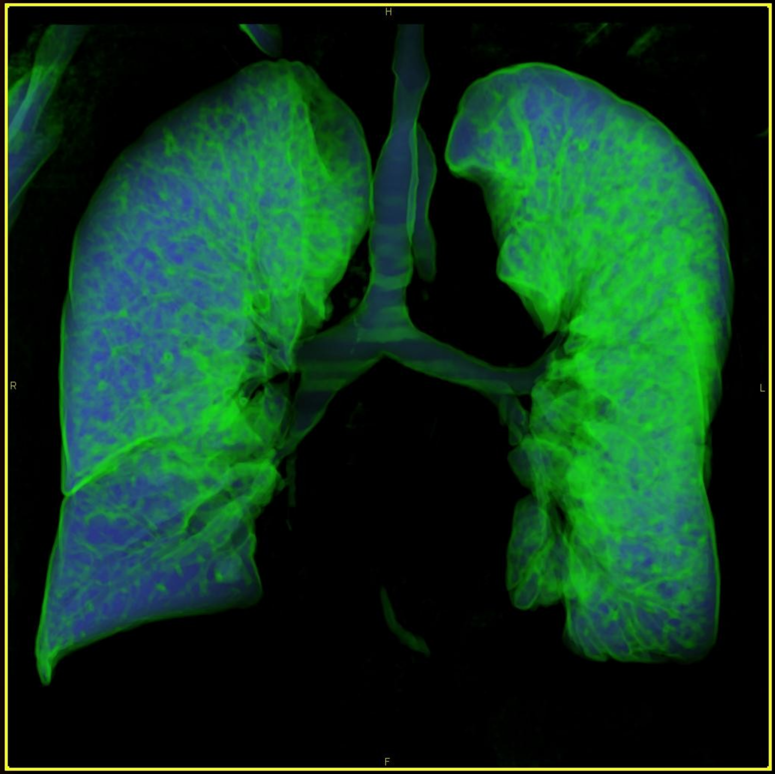


Artificial Lungs

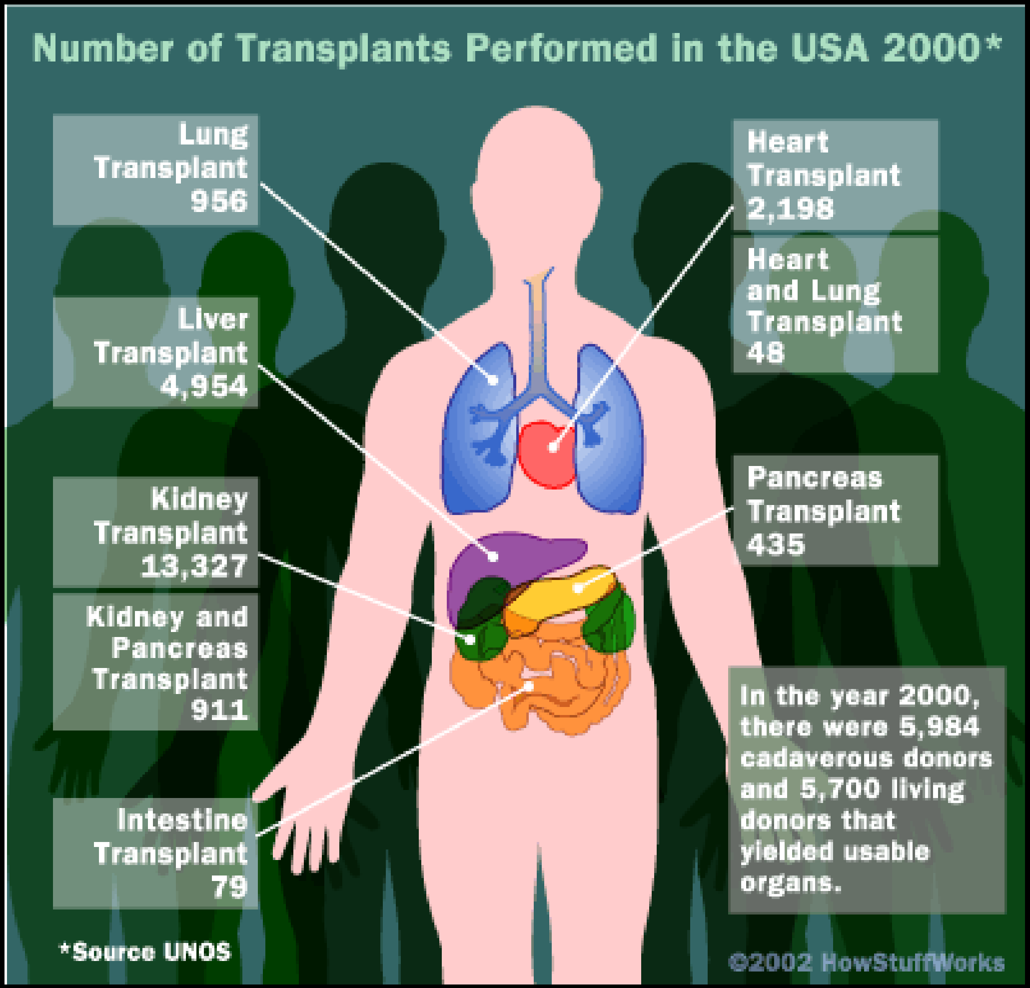
Or

"Breath Easy, We're Engineers"

Qasim Abbas

Brett Lindsay

Why Engineer Lungs?



Why Engineer Lungs?

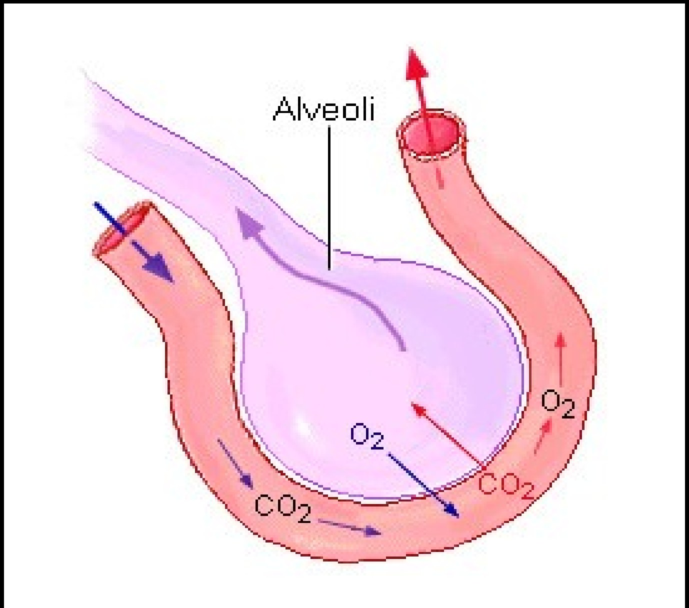
Two Main Reasons:

- The lungs have failed from disease or injury and a replacement required

- During open heart surgery, the cardiopulmonary system cannot be relied on, calling for a device to be used (Cardiopulmonary Bypass)

How Lungs Work – An Overview

- bring fresh Oxygen into the body
- remove unwanted gases from body



An animation of the process:

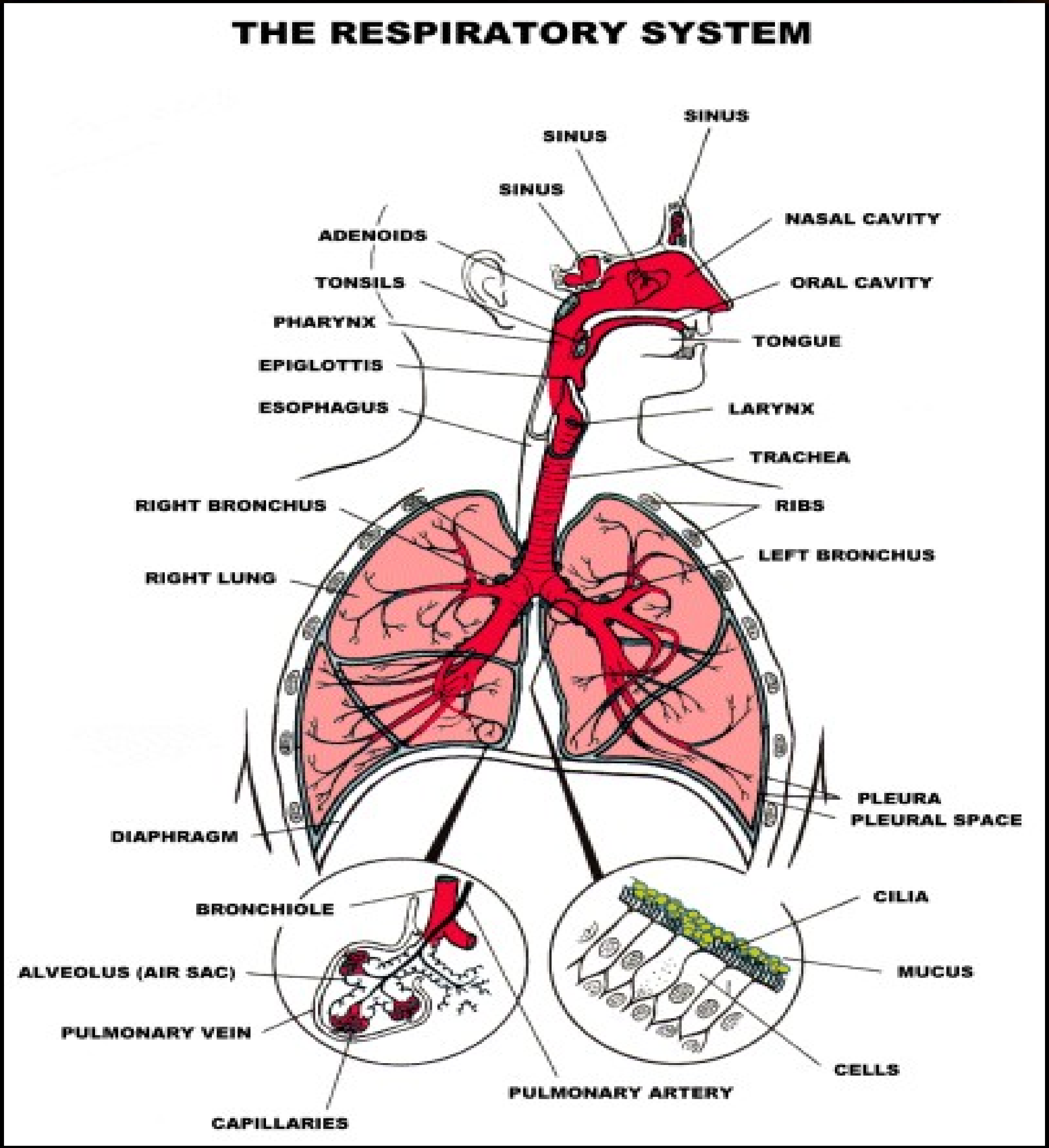
http://www.bmu.unimelb.edu.au/examples/gasxlung/

The Mechanism

- When we INHALE:
  - Diaphragm and Intercostal Muscles (between ribs) contract
  - Pressure inside chest cavity goes down (below external air pressure)
  - Air moves in, inflates lungs
- When we EXHALE:
  - Diaphragm and Intercostal Muscles (between ribs) relax
  - Pressure inside chest cavity increases (above external air pressure)
  - Air moves out
- Cycle repeats for each breath

Pathway of Air

- enters the body via mouth/nose
- goes past epiglottis, into trachea, through the larynx (containing vocal cords) and reaches the bronchi
- from the bronchi it travels through the bronchioles until it reaches the alveoli where the exchange occurs



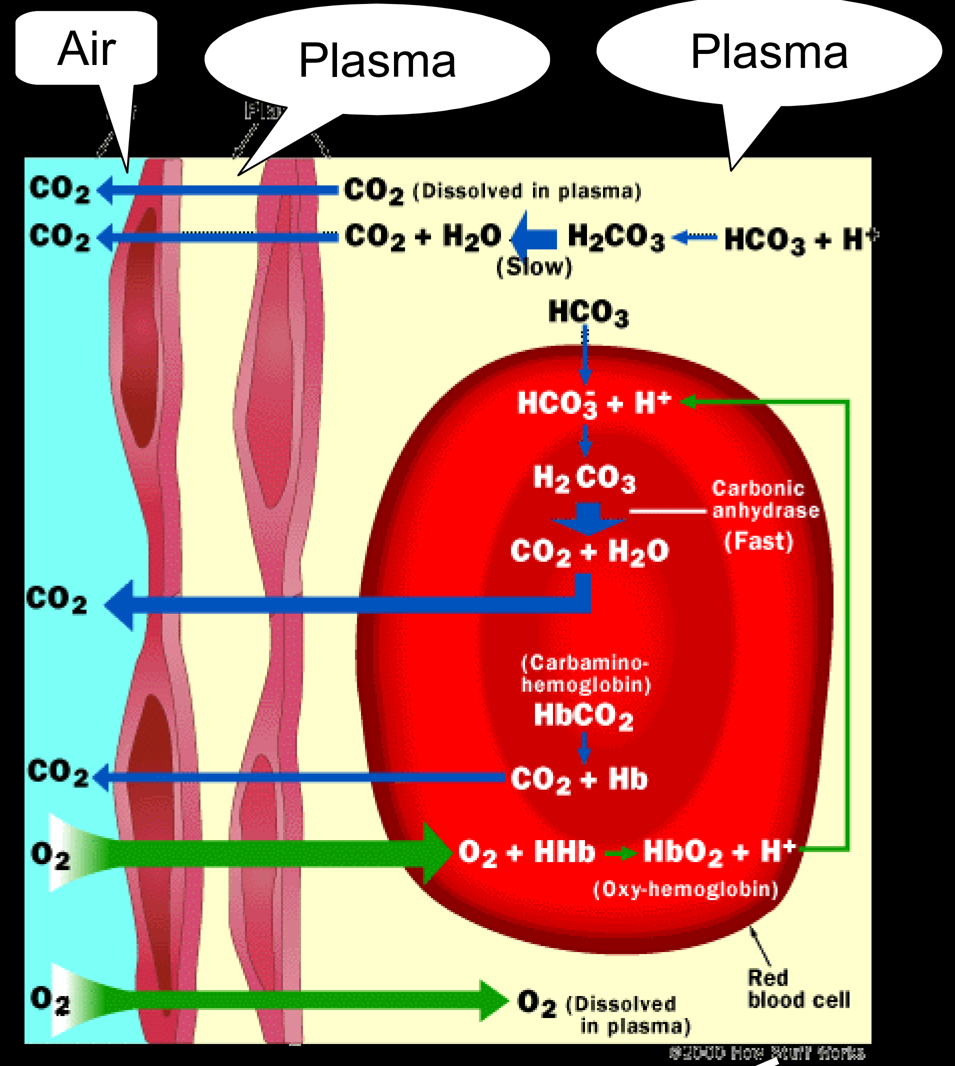
NOTE: See Appendix for details of each component of the respiratory system

