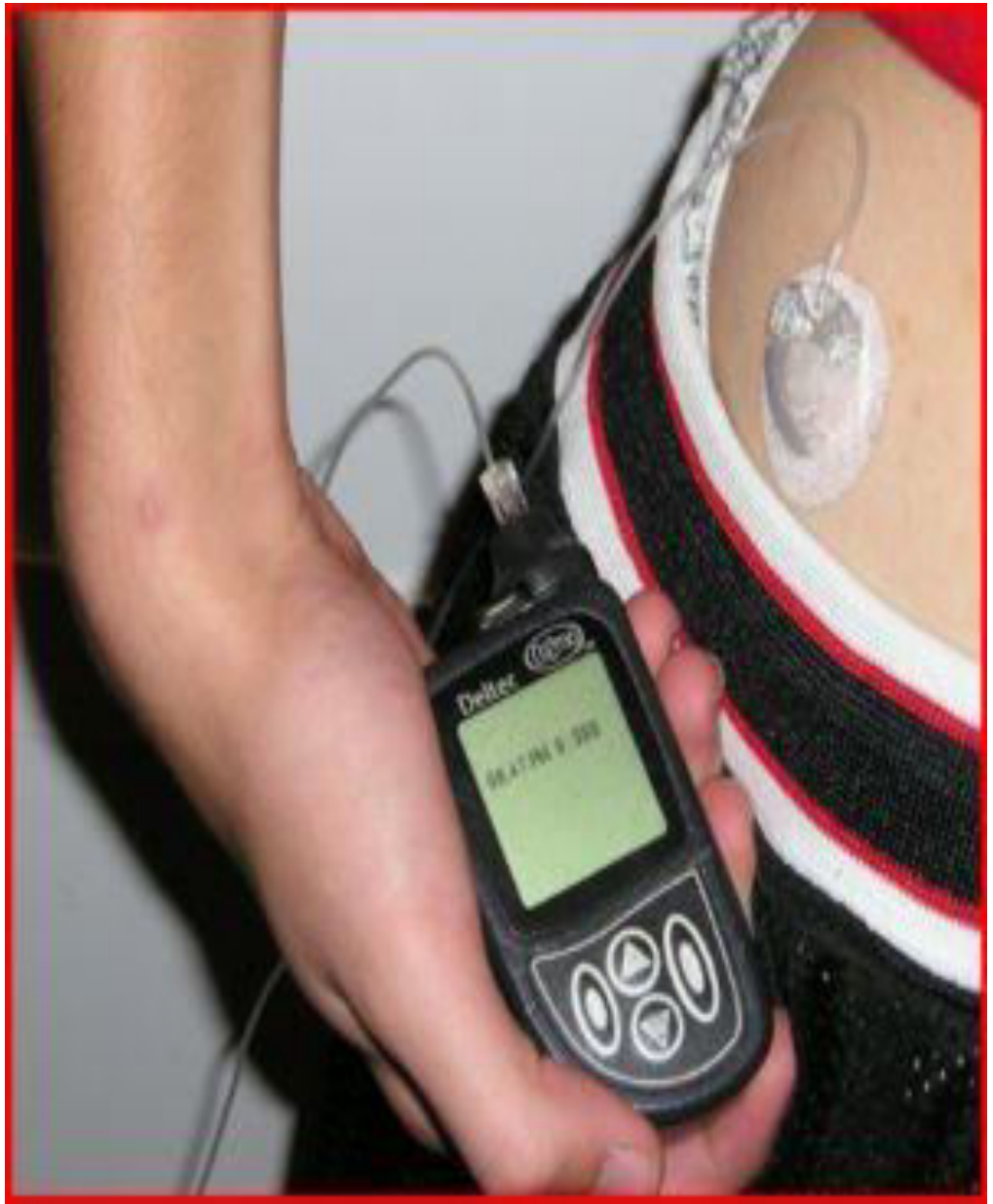
- Helps diabetics control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.
- The lack of insulin production is the motivation to develop a substitute.
- Insulin replacement therapy is appreciated for its life-saving capability, but manually managing the blood sugar level with insulin alone is arduous and inadequate.

Artificial Pancreas

- Different approaches under consideration:
- Medical equipment approach - using an insulin pump under closed-loop control using real-time data from a continuous blood glucose sensor. (nearly there)
- The biotechnology approach - the development of a bio-artificial pancreas. When surgically implanted, the device will behave as the original pancreas and will be viable for years. (Speculation)
- The gene therapy approach - the therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells. (Speculation)

Artificial Pancreas

- The Insulin pump is used to automatically deliver basal insulin continuously, and bolus insulin at meal times by pressing the buttons. Before meals, a blood glucose value is entered into the pump to calculate the correction bolus to bring the blood glucose level back to the target value



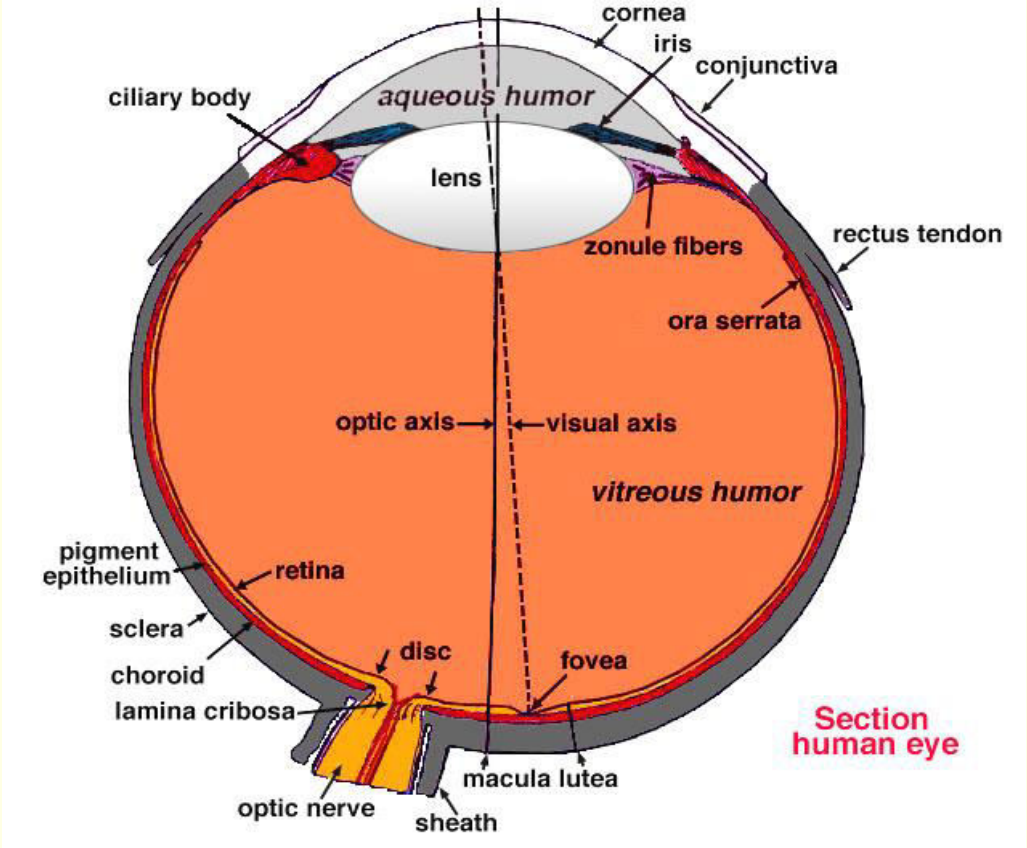
Artificial Pancreas – present day

- An insulin pump to infuse a rapid acting insulin is the first step in simulating the function of the pancreas. The pump can deliver small increments of insulin compared to an injection, and its controls match the insulin profile required for a given situation. The pump is controlled manually on command based on a *snap shot* of the recent blood glucose level and an estimate of the carbohydrate consumed. This approach is *open-loop.* Once a bolus has been calculated and delivered, the pump continues to deliver its basal rate insulin in the manner that has been programmed.
- While insulin replacement is a life saving therapy, its practical use in controlling blood glucose levels sufficiently to avoid long term complications is not ideal.
- It is a therapy!!!

BIONIC EYE ?

- Bio-electronic eye
- Electronic device which replaces functionality of a part or whole of the eye
- Used for replacing functionality (or)
- Adding functionality to the eye

Structure of the Eye

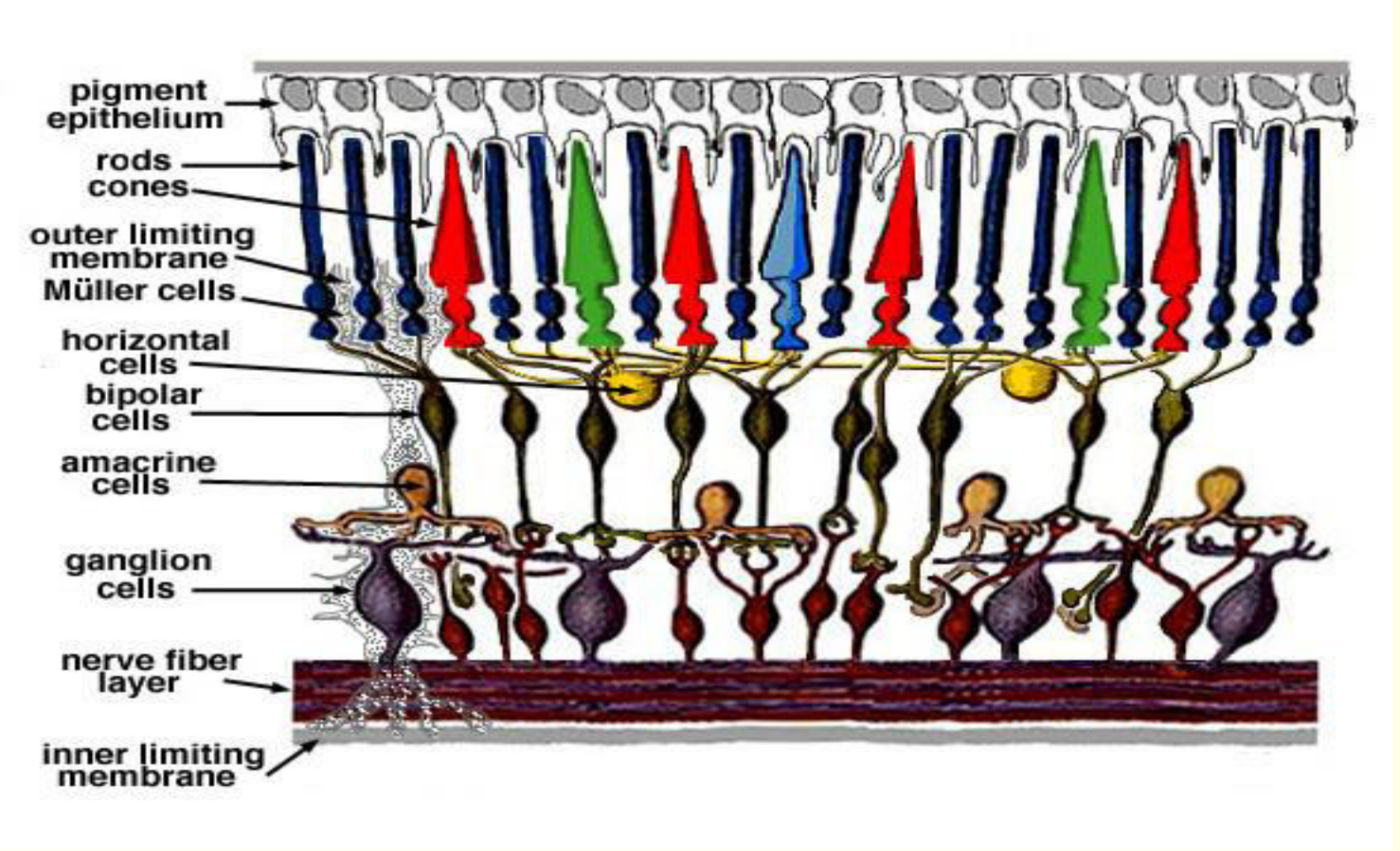


- Aqueous Humour
- The aqueous humour is a jelly-like substance located in the anterior chamber of the eye.
- Choroid
- The choroid layer is located behind the retina and absorbs unused radiation.
- Ciliary Muscle
- The ciliary muscle is a ring-shaped muscle attached to the iris.
- It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens.
- Cornea
- The cornea is a strong clear bulge located at the front of the eye (where it replaces the sclera - that forms the outside surface of the rest of the eye).
- The front surface of the adult cornea has a radius of approximately 8mm.
- The cornea contributes to the image-forming process by refracting light entering the eye.
- Fovea
- The fovea is a small depression (approx. 1.5 mm in diameter) in the retina.
- This is the part of the retina in which high-resolution vision of fine detail is possible.

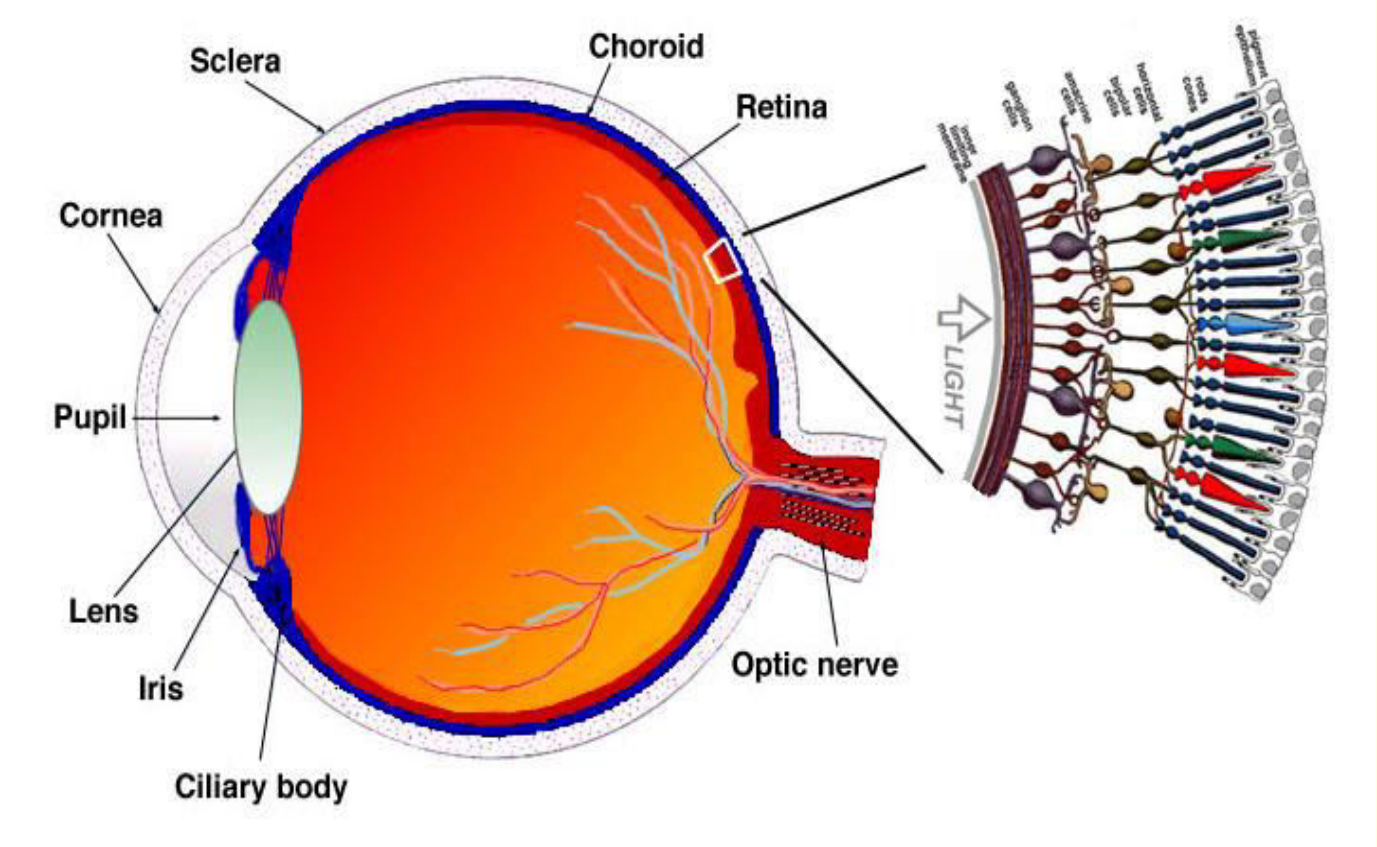
- Hyaloid
- The hyaloid diaphragm divides the aqueous humour from the vitreous humour.
- Iris
- The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye.
- The iris is the coloured part of the eye (illustrated in blue above but in nature may be any of many shades of blue, green, brown, hazel, or grey).
- Lens
- The lens of the eye is a flexible unit that consists of layers of tissue enclosed in a tough capsule. It is suspended from the ciliary muscles by the zonule fibers.
- Optic Nerve
- The optic nerve is the second cranial nerve and is responsible for vision.
- Each nerve contains approx. one million fibres transmitting information from the rod and cone cells of the retina.
- Papilla
- The papilla is also known as the "blind spot" and is located at the position from which the optic nerve leaves the retina.
- Pupil
- The pupil is the aperture through which light - and hence the images we "see" and "perceive" - enters the eye. This is formed by the iris. As the size of the iris increases (or decreases) the size of the pupil decreases (or increases) correspondingly.

- Retina
- The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, then the hyaloid and finally the vitreous humour before reaching the retina.
- The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.
- Sclera
- The sclera is a tough white sheath around the outside of the eye-ball.
- This is the part of the eye that is referred to by the colloquial terms "white of the eye".
- Visual Axis
- A simple definition of the "visual axis" is "a straight line that passes through both the centre of the pupil and the centre of the fovea". However, there is also a stricter definition (in terms of nodal points) which is important for specialists in optics and related subjects.
- Vitreous Humour
- The vitreous humour (also known as the "vitreous body") is a jelly-like substance.
- Zonules
- The zonules (or "zonule fibers") attach the lens to the ciliary muscles.

The Retina


pigment epithelium
rods
cones
outer limiting membrane
Müller cells
horizontal cells
bipolar cells
amacrine cells
ganglion cells
nerve fiber layer
inner limiting membrane

The Eye with Retina



- A **photoreceptor cell** is a specialized type of neuron found in the retina that is capable of phototransduction. The great biological importance of photoreceptors is that they convert light (visible electromagnetic radiation) into signals that can stimulate biological processes. To be more specific, photoreceptor proteins in the cell absorb photons, triggering a change in the cell's membrane potential.
- The two classic photoreceptor cells are rods and cones, each contributing information used by the visual system to form a representation of the visual world, sight. The rods are narrower than the cones and distributed differently across the retina, but the chemical process in each that supports phototransduction is similar.
- There are major functional differences between the rods and cones. Rods are extremely sensitive, and can be triggered by as few as 6 photons.[3] At very low light levels, visual experience is based solely on the rod signal. This explains why colors cannot be seen at low light levels: only one type of photoreceptor cell is active.
- Cones require significantly brighter light (i.e., a larger numbers of photons) in order to produce a signal. In humans, there are three different types of cone cell, distinguished by their pattern of response to different wavelengths of light.
- So, for example, an L cone cell contains a photoreceptor protein that more readily absorbs long wavelengths of light (i.e., more "red"). Light of a shorter wavelength can also produce the same response, but it must be much brighter to do so.
- The human retina contains about 120 million rod cells and 6 million cone cells. The number and ratio of rods to cones varies among species, dependent on whether an animal is primarily diurnal or nocturnal. Certain owls, such as the tawny owl, have a tremendous number of rods in their retinae. In addition, there are about 2.4 million to 3 million ganglion cells in the human visual system, the axons of these cells form the 2 optic nerves, 1 to 2% of them photosensitive.

