The problem of the missing organ

1. Irreversible injury (acute and chronic) destroys organ function.
2. Five basic therapies for the missing organ.
3. Examples of widespread clinical problems that have not been solved adequately.

1. Irreversible injury (acute and chronic) destroys organ function.
Various Medical Problems

• The aggressive bacterium (virus)
• The missing enzyme
• The defective gene
• The missing organ
Irreversible organ injury

• The mammalian fetus regenerates lost organs spontaneously.
• Adult mammals do not regenerate damaged or diseased organs.
• The adult response to trauma or chronic disease includes wound closure by contraction and formation of scar (repair).
Amphibian (newt) limbs regenerate spontaneously

Figure removed due to copyright restrictions.
See Figure 1.1 in [TORA].

Figure 1.1. Montage of individual newt limbs amputated across the lower or upper arms, photographed at indicated times and regenerating spontaneously. (From Goss, 1992.)
Liver: compensatory hypertrophy, not “real” regeneration of two lobes

FIGURE 1.2. Liver does not regenerate at the anatomical site of injury. When the median and left lateral lobes of a rat liver are removed (broken line shows shape of intact organ), only the caudate and right lateral lobes remain, representing about one-third of the intact organ. After three weeks, these lobes enlarge to a mass equivalent to the initial size of the liver. The shape of the intact liver is not restored. (From Goss, 1992.)
Example of adult healing response. Severe burn causes skin loss. Wound closes by contraction and scar synthesis. Photo removed due to copyright restrictions.
Figure removed due to copyright restrictions.

See Chapter 1 in [TORA] - examples of injury healing in various tissue types.
Poor organ function leads to unpleasant choices

--- scarred heart muscle: poor pumping action; congestive heart failure; drugs, heart transplant
--- scarred kidney: poor filtration; use kidney dialysis machine
--- scarred heart valve: inefficient pumping due to leaky valve; congestive heart failure
--- scarred liver: cirrhosis; poor function; liver transplant
--- scarred eye: loss of vision
2. Five therapies for the missing organ.
Five Approaches to the Problem of the Missing Organ

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<td>Skin</td>
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</table>
A. Transplantation (e.g., kidney transplant, heart transplant)

- donor organ
- donor $\Rightarrow$ $\Rightarrow$ $\Rightarrow$ $\Rightarrow$ host $\Rightarrow$ rejection? $\Rightarrow$
- $\Rightarrow$ treatment impairs immune system

Also, demand for organ transplants greatly outstrips supply
Demand for organs is growing, while the supply stays constant.

Data from United Network for Organ Sharing.
B. Autografting (e.g., heart bypass, skin grafting)

Donor = recipient

Example: In heart bypass surgery, a length of leg vein is removed and used to shunt clotted coronary artery

part host organ

Host ⇒ ⇒ ⇒ ⇒ ⇒ host ⇒ host trauma? sufficient recovery of function?
Third-degree burn: complete skin loss

Figure removed due to copyright restrictions.
6-yr-old burn victim – total skin loss on upper and lower abdomen

patient of Dr. John Burke

Figure removed due to copyright restrictions.
C. Passive Implant (e.g., hip prosthesis, pacemaker)

metallics/polymers/ceramics ⇒ device fabrication ⇒ host ⇒ long-term function?

materials used: stainless steel, Ti alloys, CoCr alloys, polylactic acid, polyglycolic acid, nylon; dacron (PET) vascular graft; polyurethane heart chamber
C. Passive Implant (cont.)

Problem #1: host attacks implant
- migration of hip prosthesis
- abrasion of polyethylene 'cup'
- tissue fluid attacks pacemaker electronics

Problem #2: implant attacks host
- hip prosthesis causes bone loss (stress shielding)
- heart valve causes blood cell rupture
- vascular graft causes blood clotting
Several slides on different implants removed due to copyright restrictions.

Cementing artificial hip with PMMA
Silicone gel breast implant
Heart pacemaker
Balloon catheter
Left ventricular assist device: responds to changes in workload by adjusting its beats per minute
Liver assist machine: passes blood through culture of human cells, provides 20% normal liver function
Artificial lung device inserted into large vein in chest, enables body to absorb oxygen
Hearing aid
D. In vitro synthesis

1. Synthesize a construct resembling the desired organ (organoid) in vitro in the presence of cells of one or more types, solutions of cytokines and one or more scaffolds.

2. Implant the organoid at the correct anatomical site.

3. If successfully synthesized, the organoid becomes incorporated in the organism and functions physiologically.

Problem: Physiological cytokine field unknown, cannot be replicated in vitro.
Several slides removed due to copyright restrictions.
Design strategy

Analyze problem of irreversible injured organ by identifying tissues in organs that regenerate spontaneously (regenerative) and those that do not (nonregenerative).