Alveoli

- Alveolar sacs rich in O_2 ⟷ diffuses across the alveolar membrane into PC*
- Incoming hemoglobin molecules (into PC) - rich in CO_2 ⟷ leaves blood, enters alveolar air sacs
- Oxygen rich blood returns to heart

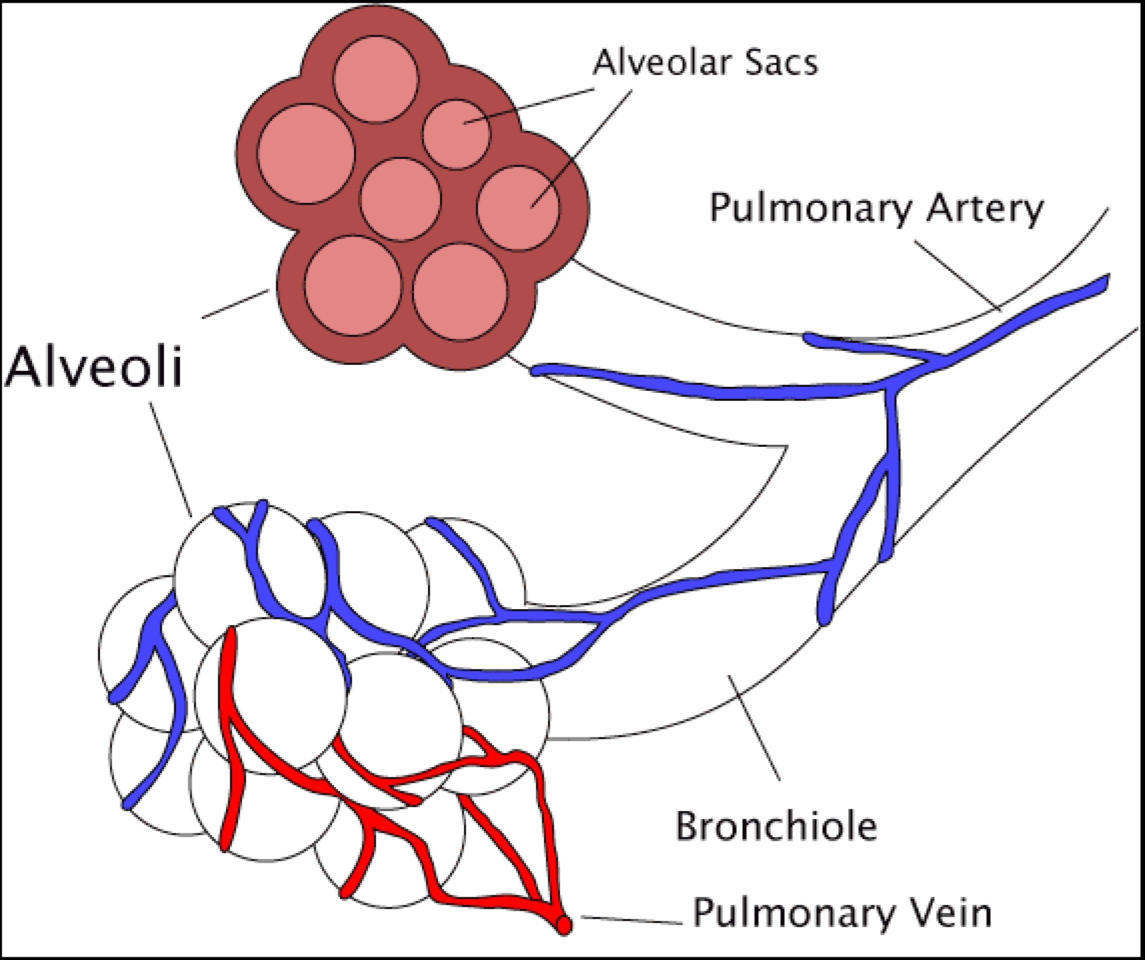
NOTES: O_2 attaches to hemoglobin, releasing CO_2.
This gas exchange occurs in fractions of a second.
* **PC** = Pulmonary Capillaries

Alveoli



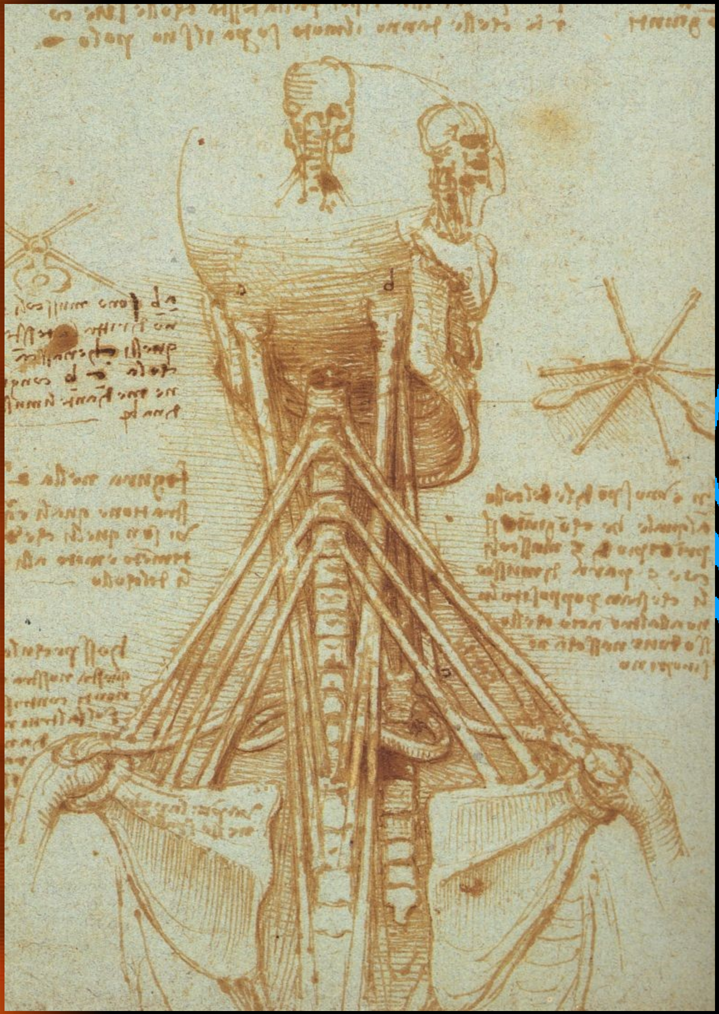
Air
Plasma
Plasma
CO_2
CO_2 (Dissolved in plasma)
CO_2
$CO_2 + H_2O$
(Slow)
H_2CO_3
$HCO_3 + H^+$
HCO_3
$HCO_3^- + H^+$
H_2CO_3
Carbonic anhydrase
(Fast)
$CO_2 + H_2O$
CO_2
(Carbamino-hemoglobin)
$HbCO_2$
CO_2
$CO_2 + Hb$
O_2
$O_2 + HHb$
$HbO_2 + H^+$
(Oxy-hemoglobin)
Red blood cell
O_2
O_2 (Dissolved in plasma)
©2000 How Stuff Works

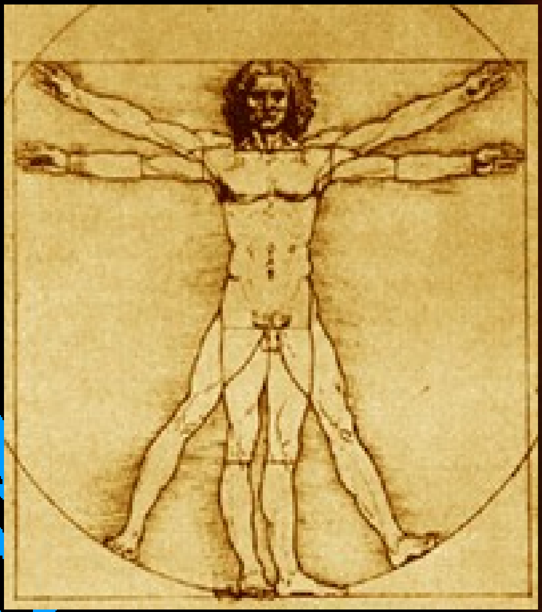
Alveoli



Alveolar Sacs
Pulmonary Artery
Alveoli
Bronchiole
Pulmonary Vein

A HISTORY LESSON



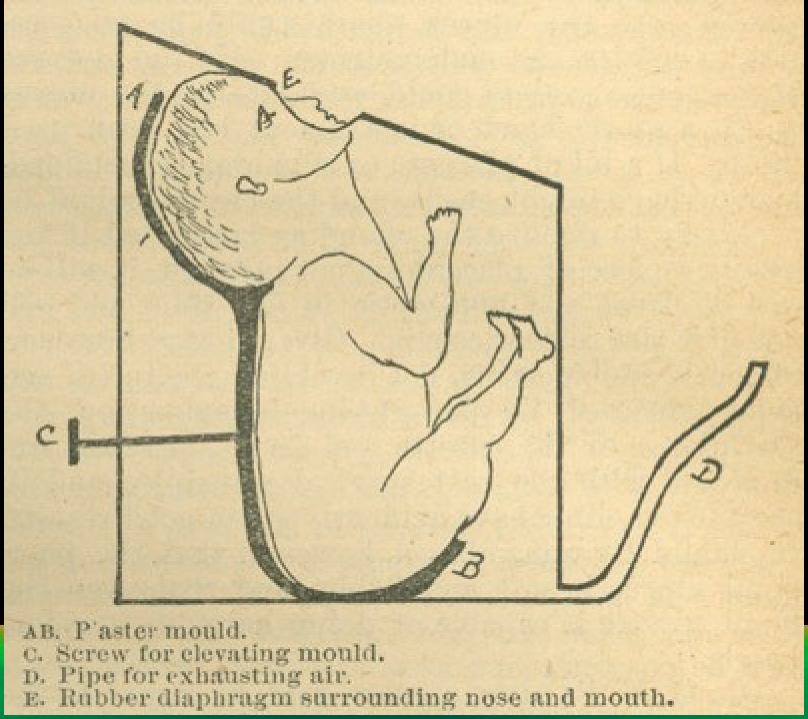


A STROLL DOWN MEMORY LANE...

Some History ...

Artificial respiration techniques have been around for centuries:

- 1782: Bellows considered the best means for artificial respiration for over 40 years
- 1889: Infant resuscitator developed by Dr. Egon Braun



Some History ...

