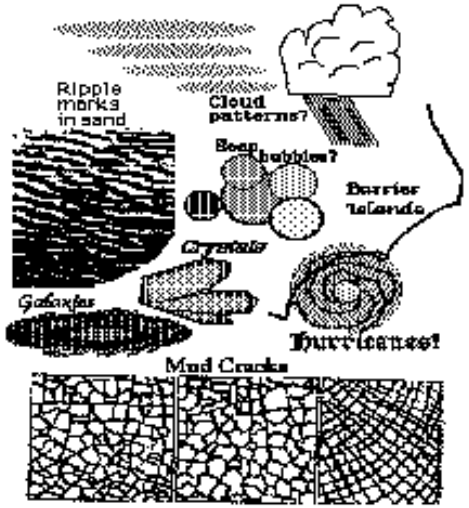
The Zeroeth Problem.

Oversimplifications that distract people from the real problems

Geometry imposed by outside forces



Geometry created by interactions of component materials

Sometimes matter is shaped
by outside forces imposed on it.

Other times, shapes arise spontanously from the properties of the materials.

The human mind
is much more familiar
with this category
of shape causation
(by external imposition)

Unfortunately for us, embryonic development belongs in this other category of mechanisms.

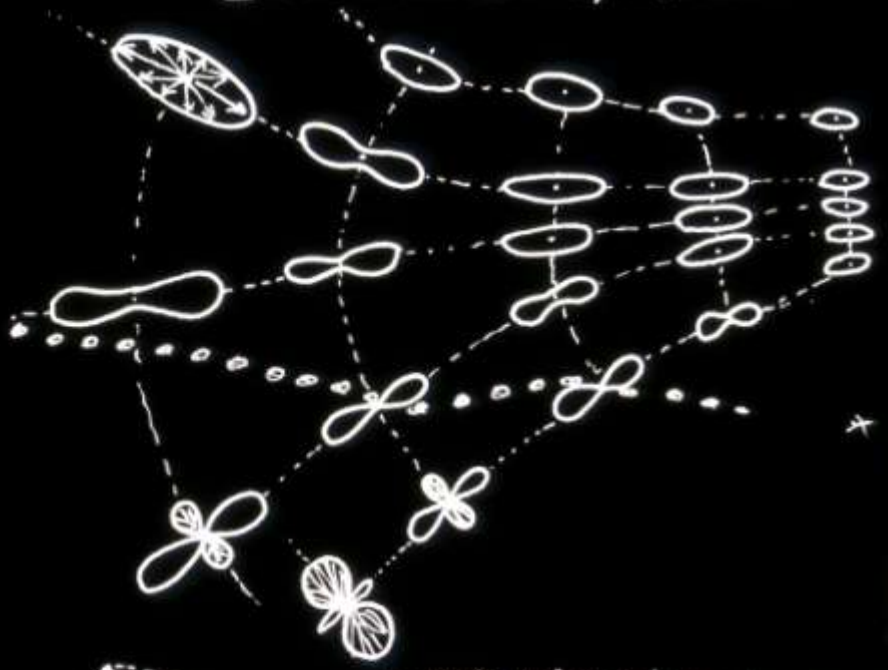
Nevertheless, most people
are much more comfortable
thinking about development
as if shape were being imposed.

**Thus, much of the history of embryology
(from preformationism, to Diesch's entelechy, to "positional information")
has consisted of efforts to make sense of spontaneous pattern formation
as if the patterns and shapes were being externally imposed on materials.**

Second Order Symmetrical Tensors

Stress, Strain, Curvature

(Also Permeability, Refractive Index + some others which can't be Negative)



* Always Equal in Opposite Directions
  → = ← ↑ = ↓
* Maxima and Minima are Always in Perpendicular Directions
* The Directions of Maxima + Minima Lie along "Principal Directions" which form a Network
* Regions where Maxima and Minima Have Same Sign (="Elliptic Regions") are separated from Hyperbolic Regions where they Have Opposite Sign by "Parabolic" Boundaries ····· where one is zero ∞

→ Vary with Direction at each point according to the Equation $T = A\cos^2\theta + B\cos^2\phi + C\cos^2$ etc