Healthy Vision

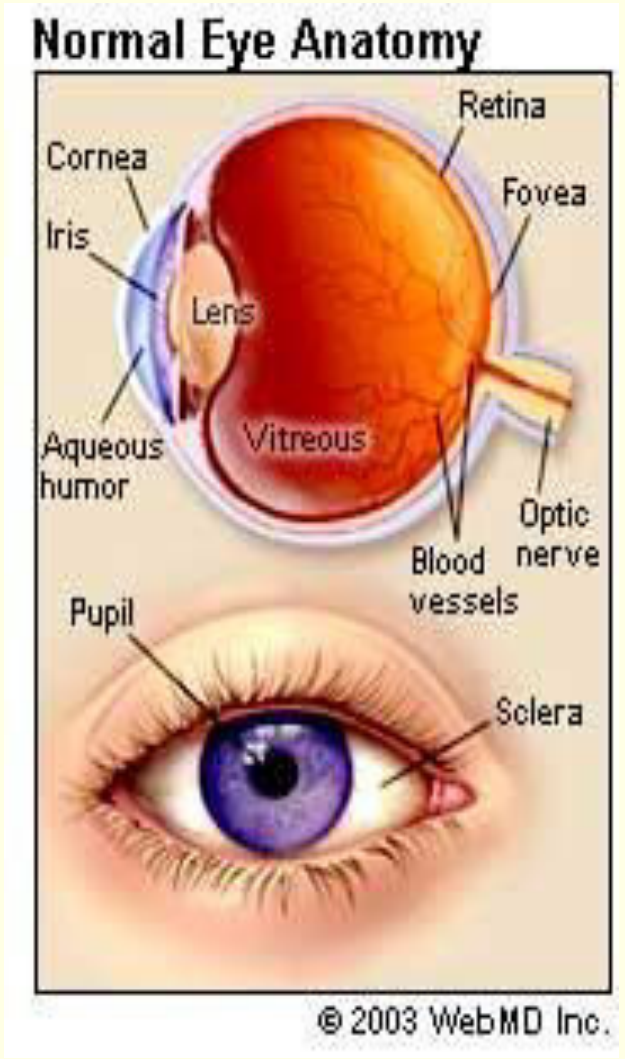
1. Reflected light enters the cornea (*Window of the eye*)

2. Light travels through the pupil
   - Contracts or dilates depending on how brightness of surroundings

3. Light enters the lens
   - Just like a camera, the lens of the eye focuses light

4. The light beams through the center of the eye to the retina

5. Retina:
   - Photoreceptors (*Specialized cells that convert light into electric impulses*)
   - Macula (*Center of the retina that contains more photoreceptors than any other part of eye*)



Diseases of the Eye

- Retinitis Pigmentosa
- Macular Degeneration

Reasons for Bionic Eye

Macular Degeneration

- Age Related
- Loss of central vision and blurred peripheral vision
- Macula deteriorates over time
- Vision becomes gray
- 10% of adults over age 55 world-wide

Retinitis Pigmentosa

- Genetic
- Loss of peripheral vision inward
- Photoreceptors in periphery deteriorate
- 1.5 million people world-wide

Retinitis Pigmentosa

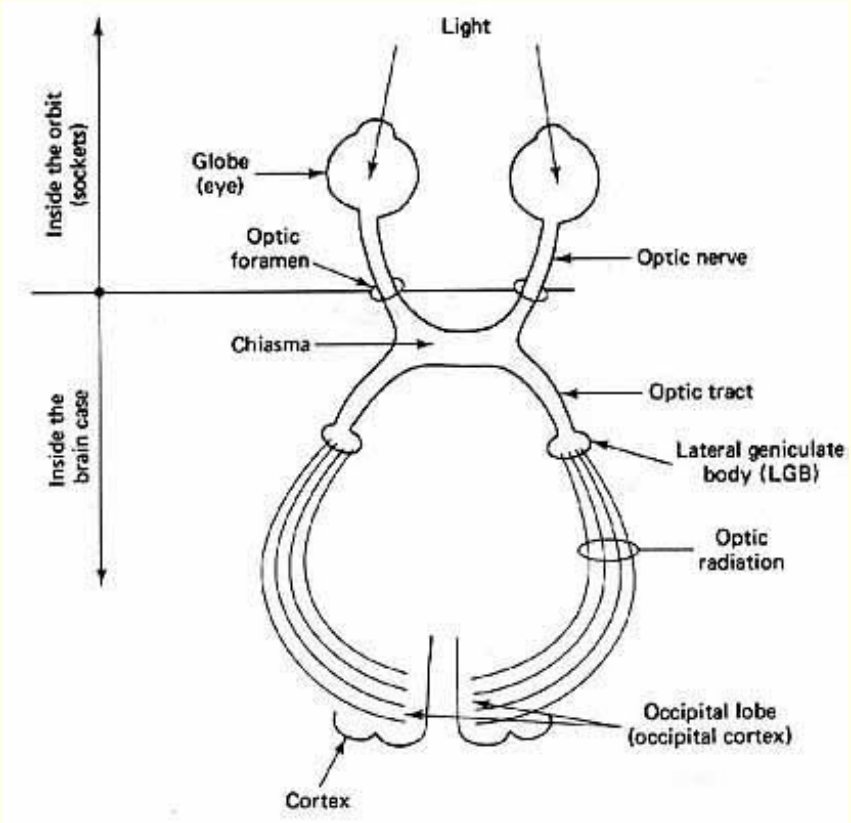
- Hereditary Genetic Disease
- Peripheral Rods degenerate
- Gradually progresses towards center of eye
- Spares the foveal region
- Tunnel vision results

Macular Degeration

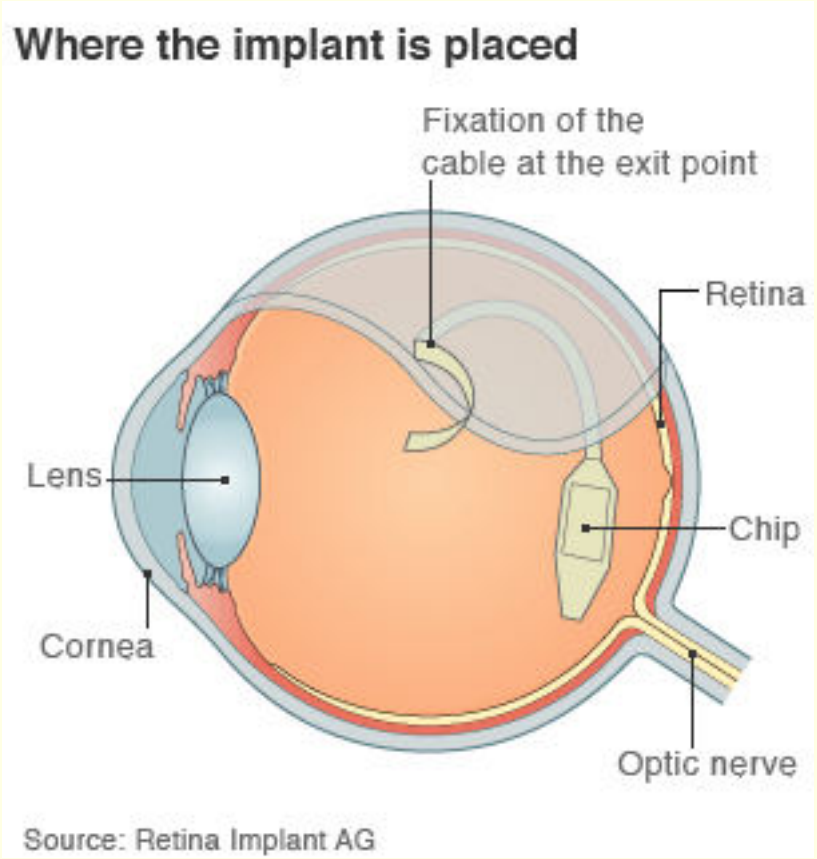
- Genetically Related
- Cones in Macula region degenrate
- Loss or damage of central vision
- Peripheral Retina spared
- Common among old people

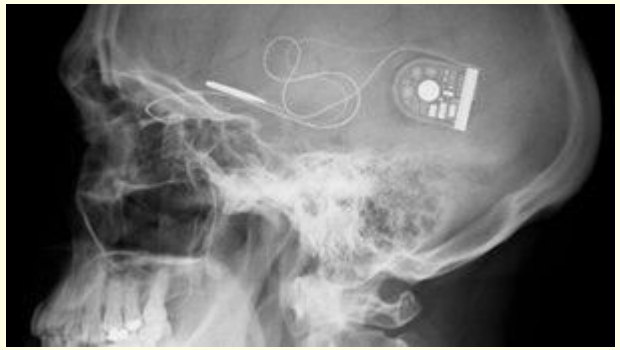
Regions of Implantation

- Retina
- Optic Nerve
- Lateral geniculate body
- Visual Cortex



Retinal Implants



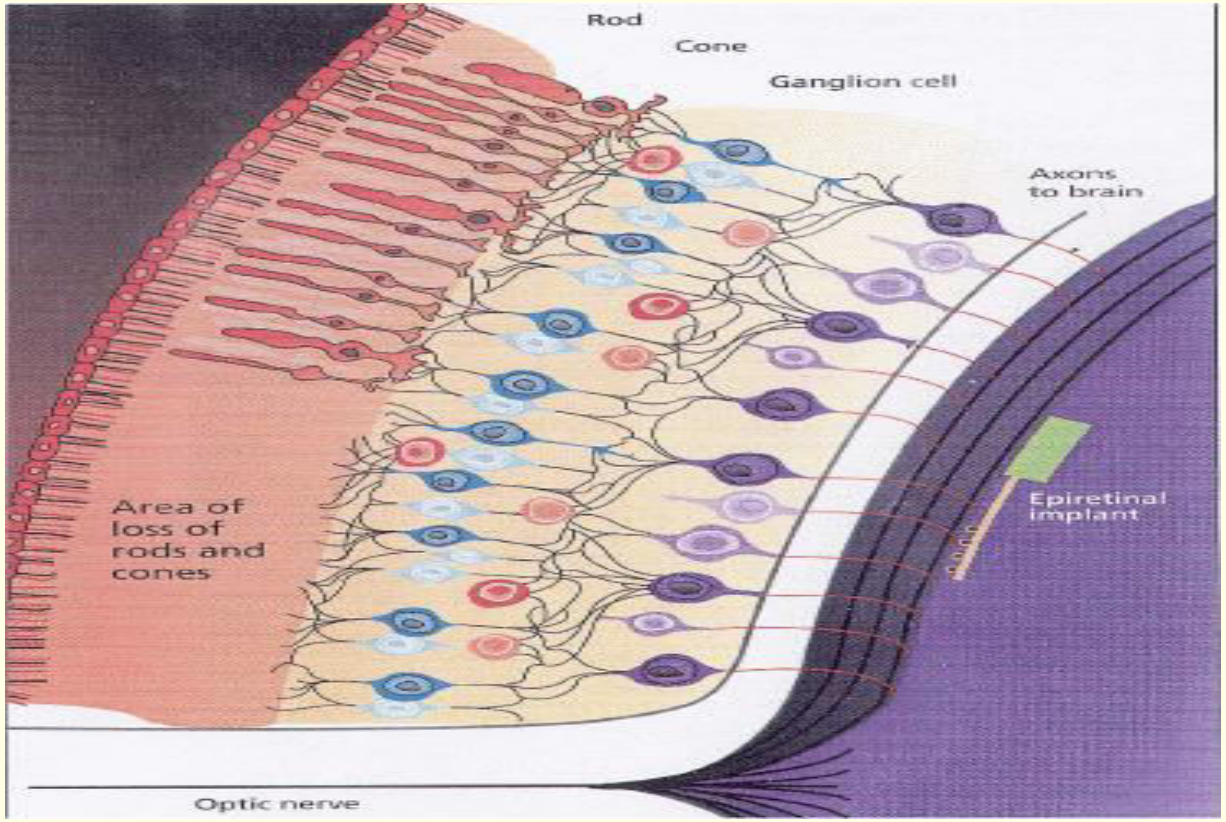


MIT-Harvard device

Features

- Epi-Retinal Approach
- Microelectrode array replaces damaged photoreceptors
- Power source – Laser(820nm wavelength)
- Image Acquisition - Using CCD Camera
- Patient spectacle holds the camera and power source

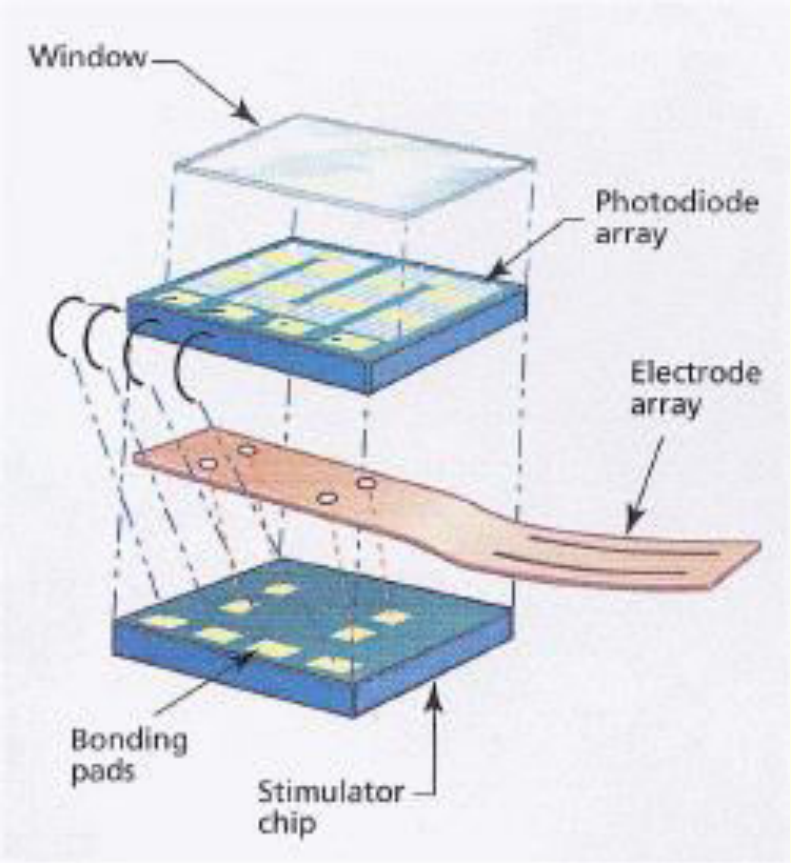
Site of Implant



Implant Structure

- Layers
  1- Photodiode Array
  2- Polyimide strip
  3- Stimulator chip

- Electrodes on other end of Polyimide strip



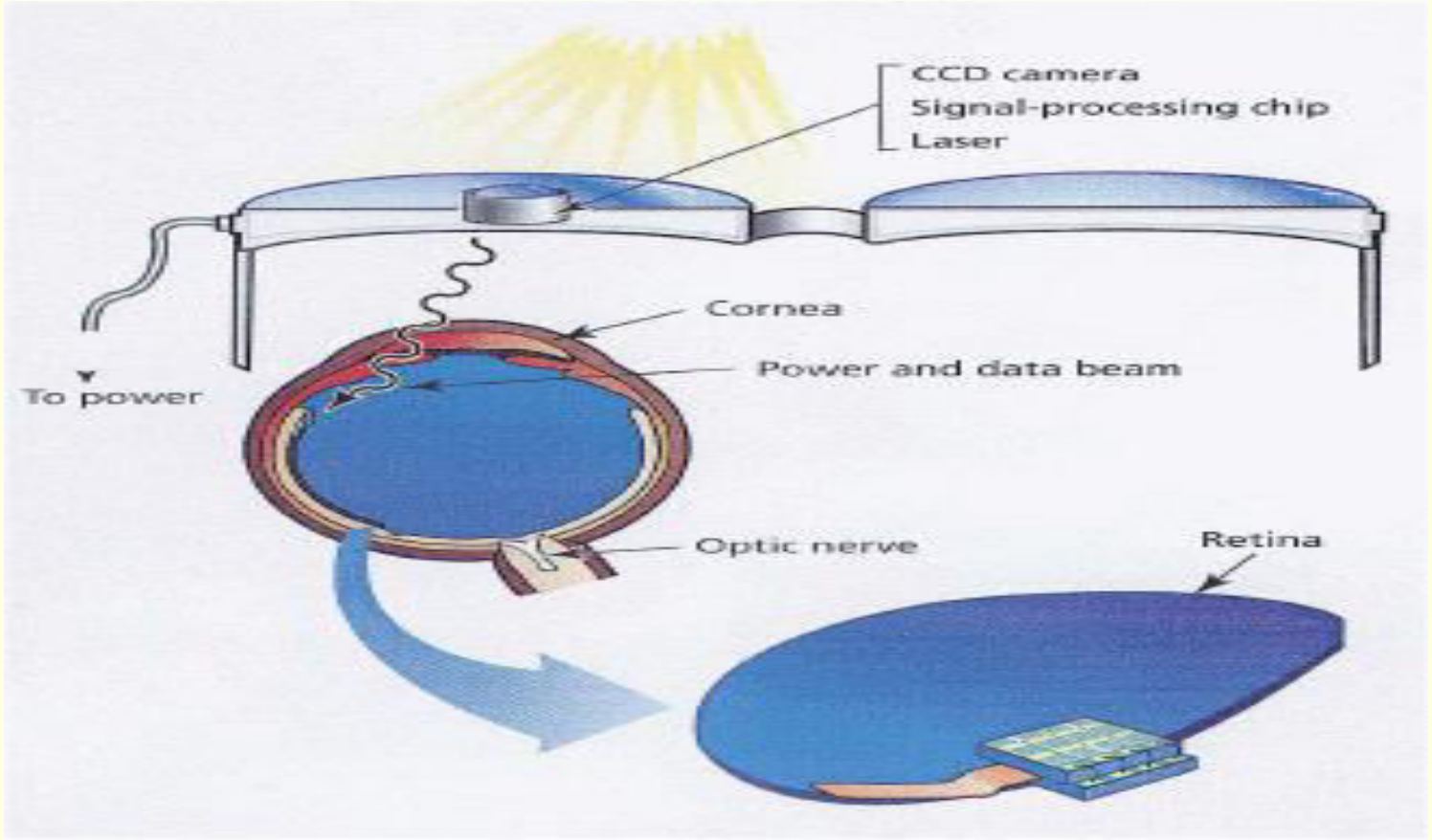
Working of the System - 1

- CCD camera input – External light intensity
- CCD output amplitude-modulates laser source
- This hits photodiode array of implant
- This in turn powers stimulator chip (SC)

Working of the System - 2

- SC drives current to electrodes facing retina
- This excites the ganglionic cells > axons > optic nerve > visual cortex in occipital lobe of brain
- Brain helps in perceiving an image

The Whole Picture



Advantages

- Very Early in the visual pathway
- No Batteries implanted within body
- No complicated surgical procedure
- Power Requirement – ¼ of milliwatt

Disadvantages

- Axons b/w electrodes and ganglionic cells
- Other axons get excited – unwanted perception of large blur
- Extra circuitry required for downstream electrical input

What is a Cochlear Implant?

-A biomedical device that presents an auditory signal using electrical stimulation of the inner ear.

Source: seattlepi.nwsource.com/ lifestyle/echo28.shtml

Cochlear Implants

The cochlear implant is the ***most significant technical advance*** in the treatment of hearing impairment since the development of the hearing aid around the turn of the century.

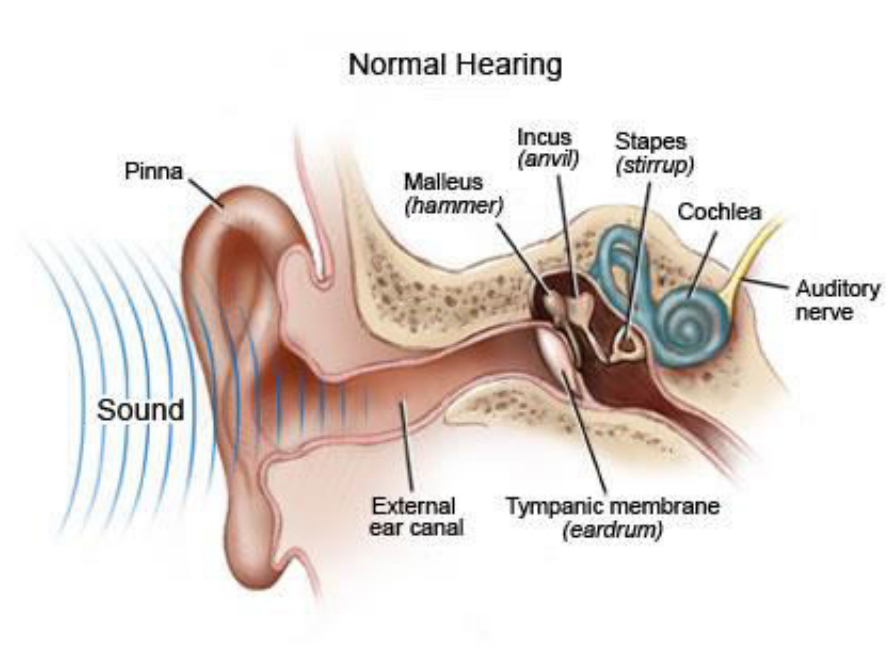
Designed to restore some sense of hearing for:

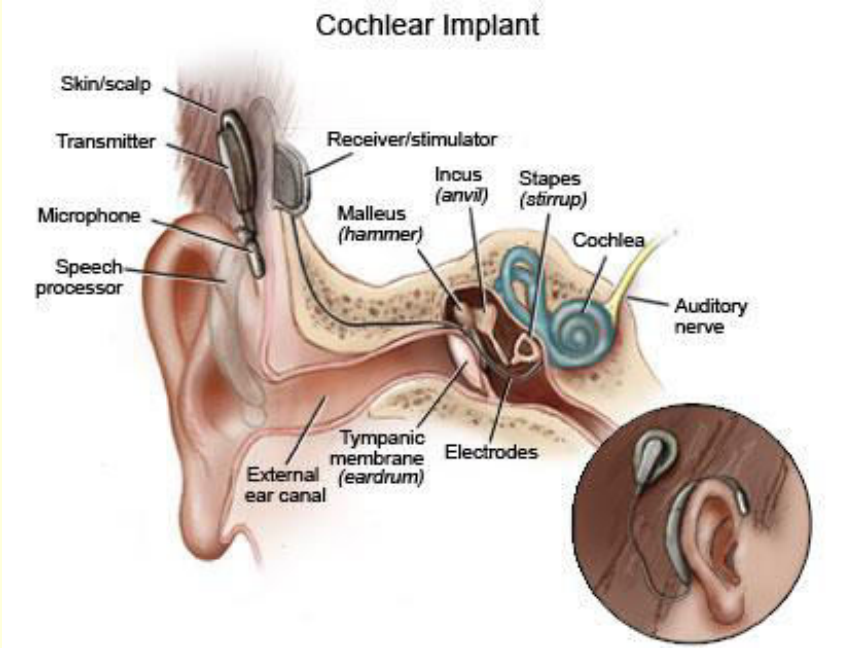
- Children or adults who receive little or no benefit from hearing aids.
- Loss must be: (a) profound, (b) bilateral, and (c) sensorineural.
- **Problem**: Auditory nerve is intact, but hair cell transducers are not functioning.