Problem with previous machines: No automation or regulation system

- 1918: Dr W. Steuart built a wooden sealed box operated by variable-speed, motor-driven bellows for artificial respiration
- 1919: Ventilation machine using electric pumps for rhythmic pressure variation tested on dog by physiologists, F. Chillingsworth and R. Hopkins
- 1926-1927: Dr K. Drinker and team developed an iron box (Iron Lung) with controllable pressure
  - artificial resuscitation test on cat successful
  - 1929: first successful use on human

Earliest Biomedical Engineering Example:
THE IRON LUNG

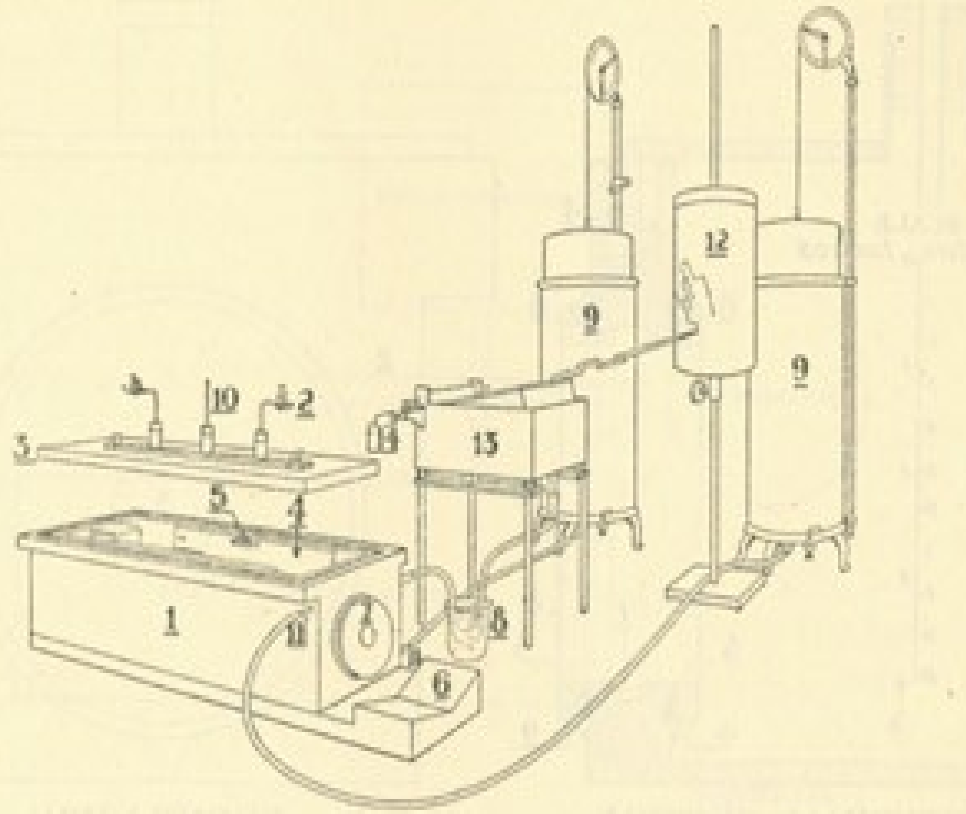
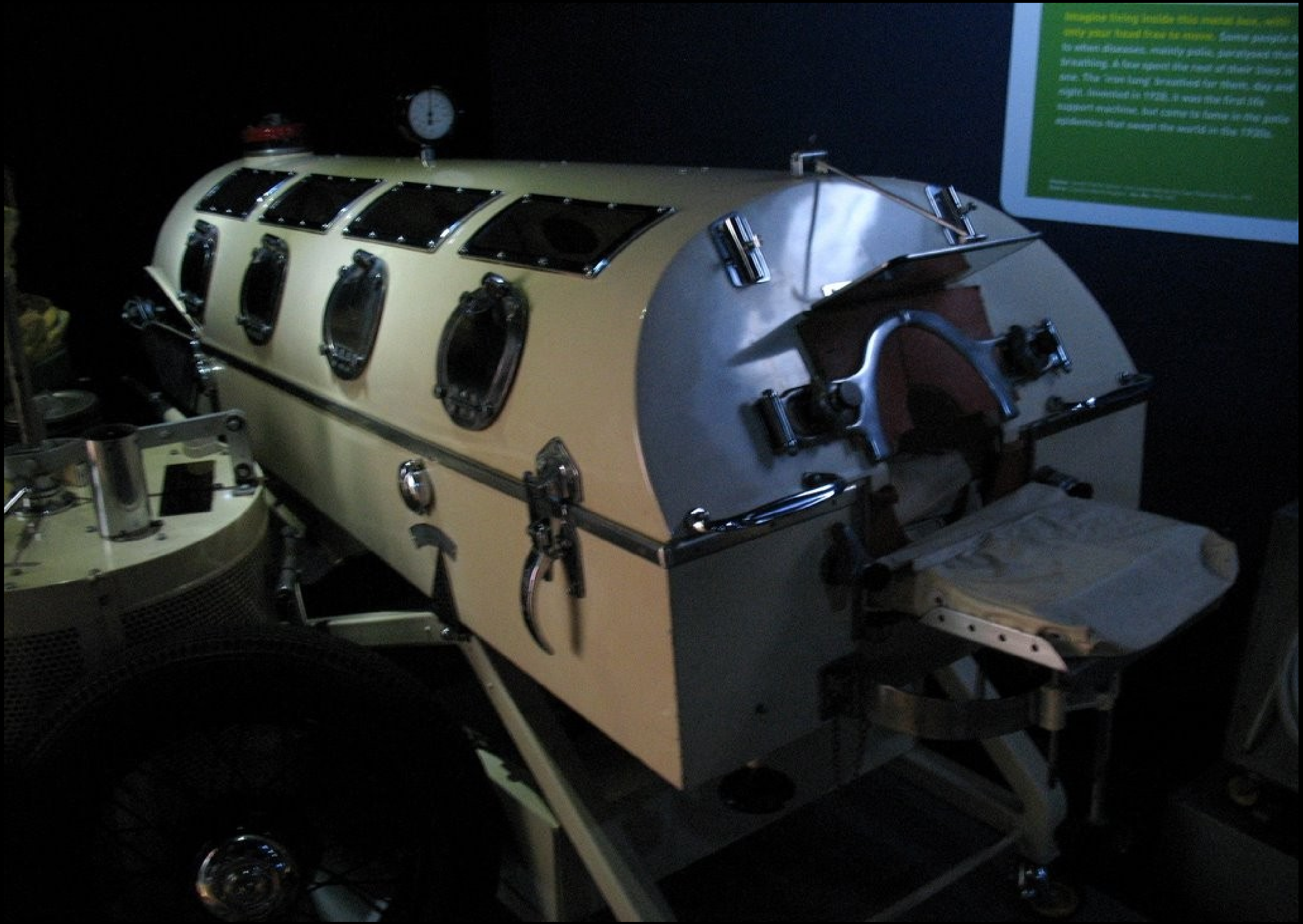
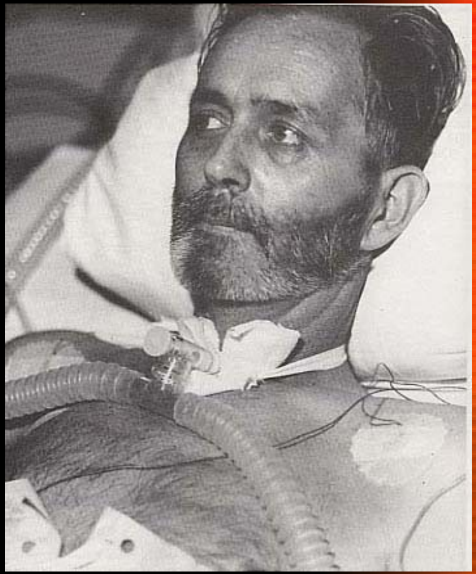


Fig. 1. Apparatus for determining cutaneous respiration. *1*, plethysmograph; *2*, gas sampling tube; *3*, cover; *4*, blocks to reduce space; *5*, cleats; *6*, head rest; *7*, head aperture; *8*, condensation chamber; *9*, mixing spirometer; *10*, thermometer; *11*, tubes entering gas seal; *12*, kymograph; *13*, Krogh spirometer; *14*, counterbalancing pin.

THE NEWER IRON LUNG



MECHANICAL VENTILATION is all good but ...



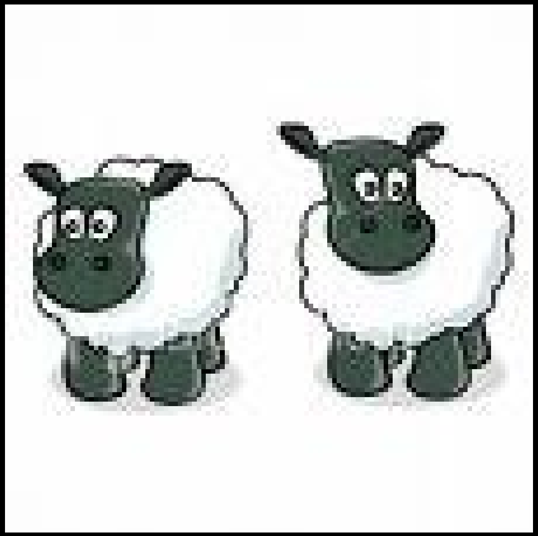
PROBLEMS!

- Inflating/Deflating Of lungs:
  - unwanted movement in some surgeries
  - May cause tearing ⟷ lungs scarred!
- Patients bed ridden, cannot speak (tracheostomy tube), must remain in ICU ⟷ increased chance of communicating a disease.

Waiting for a transplant: Ventilators vs. Paracorporeal Artificial Lungs in cases of extreme lung damage.

Test: Fourteen sheep were exposed to lethal amounts of smoke inhalation (80-100% smoke/burn = acute respiratory distress syndrome).

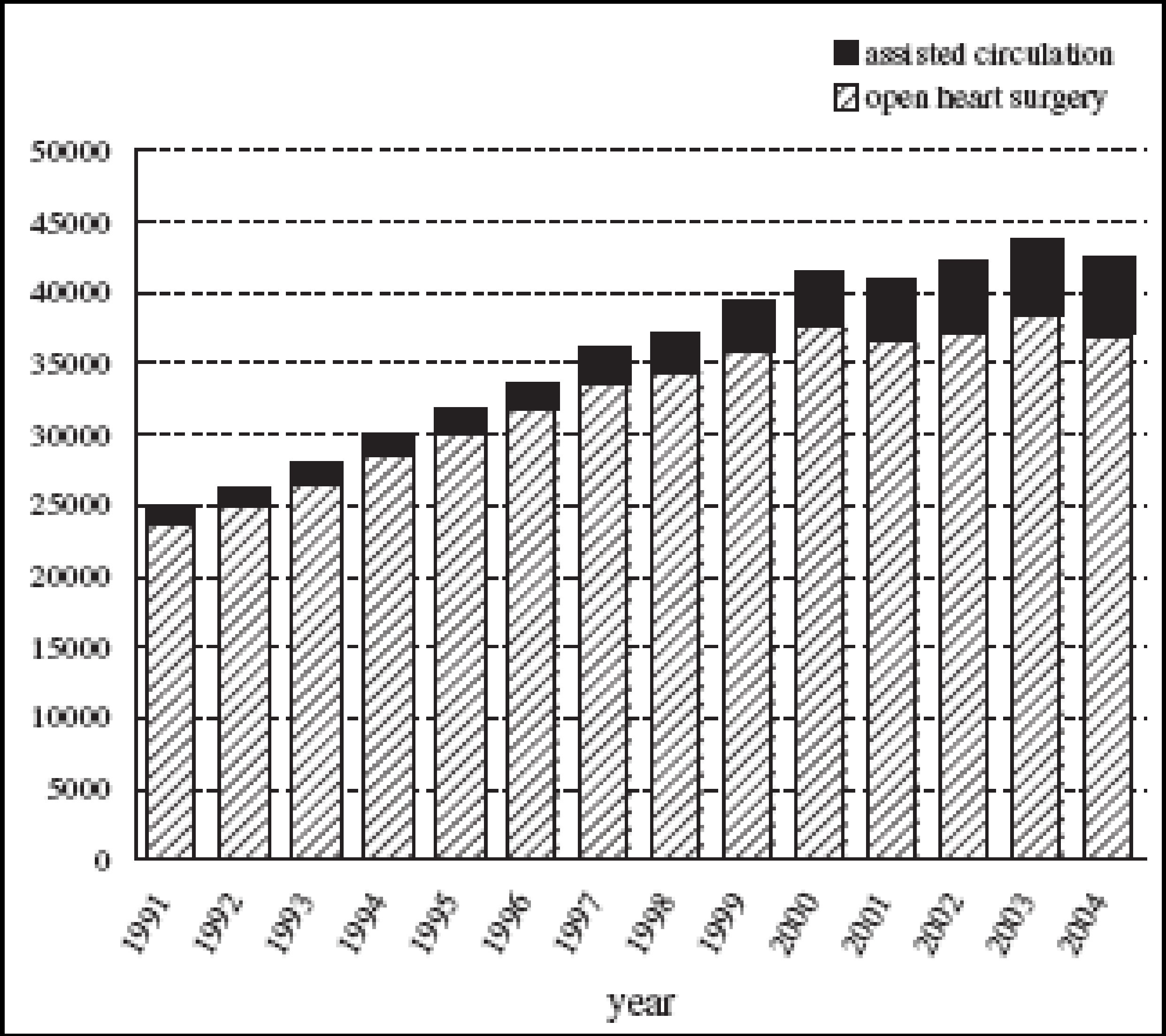
Eight were attached to a PAL, six to a Ventilator.



Results: At the end of the five day study, six of the eight sheep (75%) on a PAL were still alive, vs. one of six (16%) sheep on a ventilator.

After 48 hrs, the PaO_2 (partial pressure) and FiO_2 (fraction of inspired) returned to normal levels, while the measurements for ventilation continued to meet the criteria for Acute Respiratory Distress Syndrome.

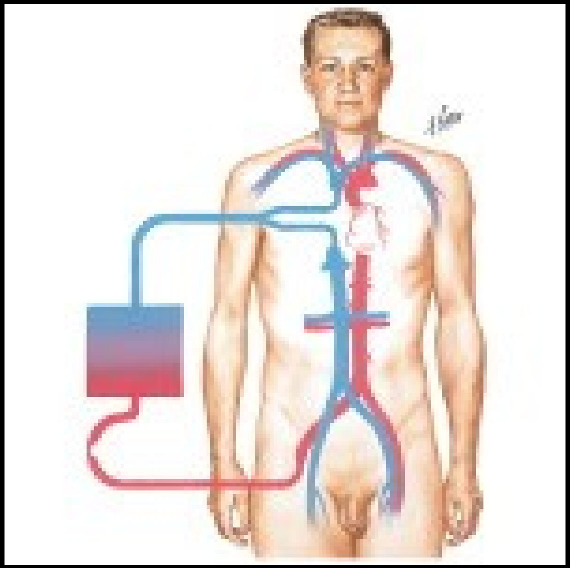
Conclusion: In many lung injuries/diseases mechanical ventilation is insufficient or disadvantageous.



