Chapter 1A.

Irreversible Healing of Extracellular Matrix.
Outline of three lectures on Irreversible Healing of Extracellular Matrix.

A. Irreversible healing of ECMs in different organs.
B. Structure and function of naturally occurring ECMs.
C. Synthesis of biologically active ECM models.
A. Injury to ECM is Irreversible

Summary:
1. After severe injury, and in contrast to the fetus, the adult heals most organs irreversibly (no regeneration).
2. Most organs are made up of three basic tissues (“tissue triad”): epithelia, basement membrane, and stroma.
3. 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.

Spontaneous regeneration of amputated limb in the newt (a small amphibian) occurs independently of severity of injury
The healed liver has the same mass, but a different shape (resected lobes are not regenerated), than the intact organ.

Image removed due to copyright considerations. See Figure 1.2 in [Yannas].
scarred heart muscle
(heart attack)

scarred kidney
(infection)

scarred heart valve
(rheumatic fever)

scarred liver
(cirrhosis)

scarred cornea
(infection)

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Spontaneous regeneration of excised epidermis
Spontaneous healing of skin excised to full thickness by contraction and scar formation. The dermis does not regenerate.
Mildly crushed nerve heals spontaneously by regeneration.
Transected nerve heals spontaneously by contraction and neuroma (neural scar) formation. No reconnection of stumps.
intact nerve with myelinated (M) axon (A) and Schwann cell (S) spontaneously healed nerve (following transection) is filled with collagen fibers (scar) but has no myelinated axon or Schwann cell.
injury mode

basic blister configuration

through epidermis: reversible healing

between epidermis and dermis: reversible healing

through dermis: irreversible healing
Cartoon of “organism” shows that basement membrane (thick solid line) appears in almost all organs.
## SUMMARY SO FAR

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
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<tr>
<td>epidermis</td>
<td>dermis</td>
</tr>
<tr>
<td><strong>NERVE</strong></td>
<td></td>
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<tr>
<td>myelin</td>
<td>endoneurial stroma</td>
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<tr>
<td><strong>BM</strong></td>
<td></td>
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<tr>
<td>BM</td>
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The Defect Closure Rule
Quantitative description of healing processes

- Initial wound area is $A_o$.
- Wound eventually closes up spontaneously. Final area is $A_f$.
- Final wound area is distributed among fractions that closed by contraction ($%C$), scar formation ($%S$) or regeneration ($%R$).
- This is the configuration of the final state.
- Wound closure rule:
  \[ C + S + R = 100 \]
<table>
<thead>
<tr>
<th>Spontaneously healing defect</th>
<th>Configuration of final state</th>
</tr>
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<tbody>
<tr>
<td>general case</td>
<td>[C, S, R]</td>
</tr>
<tr>
<td>ideal fetal healing</td>
<td>[0, 0, 100]</td>
</tr>
<tr>
<td>dermis-free skin--adult rodents</td>
<td>[96, 4, 0]</td>
</tr>
<tr>
<td>dermis-free skin--adult human</td>
<td>[37, 63, 0]</td>
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<tr>
<td>peripheral nerve--adult rat</td>
<td>[96, 4, 0]</td>
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<tr>
<td>conjunctiva--adult rabbit</td>
<td>[45, 55, 0]</td>
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Measure C

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Measure S (qualitative assay)
Kinetics of change in C

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See Figure 4.3 in [Yannas].