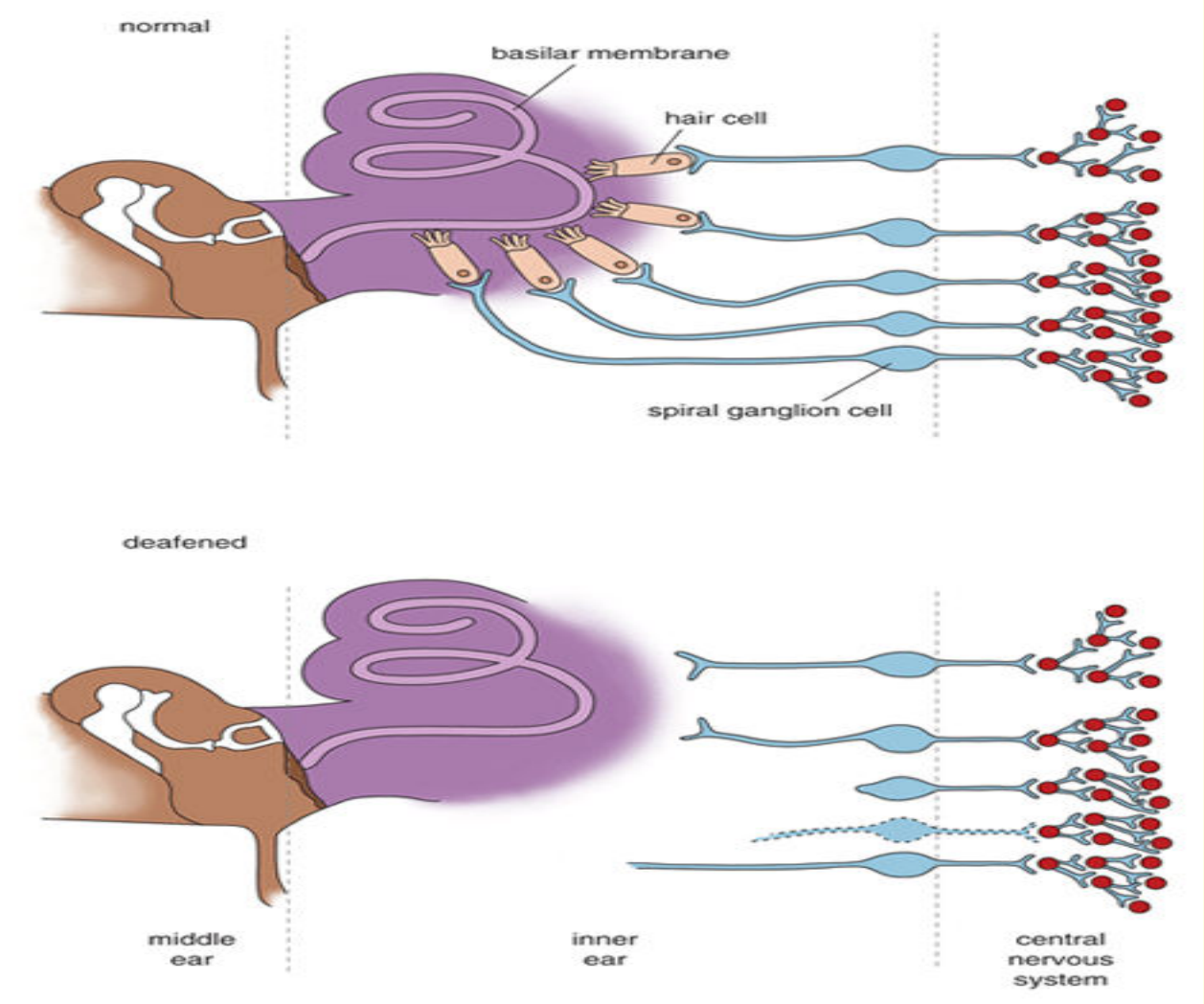
Purpose of implant: Generate electrical signals that do the job of the damaged hair cells.

- The ear has external, middle, and inner portions. The outer ear is called the pinna and is made of ridged cartilage covered by skin. Sound funnels through the pinna into the external auditory canal, a short tube that ends at the eardrum (tympanic membrane).
- The middle ear is an air-filled cavity behind the tympanic membrane, includes three bones: the malleus (or hammer), incus (or anvil), and stapes (or stirrup). The middle ear also connects to the upper throat via the Eustachian tube
- Sound causes the eardrum and its tiny attached bones in the middle portion of the ear to vibrate, and the vibrations are conducted to the nearby cochlea. The spiral-shaped cochlea is part of the inner ear; it transforms sound into nerve impulses that travel to the brain.
- The fluid-filled semicircular canals (labyrinth) attach to the cochlea and nerves in the inner ear. They send information on balance and head position to the brain. The eustachian (auditory) tube drains fluid from the middle ear into the throat (pharynx) behind the nose

Cochlear implants







Normal Ear

Deafness: Normally functioning hair cells not present; some atrophy of neural fibers.

How Does A Cochlear Implant Work?

The implant is surgically placed under the skin behind the ear. The basic parts of the device include:

External:
one or more microphones which picks up sound from the environment
a speech processor which selectively filters sound to prioritize audible speech, splits the sound into channels and sends the electrical sound signals through a thin cable to the transmitter,
a transmitter, which is a coil held in position by a magnet placed behind the external ear, and transmits power and the processed sound signals across the skin to the internal device by electromagnetic induction,
Internal:

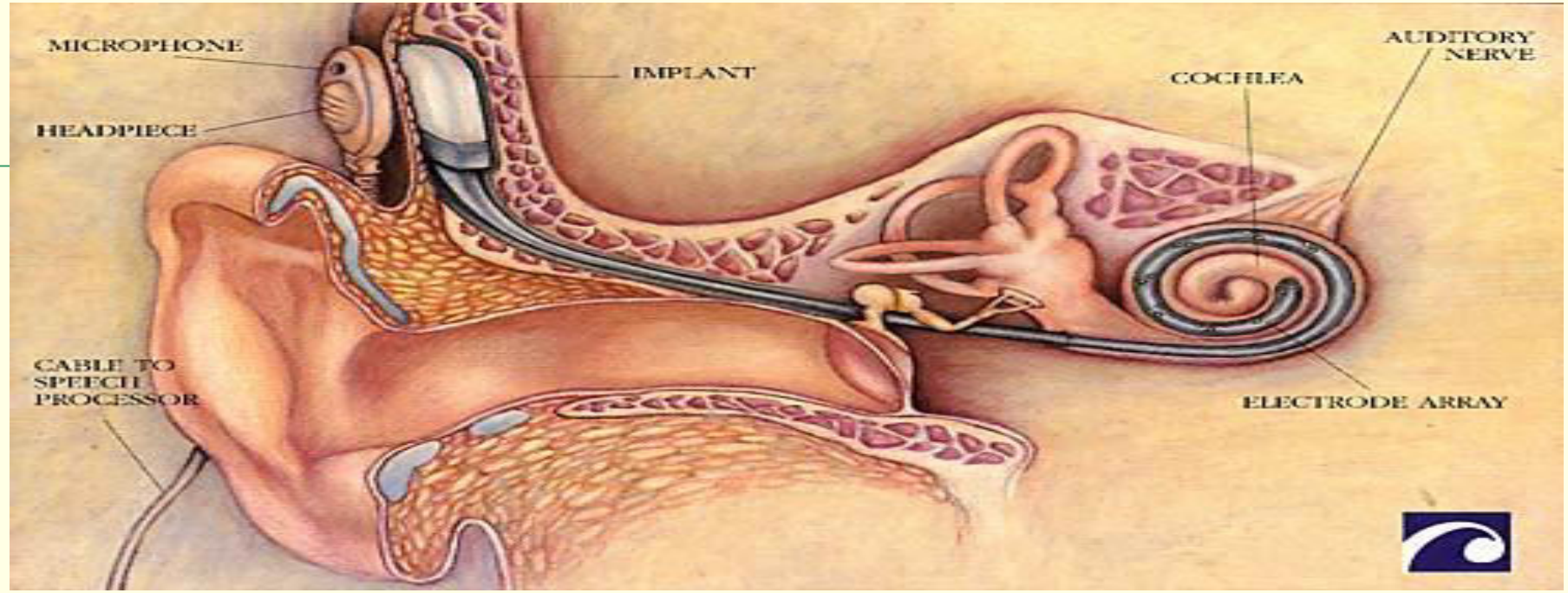
The internal part of a cochlear implant (model Cochlear Freedom 24 RE)
a receiver and stimulator secured in bone beneath the skin, which converts the signals into electric impulses and sends them through an internal cable to electrodes,
an array of up to 22 electrodes wound through the cochlea, which send the impulses to the nerves in the scala tympani and then directly to the brain through the auditory nerve system. There are 4 manufacturers for cochlear implants, and each one produces a different implant with a different number of electrodes. The number of channels is not a primary factor upon which a manufacturer is chosen; the signal processing algorithm is also another important block.

How Does a Cochlear Implant Work?

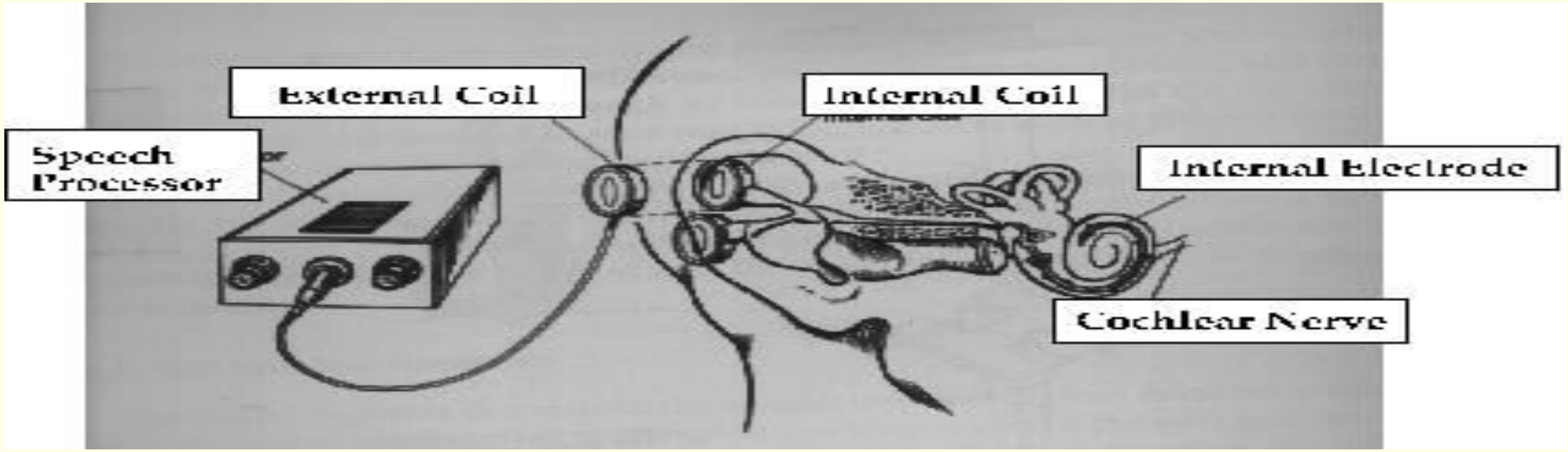
- Electrical pulses are sent to the metal bands on the **electrode array**
- Precisely controlled current flows between the active electrode(s) and return electrode(s)

→ Spiral ganglion cells are stimulated

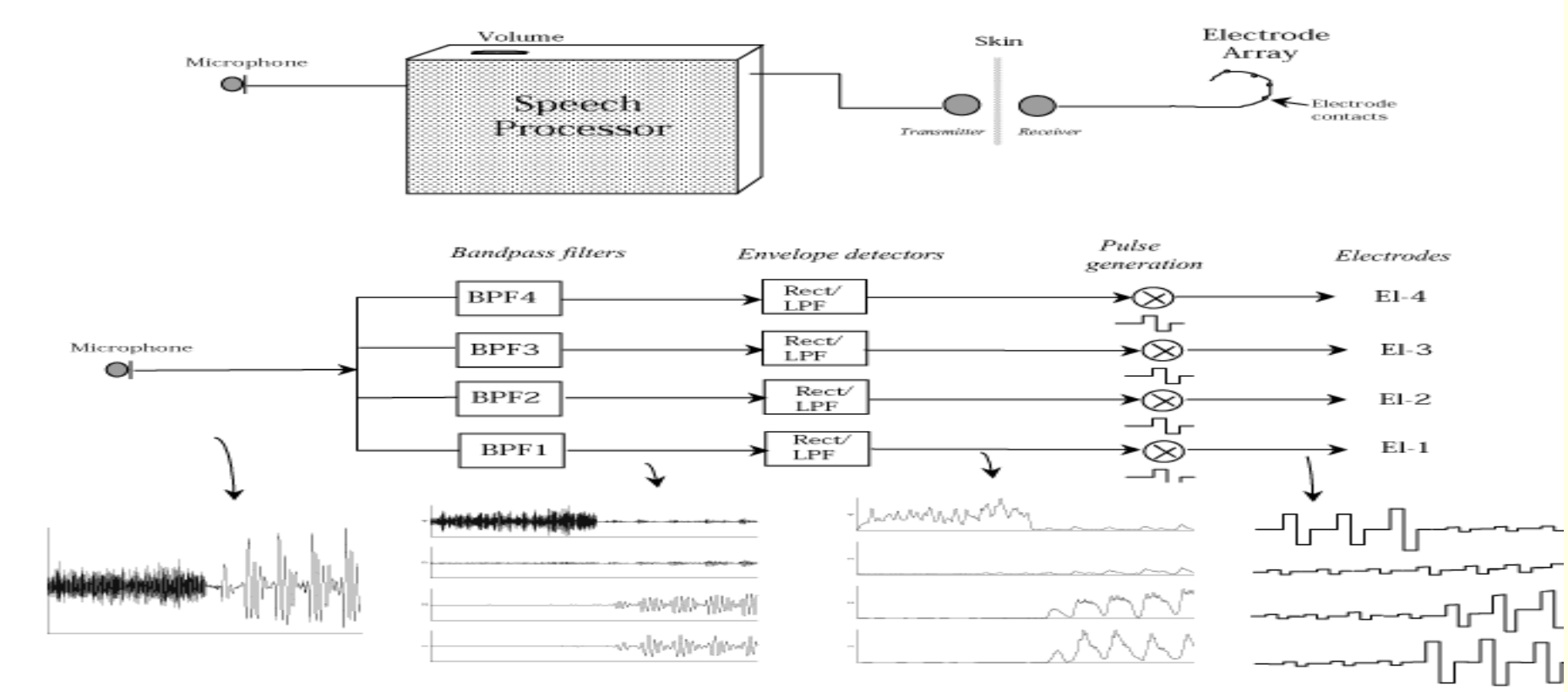
Source: www.cochlear.com


MICROPHONE
IMPLANT
COCHLEA
AUDITORY NERVE
HEADPIECE
CABLE TO SPEECH PROCESSOR
ELECTRODE ARRAY


Nucleus® 24
Implants
Speech Coding Strategies
Speech Processors
NRT™
Request Information



The speech processor uses a bank of bandpass filters (or a Fourier analyzer) to analyze the signal before passing it along to the array of electrodes.


Microphone
Volume
Speech Processor
Skin
Transmitter
Receiver
Electrode Array
Electrode contacts
Bandpass filters
Envelope detectors
Pulse generation
Electrodes
Microphone
BPF4
BPF3
BPF2
BPF1
Rect/ LPF
Rect/ LPF
Rect/ LPF
Rect/ LPF
EI-4
EI-3
EI-2
EI-1

GOOD NEWS, BAD NEWS

First the Bad News

- Implant ***based primarily on place theory***. If we make the most generous assumption that place theory is correct (it probably isn't), how many stimulating electrodes should there be?
- The CI ***restores some sense of hearing***, but it is ***nowhere near the hearing sensation that is produced in a normal ear***. (There are no "bionic parts" that work as well as the original.)
- Subjects vary wildly in the amount of benefit they derive from a CI -- mostly for unknown reasons.

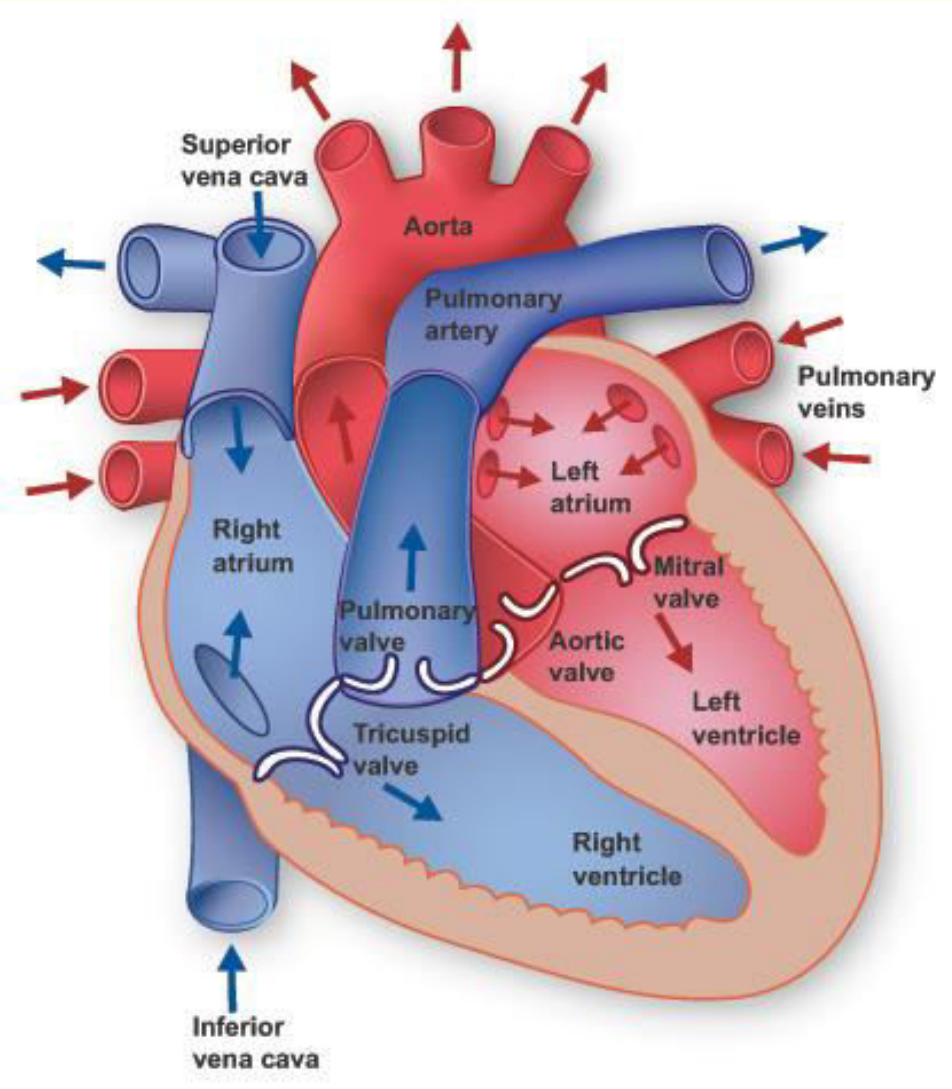
Now the Good News

Despite these drawbacks, CIs work. Research shows:

- Ability to understand speech improves.
- Children acquire speech and language skills more quickly.
- Post-lingually deafened adults (the largest deaf population) maintain their speech production skills better -- especially control of pitch and loudness, which improves immediately most of the time.

The human heart

The heart pumps blood through both circulatory systems. Blood low in oxygen from the systemic circulation enters the right atrium from the superior and inferior vena cavae and passes to the right ventricle. From here it is pumped into the pulmonary circulation, through the lungs where it receives oxygen and gives off carbon dioxide. Oxygenated blood then returns to the left atrium, passes through the left ventricle and is pumped out through the aorta to the systemic circulation–where the oxygen is used and metabolized to carbon dioxide. In addition the blood carries nutrients from the liver and gastrointestinal tract to various organs of the body, while transporting waste to the liver and kidneys. Normally with each heartbeat, the right ventricle pumps the same amount of blood into the lungs as the left ventricle pumps out into the body. Veins transport blood to the heart, while arteries transport blood away from the heart. Veins normally have lower pressures than arteries.