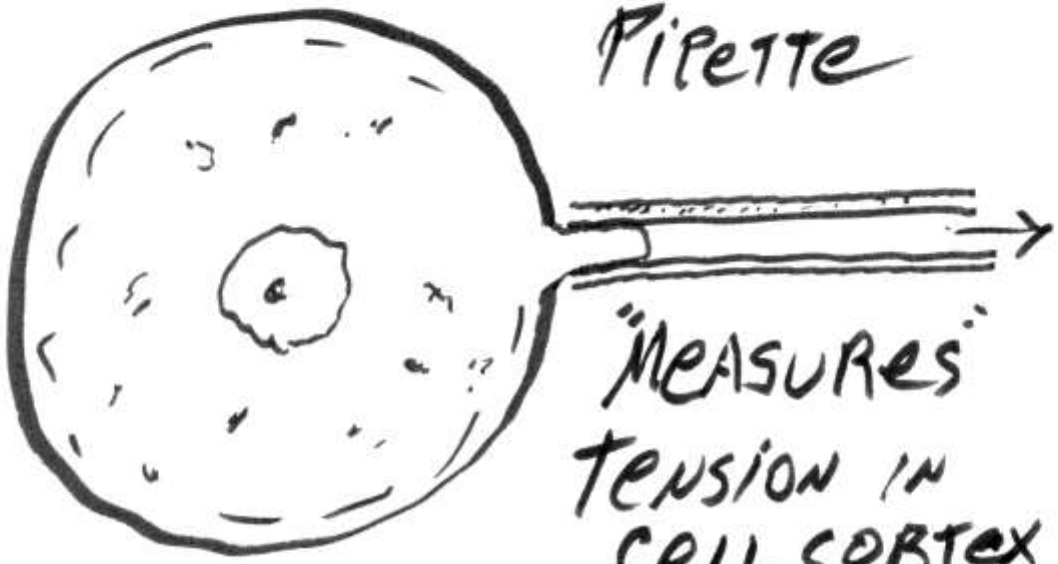
→ Described by a Two Dimensional Matrix

2 by 2 for 2 Dimensions

$$\begin{vmatrix} A & \# \\ \# & B \end{vmatrix}$$

3 by 3 for 3 Dimensions

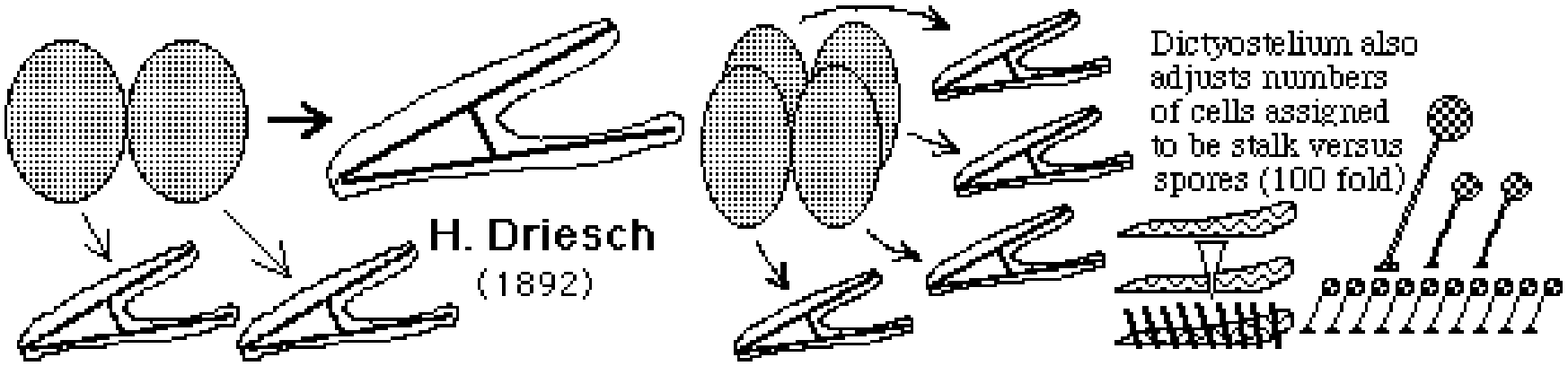
$$\begin{vmatrix} A & \# & \# \\ \# & B & \# \\ \# & \# & C \end{vmatrix}$$



BUT CAN'T DETECT
DIRECTIONAL DIFFERENCES.
(YIELDS AN ANSWER THAT IS SCALAR.)

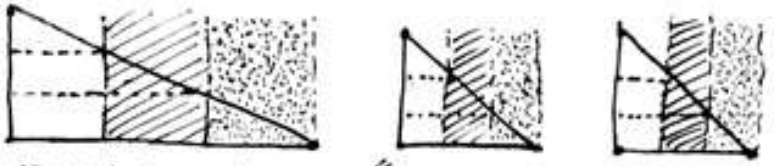
The First Problem.

- The Driesch Phenomenon, or “Embryonic Regulation”


H. Driesch
(1892)
Dictyostelium also
adjusts numbers
of cells assigned
to be stalk versus
spores (100 fold)

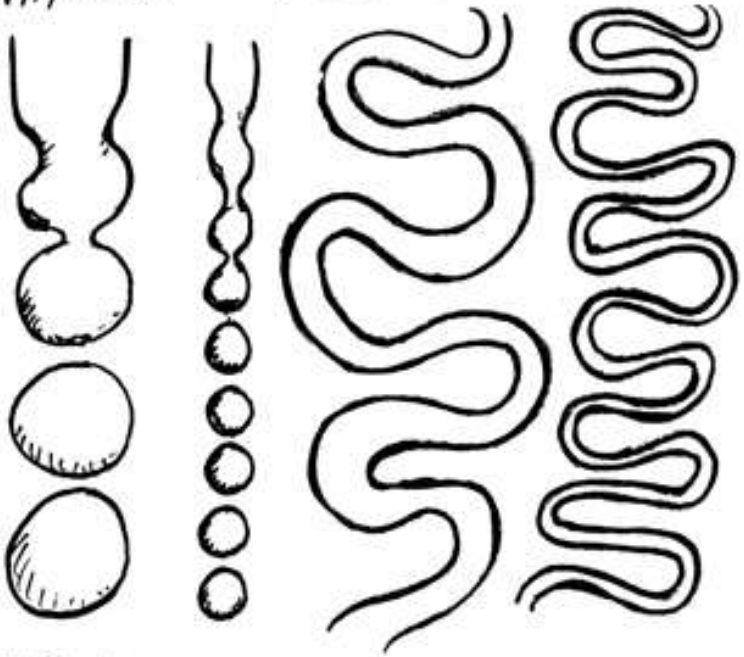
"Size Invariance" (L. Wolpert)

Proportional Adjustment of Dimensions



As Explained in Terms of "Positional Information"