Rather than planning a device that can synthesize the entire organ, the designer’s task is made simpler if the design focuses on synthesis of just those tissue(s) that do not regenerate by themselves. Which are they?
Identify nonregenerative tissues

1. Every organ is different, but....
2. Generalize by focusing on individual tissues that comprise organ.
3. Most organs are made up of three basic tissues ("tissue triad"): epithelia, basement membrane, and stroma.
4. Epithelia and basement membrane are spontaneously regenerative; the stroma is not.
4. Therefore, the central problem in biomaterials selection for organ replacement by regeneration is synthesis of the stroma.
Members of the tissue triad

• EPITHELIA
  100% cells. No matrix. No blood vessels.

• BASEMENT MEMBRANE
  No cells. 100% matrix. No blood vessels.

• STROMA (CONNECTIVE TISSUE)
The tissue triad in skin and nerves

Skin

Nerve

Figure by MIT OCW.
The tissue triad in the organism

Figure by MIT OCW.
The epidermis is regenerative

Spontaneous regeneration of excised epidermis

Left: a controlled injury (e.g. stripping or blistering) which leaves the dermis intact. Right: the epidermis recovers completely at the defect site. Hair follicles are lined with epidermal tissue and also regenerate.
The dermis is nonregenerative

Spontaneous healing of skin excised to full thickness by contraction and scar formation. The dermis does not regenerate.

Left: Excision of the epidermis and dermis to its full thickness. Right: Wound edges contract and close, while scar tissue forms simultaneously in place of a physiological dermis. The epidermis that forms over the scar is thinner and lacks undulations (rete ridge).
Evidence that epidermis and basement membrane in skin are regenerative.
crushed nerve heals spontaneously by regeneration

Within the nerve fiber, axons and their myelin sheath are regenerative. Top: Following mild crushing injury, the axoplasm separates and the myelin sheath degenerates at the point of injury. However, the basement membrane stays intact. Bottom: The nerve fiber regenerates after a few weeks.
The endoneurium (= stroma) is nonregenerative

Transected nerve heals spontaneously by contraction and neuroma (neural scar) formation. No reconnection of stumps.

Most supporting tissues (stroma) that surround nerve fibers are not regenerative. Thus, while nerve fibers can regenerate following a transection, the other tissues in the nerve trunk cannot regenerate. After transection, the nerve trunk stumps become neuromas - clumps of scarred tissue that close largely by contraction.
A completely transected nerve fiber is nonregenerative.
### Table: Regenerativelty Similar Tissues in Skin and Peripheral Nerves

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<tr>
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<th>Skin</th>
<th>Peripheral Nerves</th>
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<tbody>
<tr>
<td>1. Regenerative</td>
<td>Epidermis</td>
<td>Myelin sheath basement membrane (perineurium, in part only)</td>
</tr>
<tr>
<td>tissues</td>
<td>Basement membrane</td>
<td></td>
</tr>
<tr>
<td>2. Nonregenerative</td>
<td>Dermis</td>
<td>Endoneurial stroma</td>
</tr>
<tr>
<td>tissues</td>
<td></td>
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</tbody>
</table>

*Figure by MIT OCW.*

See [TORA] Chapter 2.

*Regeneratively similar tissues in skin and peripheral nerves.*
The central question is…

- Epithelia and basement membrane (BM) are synthesized from remaining epithelial cells.
- The stroma is not synthesized from remaining stromal cells. Instead these cells induce closure of the injury by contraction and synthesis of scar.
- Therefore, the key process is synthesis of the stroma.
- Once the stroma has been synthesized, epithelial cells can synthesize both epithelia and BM over it (“sequential” synthesis).
- Also, consider “simultaneous” synthesis.
Skin: In vitro or in vivo synthesis?

IRREDUCIBLE PROCESSES FOR SYNTHESIS OF SKIN AND PERIPHERAL NERVES

(A) In Vitro Synthesis

- Culture
- Cells
- Soluble & Insoluble Regulators
- Tissue bi-layer
- Host
- Remodeled & Regenerated

(B) In Vivo Synthesis

- Cells
- Scaffold
- Host
- Remodeled & Regenerated

Figure by MIT OCW.
Peripheral nerves: In vitro or in vivo synthesis?

(A) In Vitro Synthesis
- Culture
- Cells
- Soluble & Insoluble Regulators
- Host
- Remodeled & Regenerated

(B) In Vivo Synthesis
- Tube
- Cells
- Host
- Matrix
- Remodeled & Regenerated

Figure by MIT OCW.
Example of scaffold studied for possible use with in vitro synthesis: synthetic and natural polymers used together

Alcohols react readily with carbonyldiimidazole to produce reactive imidazole-N-carboxylates for coupling to amine-containing ligands.

Figure by MIT OCW.
3. Examples of widespread clinical problems that have not been solved adequately
Arthritis

Several slides describing unsolved clinical problems removed due to copyright restrictions. These slides described:
- Arthritis
- Alzheimer's Disease
- Cataracts
- Glaucoma
- Digestive system disorders
- Obesity
- Back pain
- Ischemic and hemorrhagic strokes
- Prostate problems
- Impaired lung function and lung diseases
- Heart arrhythmias
- Heart attack