Some Numbers

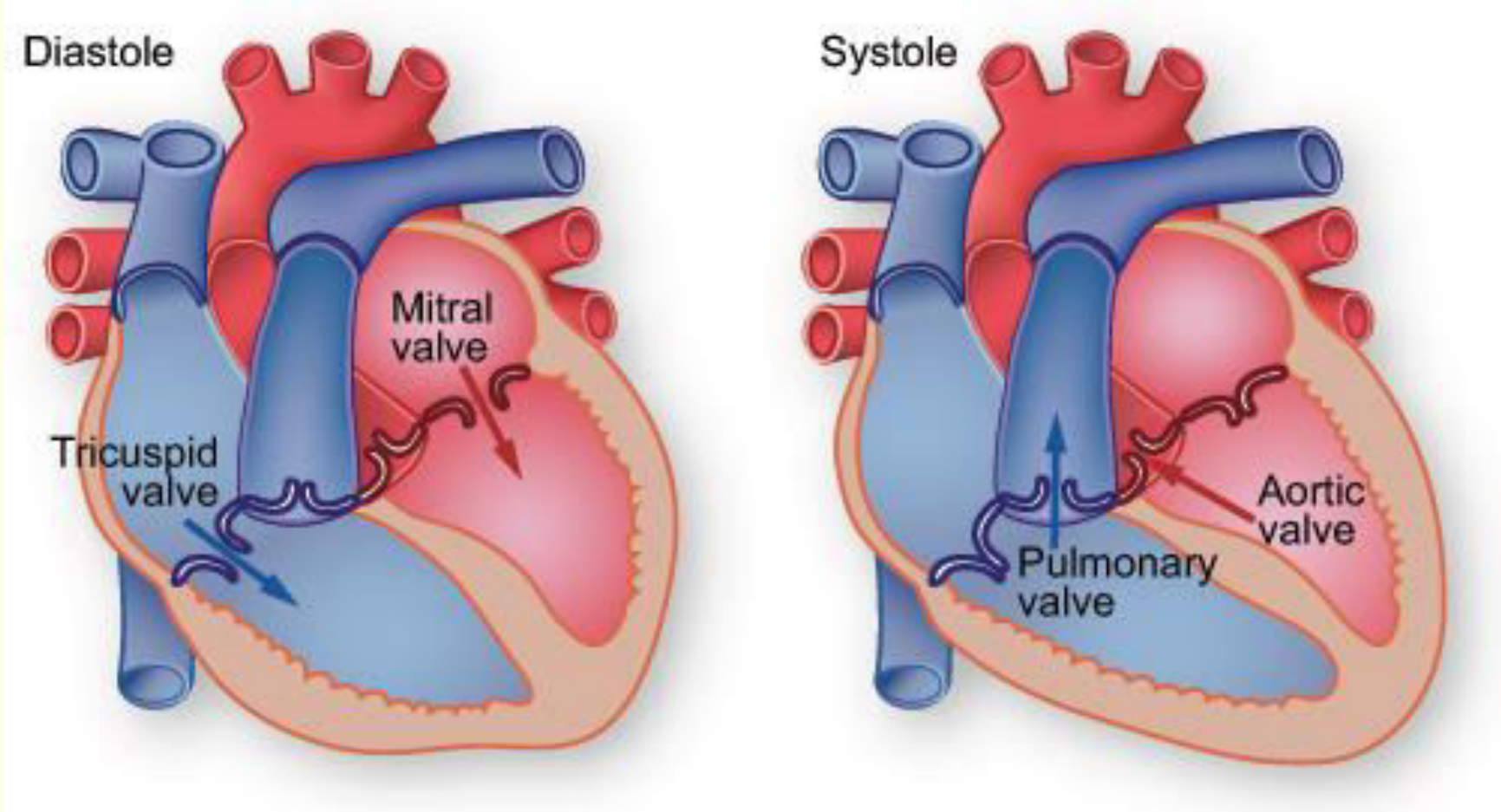
Normal Heart Rate : 72 beats per minute

- Per day : 1,03,680 … almost 1 lakh
- Per year : 3,78,43,200 … about 3.75 Crores
- Over a lifetime : 245 Crores (in about 65 years).

Volume Pumped per Beat : about 70ml (Stroke Volume)

- Per minute : 5040 ml (approximately total blood volume in body)
- Per day : 7260 litres *(daily per capita requirement of water in India 135 l)*
- Per year : 26.6 lakh litres
- In a life time : 17 Crore litres

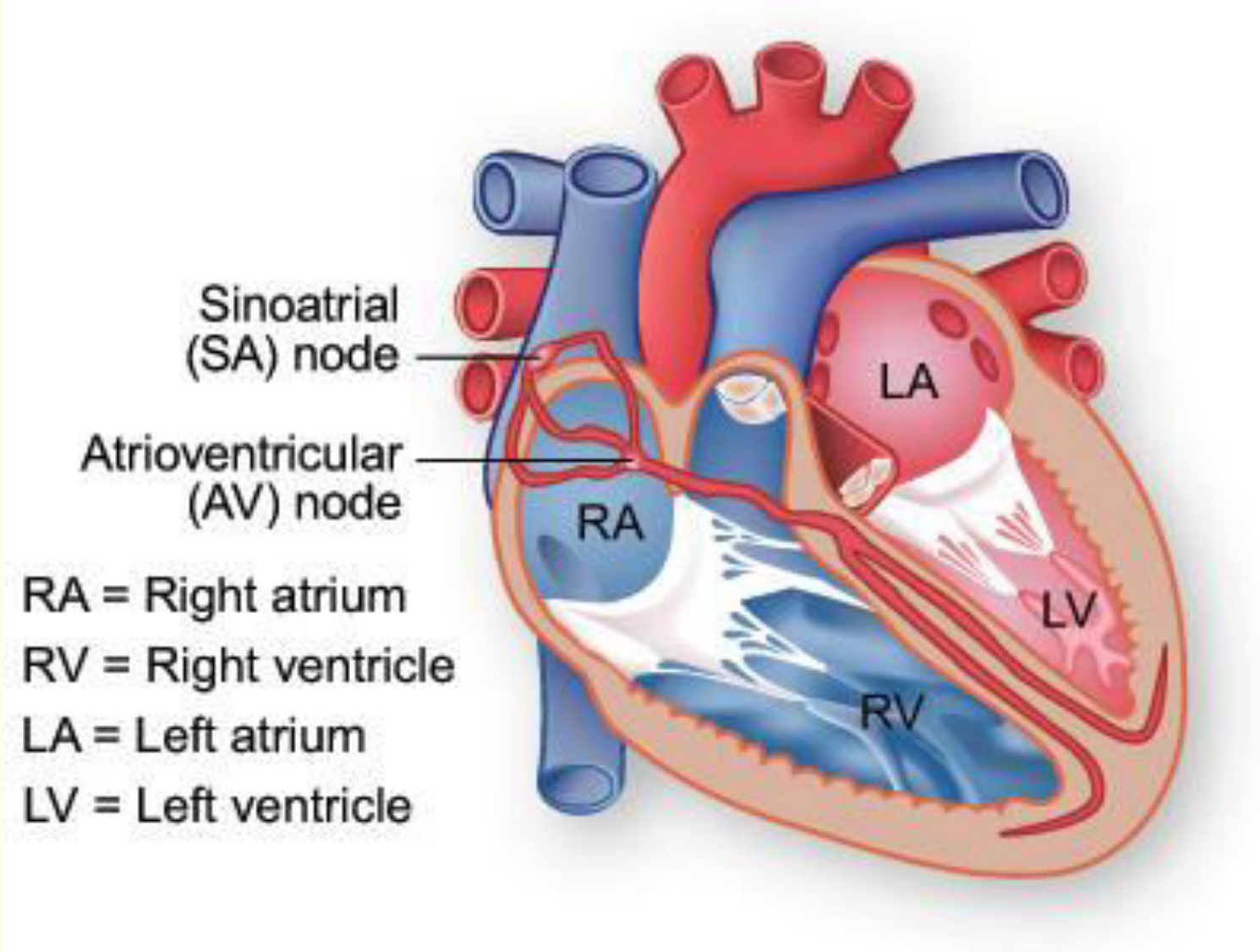
Heart Beat and Valves



Heart Valves

- Four valves regulate blood flow through your heart: The tricuspid valve regulates blood flow between the right atrium and right ventricle.
- The pulmonary valve controls blood flow from the right ventricle into the pulmonary arteries, which carry blood to your lungs to pick up oxygen.
- The mitral valve lets oxygen-rich blood from your lungs pass from the left atrium into the left ventricle.
- The aortic valve opens the way for oxygen-rich blood to pass from the left ventricle into the aorta, your body's largest artery.

Heart Conduction Pathway



- Electrical impulses from your heart muscle (the myocardium) cause your heart to beat (contract). This electrical signal begins in the sinoatrial (SA) node, located at the top of the right atrium. The SA node is sometimes called the heart's "natural pacemaker." When an electrical impulse is released from this natural pacemaker, it causes the atria to contract. The signal then passes through the atrioventricular (AV) node. The AV node checks the signal and sends it through the muscle fibers of the ventricles, causing them to contract.
- The SA node sends electrical impulses at a certain rate, but your heart rate may still change depending on physical demands, stress, or hormonal factors.

Heart Beat

- A heartbeat is a two-part pumping action that takes about a second. As blood collects in the upper chambers (the right and left atria), the heart's natural pacemaker (the SA node) sends out an electrical signal that causes the atria to contract. This contraction pushes blood through the tricuspid and mitral valves into the resting lower chambers (the right and left ventricles). This part of the two-part pumping phase (the longer of the two) is called **diastole**.
- The second part of the pumping phase begins when the ventricles are full of blood. The electrical signals from the SA node travel along a pathway of cells to the ventricles, causing them to contract. This is called **systole**.

Heart Beat

- As the tricuspid and mitral valves shut tight to prevent a back flow of blood, the pulmonary and aortic valves are pushed open. While blood is pushed from the right ventricle into the lungs to pick up oxygen, oxygen-rich blood flows from the left ventricle to the heart and other parts of the body.
- After blood moves into the pulmonary artery and the aorta, the ventricles relax, and the pulmonary and aortic valves close. The lower pressure in the ventricles causes the tricuspid and mitral valves to open, and the cycle begins again. This series of contractions is repeated over and over again, increasing during times of exertion and decreasing while you are at rest. The heart normally beats about 60 to 80 times a minute when you are at rest, but this can vary. As you get older, your resting heart rate rises. Also, it is usually lower in people who are physically fit.

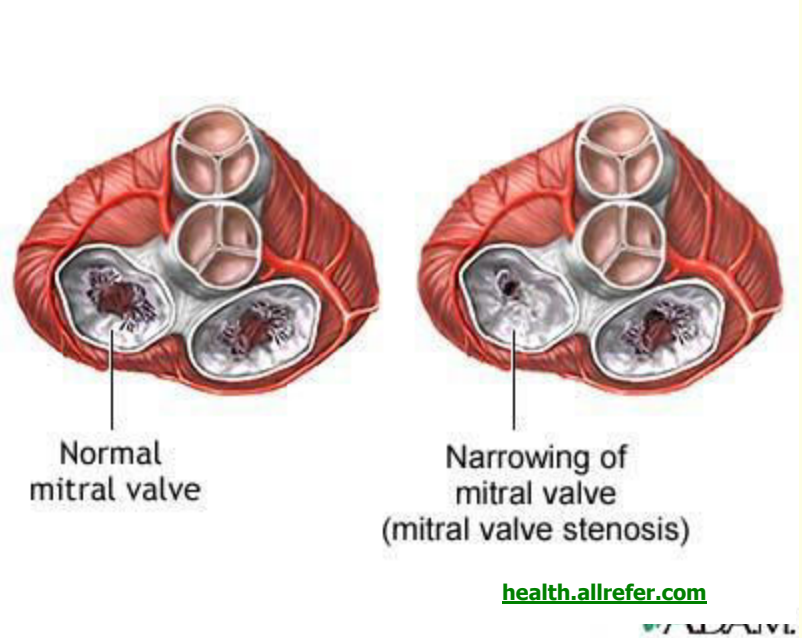
Valve Disorders

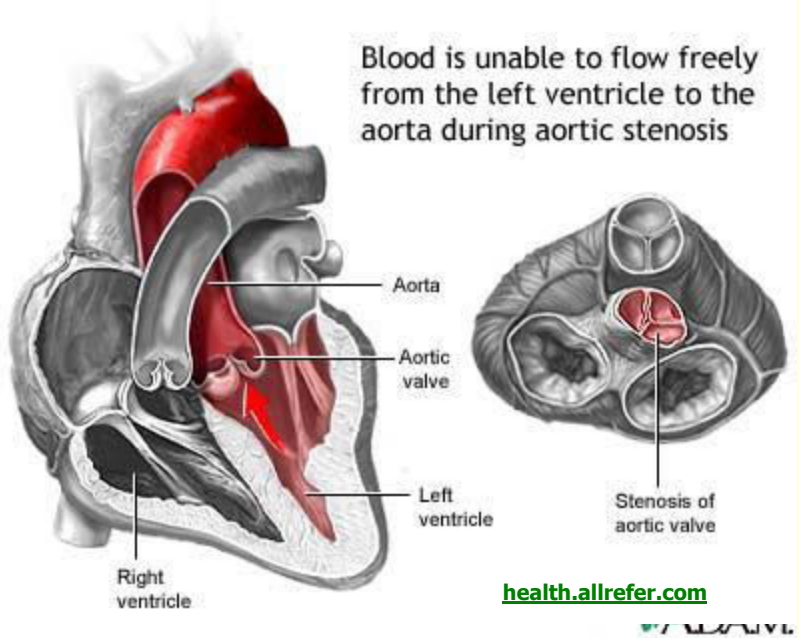
Valve disorders can be categorized into the following types:

- **Stenosis (narrowing)**
  Sometimes age or disease can prevent heart valves from opening properly. The narrowing of heart valves is known as stenosis. When the opening narrows, the heart cannot push the required amount of blood through the valve. Because stenosis makes the heart work harder to pump the same volume of blood, it may also lead to an increase in the size of the heart muscle. Enlargement of the heart muscle may lead to serious complications.
- **Pulmonary valve stenosis**
  Pulmonary valve stenosis is a narrowing or obstruction that partly or completely blocks the flow of blood. Obstructions can occur in heart valves, arteries or veins. This condition results in the narrowing of the pulmonary valve (which lets blood flow from the right lower chamber of the heart to the lungs). As a result, the right lower chamber (right ventricle) must pump harder than normal to overcome the obstruction. This may cause stress on, and enlargement of, the right ventricle.

Valve problems

- Mitral stenosis
- Aortic stenosis
  - Stenosis is the obstruction or narrowing of valve opening
  - More pressure on atria and ventricles (respectively) to deliver sufficient blood



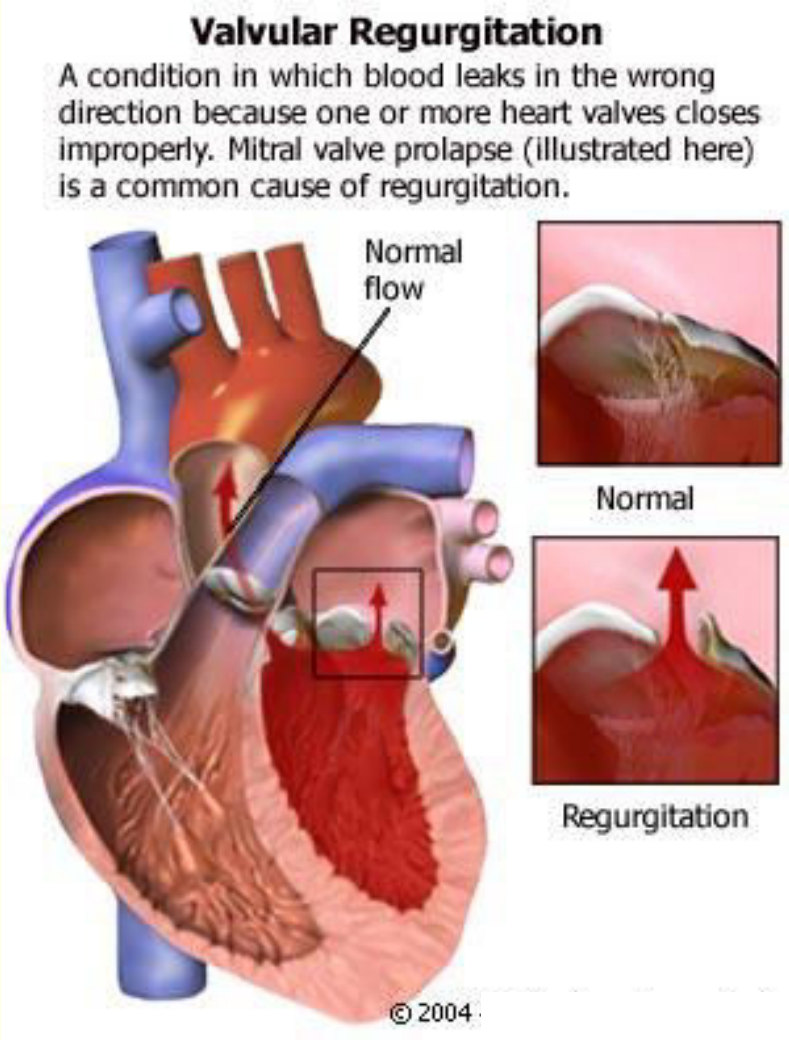


Valve Disorders

- **Prolapse (slipping out of place)**
  In valve prolapse, the valve flaps do not close smoothly or evenly. Instead, they collapse backwards into the heart chamber they are supposed to be sealing off. This sometimes makes a clicking noise and allows a small amount of blood to leak backward through the valve. This group of conditions may be called mitral valve prolapse, click-murmur syndrome, Barlow's syndrome, balloon mitral valve and floppy valve syndrome.
- **Regurgitation (backward flow)**
  Another common problem occurs when a heart valve doesn't close securely. This is called regurgitation (or sometimes called valvular insufficiency). This condition reduces the heart's pumping efficiency. When the heart contracts, blood is pumped forward in the proper direction and is also forced backwards through the damaged valve. This not only limits the heart's ability to supply the body with blood, but may also cause lung problems.

Valve problems

- Mitral insufficiency
- Atrial insufficiency
  - Inability of the valve to close completely



http://www.heartcenteronline.com/myheartdr/common/articles.cfm?ARTID=187

Valve replacement

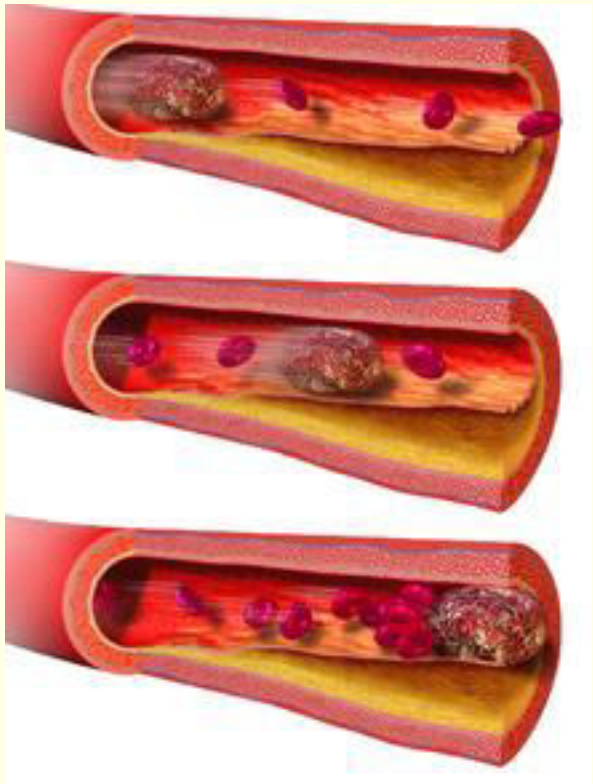
- Various types of valves used falls under ‘biomaterials and prosthetics’
- Valve replacement involves
  - Incision of chest wall, hence disrupting vacuum system in the thoracic cavity essential for breathing
  - Disrupting the function of heart itself hence the supply of blood to capillaries
- Various accessories needed during the surgery
  - Extra corporeal circulation or heart lung bypass machine
    - Pump that replaces heart
    - Oxygenator that replaces lungs

What is it?