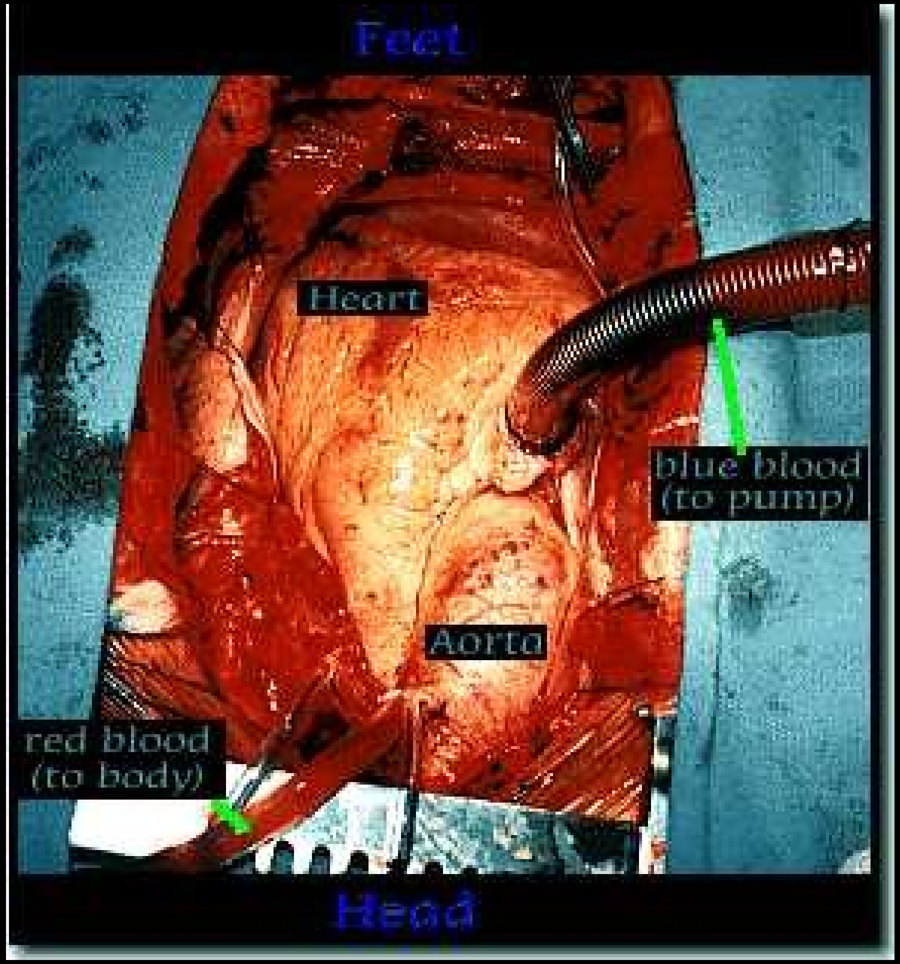
Annual shipment of artificial lungs in Japan.

Cardiopulmonary Bypass

In order to do surgery on the heart, you need it to remain steady.



Paralyze the heart, and route the blood through an external device.


Feet
Heart
blue blood
(to pump)
Aorta
red blood
(to body)
Head

Three parts to device:

A circuit which delivers a cardioplegia inducing agent to the heart.

- stops heart from beating without tissue death.

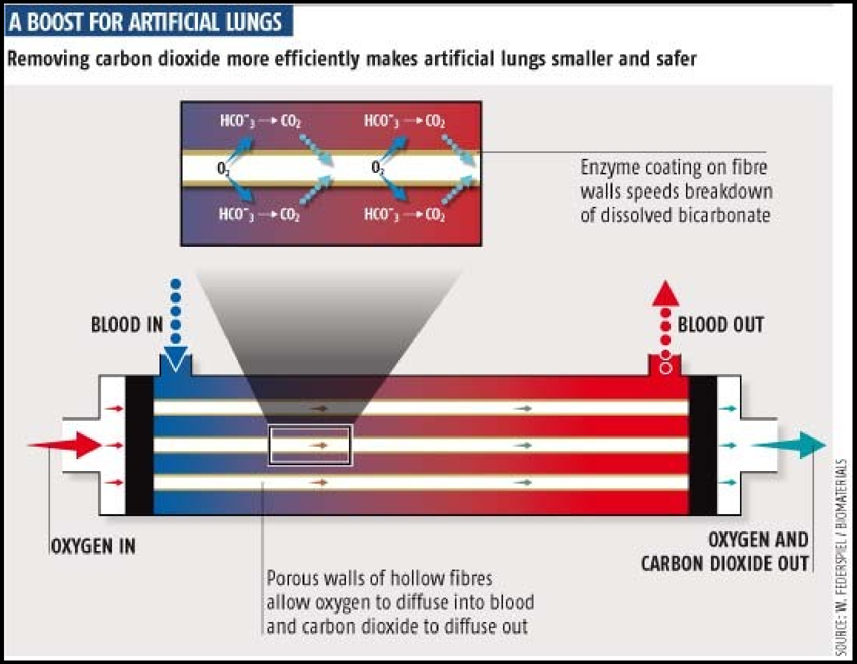
Pump to keep blood flowing throughout the body.

Oxygenator or "Artificial Lung" to remove CO_2 from the blood, and add necessary O_2.

Artificial Lungs

Bubble Oxygenators

Membrane Oxygenators



Bubble Oxygenators

Invented in the mid 50s (not used as much now).

Deoxygenated blood enters the device.

Oxygen is bubbled out through needles.

[Aquarium.]

Oxygen diffuses from the bubbles into the blood film, and vice versa for CO_2.

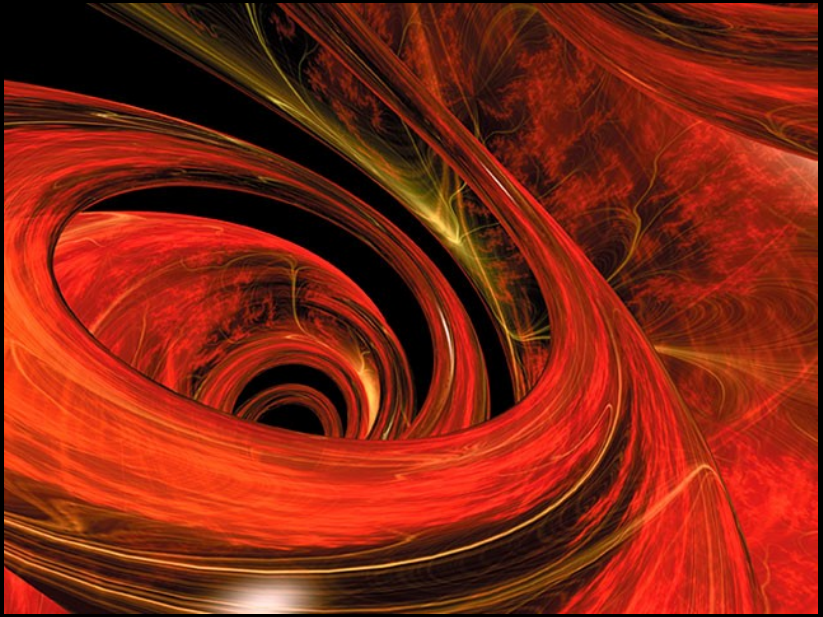
Byproduct: tends to denature proteins.

There is a gas outlet at the top of the device.

The gas exchange needs to be followed by a defoaming stage.

Polyurethane mesh sponge coated with silicone.

Finally an arterial reservoir designed to return blood to the body without any vortexing.



Membrane Oxygenators

Basic idea is to copy the way O_2/CO_2 exchange happens in the lungs: across a barrier which allows gases to pass, but not things like red blood cells.

Oxygenators can utilize supplied O_2 as opposed to air intake.

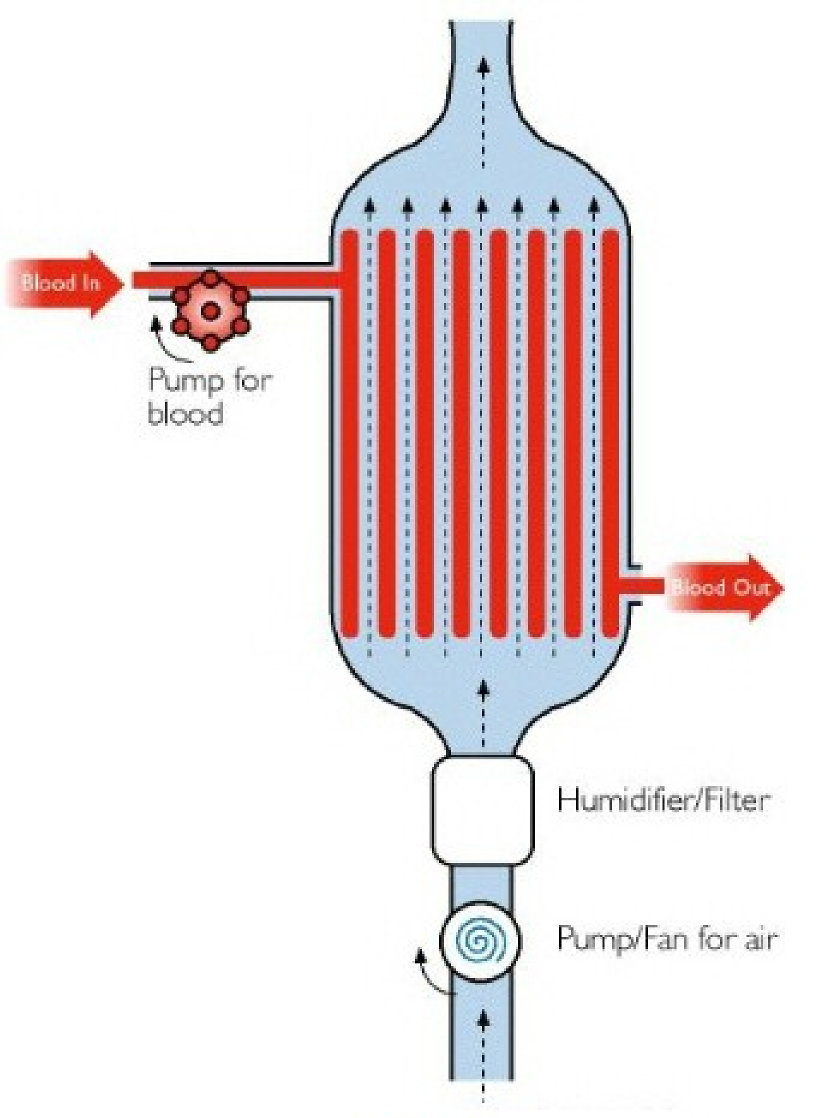
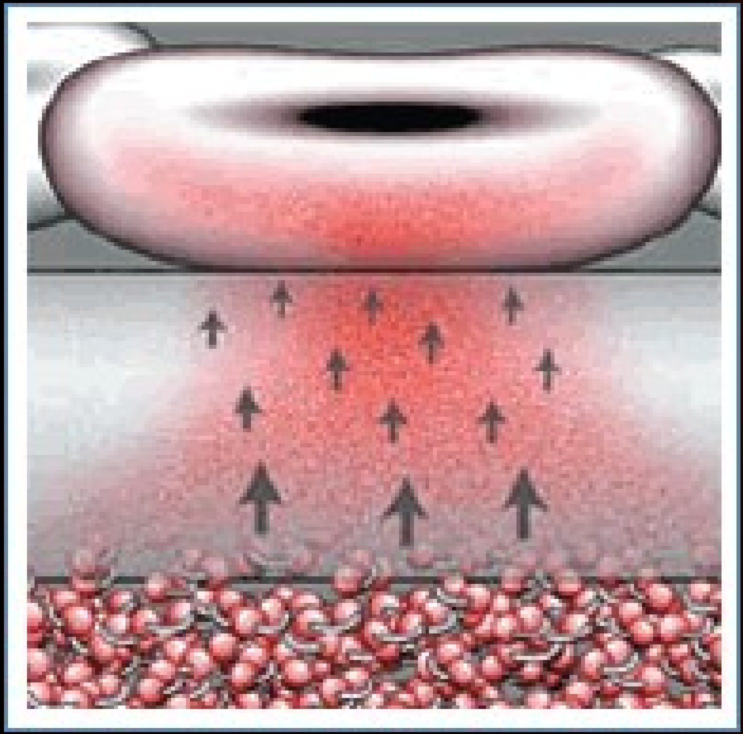


Figure 2

Semi-Permeable Membrane

Made of a reinforced silicone (other possibilities).

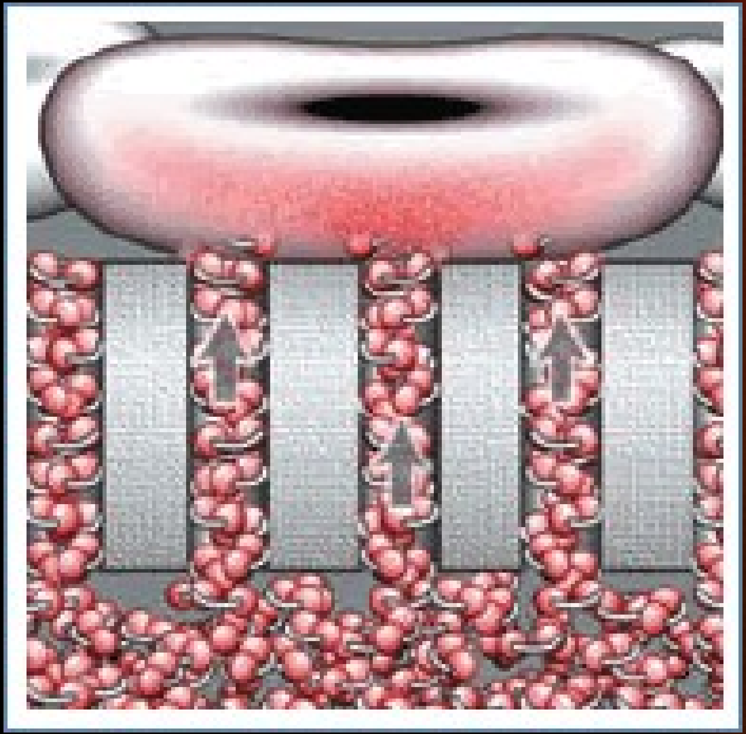
No direct blood/gas contact.