Physical or Mechanical Analogies

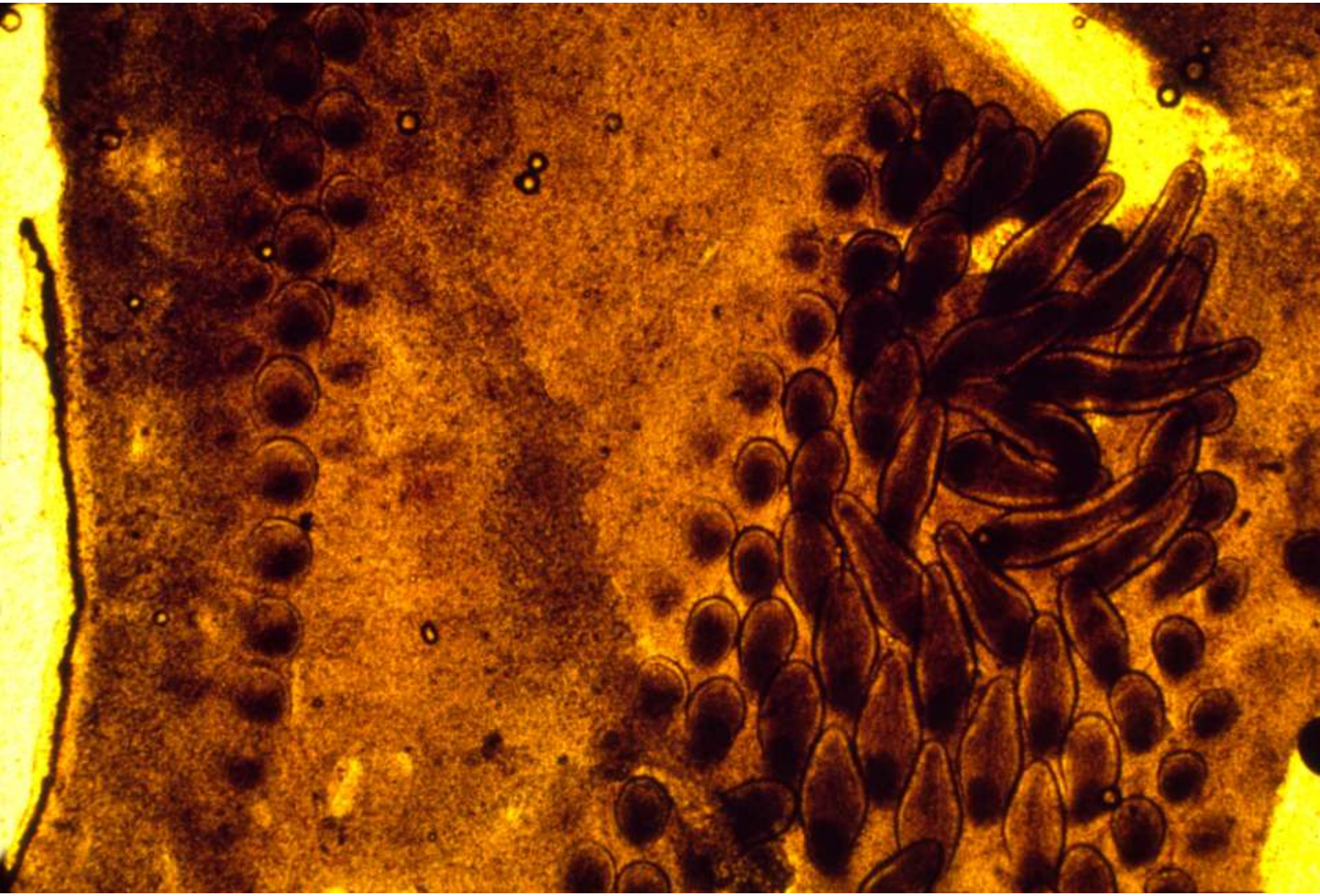


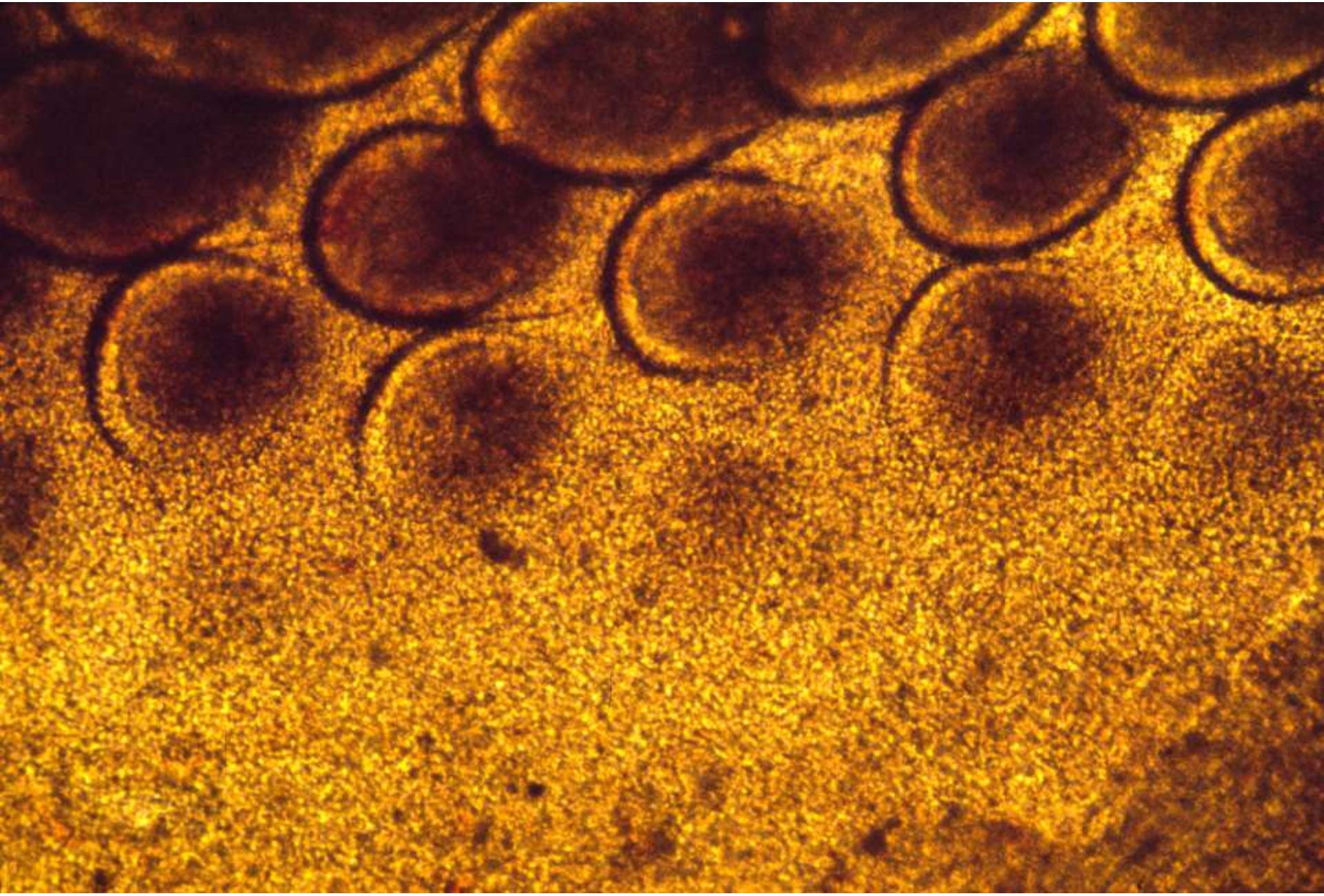
Water Drops