- An artificial heart valve is a mechanism that mimics the function of a human heart valve
- It’s used for patients with a heart valvular disease or have a damaged valve
- Heart valves are used to provide the heart with a unidirectional blood flow
- They act as pumps

"An ideal Prosthetic valve"

- Unidirectional flow
- Durable : 40million cycles/year
- Blood compatible: no thrombus, embolus
- An embolus is any detached, traveling intravascular mass carried by circulation, which is capable of clogging arterial capillary beds (create an arterial occlusion) at a site distant from its point of origin.
- Central flow: Laminar not turbulent
- Closing not damaging blood cells
- Last but not the least important – It should be quiet



Evolution of Prosthetic Heart Valves

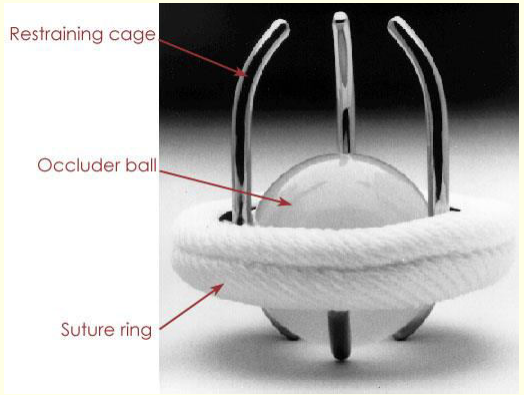
The development of the original ball-and-cage valve design can be attributed to the bottle stopper in 1858

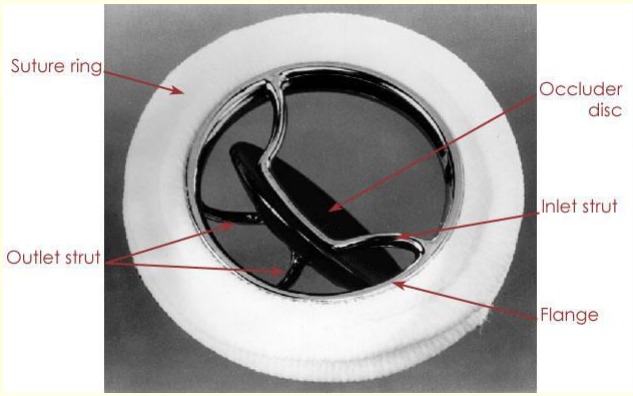
In the early 1950's, it led to the idea of a prosthetic heart valve consisting of a cage with a mobile spherical poppet

First implanted in a human in a closed procedure in September of 1952. In 1953, marked successful use of the heart and lung machine, paving the way for the 1st open heart operations

Types of Artificial Heart Valves

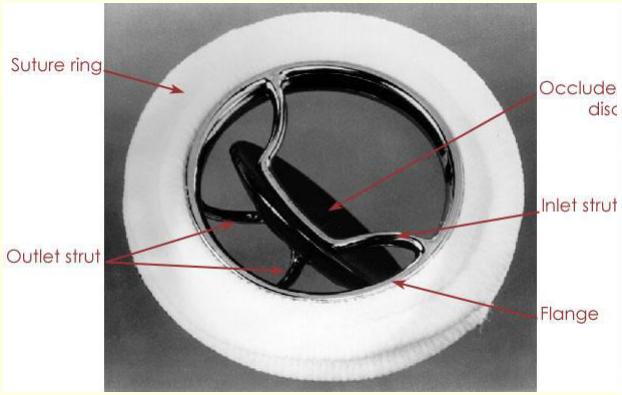
- Mechanical- There are three types. The caged ball, tilting disk, and bileaflet
- Tissue(biological)- valves that are used from animals to implant them back into humans

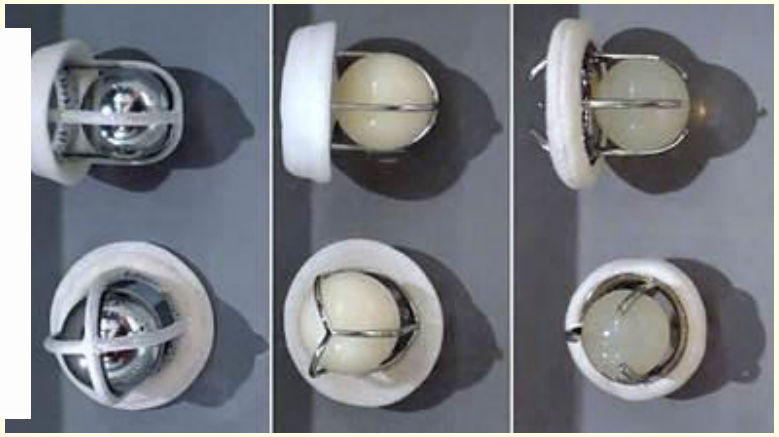




Mechanical Heart Valves

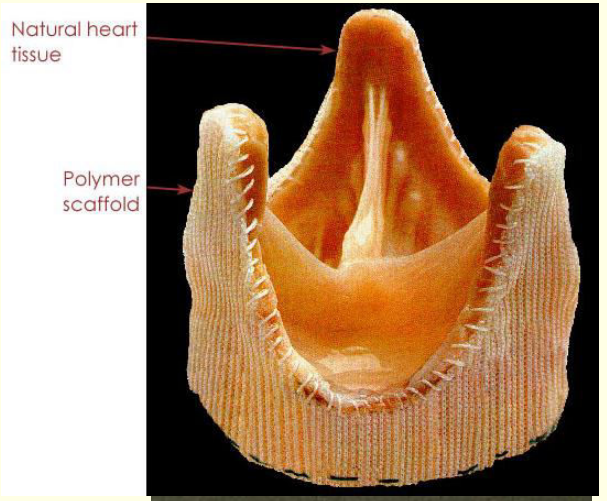
- All the types of mechanical heart valves are still in use today.
- Usually made of titanium or carbon which makes them strong and very durable
- Three types of mechanical heart valves





Tissue Heart Valves (biological valves)

- Using valves from other animals. The porcine valve of a pig is the most comparable valve to a human.
- Xenotransplantation
- Xenotransplantation, is the transplantation of living cells, tissues or organs from one species to another. Such cells, tissues or organs are called xenografts or xenotransplants. In contrast, the term allotransplantation refers to a same-species transplant. Human xenotransplantation offers a potential treatment for end-stage organ failure, a significant health problem in parts of the industrialized world. A continuing concern is that many animals, such as pigs, have a shorter lifespan than humans, meaning that their tissues age at a quicker rate.
- Pericardial valves: The pericardial heart valve was invented by Marian Ionescu, a British surgeon working at the General Infirmary in Leeds, England. He created this artificial bioprosthetic heart valve as a three-cusp structure made of chemically treated bovine pericardium attached to a Dacron cloth-covered titanium frame.

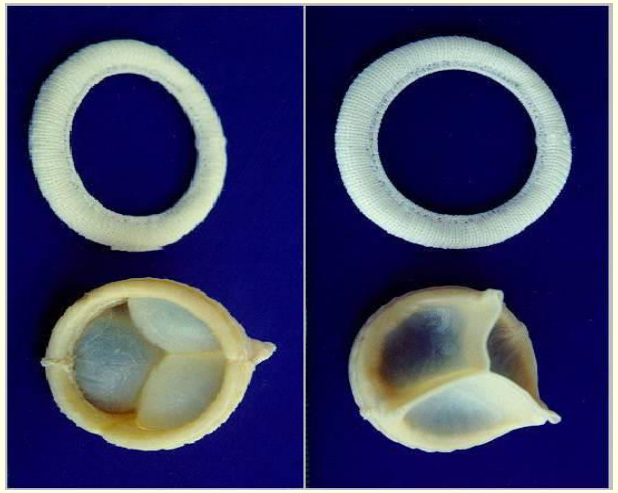


Bileaflet valves

- Two semicircular leaflets that rotate about struts attached to the valve housing
- Good hemodynamic performance - improved flow characteristics, lower transvalvular pressure gradients, less blood flow turbulence, improved hemodynamics at a given annular diameter, a larger orifice area and low bulk and flat profile
- the least thrombogenic of the artificial valves
- **most commonly implanted mechanical valves**

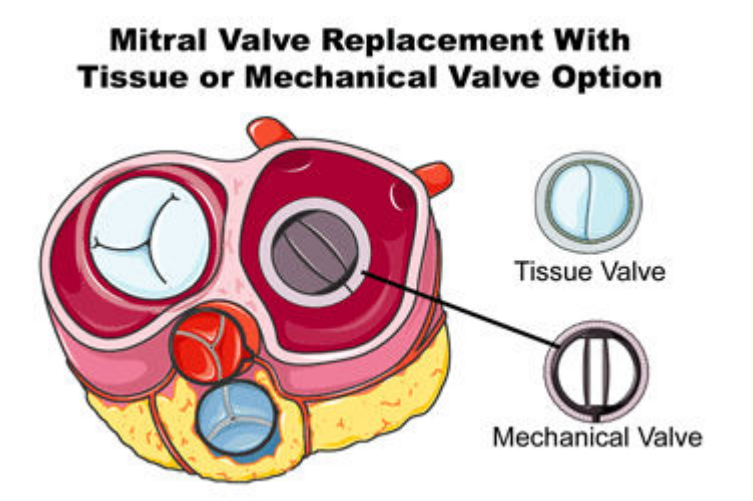
Advantages

- Mechanical heart valves: The biggest advantage is the durability. While the tissue heart valves are estimated to last about 10-15 years, a mechanical heart valve can last 30 year
- Tissue heart valves: There is minimal blood regurgitation, minimal transvalvular pressure gradient, self repairing.
- Does not require and anti-coagulant drug.



Disadvantages

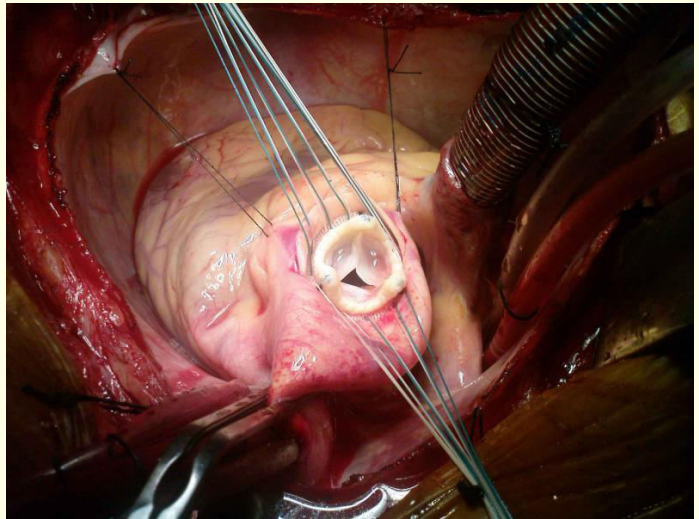
- Mechanical heart valves – In order to decrease the risk of blood clotting, the patient must take blood thinners. Some patients can hear their mechanical heart valve open and close.
- Tissue heart valves – Wear, there is a small possibility that the body will reject the valve, inability to implant them into infants and children.



Implanting

- Both mechanical and tissue heart valves require open heart surgery
- It’s more common in tissue valves for a re-operation
- Complete recovery from surgery could be a couple of weeks to several months
- Currently: 55% mechanical valves

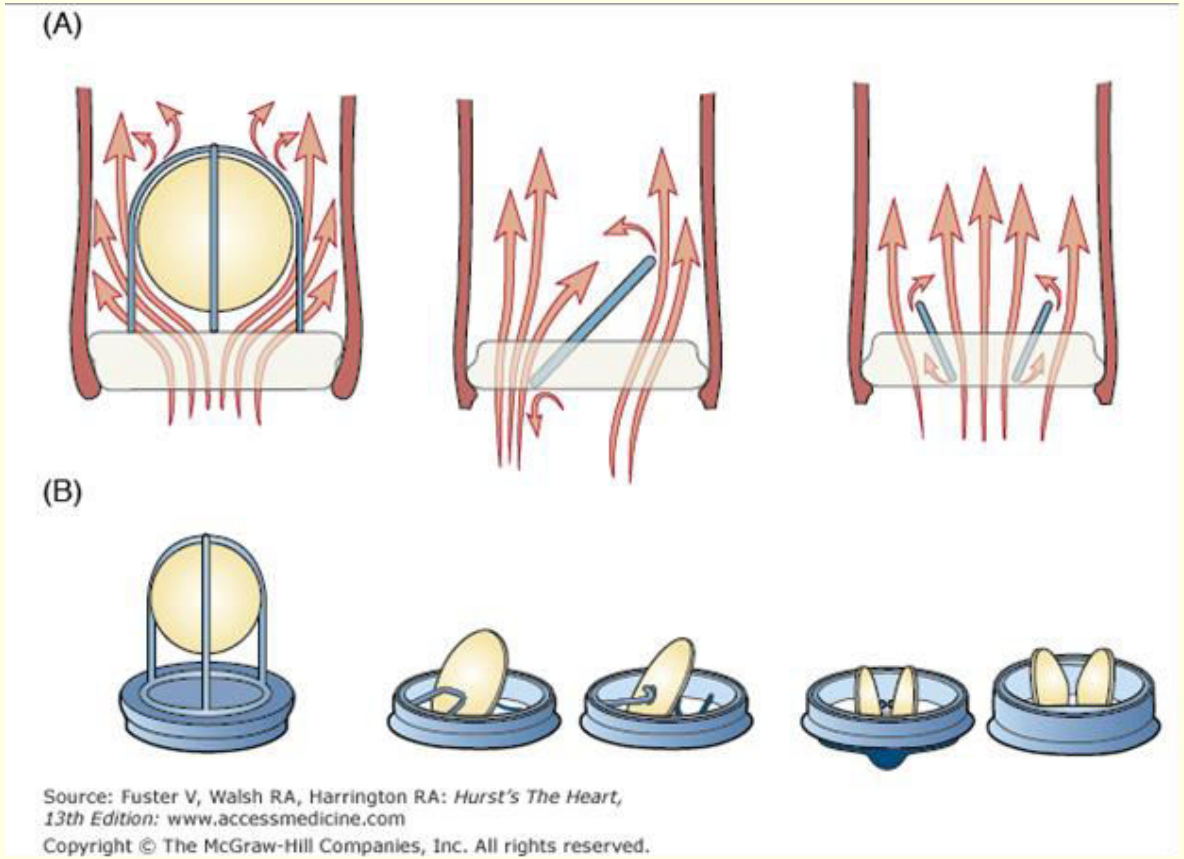
  45% tissue valves



FDA-approved prosthetic heart valves

Type	Manufacturer	Model	Year of first clinical use	Implants* (thousands)
Mechanical				
Ball	Baxter Edwards	Starr-Edwards	1965	200
Disk	Medtronic	Medtronic Hall	1977	178
	Medical Inc.	Omniscience	1978	48
	Alliance	Monostrut	1982	94
Bileaflet	St. Jude	St. Jude	1977	580
	Baxter Edwards	Duromedics	1982•	20
	CarboMedics	CarboMedics	1986	110
Biological				
Porcine	Medtronic	Hancock Standard	1970	177
		Hancock MO	1978	32
	Baxter Edwards	CE Standard	1971	400
		CE SupraAnnular	1982	45
	St. Jude	Toronto Stentless (TSP)	1991	5
	Medtronic	Free Style	1992	5
Pericardial	Baxter Edwards	CE	1982	35
Homograft	Noncommercial△		1962	12
	Cryolife△		1984	14
Autologous	noncommercial△	Pulmonary autograft	1967	2

Haemodynamics of blood flow



Profile and hemodynamics of each main valve type. **A.** Whereas ball and cage valves are associated with a lack of central blood ejection fraction, tilting disc valves are associated with turbulent blood flow at the lesser orifice. **B.** Bileaflet valves have the lowest profile compared with ball and cage valves and tilting disc valves – better transvalvular gradient. However prone to backflow

- However, inspite of improved design and haemodynamics – still haunted by numerous complications and the most dreaded one of valve thrombosis

Why not always use a Bioprosthetic valve !!

- Developed primarily to overcome the risk of thromboembolism that is inherent in all mechanical prosthetic valves
- Major problem – DURABILITY. Cuspal tears, degeneration, fibrin deposition, perforation, fibrosis, and calcification.
- Rate of tissue failure – by 10 years 30% and upto 60% by 15 years.

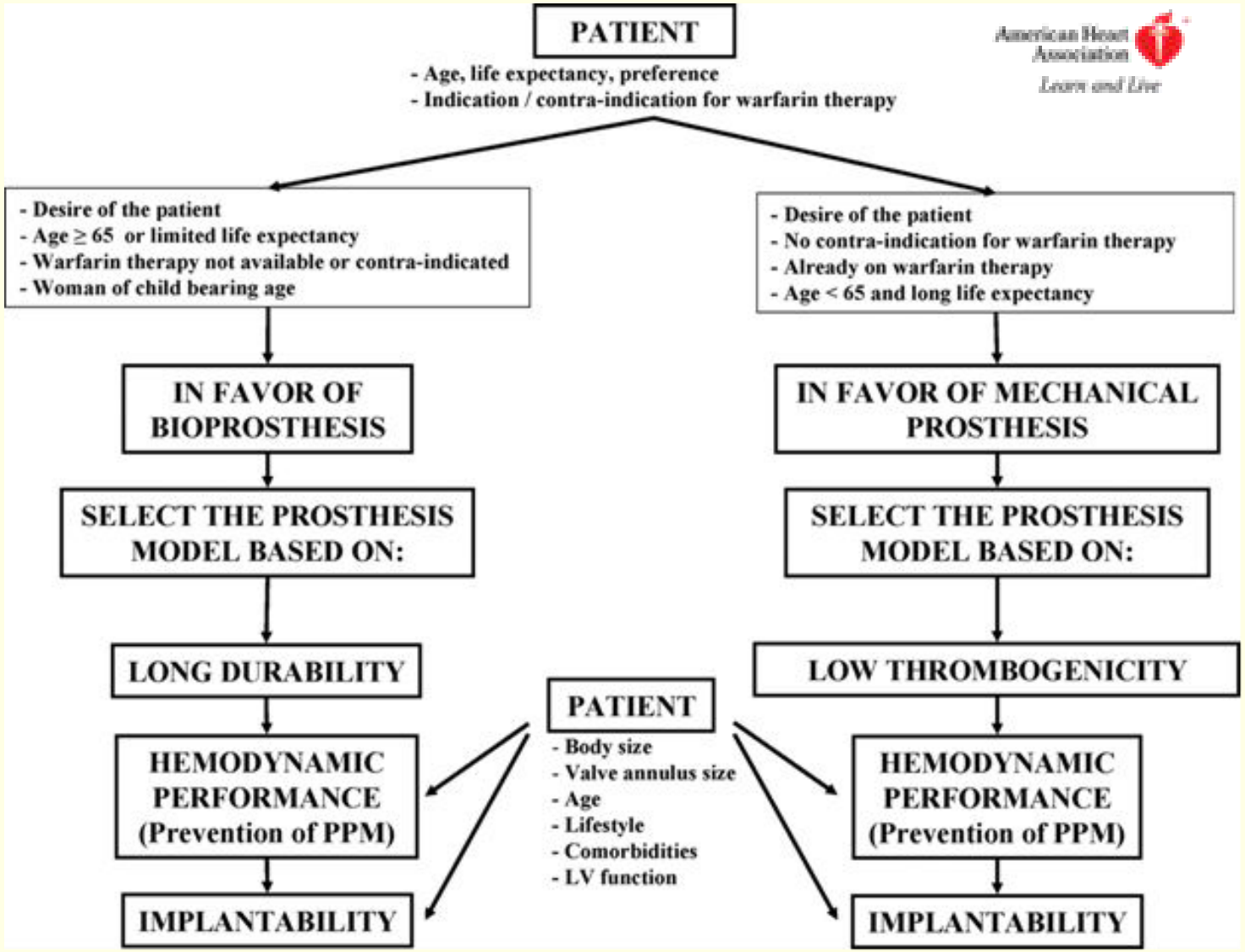
Choice of Valves

- Major task is to weigh the advantage of durability and the disadvantages of the risks of thromboembolism and anticoagulant treatment inherent with mechanical valves
- Warfarin (also known by the brand names Coumadin, Jantoven, Marevan, Uniwarfin) is an anticoagulant normally used in the prevention of thrombosis and thromboembolism, the formation of blood clots in the blood vessels and their migration elsewhere in the body, respectively.
- The next step is to choose a prosthesis model that provides superior hemodynamic performance to prevent prosthesis-patient mismatch (PPM) and thereby minimize postoperative trans-prosthetic gradients.

Thrombosis with Mechanical valve

- Mechanical prostheses remains burdened with the risk of thrombosis – potentially fatal
- Valve thrombosis is any thrombus in the absence of infection attached to or near an operated valve that occludes part of the blood flow path or that interferes with the function of the valve.
- Risk factors:
  - **inadequate or discontinued anticoagulant therapy**
  - **previous endocarditis:**
  - Endocarditis is an infection of the inner lining of your heart (endocardium).
  - Endocarditis generally occurs when bacteria or other germs from another part of your body, such as your mouth, spread through your bloodstream and attach to damaged areas in your heart. Left untreated, endocarditis can damage or destroy your heart valves and can lead to life-threatening complications. Treatments for endocarditis include antibiotics and, in certain cases, surgery.
  - Endocarditis is uncommon in people with healthy hearts. People at greatest risk of endocarditis have damaged heart valves, artificial heart valves or other heart defects.
  - **the prosthetic valve model used**

Patient tailored prosthesis



Measurement System and Diagnostic Devices

Biomedical Instrumentation

- Diagnosis and therapy depend heavily on the use of medical instrumentation.
- Medical procedures:

  Medicine can be defined as a multistep procedure on an individual by a physician, group of physician, or an institute, repeated until the symptoms disappear

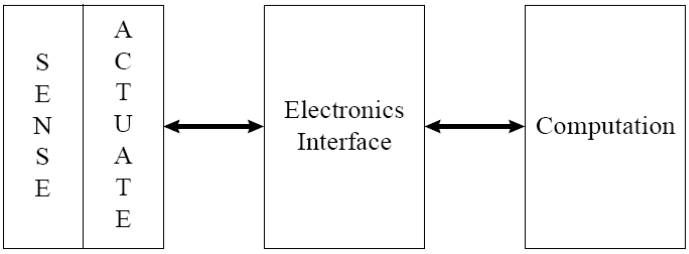
2

The Importance of Biomedical Instrumentation

- **Medical procedure**
  1. Collection of data - qualitative and/or quantitative
  2. Analysis of data
  3. Decision making
  4. Treatment planning based on the decision

3

Biomedical Instrumentation System



- All biomedical instruments must interface with biological materials. That interface can by direct contact or by indirect contact

4

Sensor

- A sensor converts one form of energy to another, and in so doing detects and conveys information about some physical, chemical or biological phenomena.
- More specifically, a sensor is a transducer that converts the measurand (a quantity or a parameter) into a signal that carries information.