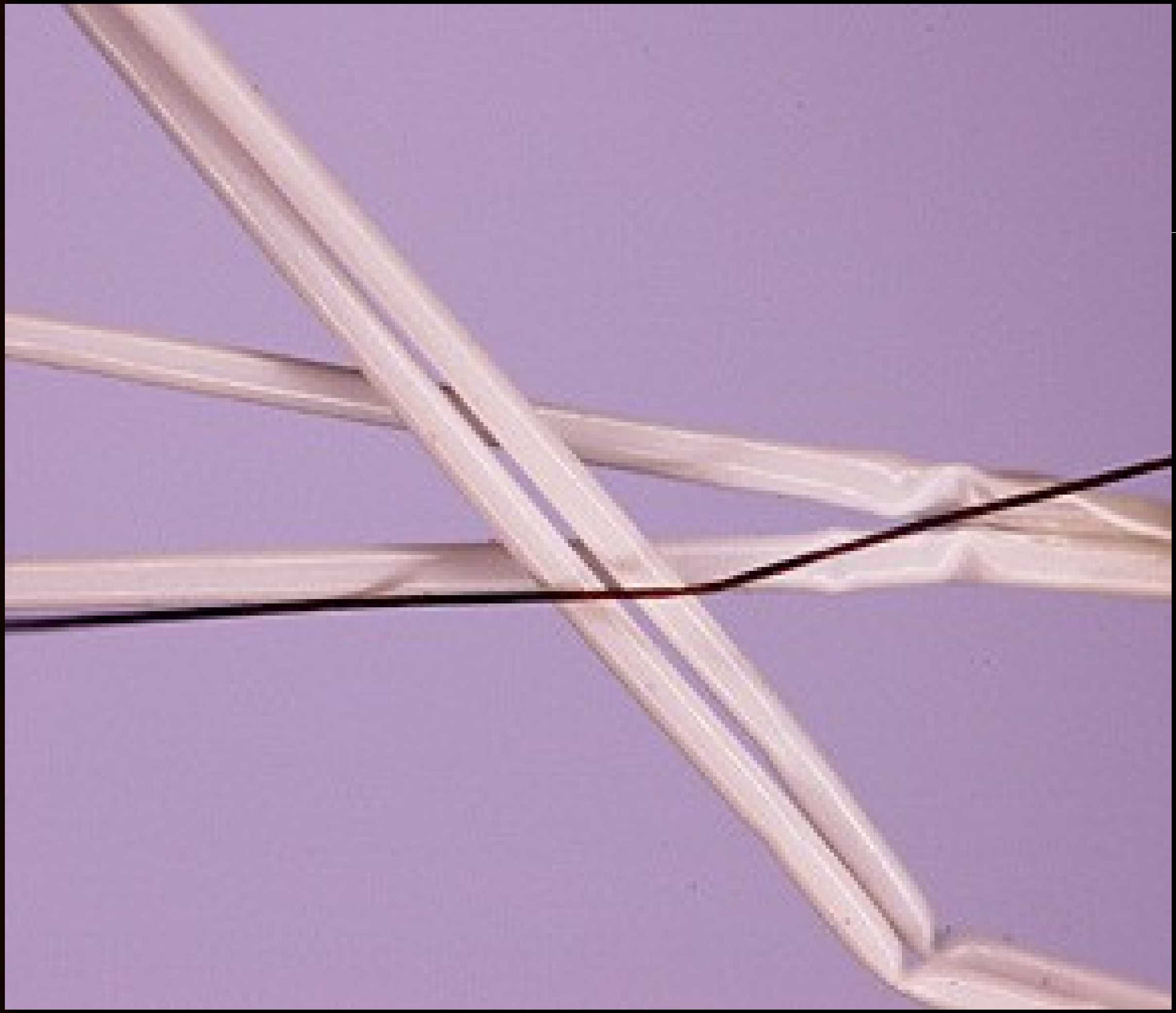


- Physiologically inert
- Thromboresistant (blood clotting).
- Non-toxic/Biocompatible
- Electrochemically identical to the normal capillary
- Effective gas transfer characteristics

Micro-Porous Membrane

- Most common.
- Various materials, eg.:
  polypropylene
  poly-4-methylpentene-1
- Direct blood/gas contact.
- Pore sizes can be under 0.03 microns (diameter). Red Blood Cell: 7 microns.



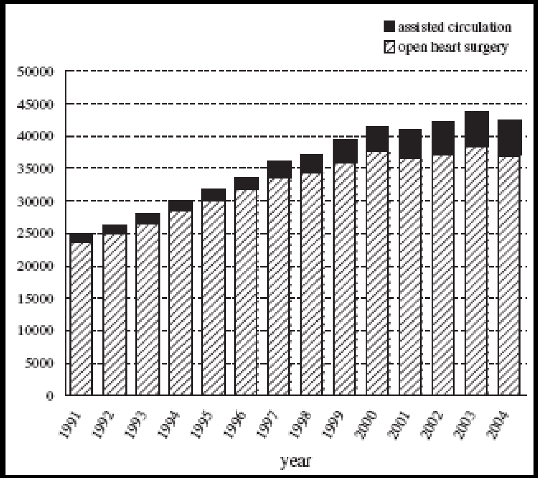


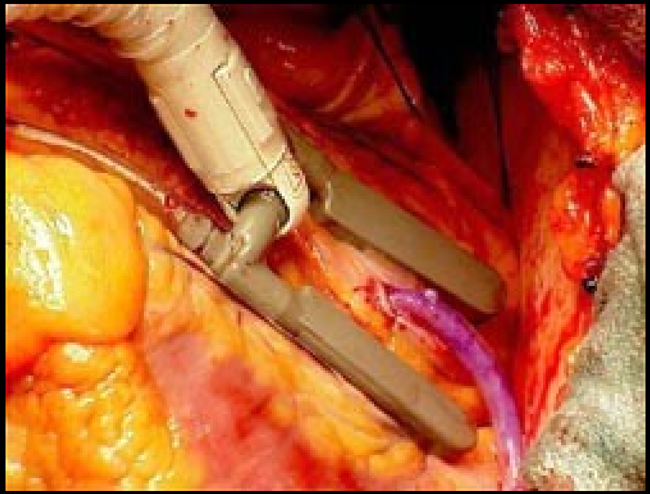
Oxygenator fibres from a Welsh AL prototype set beside a human hair.

Roughly 10,000 fibres in an artificial lung

Cardiopulmonary Bypass falling out of favour.

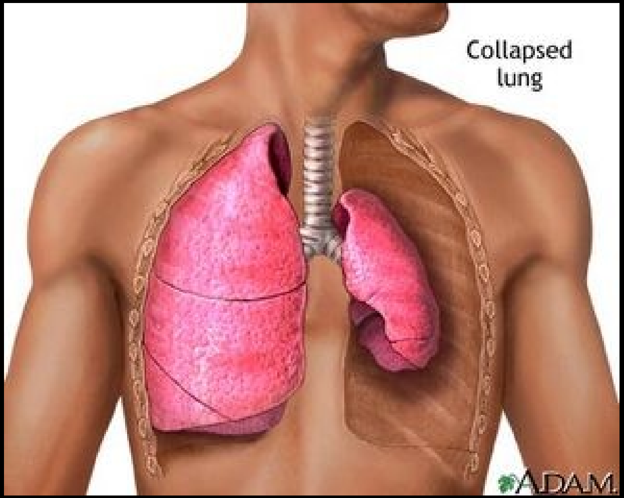
Replaced by Off Pump Coronary Artery Bypass Grafting, which allows the heart and lungs to function normally while the part being worked on is stabilized by a device.



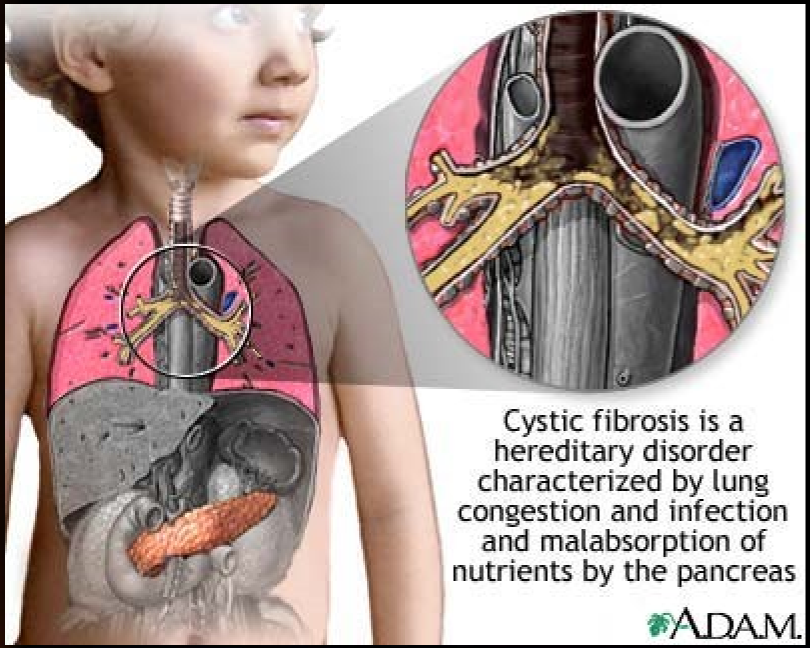


On the other hand, the miniaturization and increased efficiency of artificial lungs is creating a growing trend in assisted circulation.

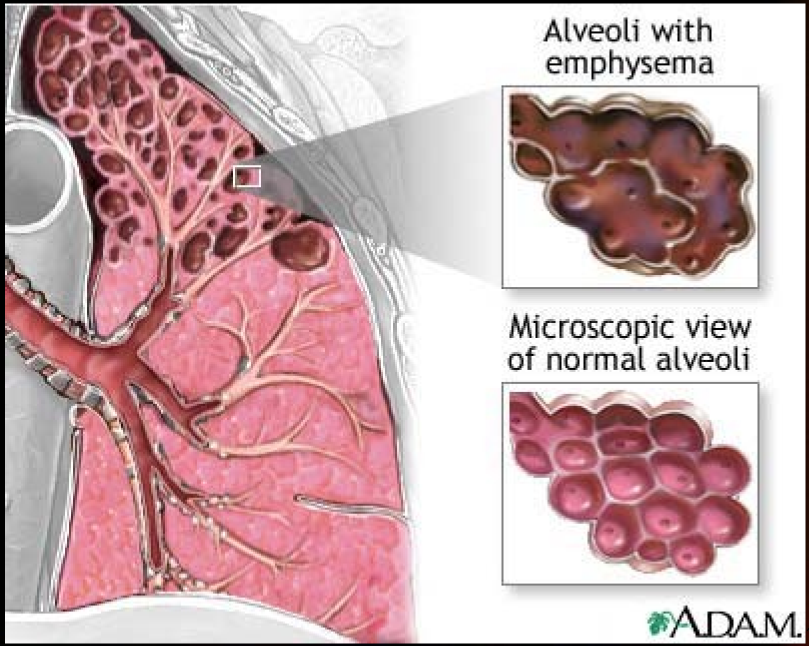
What if...



Collapsed lung
A.D.A.M.

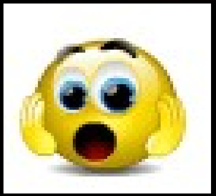


Cystic fibrosis is a hereditary disorder characterized by lung congestion and infection and malabsorption of nutrients by the pancreas
A.D.A.M.



Alveoli with emphysema
Microscopic view of normal alveoli
A.D.A.M.

When Lungs Fail!!



Diseases fall into two categories:

- Mechanics of Breathing
- Gas Exchange

When Lungs Fail!!

Diseases fall into two categories:

- Mechanics of Breathing (air flow restricted)
  - Asthma: airways constrict, size reduced
  - Emphysema: lung elasticity reduced (more fibers)
  - Bronchitis: narrower, inflamed airways
  - Pneumothorax: Lungs collapse, air pressure in pleural cavity becomes equal to that outside
  - Apnea: breathing stops/slows – usually due to problems in brain's respiratory centres
- Gas Exchange

When Lungs Fail!!

Diseases fall into two categories:

- Mechanics of Breathing
- Gas Exchange (O_2 delivery reduced)
  - Pulmonary edema: fluid between PC and Alveoli builds up, distance for exchange increases
  - Smoke inhalation: particles coat alveoli
  - Carbon Monoxide poisoning: CO binds tightly to hemoglobin than either CO_2 or O_2

When Lungs Fail!! 

Severe cases, lung transplants recommended:

- Emphysema (described earlier)
- Cystic Fibrosis: thick/sticky mucus builds up in lungs (and digestive tract)
- Sarcoidosis: abnormal inflammation of organs including lungs
- Idiopathic Pulmonary Fibrosis: scarring/thickening of tissues deep within lungs
- ... and the list goes on

Advances Not So Long Ago...

- 1983 – first successful single lung transplant
- 1986 – first successful double lung transplant
- 1988 – introduced as a treatment option for cystic fibrosis patients

Where? TORONTO!!!

For details, visit:

- http://www.torontotransplant.org/patients/lungs.cfm


Original Question:

If we can get donations of lungs, why engineer them?

The following might convince you...