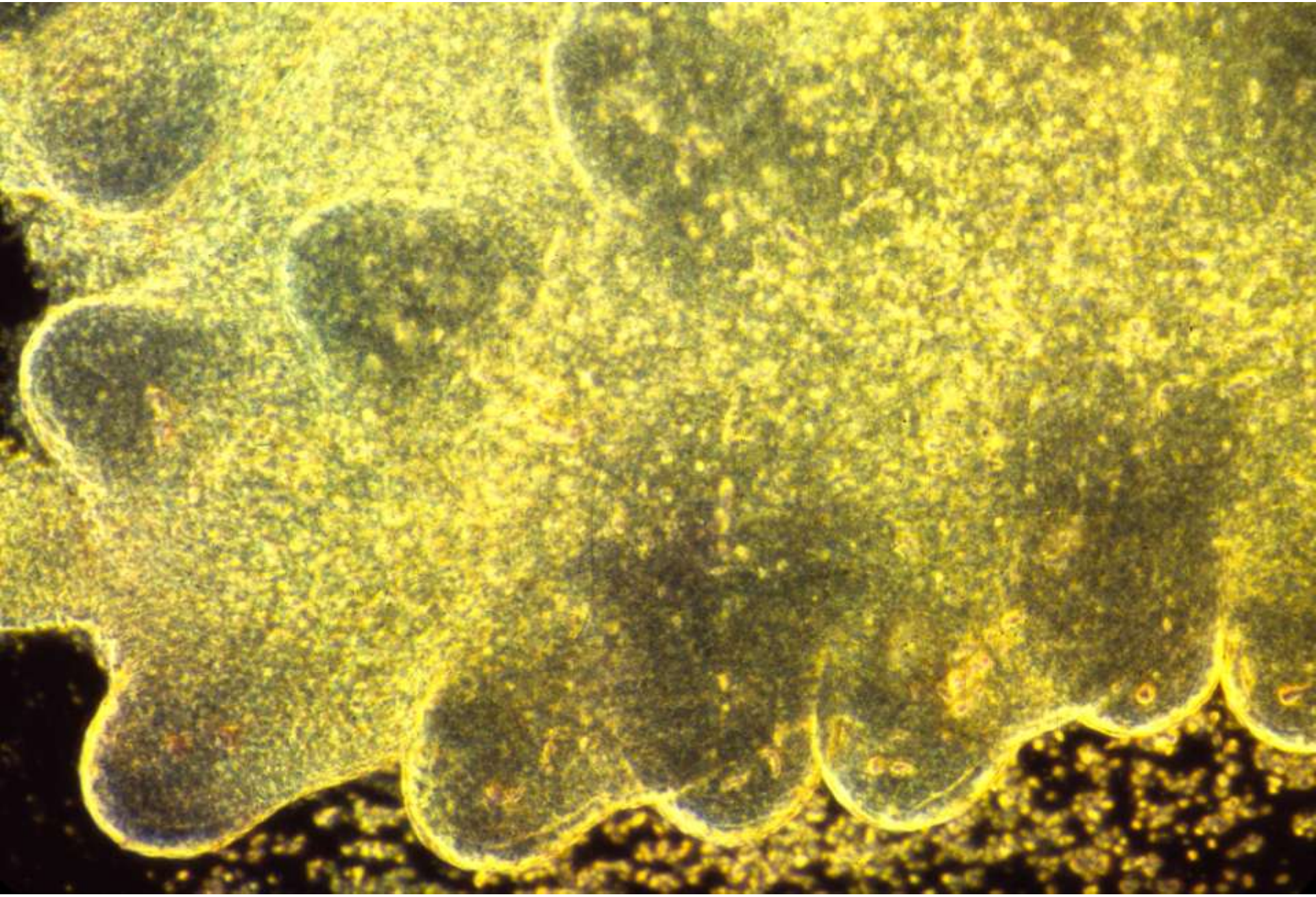
River Meanders

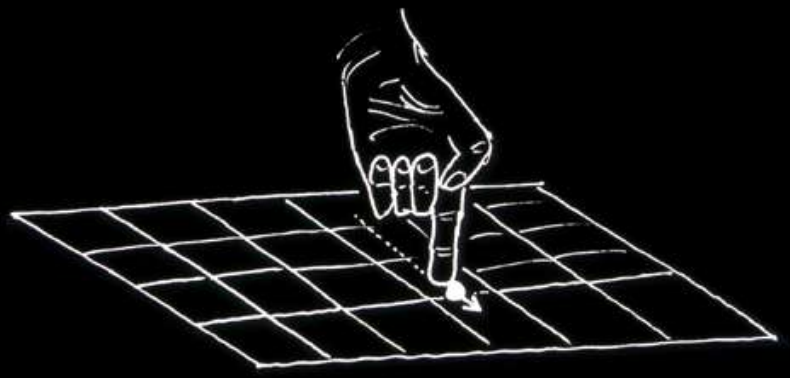
The Second Problem.