5

What is a Biosensor

- Biosensors are 簡nalytical devices that combine a biologically sensitive element with a physical or chemical transducer to selectively and quantitatively detect the presence of specific compounds in a given external environment篤[Vo-Dinh and Cullum, 2000].
  - Antibodies
  - Enzymes
  - DNA, RNA
  - Whole cells

6

Components of BM Instrumentation System…

- A sensor
  - Detects biochemical, bioelectrical, or biophysical parameters
  - Provides a safe interface with biological materials
- An actuator
  - Delivers external agents via direct or indirect contact
  - Controls biochemical, bioelectrical, or biophysical parameters
  - Provides a safe interface with biologic materials

7

…Components of BM Instrumentation System…

- The electronics interface
  - Matches electrical characteristics of the sensor/actuator with computation unit
  - Preserves signal to noise ratio of sensor
  - Preserves efficiency of actuator
  - Preserves bandwidth (i.e., time response) of sensor/actuator
  - Provides a safe interface with the sensor/actuator
  - Provides a safe interface with the computation unit
  - Provides secondary signal processing functions for the system

8

…Components of BM Instrumentation System

- The computation unit
  - provides primary user interface
  - provides primary control for the overall system
  - provides data storage for the system
  - provides primary signal processing functions for the system
  - maintains safe operation of the overall system

9

Classifications of Biomedical Instruments

- The sensed quantity
- The principle of transduction
- The organ system for measurement
- The clinical medicine specialties
- Based on the activities involved in the medical care, medical instrumentation may be divided into three categories:
  - Diagnostic devices
  - Therapeutic devices
  - Monitoring devices

10

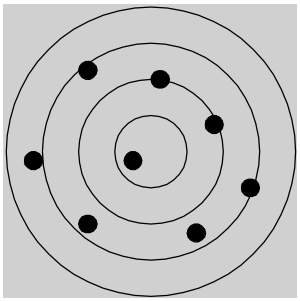
Accuracy and precision…

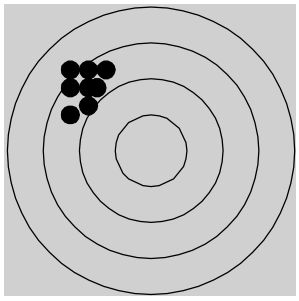
- Resolution
  - the smallest incremental quantity that can be reliably measured.
    - a voltmeter with a larger number of digits has a higher resolution than one with fewer digits.
  - However, high resolution does not imply high accuracy.
- Precision
  - the quality of obtaining the same output from repeated measurements from the same input under the same conditions.
  - High resolution implies high precision.
- Repeatability
  - the quality of obtaining the same output from repeated measurements from the same input over a period of time.

11

…Accuracy and precision…

- Data points with
  (a) low precision and (b) high precision.





12

…Accuracy and precision…

- Accuracy
  - the difference between the true value and the measured value divided by the true value.

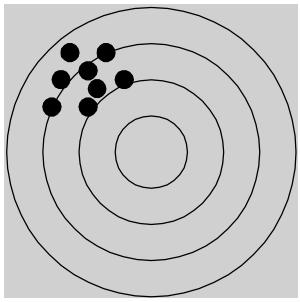
- **Obtaining the highest possible precision, repeatability, and accuracy is a major goal in bioinstrumentation design.**

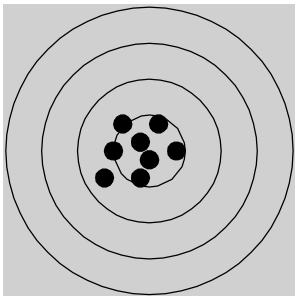
13

…Accuracy and precision…

- Data points with

(a) low accuracy and (b) high accuracy





14

Lateral Flow Immunoassay

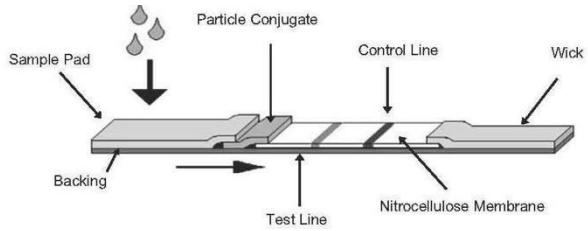


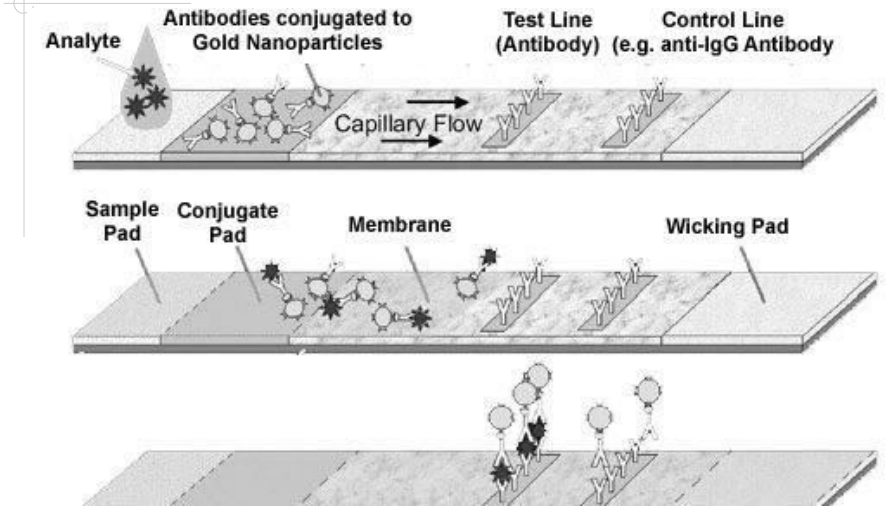
FIGURE 1 Typical lateral flow test strip configuration. (The color version of this figure may be viewed at www.immunoassayhandbook.com).

Lateral flow tests also known as lateral flow immunochromatographic assays, are simple devices intended to detect the presence (or absence) of a target analyte in sample (matrix) without the need for specialized and costly equipment, though many lab based applications exist that are supported by reading equipment. Typically, these tests are used for medical diagnostics either for home testing, point of care testing, or laboratory use. A widely spread and well known application is the home pregnancy test.

Lateral Flow Immunoassays

- A typical lateral flow rapid test strip consist of the following components:
- Sample pad - an adsorbent pad onto which the test sample is applied.
- Conjugate or reagent pad – this contains antibodies specific to the target analyte conjugated to coloured particles (usually colloidal gold nanoparticles, or fluorescent particles).
- Reaction membrane – typically a nitrocellulose or cellulose acetate membrane onto which anti-target analyte antibodies are immobilized in a line that crosses the membrane to act as a capture zone or test line (a control zone will also be present, containing antibodies specific for the conjugate antibodies).
- Wick or waste reservoir – a further absorbent pad designed to draw the sample across the reaction membrane by capillary action and collect it.
- The components of the strip are usually fixed to an inert backing material and may be presented in a simple dipstick format or within a plastic casing with a sample port and reaction window showing the capture and control zones.

Lateral Flow Immunoassays

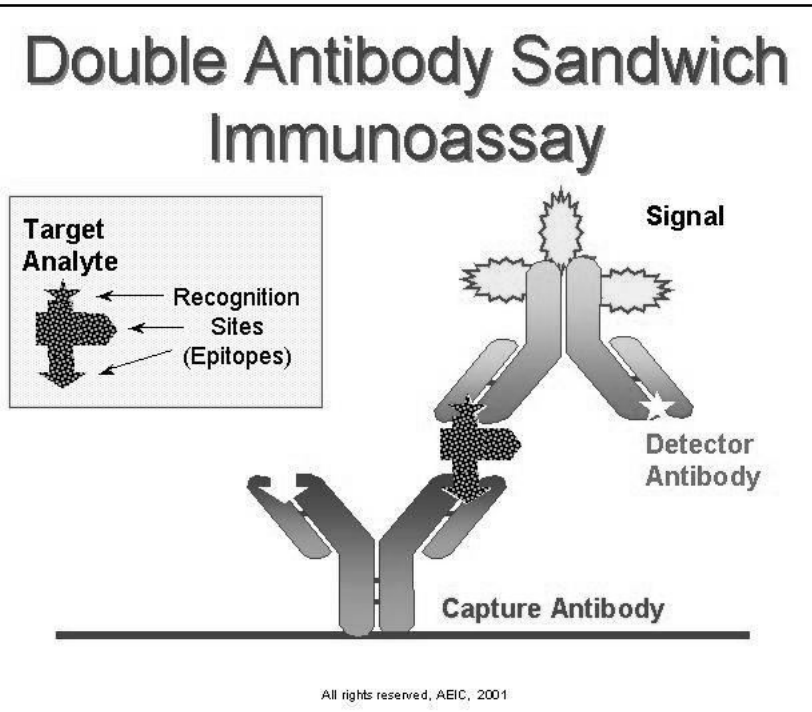


Double antibody sandwich assays

- In this format the sample migrates from the sample pad through the conjugate pad where any target analyte present will bind to the conjugate. The sample then continues to migrate across the membrane until it reaches the capture zone where the target/conjugate complex will bind to the immobilized antibodies producing a visible line on the membrane. The sample then migrates further along the strip until it reaches the control zone, where excess conjugate will bind and produce a second visible line on the membrane.

Double antibody sandwich assays

- This control line indicates that the sample has migrated across the membrane as intended. Two clear lines on the membrane is a positive result. A single line in the control zone is a negative result. Double antibody sandwich assays are most suitable for larger analytes, such as bacterial pathogens and viruses, with multiple antigenic sites.



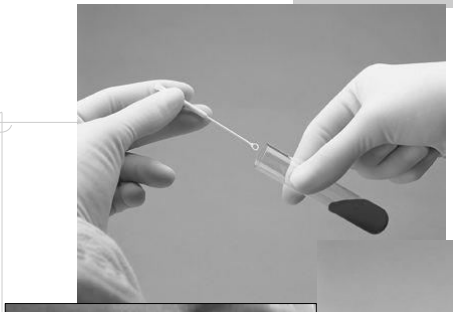
Competitive assays

- Competitive assays are primarily used for testing small molecules and differ from the double antibody sandwich format in that the conjugate pad contains antibodies that are already bound to the target analyte, or to an analogue of it. If the target analyte is present in the sample it will therefore not bind with the conjugate and will remain unlabeled. As the sample migrates along the membrane and reaches the capture zone an excess of unlabeled analyte will bind to the immobilized antibodies and block the capture of the conjugate, so that no visible line is produced. The unbound conjugate will then bind to the antibodies in the control zone producing a visible control line.

Competitive assays

- A single control line on the membrane is a positive result. Two visible lines in the capture and control zones is a negative result. However, if an excess of unlabeled target analyte is not present, a weak line may be produced in the capture zone, indicating an inconclusive result. Competitive assays are most suitable for testing for small molecules, such as mycotoxins, unable to bind to more than one antibody simultaneously. There are a number of variations on lateral flow technology. The capture zone on the membrane may contain immobilized antigens or enzymes - depending on the target analyte - rather than antibodies. It is also possible to apply multiple capture zones to create a multiplex test.

Why do rapid HIV testing?



- Accurate & simple
- Deliver results to everyone
- Convenient for patients

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HIV Rapid Tests

- Qualitative assay to detect HIV antibodies
- Most detect HIV 1 and HIV 2
- As reliable as EIAs
- Issues:
  - Small volumes
  - Validation of use
  - Appropriate training

HIV Rapid Tests: Advantages

- Increases access to prevention and interventions
- Supports increased number of testing sites
- Same-day diagnosis and counseling
- Robust and easy to use
- Test time under 30 minutes
- Most require no refrigeration
- None or one reagent
- Minimal or no equipment required
- Minimum technical skill

Body Fluids Used for HIV Rapid Testing

- Serum
- Plasma
- Whole blood
- Oral fluids

Three Formats of HIV Rapid Tests

- Immunoconcentration (flow-through device)
- Immunochromatography (lateral flow)
- Particle agglutination

Immunoconcentration

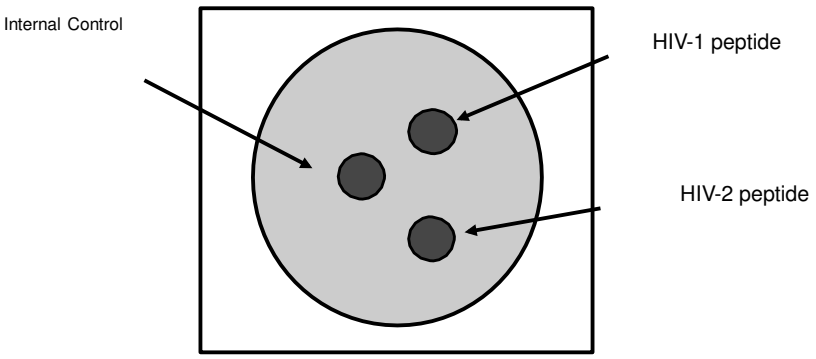
- Microscopic particles are separately coated with the antigens that represent portions of the transmembrane proteins HIV-1 and HIV-2, respectively. The microparticles are immobilized on the reaction membrane of the Cartridge and form the Test Spots. The reaction membrane also contains a Procedural Control Spot that serves as a control spot to ensure that the entire test procedure was properly executed. If antibodies against HIV-1 and/or HIV-2 are present in the specimen, they bind to the antigens on the microparticles in the specific spots on the cartridge membrane. The Conjugate, which contains alkaline phosphatase-labeled goat anti-human IgG, is then added to the Cartridge. The Conjugate binds to the human antibody-antigen complexes that are immobilized in the spots on the cartridge membrane.

Immunoconcentration

- Next, Development Reagent is added to the Cartridge. A purple color develops on the Test Spots in proportion to the amount of antibodies against HIV-1 and/or HIV-2 that have been bound to the antigen-coated microparticles and detected by the Conjugate. A purple color will also develop on the Procedural Control Spot when the test has been performed correctly. Color development is stopped by the addition of Stop Solution. The membrane is examined visually for the presence of purple color on the Procedural Control Spot and on the Test Spots.

How Immunoconcentration Works

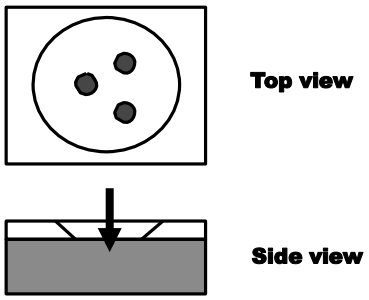
HIV antibody links to bound HIV peptide antigens forming the color spot



Tests Based on Immunoconcentration

Flow-Through Devices:

- Multi-Spot
- Genie II



Multispot HIV-1/2

- Serum
- Plasma

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Multispot

- Pros
  - -can distinguish between HIV-1 and 2
  - -approx. 10 minutes to complete process
  - -can read results immediately or up to 24 hours after completion
- Cons
  - -more difficult processing steps
  - -once test process started, must complete

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Reading Results: Genie II

Non-reactive Reactive

FDA-approved Rapid Tests

- Reveal (MedMira)
- OraQuick (OraSure Technologies)
- Uni-Gold (Trinity Biotech)
- Multispot (Bio-Rad)

All test for HIV antibodies

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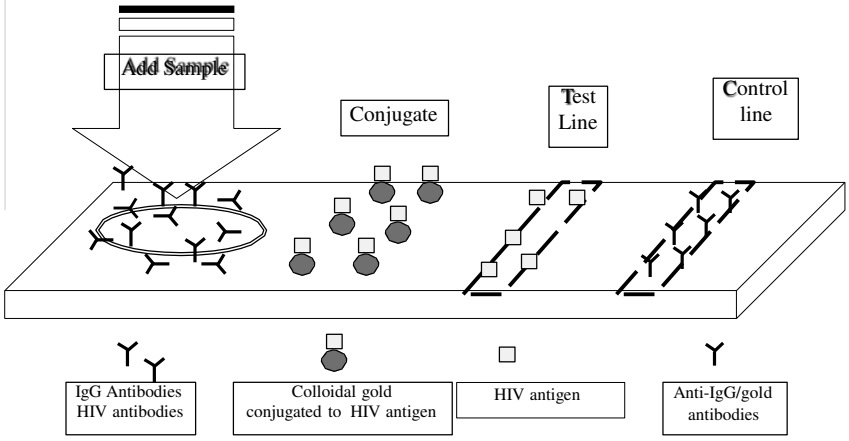
How Immunochromatography Works

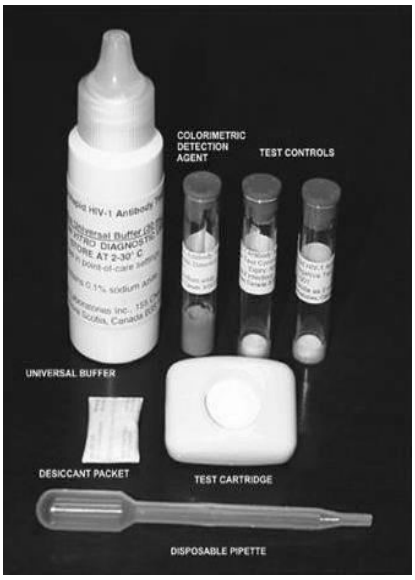


Reveal G-2 HIV-1 Test

- The RevealTM G2 Rapid HIV-1 Antibody Test is a manually performed, visually interpreted, rapid immunoassay. The RevealTM G2 Rapid HIV-1 Antibody Test is comprised of a single-use test cartridge containing an immunoreactive test membrane. The immunoreactive test membrane is comprised of a combination of synthetic peptides corresponding to conserved regions of HIV structural proteins coated onto a membrane matrix, which functions to capture anti-HIV-1 antibodies present in human serum or plasma when a drop of the specimen is applied. In addition, the test membrane has a procedural and reagent Control Line comprised of protein A. Following the application of the sample, the membrane is washed with MedMira Universal Buffer to remove any non-specifically bound antibodies. Captured anti-HIV-1 antibodies are visualized through a reaction with the MedMira Colorimetric Detection Agent (a proprietary protein A-colloidal gold conjugate) followed by a second washing step with MedMira Universal Buffer for clarification of the test result. A Reactive test result occurs only when the protein A portion of the conjugate binds to the captured antibodies, producing a distinctive red dot in the test (T) zone and a vertical red Control Line in the control (C) zone of the test membrane upon completion of the test procedure. In contrast, a Non-Reactive test result, due to the absence of the HIV -1 antibody/antigen complex, is indicated by the presence of only the vertical red Control Line on the test membrane. If the vertical red Control Line is not present, the test result is considered invalid and testing must be repeated with a new cartridge

Reveal G-2 HIV-1 Test

- Serum & Plasma



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Reveal G2

- Pros:
  - Fastest processing time
- Cons:
  - Somewhat complicated
  - Lower specificity
  - Serum or plasma only - requires centrifuge equipment
  - Requires operator attention during entire process

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OraQuick Advance

- Oral Fluid
- Whole blood
- Plasma

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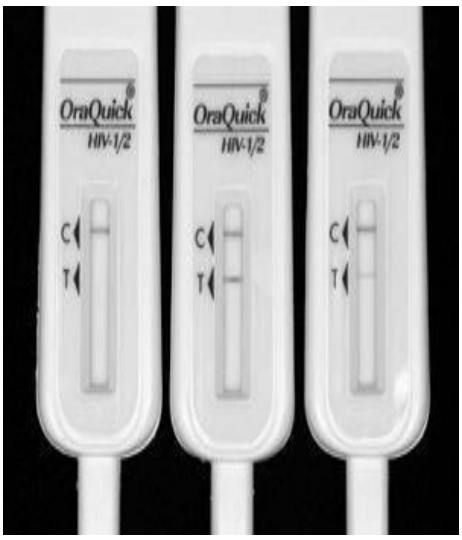
OraQuick Advance

- The OraQuick ADVANCE Rapid HIV-112 Antibody Test is a manually performed, visually read, 20 minute immunoassay for the qualitative detection of antibodies to HIV-1 and HIV-2 in human oral fluid, whole blood obtained from a finger puncture or a venipuncture, and plasma.
- The OraQuick ADVANCE rapid test is comprised of a single use test device and a single use vial containing a pre-measured amount of a buffered developer solution.
- Each component is sealed in separate compartments of a single pouch to form the test. The OraQuick ADVANCE rapid test utilizes a proprietary lateral flow immunoassay procedure. The device plastic housing holds an assay test strip comprised of several materials that provide the matrix for the immunochromatography of the specimen and the platform for indication of the test results.