ISSUES AT HAND:

- Lung Transplant requires donors
- Donor pool is limited
- Criteria for matching donors is strict (health, size age, blood type, etc)
- Recipient criteria (no smoking/drug/alcohol, no chronic medical condition, financial status, age)
- Due to the requirement of ongoing care in the ICU and limited room for patients, the waiting lines are long – often up to 2 years

ISSUES AT HAND:

- Survival rates:
  - 80% at year 1 and 60% at 4 years
- The transplanted organ is considered an invader for the rest of life
  - Anti-rejection drugs required to suppress immune system ⟷ weakens immune system over time
- Donated lungs usually taken from living people – may cause financial problems for them, but mortality rate is less than 0.5% - 1%

ISSUES AT HAND:

In 2005, 3500 patients were on the US waiting list for a lung transplant.

Only 1000 received said transplant.

People can wait on the list for several years.

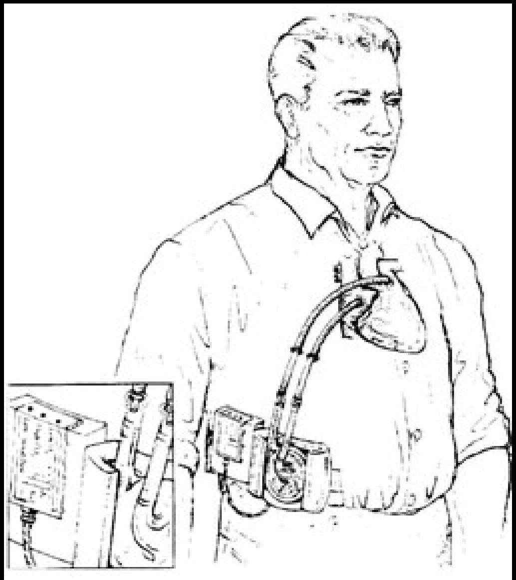
In 2004, 533 people died before a donor could be found.

Lung Disease is third most frequent cause of death in Europe and USA, yet it doesn't get as much attention as heart disease or cancer.

http://www.webmd.com/video/artificial-portable-lung

By developing portable temporary artificial lungs, capable of being worn on a belt, we can greatly improve the quality of life for people awaiting lung transplants.

It will also allow patients to maintain their strength, an important factor in successful surgery.



TAKING STEPS TO INCREASE EFFICIENCY

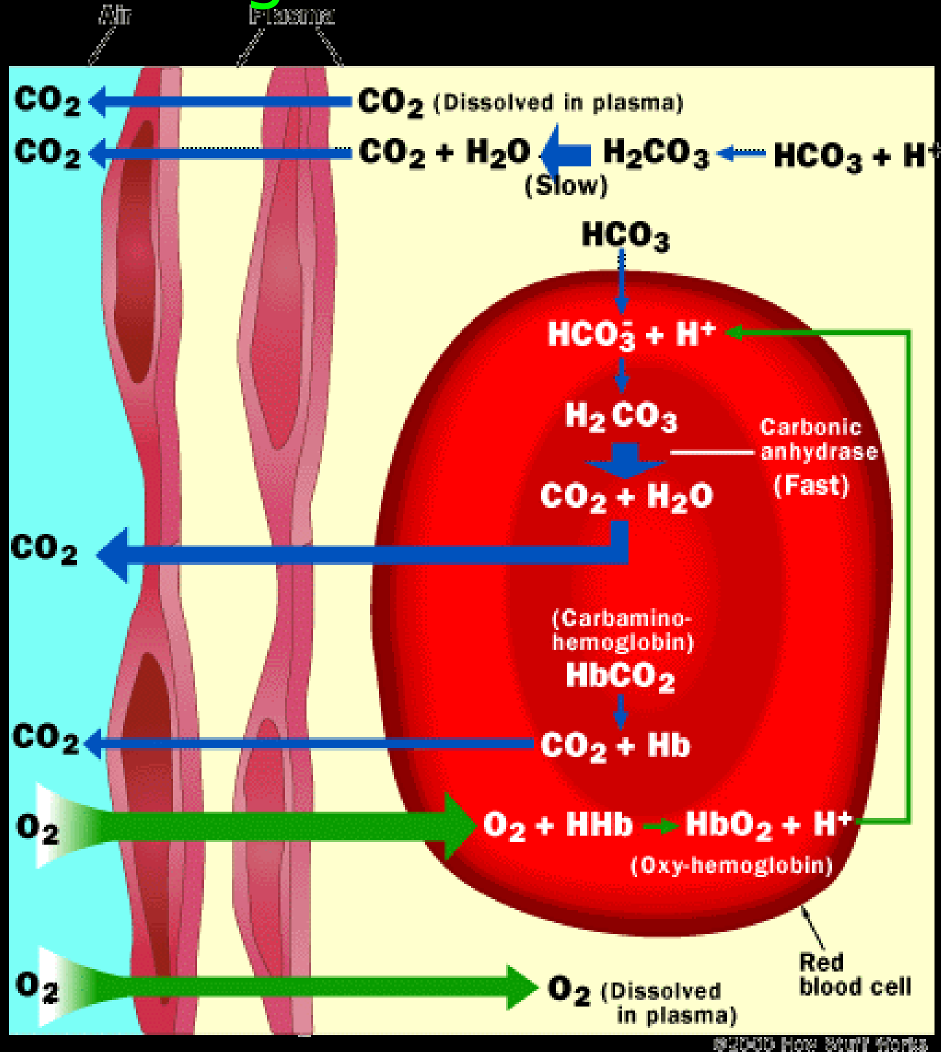
SOME PROBLEMS AND THEIR SOLUTIONS...

CO_2 in Blood

Earlier, we showed you this image.

Four pathways for CO_2 expulsion.

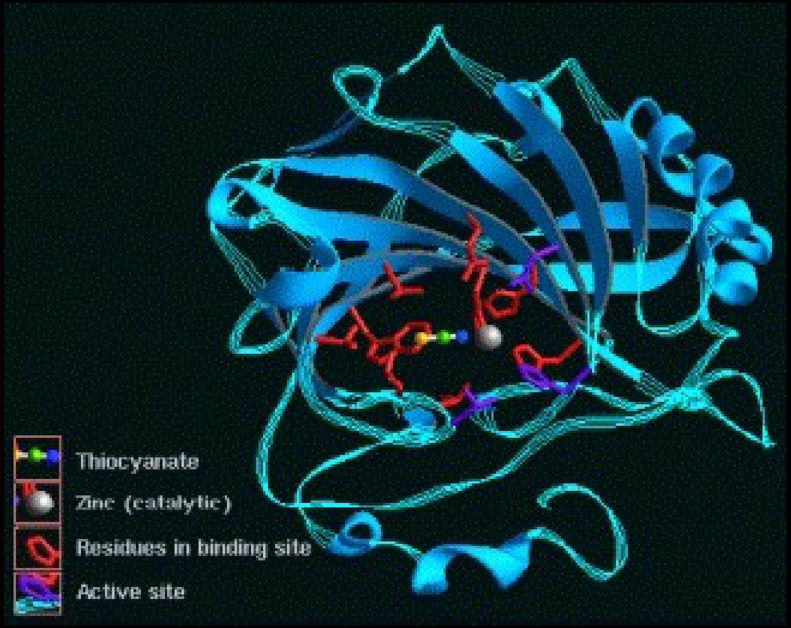
Three of those pathways involve the breakdown of bicarbonate.



CO_2 in Blood

PROBLEM!

90% of CO_2 in the blood is in the form of bicarbonate!

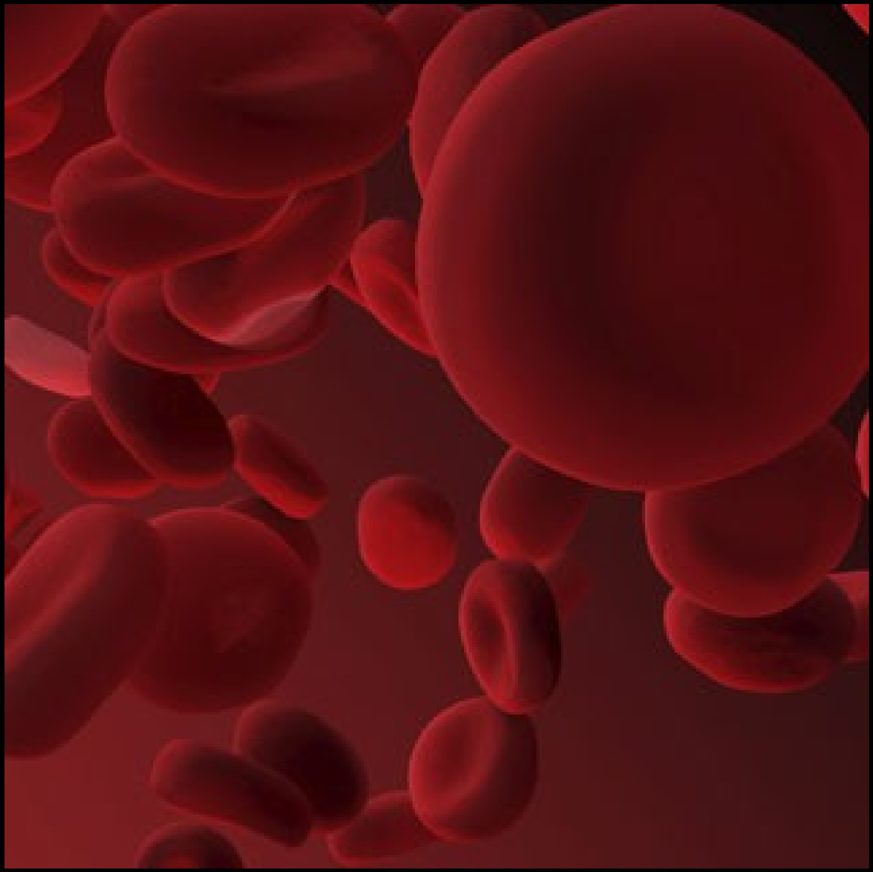


Carbonic Anhydrase is the enzyme in red blood cells responsible for breaking the majority of HCO_3 into CO_2.

CO_2 in Blood

Because most CO_2 is produced at the site of exchange by red blood cells, artificial lungs require very large volumes of blood to be passing through them at any given time.

William Federspiel of the University of Pittsburgh has experimented with coating the oxygenator fibres with Carbonic Anhydrase.



CO_2 in Blood

Early tests:

Flowing bicarbonate solution over coated vs uncoated oxygenator fibres.

Result:

75% increase in rate of CO_2 uptake in coated fibres.

Later tests on blood also proved beneficial.

This will allow for a lower rate of blood flow through the artificial lung.

Blood through the device ...

Blood is passing through a complex alien environment for long periods.

PROBLEM!

Coagulation and other Immune Responses

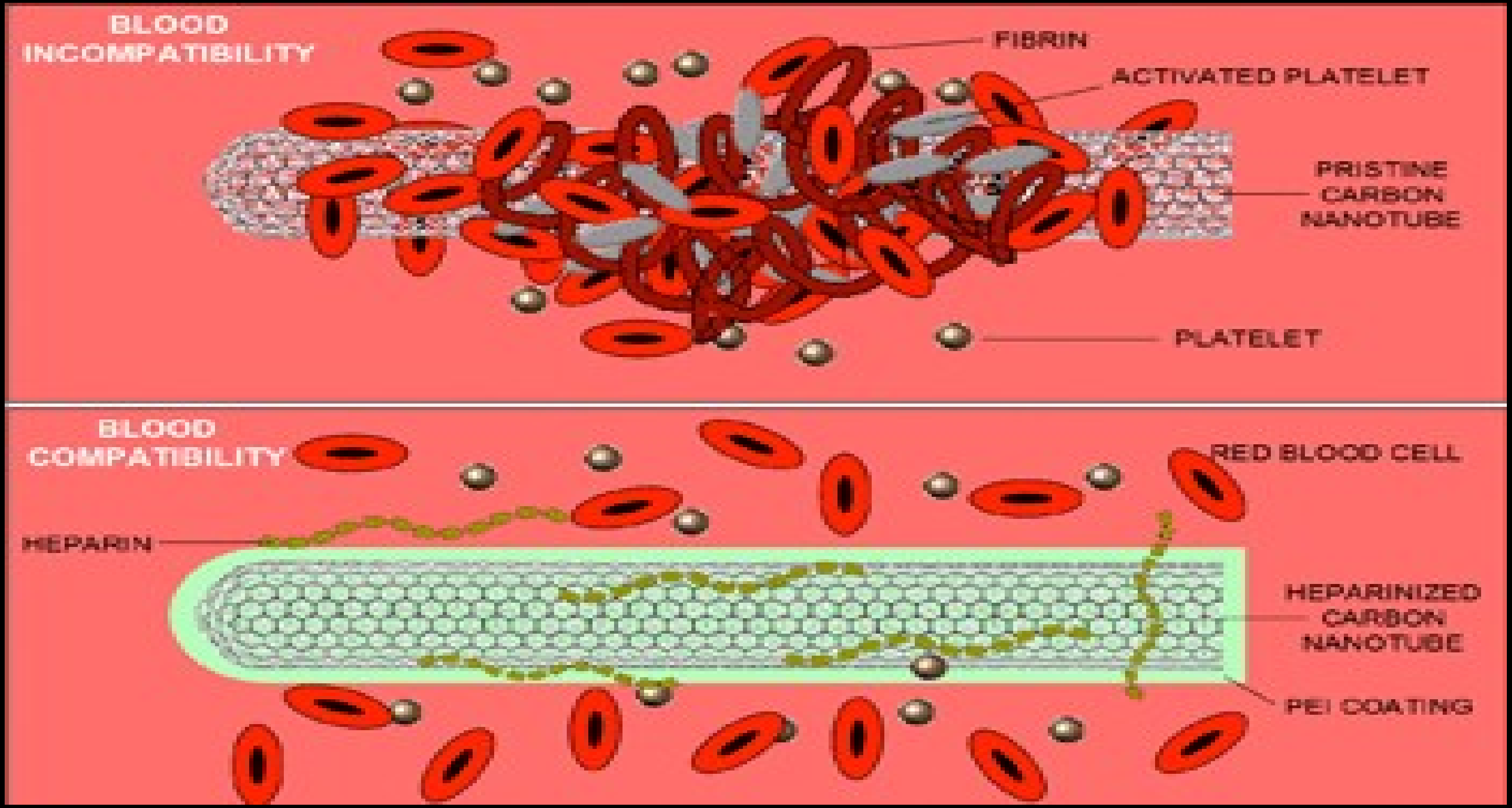
PROBLEM!