Consistent repetition of shapes



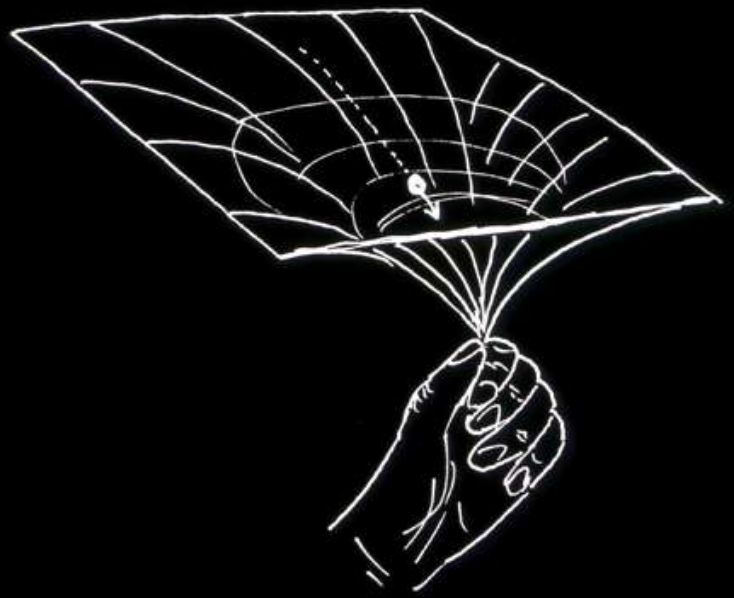






Two kinds of

Causality



The Third Problem.

Reaction diffusion systems?

Turing's Original Equations

$$\frac{\partial[x]}{\partial T} = R_x\left(5[x] - 6[y] + 1\right) + D_x \frac{\partial^2[x]}{\partial s^2}$$

$$\frac{\partial[y]}{\partial T} = R_y\left(6[x] - 7[y] + 1\right) + D_y \frac{\partial^2[y]}{\partial s^2}$$