Reading Results: OraQuick

Non-Reactive



Reactive

OraQuick

- Pros:
  - Simplest procedure
  - Flexible read time
  - Tests for HIV-2, oral fluid
  - Internal control verifies addition of sampl
- Cons:
  - Longest [passive] processing time

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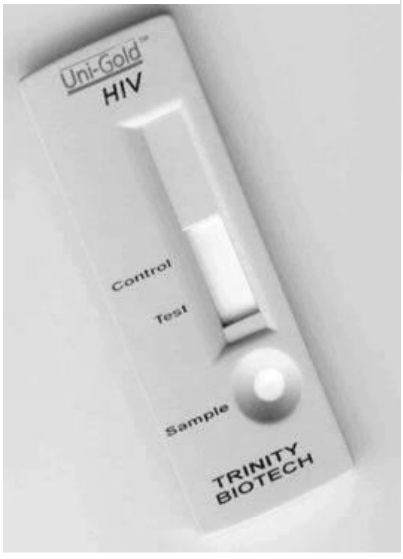
Uni-Gold

- Whole blood
- Plasma & Serum



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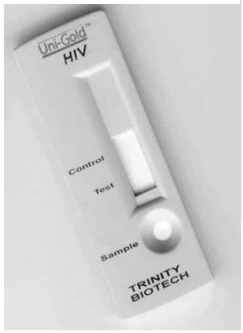
Uni-Gold

- Uni-Gold Recombigen® HIV-1/2 was designed as a rapid immunoassay and is intended to detect antibodies to HIV-1 and/or HIV-2 in human serum, plasma and whole blood (venipuncture and fingerstick).
- Uni-Gold Recombigen® HIV-1/2 uses proteins representing regions of the HIV virus. If antibodies to HIV-1 and/or HIV-2 are present in the sample, they combine with these proteins and a color reagent and this complex binds to the proteins in the test forming a visible pink/red band in the test region of the device adjacent to the word 'Test'.
- The control line should always appear as a visible pink/red band in the control region of the device to indicate that the test device is functioning correctly. A reactive result is indicated by a pink/red band in the test region of the device. A non-reactive result occurs in the absence of detectable levels of antibodies to HIV-1 and/or HIV-2 in the specimen; consequently no visually detectable band develops in the test region of the device.

UniGold



- Pros:
  - Relatively simple procedure
  - 10 minute processing time
- Cons:
  - No flexibility in read time
  - Internal control does not verify addition of sample (03.04 PI)

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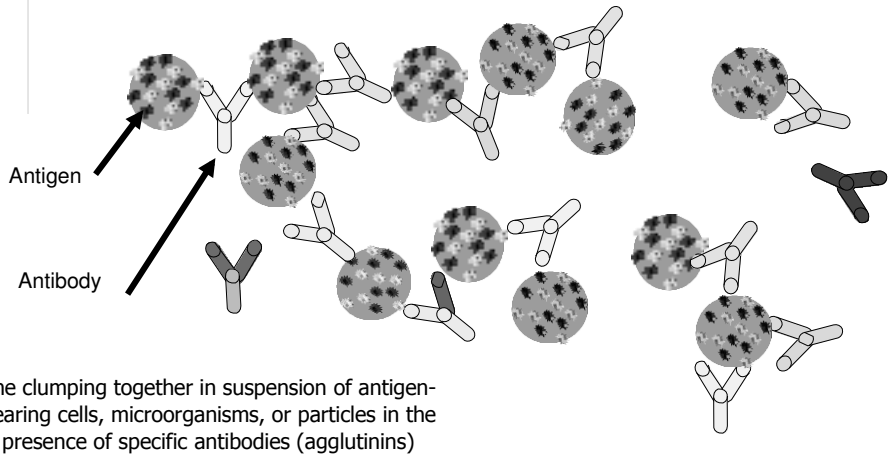
How Particle Agglutination Works

Anti-HIV antibodies bind to the antigen-coated latex particles.



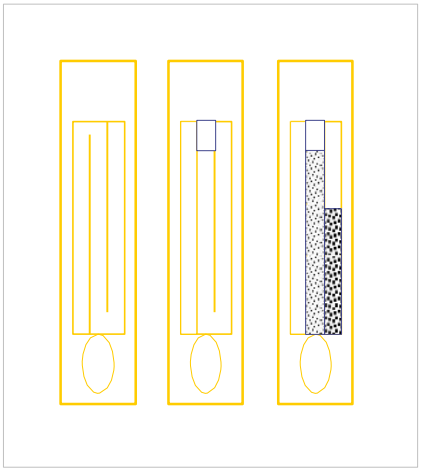
The clumping together in suspension of antigen-bearing cells, microorganisms, or particles in the presence of specific antibodies (agglutinins)

Tests Based On Agglutination

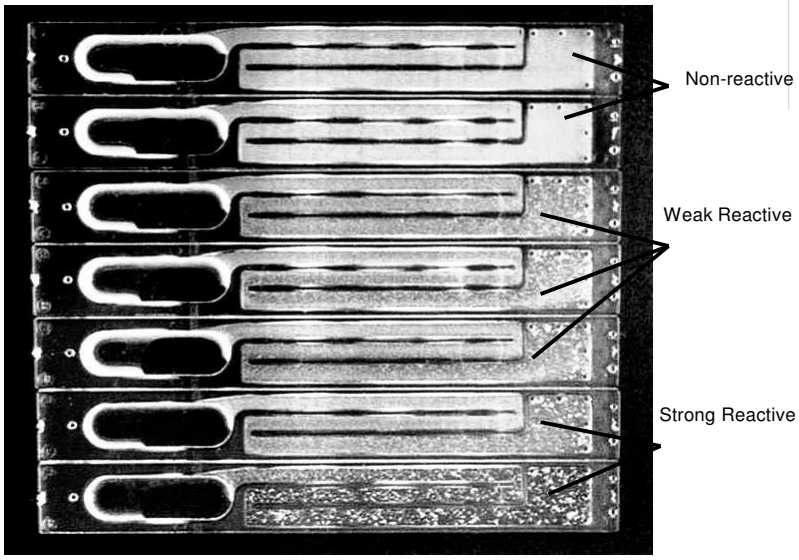
Agglutination devices:

- Capillus
- Serodia

A particle agglutination (PA) test, the Serodia HIV-1/2 test, is a low-cost, simple-to-perform agglutination assay capable of detecting antibodies to HIV-1 and HIV-2. The test incorporates viral lysate antigens coated on gelatin microbeads (particles) that agglutinate in the presence of specific antibodies



Reading Results: Capillus



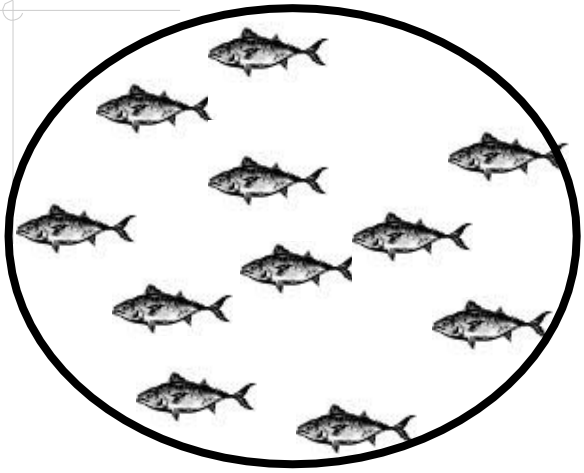
There Are Only Three Possible Outcomes for Single HIV Antibody Tests

Reactive or "Positive"
- Test band
- Control band

Non-reactive or "Negative"
- Control band only

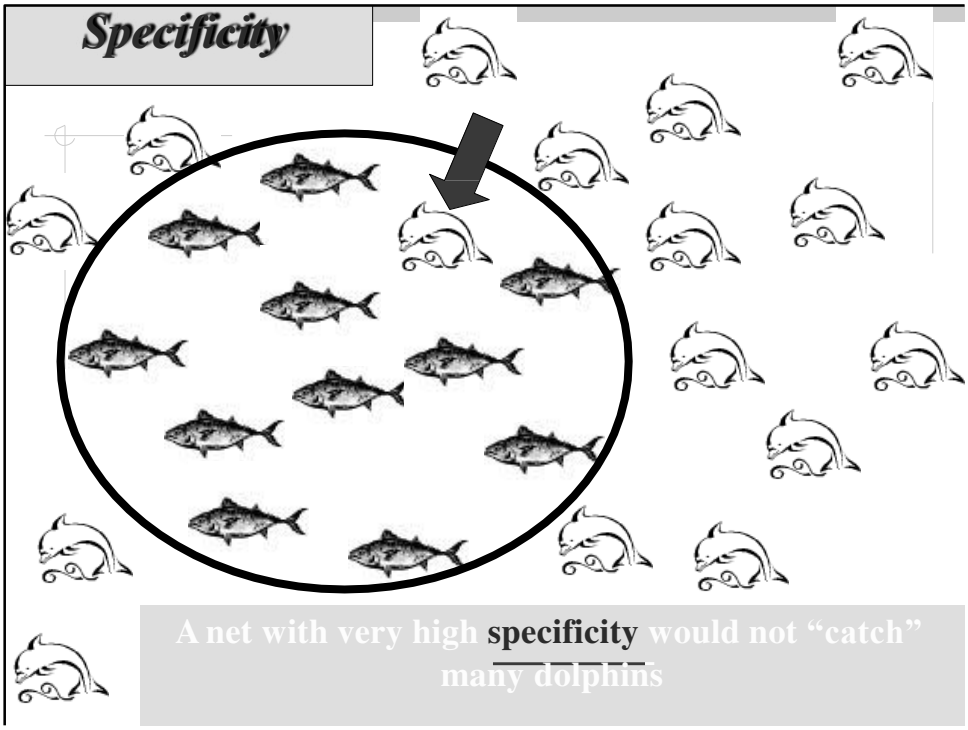
Invalid
- No control band present
- Test has failed. Repeat with new device.

Sensitivity



A net with very high **sensitivity** would not "miss" (m)any tuna

Specificity



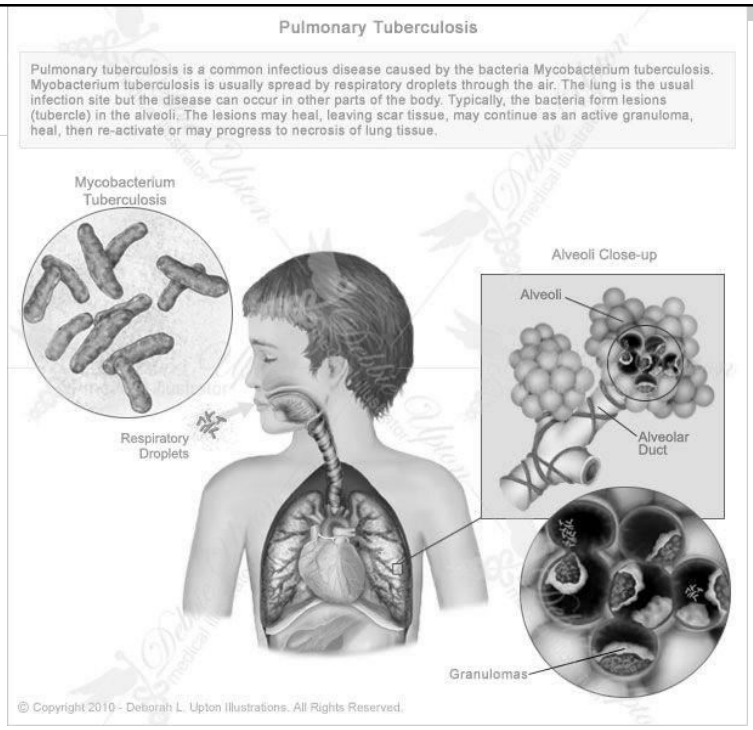
A net with very high **specificity** would not "catch" many dolphins

Human Lungs

- The lungs are a pair of spongy, air-filled organs located on either side of the chest (thorax). The trachea (windpipe) conducts inhaled air into the lungs through its tubular branches, called bronchi. The bronchi then divide into smaller and smaller branches (bronchioles), finally becoming microscopic.
- The bronchioles eventually end in clusters of microscopic air sacs called alveoli. In the alveoli, oxygen from the air is absorbed into the blood. Carbon dioxide, a waste product of metabolism, travels from the blood to the alveoli, where it can be exhaled. Between the alveoli is a thin layer of cells called the interstitium, which contains blood vessels and cells that help support the alveoli.
- The lungs are covered by a thin tissue layer called the pleura. The same kind of thin tissue lines the inside of the chest cavity -- also called pleura. A thin layer of fluid acts as a lubricant allowing the lungs to slip smoothly as they expand and contract with each breath.

Lung Diseases - Tuberculosis

- Tuberculosis (TB) is a serious disease caused by breathing in a bacteria called Mycobacterium tuberculosis. TB usually infects the lungs. TB can also infect other parts of the body, including the kidneys, spine and brain.
- People can have TB and not be sick, this is called latent TB. Latent TB is when a person has the TB bacteria in their body but it is not growing. The latent TB can become active TB at any time and make them very sick. If they have inactive TB infection they need to get treatment to cure their TB infection.
- TB is contagious. People who are sick with active TB disease spread TB germs through the air. It's important for people with TB to get treatment right away. TB treatments can cure TB and prevent it from spreading to others.



Global Burden of TB

- 1/3 world population is latently infected with M. tuberculosis
- 10% will develop active disease at some point in their lifetime
- In 2009, there were 9.4 million new cases of TB across the globe, and 1.7 million deaths
- TB –HIV co-infection
- Drug-resistant TB: MDR/XDR-TB

Drug Resistant TB

- Among TB patients notified in 2009, an estimated 250,000 had MDR-TB. Of these, slightly more than 30 000 (12%) were XDR-TB (WHO Global Tuberculosis Control 2010)
- Current phenotypic DST tests for drug resistance can take > 4 weeks, leading to higher mortality and spread of MDR strains
- Need for molecular diagnosis of MDR/XDR-TB

—Minimizing side effects

—Highly economic, expensive and ineffective drugs can be avoided

— Guiding treatment

Treatment for Tuberculosis

Treatment for inactive TB infection

If you have inactive TB infection, there are TB bacteria in your body, but you do not have any symptoms. Inactive TB must be cured to kill the TB bacteria before it becomes active TB and makes you very sick.

Inactive TB is often treated with a medicine called isoniazid (INH). Most people are prescribed this medication daily for 9 months. Inactive TB is also treated with the medicine isoniazid (INH) for 6 months and 3 months with INH and rifampin (PMP) for 3-4 months.

It's very important to take your TB medicine exactly as your doctor or nurse says, for as long as they say. If you stop taking your TB medicine or skip doses, these things could happen:

Your TB infection could come back.

Your TB infection could turn into active TB disease. With active TB, you will have symptoms and feel sick and you can pass TB on to your friends and family.

You could accidentally make the TB germ even stronger, so your TB infection is harder to treat. This is called drug-resistant TB and it is very dangerous and it can be deadly.

Treatments for active TB infection

If you have active TB, your doctor will prescribe medicine to cure you.

To get TB medicine, you need a prescription. TB medicine and treatment are free for most people in India.

Some antibiotic medicines (antibiotics) can cure TB. They kill the tuberculosis germs. It usually takes two or more TB medicines to cure active TB disease.

These are the most common medicines to cure TB:

Isoniazid (INH), also called Dom-Isoniazid®, Isotamine®, or PMS-Isoniazid®. It comes as pills or syrup.

Rifampin (RMP), also called Rifadin® or Rofact®. It comes as pills.

Pyrazinamide (PZA), also called PMS-Pyrazinamide® or Tebrazid®. It comes as pills.

Ethambutol (EMB), also called Etibi®. It comes as pills.

Your doctor may put you on all four medications at first. Your doctor will decide which medicines are best for you, and how long you must take them to be cured. TB germs are hard to kill. That's why it's very important that you take all your medicine.

TB Diagnostics

- For decades, researchers and the industry had pinned their hopes on serological antibody-detection methods for POC test development. Indeed, dozens of serological rapid (lateral flow assays) and ELISA tests got commercialized, even though no international guideline recommended their use. Today, these tests are on the market in at least 17 of the 22 highest tuberculosis burden countries, and millions of patients in the private sector undergo serological testing. Unfortunately, TB serological tests are neither accurate nor cost-effective, prompting the WHO to issue a strong negative recommendation against their use. The WHO policy, announced on July 20, 2011, states that, since the "the harms/risks [of commercial serodiagnostic tests] far outweigh any potential benefits (strong recommendation) …these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status".

TB Diagnostics

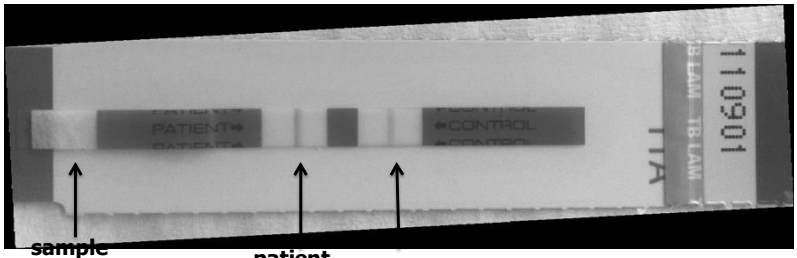
- The failure of antibody-based approaches spurred interest in antigen-detection. While many candidate antigens have been evaluated, urine lipoarabinomannan (LAM) detection assay was the first and, to date, the only antigen detection test to be commercialized, based on promising results from early studies. Two recent studies have evaluated the Determine® TB-LAM (Alere Inc., Waltham, MA, USA), a low-cost, POC version of the urine LAM test, in HIV-infected persons in South Africa.

Lipoarabinomannan, also called LAM, is associated with Mycobacterium tuberculosis, the bacteria responsible for tuberculosis. Its primary function is to inactivate macrophages and scavenge oxidative radicals.

The inactivation of macrophages allows for the dissemination of mycobacteria to other parts of the body. The destruction of oxidative radicals allows for the survival of the bacteria, as oxidative free radicals are an important mechanism by which our bodies try to rid ourselves of infection.

Determine LAM lateral flow assay (Alere)

- Uses Determine testing platform
- No sample processing; results in 25 minutes
- Analytical sensitivity reported to be 0.25 ng/ml
- Uses urine samples



Determine TB-LAM

Author/ Year	N	Setting	Sensitivity		Specificity
			Overall	**CD4<100**	
Peter, 2012	335	Inpatients	45%		96%
Lawn, 2012	516	ART clinic	28%	52%	99%
Dorman S, 2012	561	Outpatients Inpatients	45%	80%	90%

TB Diagnostics

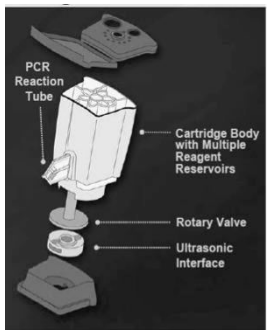
- Consistent with previous studies, the overall sensitivity of Determine® TB-LAM was low in patients with culture-confirmed TB. However, these studies showed that a combination of POC LAM test and sputum smears may offer value in screening for TB among severely immune-compromised HIV-infected patients, a subgroup of high-risk patients for whom diagnostic delays can be fatal. Because the Determine® TB-LAM test may have value only in those with low CD4 counts (CD4 cells or T-cells are a type of white blood cells that play a major role in protecting your body from infection. They send signals to activate your body's immune response when they detect "intruders," like viruses or bacteria), the test must be evaluated as part of an algorithm which includes, ideally, HIV and CD4 testing at the point-of-care.

TB Diagnostics

- The recent WHO endorsement of Xpert MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA), an automated, cartridge-based nucleic acid amplification test (NAAT), has greatly stimulated resurgent interest in using molecular tests for rapid diagnosis of active TB and drug. While the Xpert MTB/RIF assay is accurate and can potentially be used outside of a laboratory setting by a minimally trained health worker, it falls short of meeting the ideal POC requirements on two important grounds: at current prices, it is expensive and unaffordable in many settings, and it requires sophisticated equipment that cannot be deployed at the community level. Also, the pricing of Xpert MTB/RIF assay in the private sector in developing countries is substantially higher than the pricing for the public sector, imposing additional barriers for scale-up.