Blood thinners are problematic long term.

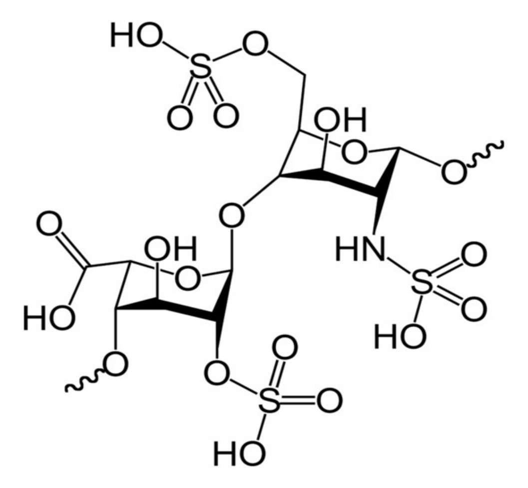
Solution: hemocompatible coatings.

Heparin

- Most commonly used to avoid compatibility issues



Heparin



Discovered in 1916.

Widely used anticoagulant.

Made from mucus membranes in pig intestine and cow lung.

Increases activity of the enzyme inhibitor Antithrombin → inactivates Thrombin, Factor Xa, and various coagulating proteases.

Heparin

Side effects:

1) Heparin-Induced Thrombocytopenia

Platelets under immunological attack.

2) Elevated Aminotransferase Levels

Removes amino groups from amino acids.

3) Hyperkalemia

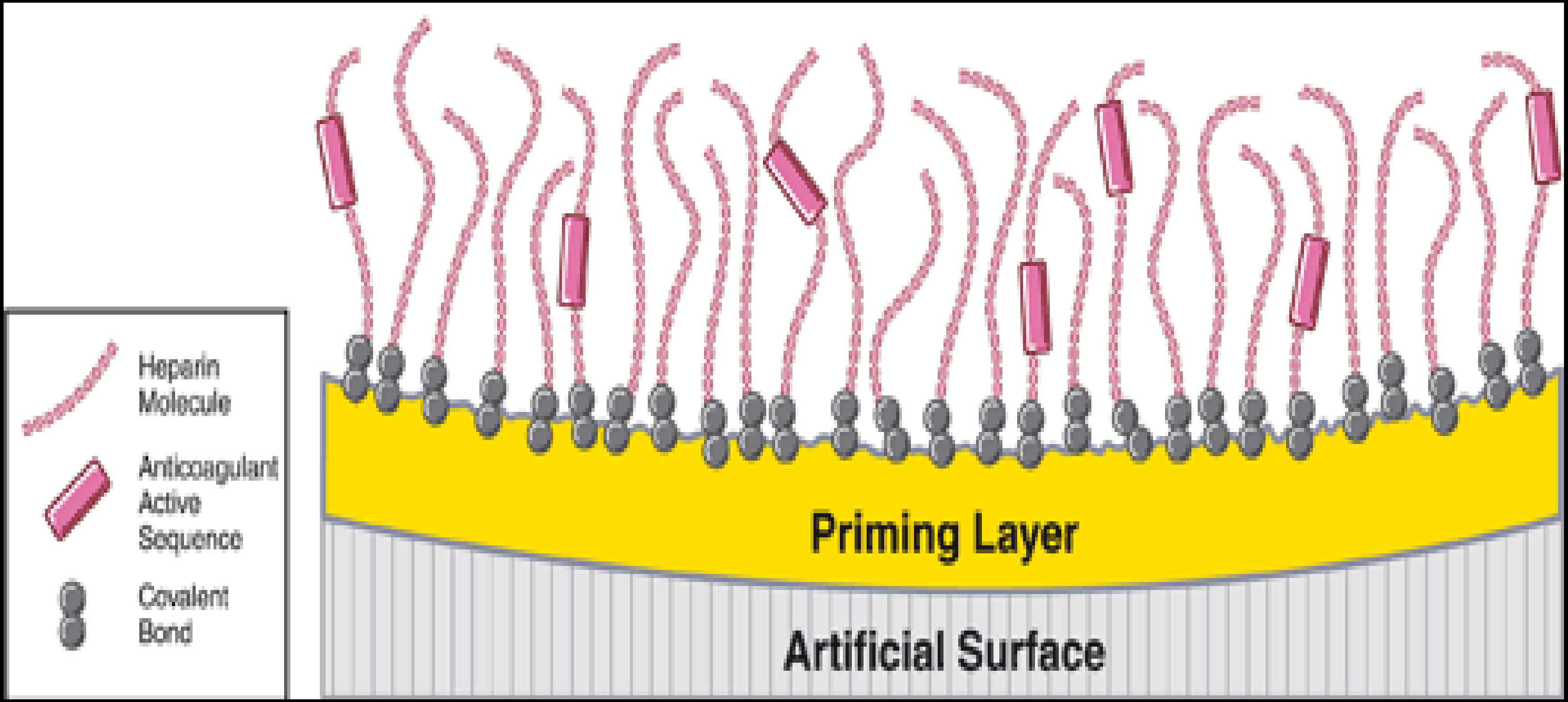
Increased Potassium ions in the blood.

Alleviated by end of Heparin use.

Heparin

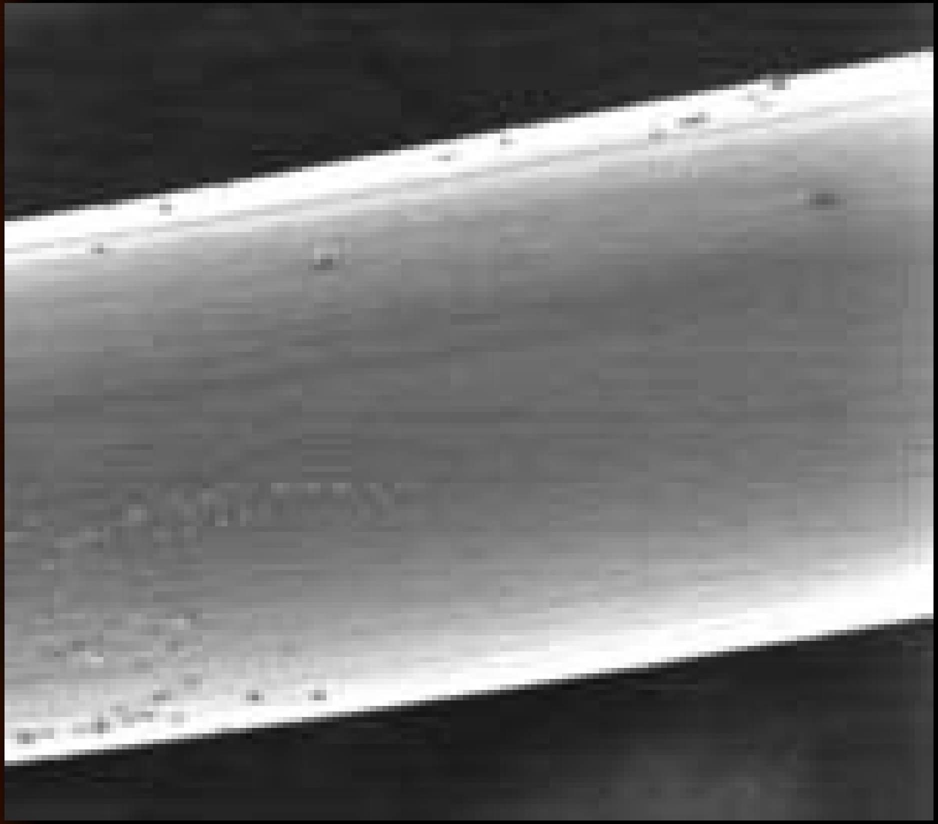
By coating devices, one largely localizes effects.

Trade secrets further reduce problems.

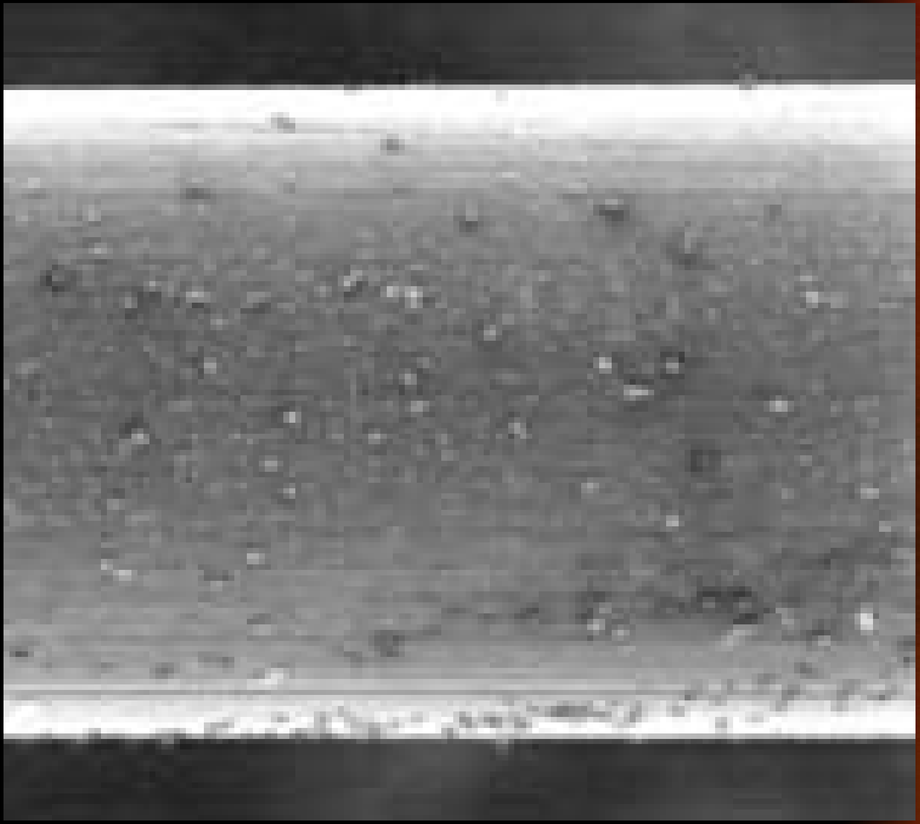


Carmeda® BioActive Surface

Heparin



Carmeda® coated



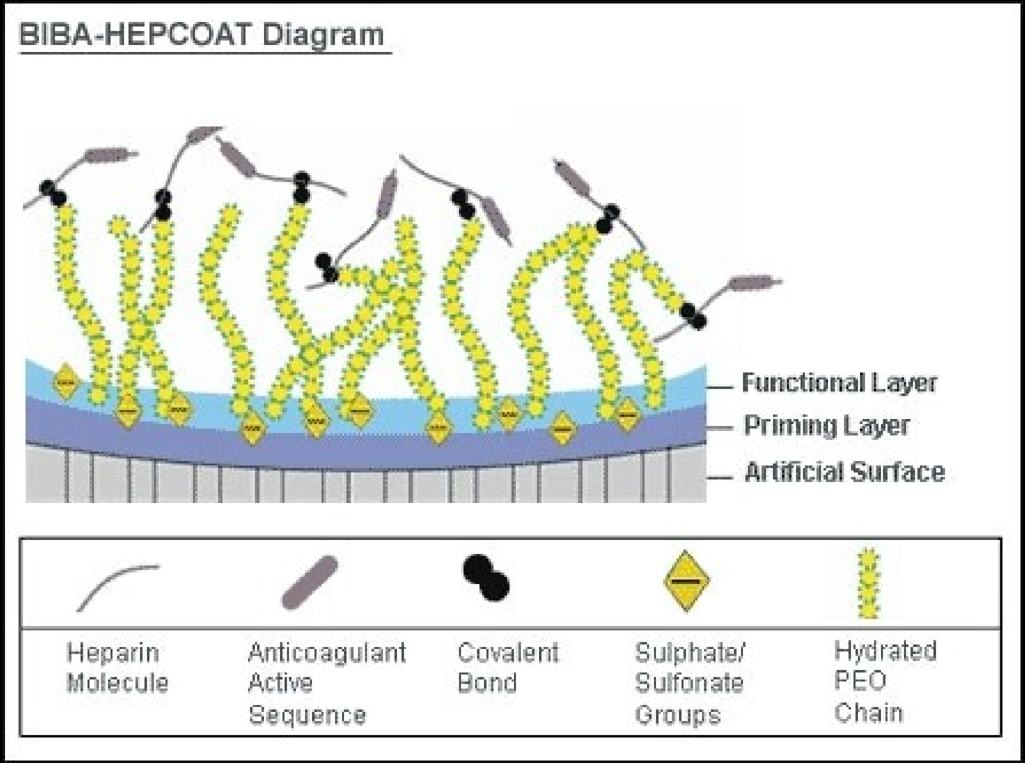
Uncoated

Scanning Electron Micrographs of oxygenator fiber surfaces after one hour in vitro (100X magnification).

Heparin

Largest challenge of manufacturing Heparin coatings is connecting it to the artificial surface:

- Heparin requires intact three dimensional structure to express proper activity.