$$D_y = 9\ D_x$$

Turing's Examples of Chemical Reactions which would obey these Equations

$A \rightarrow X$ at rate $10^{-3}[A]$; $[A] = 10^3$

$X + Y \rightarrow C$ at rate $10^3[X][Y]$

$C \rightarrow X + Y$ at rate $10^6[C]$

$C \rightarrow D$ at rate $62.5[C]$

$B + C \rightarrow W$ at rate $0.125[B][C]$; $[B] = 10^3$

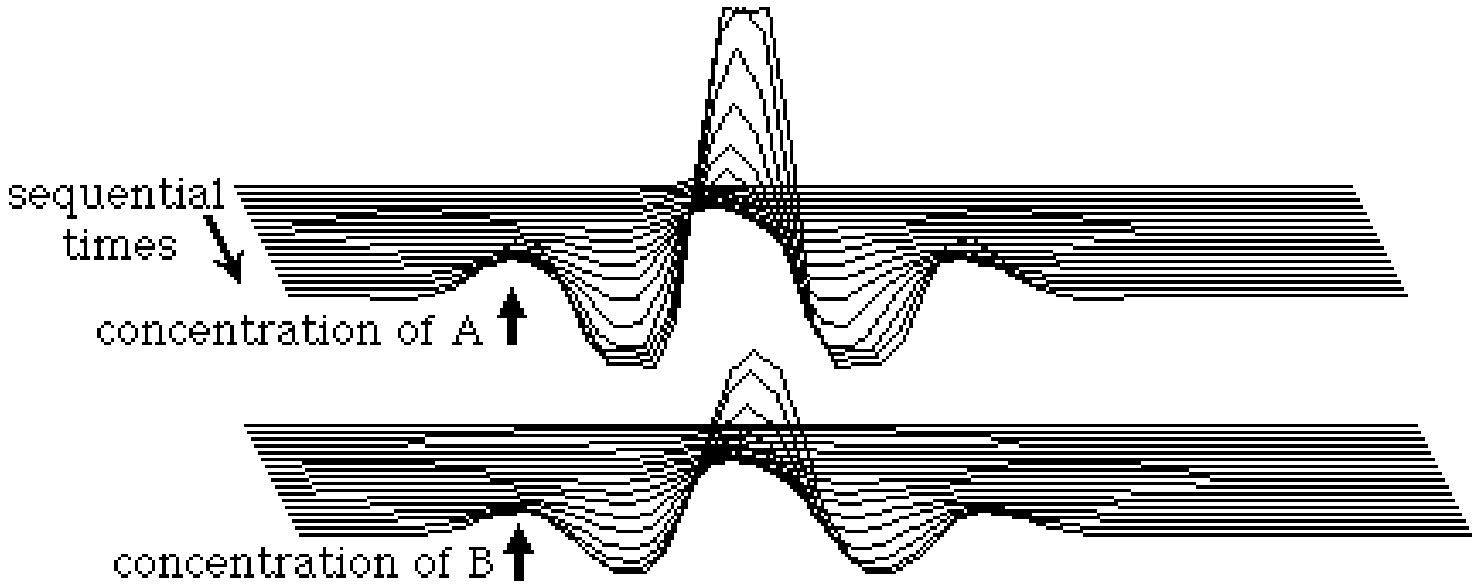
$W \rightarrow Y + C$ instantly

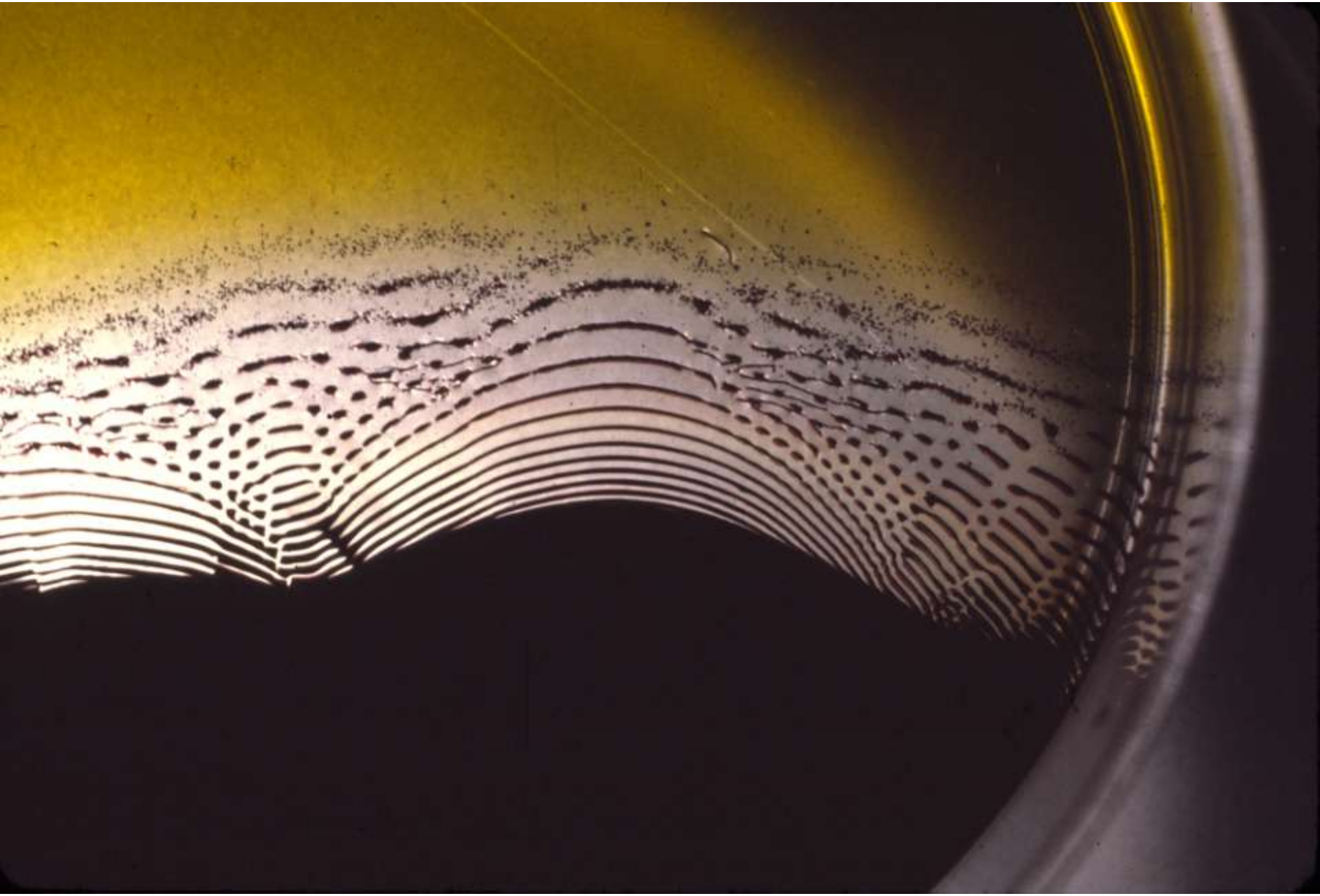
$Y \rightarrow E$ at rate $0.0625[Y]$

$Y + V = V'$ instantly

$V' \rightarrow E + V$ at rate $62.5[V']$; $[V'] < 10^{-3}[V]$

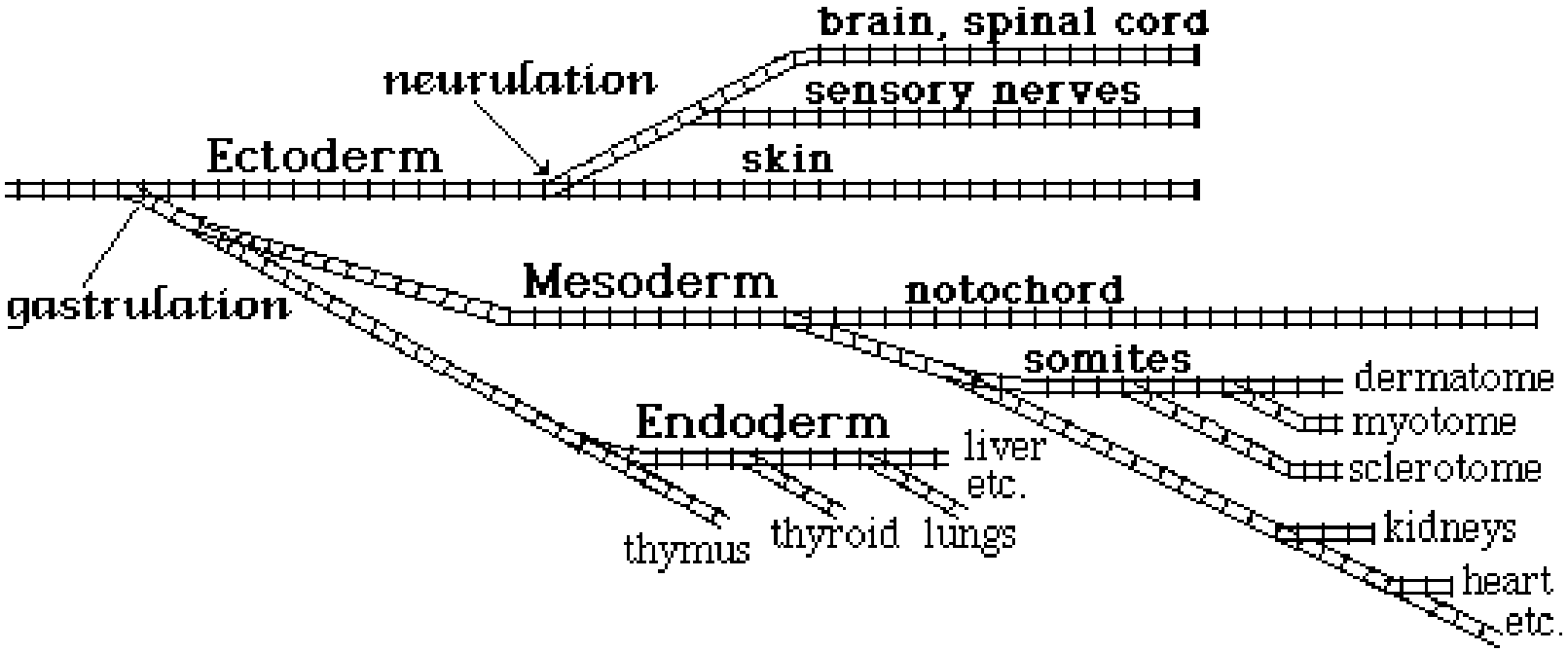
But any other reactions which obeyed these or similar equations would generate the same patterns