GeneXpert® - a Molecular Lab in a Cartridge Fully-Integrated Sample Preparation, Amplification and Detection

- **Universal sample prep**
- **Closed test system provides:**
  - **Nested PCR**
  - **Reflexive test capability**
- **Same Basic Cartridge works With all Tests and GeneXpert® Systems**

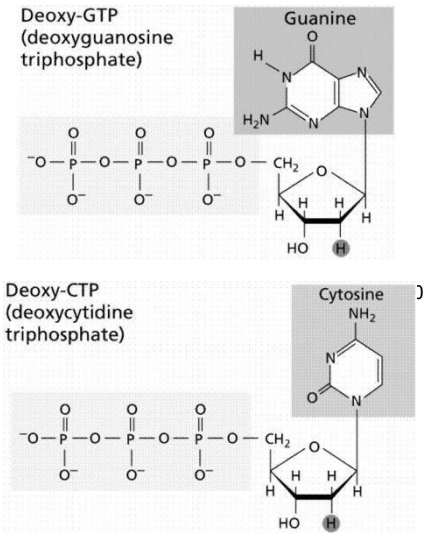


Xpert MTB/RIF

- Detects M. tuberculosis and common mutations that confer resistance to rifampin
- Fully automated
- Uses GeneXpert platform (Cepheid, CA)

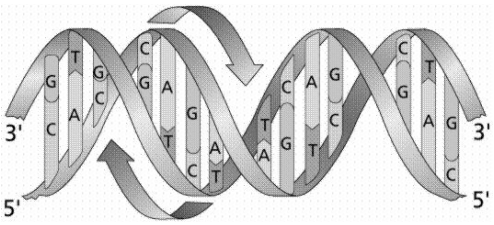
DNA Review

- DNA molecule:
  DNA molecules are linear, unbranched polymers composed of nucleic acid molecules – deoxyribonucleic acid molecules.
- Nucleic acid molecule consists of nucleotides: a purine (guanine, G, and adenine, A) or pyrimidine base (thymine, T, cytosine, C) covalently bound to deoxyribose phosphate



DNA Review

- DNA molecule:
  DNA molecule has a double helix structure
- Two DNA strands bound together
- Single stranded DNA – polymer consisting of a series of bases (A, C, G, T)
- Double stranded DNA – base pairs



DNA	Sequence	Length
Single-stranded	A-C-G-T-C	5 bases
Double-stranded	A-C-G-T-C T-G-C-A-G	5 base pairs

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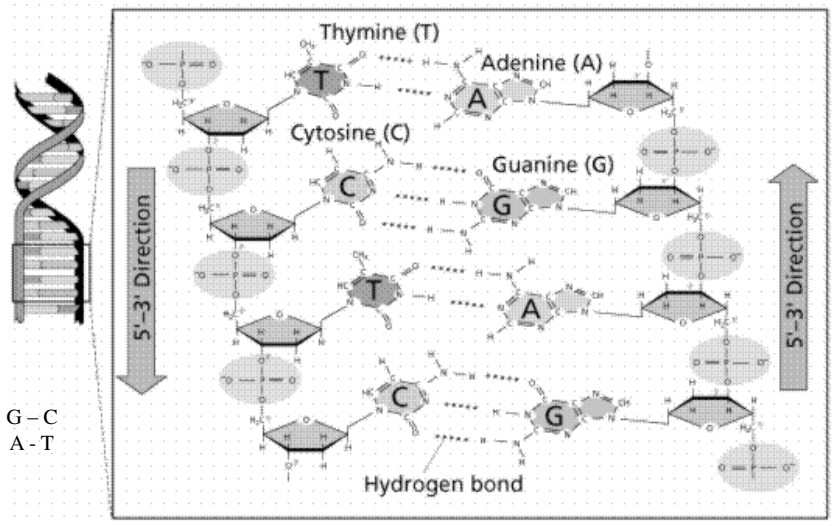
DNA Review



Complementary pair of polymer strands held by hydrogen bonds

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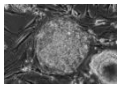
DNA Detection process

Sample preparation



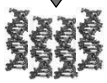
DNA/RNA extraction from the cells or microorganisms

- Chemical extraction (alkali)
- Mechanical disruption (ultrasonics)

DNA/RNA purification

- Filters (size exclusion)
- Commercial kits

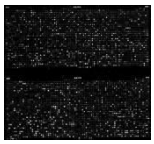
DNA amplification



- PCR (polymerase chain reaction)
- On-chip amplification

Detection

Target DNA hybridization to complementary probes on the DNA microarray



- Labeled target or additional reporter probe
- Fluorescent detection

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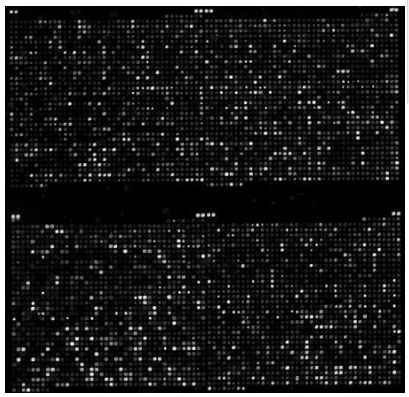
DNA Microarrays

- DNA microarrays rely on the hybridization properties of nucleic acids to monitor DNA or RNA abundance on a genomic scale in different types of cells, microorganisms
- Consist of a large number of spots on a substrate (glass, polymer, silicon) to which the probes are attached
- Probes: Oligonucleotide sequences spotted on the array / immobile substrate
- Oligonucleotides are short sequences of nucleotides (RNA or DNA), typically with twenty or fewer base pairs. Oligonucleotides are often used as probes for detecting complementary DNA or RNA because they bind readily to their complements.
- Target: Nucleic acid sample which is hybridized to the complementary probes on spotted array



Signal: Fluorescence from fluorophore probes (Cy3, Cy5, TR, fluorescein) attached to probes or targets

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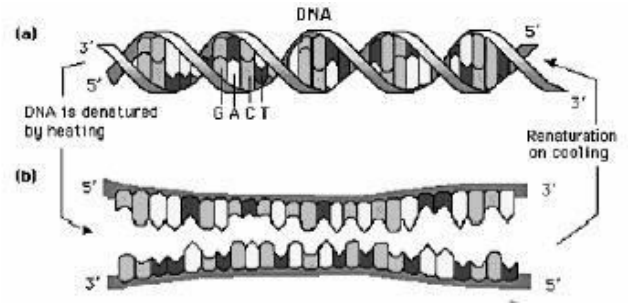
Hybridization



- Hybridization refers to the annealing of two nucleic acid strands following the base-pairing rules.
- Nucleic acid strands in a duplex can be separated, or denatured, by heating to destroy the hydrogen bonds.

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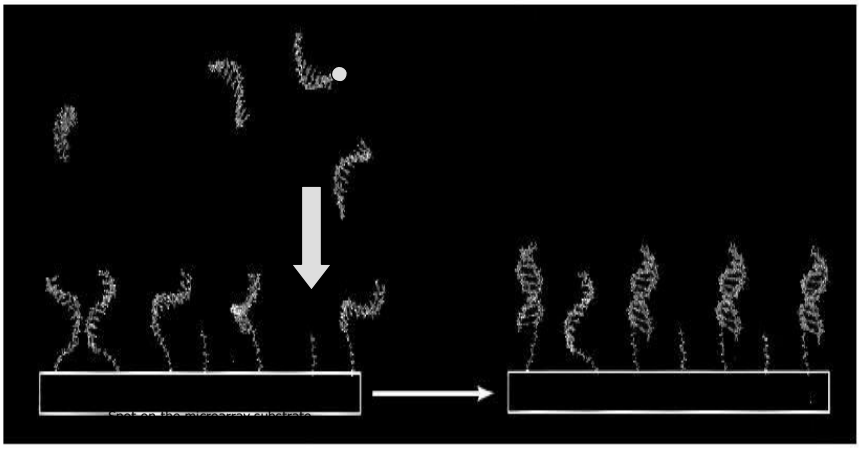
Hybridization



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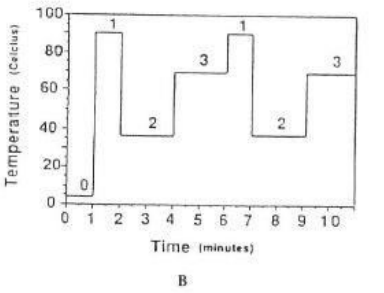
PCR

- Technique used to produce a large number of copies from a target DNA sequence
- Repetitive 3 step process
  - Denaturation (~95°C)
  - Annealing (~55°C)
  - Chain Extension (~ 72°C)



B

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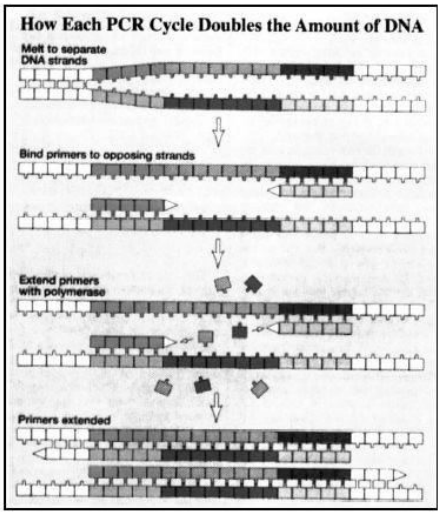
How PCR Works

How PCR Works

- High temperature to split strands
- Low temperature to anneal (primers in high concentration)
- Medium temperature to extend
- Repeat



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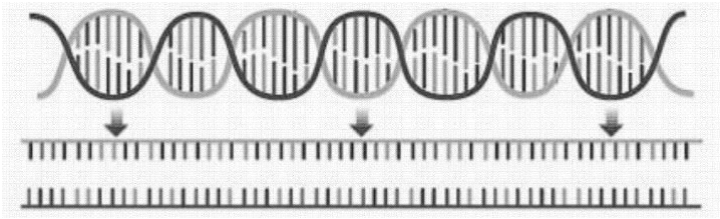
How PCR Works



step 1 - Denaturation (optimal temperature is 95°C)
By heating the DNA, the double strand melts and open to single stranded DNA.

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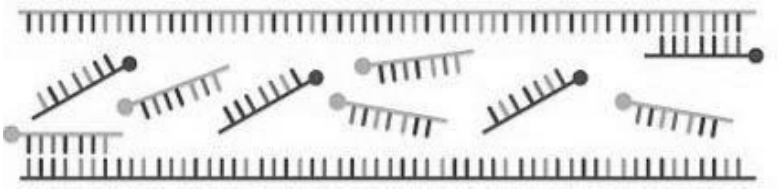
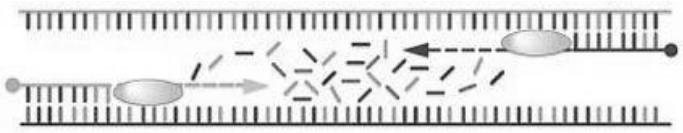
How PCR Works



step 2 - Annealing (optimal temperature is 55°C)
The single-stranded primers bind to their complementary single-stranded bases on the denaturated DNA.

100

How PCR Works



step 3 - Extension
72°C is the ideal temperature for the Taq polymerase to attach and start copying the template. The result is two new helixes in place of the first.

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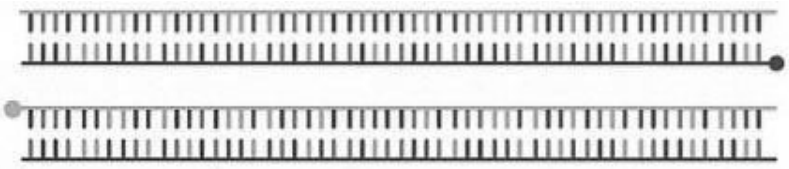
How PCR Works



By applying several times this cycle, the quantity of DNA obtained is quickly enough to perform any analysis. Starting with one DNA molecule after just 20 cycles there will be a million copies and after 30 cycles there will be a billion copies.

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Basic PCR Reagents

- Template DNA
- Complementary Primers (~20 nucleotides)
- Thermostable Polymerase Enzyme (TAQ)
- Single nucleotides (A,C,G,T)
- Buffers (pH and ionic concentrations)

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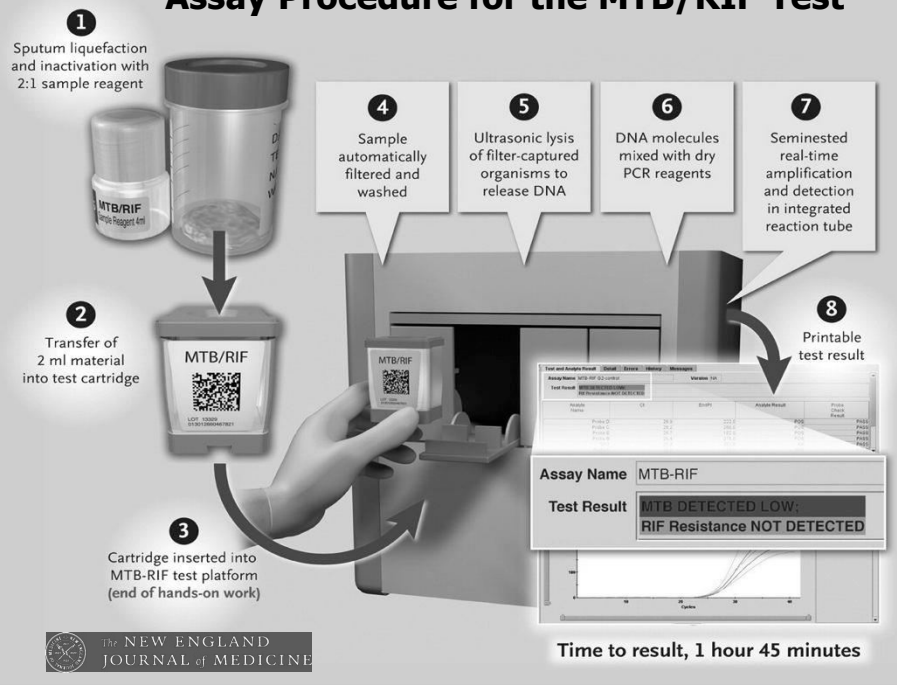
Assay Procedure for the MTB/RIF Test



Xpert MTB/RIF

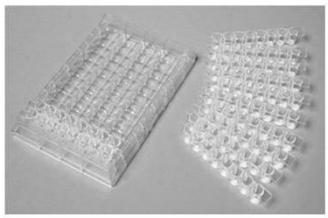
Attributes & Advantages

- Simple to perform, minimal training required
- Not prone to cross-contamination
- Requires minimal biosafety facilities
- "Near-care"

Shortcomings & Disadvantages

- Complex instrument (calibration, power supply)
- Cost for instrument
  - Cost of cartridges reduced to ~$10
  - Single supplier

T-SPOT.*TB* Test Kit



- Flexible, 96-well format
  - Twelve, 8-well strips
  - 4 wells used per patient; 24 patients per kit
  - Positive and Negative control for each patient test
- Utilizes standard blood collection tubes
- No special lab equipment required

T Spot TB test

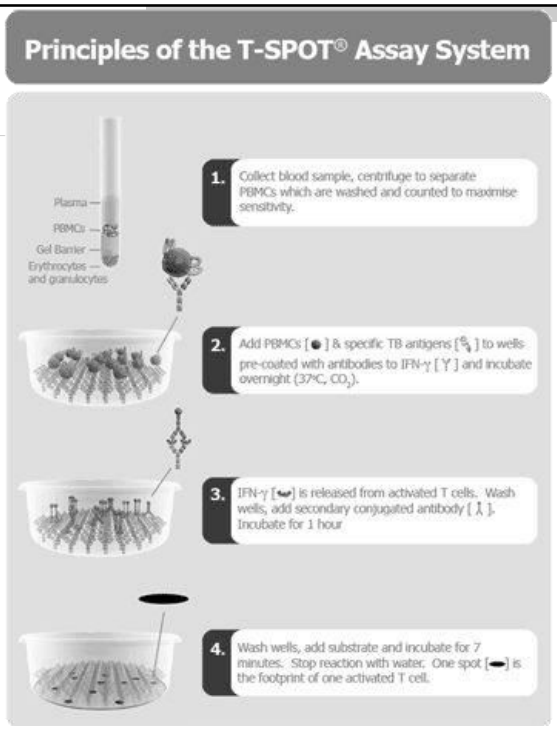
- The T–SPOT.TB test is a revolutionary in vitro diagnostic assay that measures T cells primed to Mycobacterium tuberculosis (MTB) antigens. It was developed for diagnosing both latent TB infection and TB disease in humans. The T-SPOT.TB test sets new clinical standards of sensitivity and reliability, even in the immunocompromised. The product was licensed in the European Union in July 2004, received FDA premarket approval in July 2008. It is replacing the tuberculin skin test, bringing effective TB testing to many new patient groups where the skin test gives poor results.

T Spot TB test

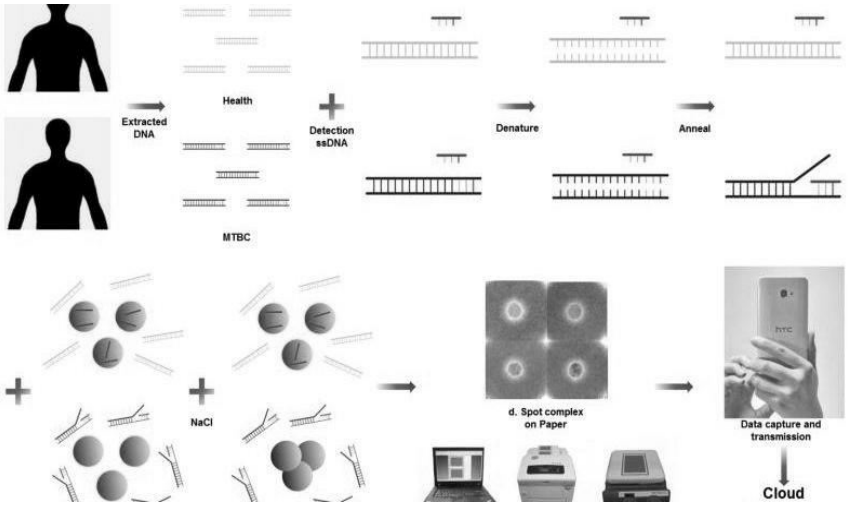
- The principles of T-SPOT assay system, are shown below, using blood as the body fluid in the example. The process starts with a blood sample, from which PBMCs (specifically Peripheral Blood Mononuclear Cells which is any blood cell having a round nucleus (as opposed to a lobed nucleus). For example: a lymphocyte, a monocyte or a macrophage. These blood cells are a critical component in the immune system to fight infection and adapt to intruders) or WBC components containing T cells (T lymphocytes are a type of lymphocyte or a type of white blood cell) that plays a central role in cell-mediated immunity. They can be distinguished from other lymphocytes, such as B cells and natural killer cells (NK cells), by the presence of a T-cell receptor (TCR) on the cell surface. They are called T cells because they mature in the thymus (although some also mature in the tonsils) are separated, washed and counted.

T Spot TB test

- A pre-determined number of PBMCs and antigens specific to the disease or condition of interest are then added to the wells of a microtiter plate to which antibodies to interferon-gamma, or IFN-γ, are bound. The test is based on the principle that the T cells of an individual who carries an active infection will respond to the antigens and secrete interferon-gamma. The secretion of interferon-gamma by the T cells of the subject is captured by the anti-interferon-gamma antibodies coated to the floor of each well. The numbers of individual reacting T cells are enumerated through visualizing the footprint of each T cell by this secretion of interferon-gamma.



Paper Based Diagnostics for TB



Schematic of the proposed TB diagnosis. Unknown extracted human DNA sequences are first hybridized with detection oligonucleotide sequences, followed by addition of colloidal gold nanoparticles and triggering of the colorimetric sensing with a sodium chloride solution. If the extracted DNA sequences consist of IS6110 target sequences then the detection oligonucleotide sequences will hybridize with them, and only a few ssDNA sequences will be absorbed on the gold nanoparticles to avoid aggregation after the addition of salt. In the absence of IS6110 target sequences, the color of the mixture remains red after hybridization and does not change. The mixture is then spotted and concentrated on the chromatography paper confined by solid wax hydrophobic barriers. Diagnostic results can be photographed with a smartphone and sent to a server for cloud computing.

Paper Based Diagnostics for TB

- This technique describes a colorimetric sensing strategy employing unmodified gold nanoparticles (AuNPs) and microfluidic paper-based analytical devices (μPAD) for tuberculosis (TB) diagnosis. After mixing with the AuNPs colloid and then being triggered with sodium chloride solution, unmodified single-stranded deoxyribonucleic acid (ssDNA) detection sequences were directly hybridized with extracted double-stranded DNA (dsDNA) from TB patients or healthy persons without complicated AuNP probe preparation processes.

Paper Based Diagnostics for TB

- The specific IS6110 dsDNA sequence of Mycobacterium tuberculosis complex (MTBC) was chosen as the diagnostic target for recognition. When the target DNA sequences were absent, the detection ssDNA sequences were absorbed on the AuNP surfaces and protected unmodified AuNPs from aggregation in the high salt solution. The detection ssDNA sequences were hybridized with target DNA when the target DNA sequences were present, and the color of the unprotected AuNPs colloid turned from red to blue.

Compliance

- A new monitoring system that combines cheap, paper-based diagnostics with text-messaging technology could help health organizations, with the cooperation of telecommunications companies, give patients another incentive to adhere to the drug regimen. José Gómez-Márquez, program director for the Innovations in International Health program at MIT, and his collaborators developed a simple paper-based test that detects metabolites of the TB drug in urine. The metabolite reacts with chemicals in the paper, revealing a simple numerical code. A patient would take the test daily and text the code to a central database. Those who take the drugs consistently for 30 days would be rewarded with cell-phone minutes.

Compliance

Take your meds: Paper tests reveal hidden codes (above) when exposed to the urine of patients who have taken tuberculosis medication. The codes can be numerical sequences or bar codes

Why we Fail to Diagnose TB?

- Lack of health infrastructure
- TB control is plagued with lack of accurate, robust and rapid diagnostic methods
- Patients are diagnosed late, many are never diagnosed before death
- In HIV infected patients, on many occasions microscopy may prove negative in spite of presence of bacilli, as only a few bacilli are expectorated