Trillium™ Biopassive Surface

Polyethylene Oxide (PEO)

Heparin

Commercialized by several companies.

Baxter International Inc.
Heparin in liquid form.

Percentage of Percutaneous Cardiopulmonary Support devices which utilize Heparin coatings*:

71.9% in1997

84.9% in 1999

91.5% in 2002

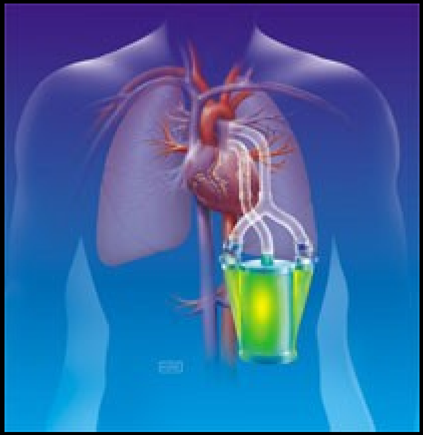
*In Japan

What is in the works ...

Interventional Lung Assist

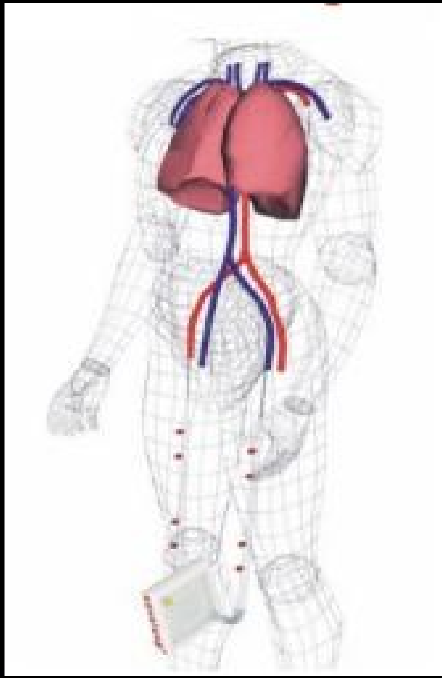
OR

Biolung!



Modern Advances ...

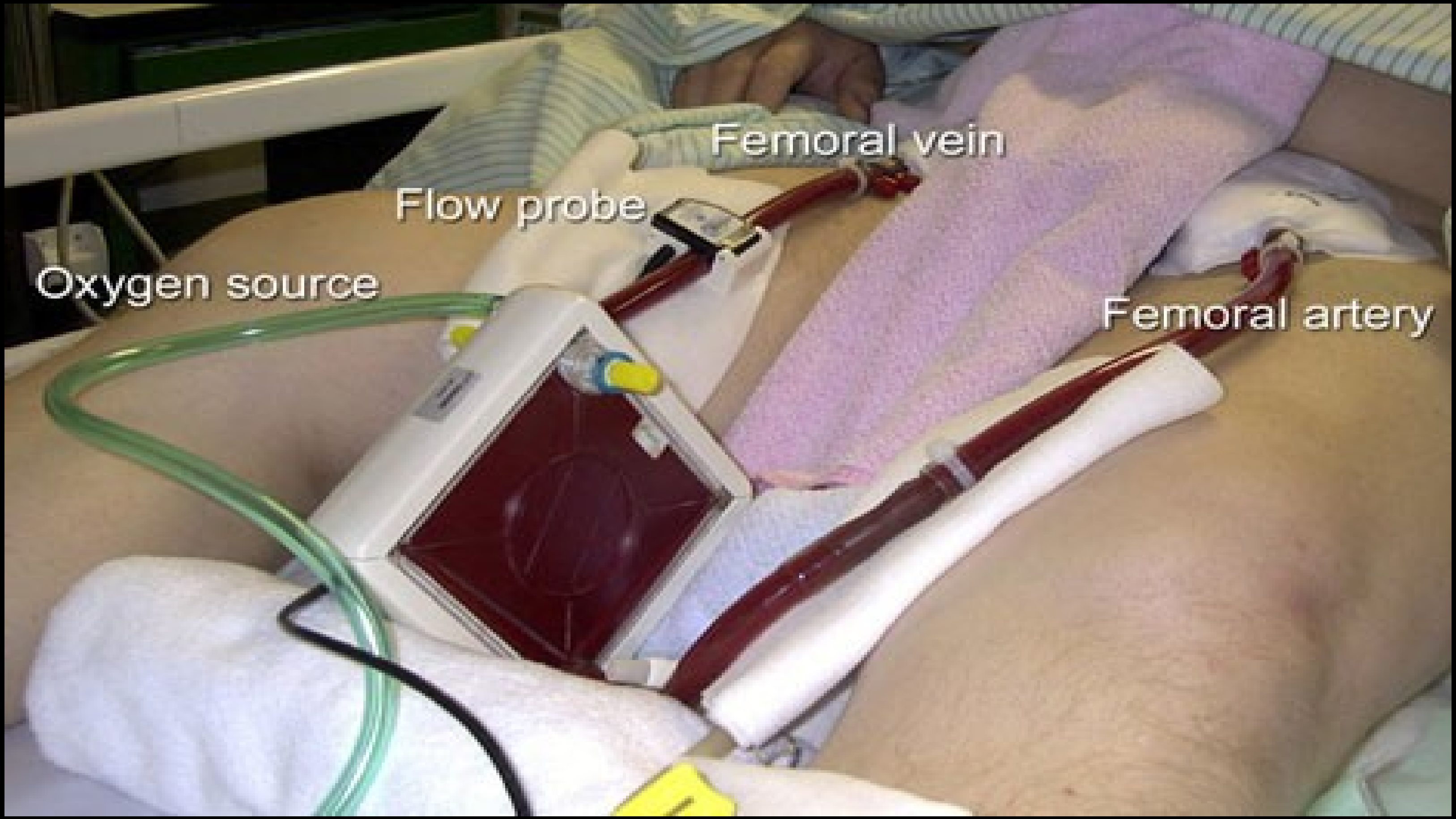
- 2002: Medical technology Company, NovaLung founded
  - 2002-2006: Interventional Lung Assist (ILA) developed by NovaLung and has been used on over 500 patients in Europe.
  - Awaiting approval in USA



At 14X14 cm, the “BioLung” from Novalung GmbH is the first of its kind to be naturally supplied with blood from the human heart.

• *Capable of replacing human lung!!!*

NovaLung ILA

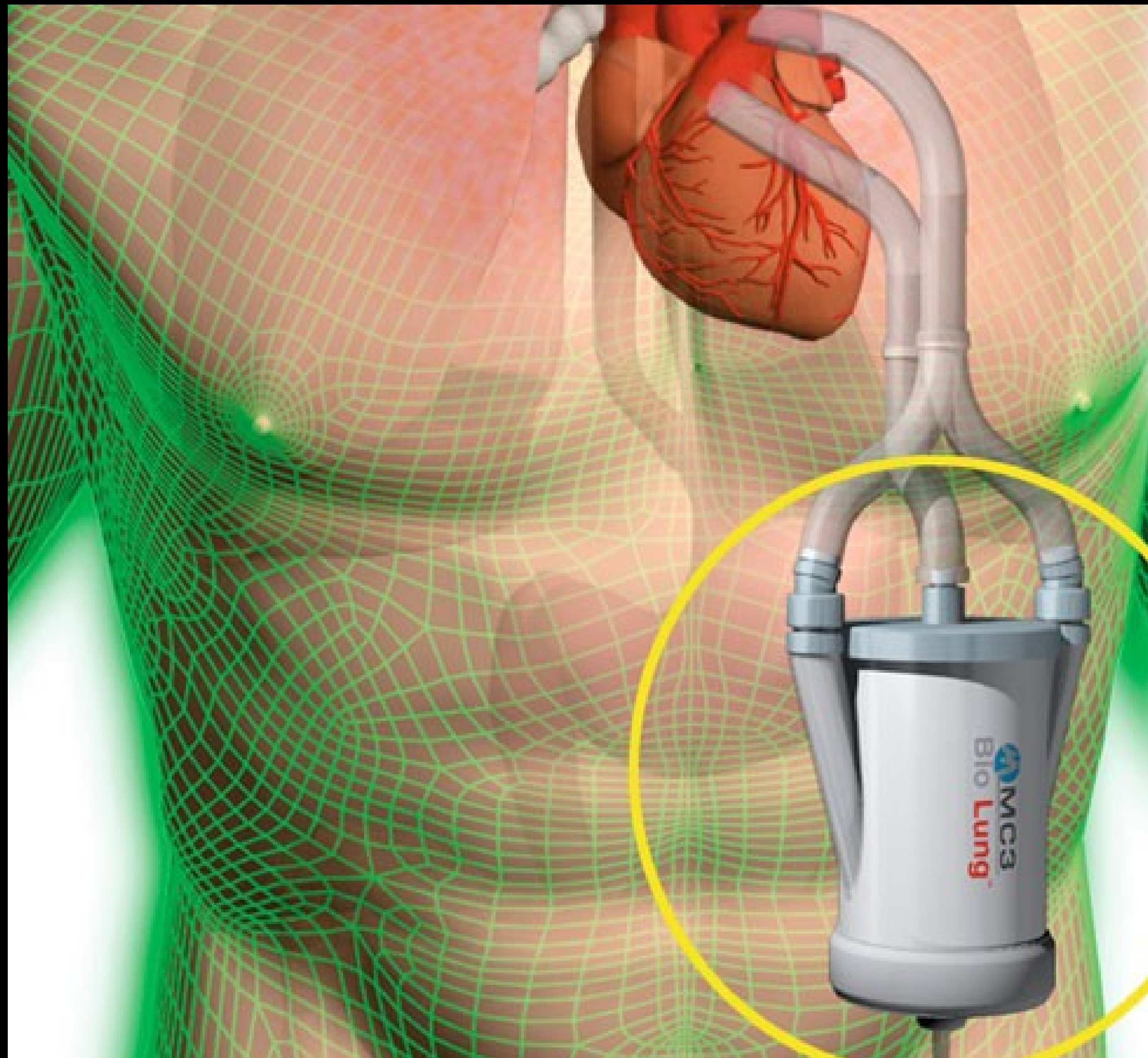


Device does require invasive tubing but is small and portable

Biolung (ILA)

... world's first artificial lung

- capable of complementing/replacing traditional mechanical ventilation AND gas exchange function of human lung!
- With mechanical ventilators creating pressure and respirators forcing air into lungs, lung damage can occur
- Also Waiting times for Lung transplants can take months ⟷ ILA device is a safe and cost-effective alternative
  - $8,000 – $10,000 + disposable costs vs $708/day for a ventilator
    - Novalung is continuing to further develop its artificial lung


MC3
Bio Lung

Appendix

The **SINUSES** are hollow spaces in the bones of the head. Small openings connect them to the nasal cavity. The functions they serve are not clearly understood, but include helping to regulate the temperature and humidity of air breathed in, as well as to lighten the bone structure of the head and to give resonance to the voice.

The **NASAL CAVITY** (nose) is the preferred entrance for outside air into the Respiratory System. The hairs that line the inside wall are part of the air-cleansing system.

Air also enters through the **ORAL CAVITY** (mouth), especially in people who have a mouth-breathing habit or whose nasal passages may be temporarily obstructed, as by a cold.

The **ADENOIDS** are overgrown lymph tissue at the top of the throat. When they interfere with breathing, they are generally removed. The lymph system, consisting of nodes (knots of cells) and connecting vessels, carries fluid throughout the body. This system helps resist body infection by filtering out foreign matter, including germs, and producing cells (lymphocytes) to fight them.

The **TONSILS** are lymph nodes in the wall of the pharynx that often become infected. They are an unimportant part of the germ-fighting system of the body. When infected, they are generally removed.

The **PHARYNX** (throat) collects incoming air from the nose and passes it downward to the trachea (windpipe).

The **EPIGLOTTIS** is a flap of tissue that guards the entrance to the trachea, closing when anything is swallowed that should go into the esophagus and stomach.

The **LARYNX** (voice box) contains the vocal cords. It is the place where moving air being breathed in and out creates voice sounds.

The **ESOPHAGUS** is the passage leading from the mouth and throat to the stomach.

The **TRACHEA** (windpipe) is the passage leading from the pharynx to the lungs.

Appendix

The **RIBS** are bones supporting and protecting the chest cavity. They move to a limited degree, helping the lungs to expand and contract.

The trachea divides into the two main **BRONCHI** (tubes), one for each lung. These, in turn, subdivide further into bronchioles.

The **RIGHT LUNG** is divided into three **LOBES**, or sections.

The **LEFT LUNG** is divided into two **LOBES**.

The **PLEURA** are the two membranes, that surround each lobe of the lungs and separate the lungs from the chest wall.

The bronchial tubes are lined with **CILIA** (like very small hairs) that have a wave-like motion. This motion carries **MUCUS** (sticky phlegm or liquid) upward and out into the throat, where it is either coughed up or swallowed. The mucus catches and holds much of the dust, germs, and other unwanted matter that has invaded the lungs and thus gets rid of it.

The **DIAPHRAGM** is the strong wall of muscle that separates the chest cavity from the abdominal cavity. By moving downward, it creates suction to draw in air and expand the lungs.

The smallest subdivisions of the bronchi are called **BRONCHIOLES**, at the end of which are the alveoli (plural of alveolus).

The **ALVEOLI** are the very small air sacs that are the destination of air breathed in. The **[PULMONARY] CAPILLARIES** are blood vessels that are imbedded in the walls of the alveoli. Blood passes through the capillaries, brought to them by the **PULMONARY ARTERY** and taken away by the **PULMONARY VEIN**. While in the capillaries the blood discharges carbon dioxide into the alveoli and takes up oxygen from the air in the alveoli.

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