sequential
times
concentration of A
concentration of B



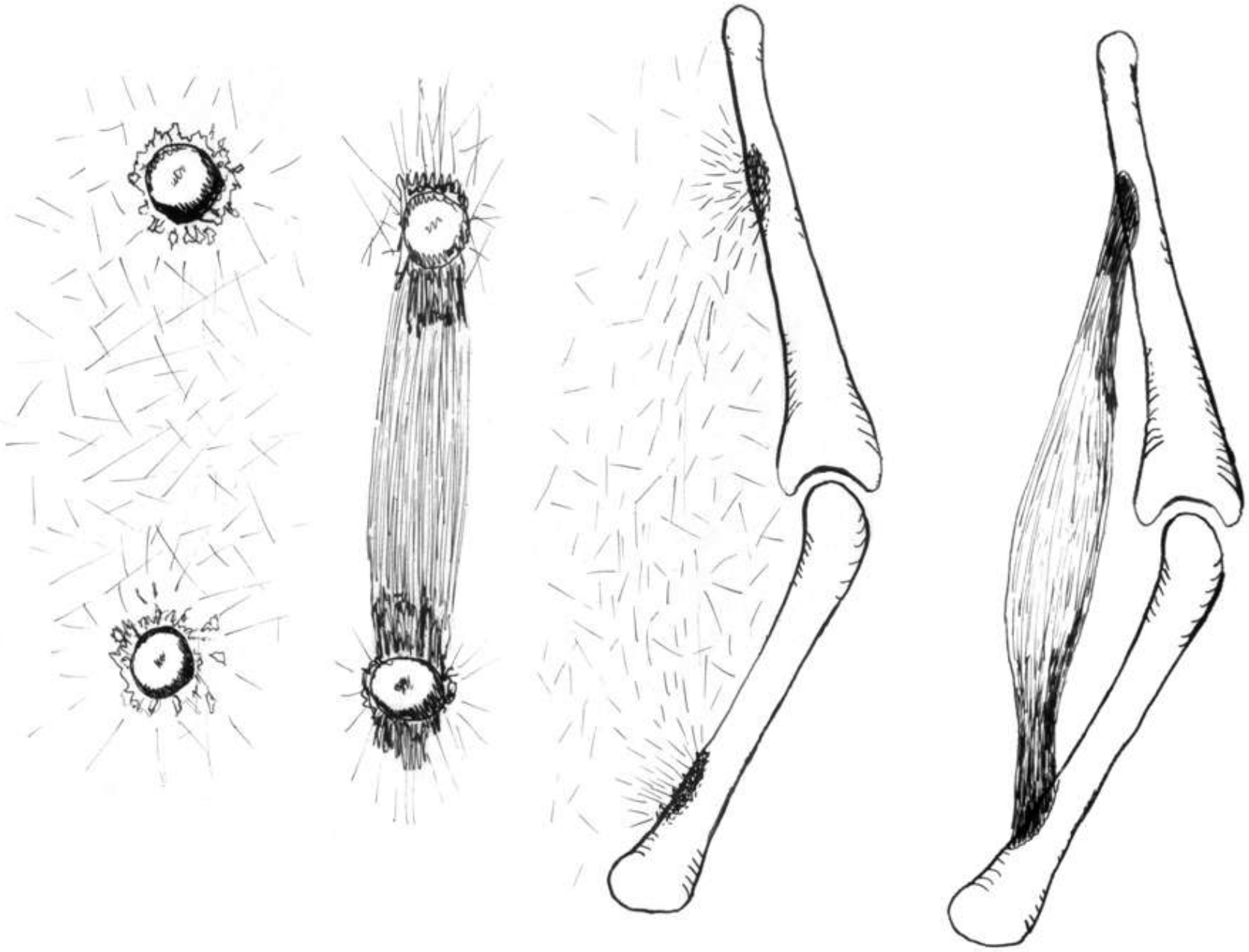
The Fourth Problem.

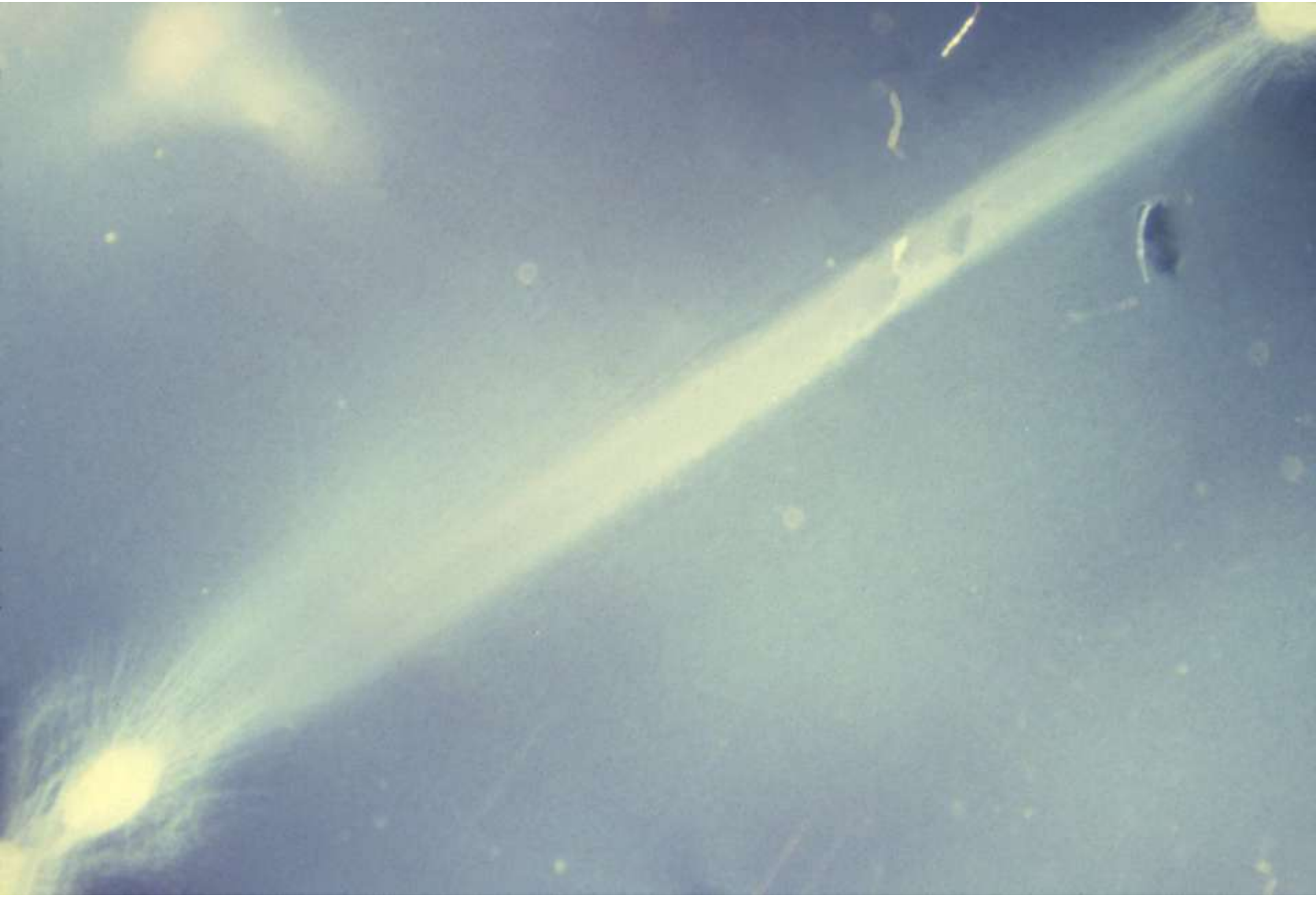
The molecular mechanism that controls cell differentiation

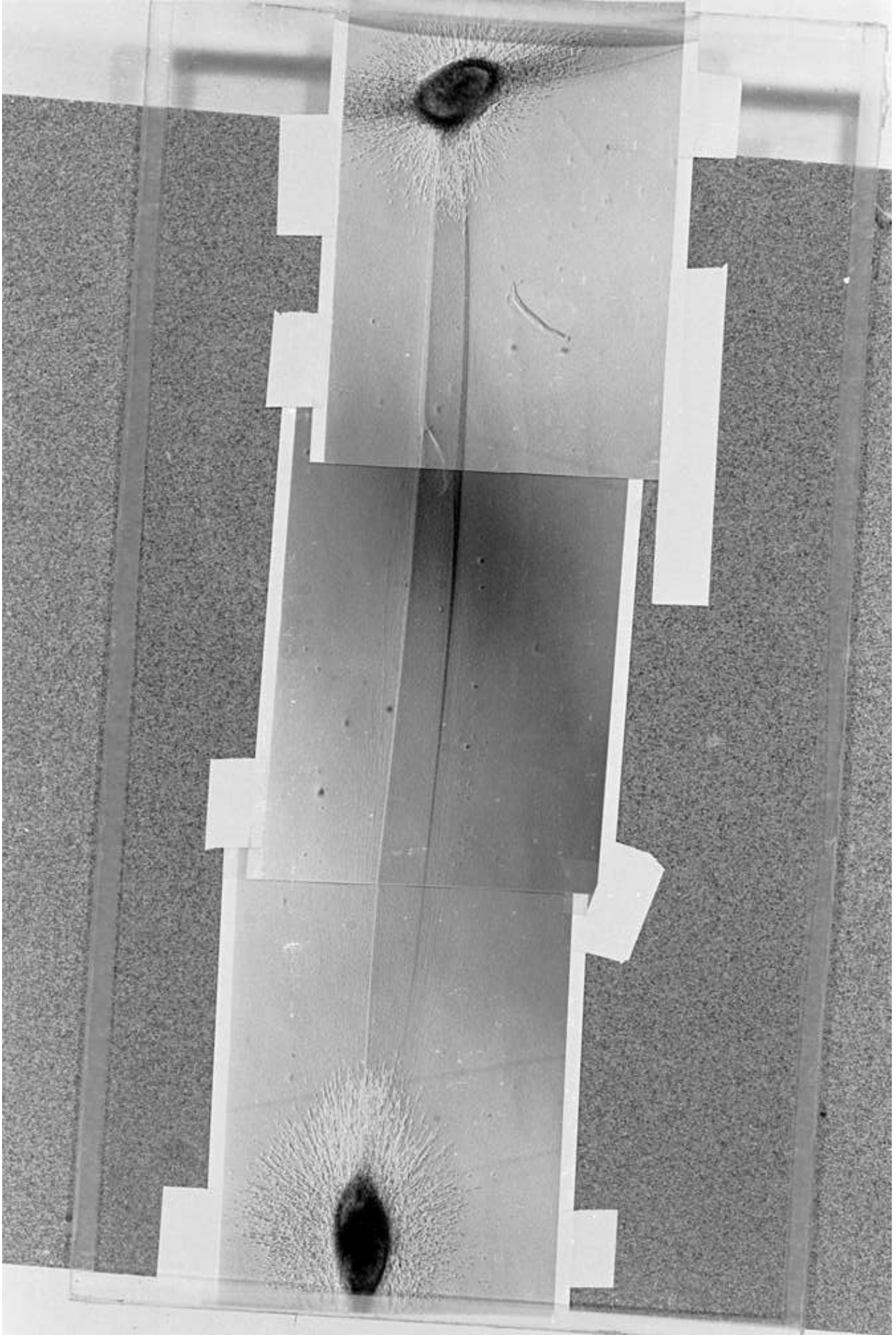

brain, spinal cord
neurulation
sensory nerves
Ectoderm
skin
gastrulation
Mesoderm
notochord
somites
dermatome
myotome
sclerotome
Endoderm
liver
etc.
kidneys
heart
etc.
thymus
thyroid
lungs

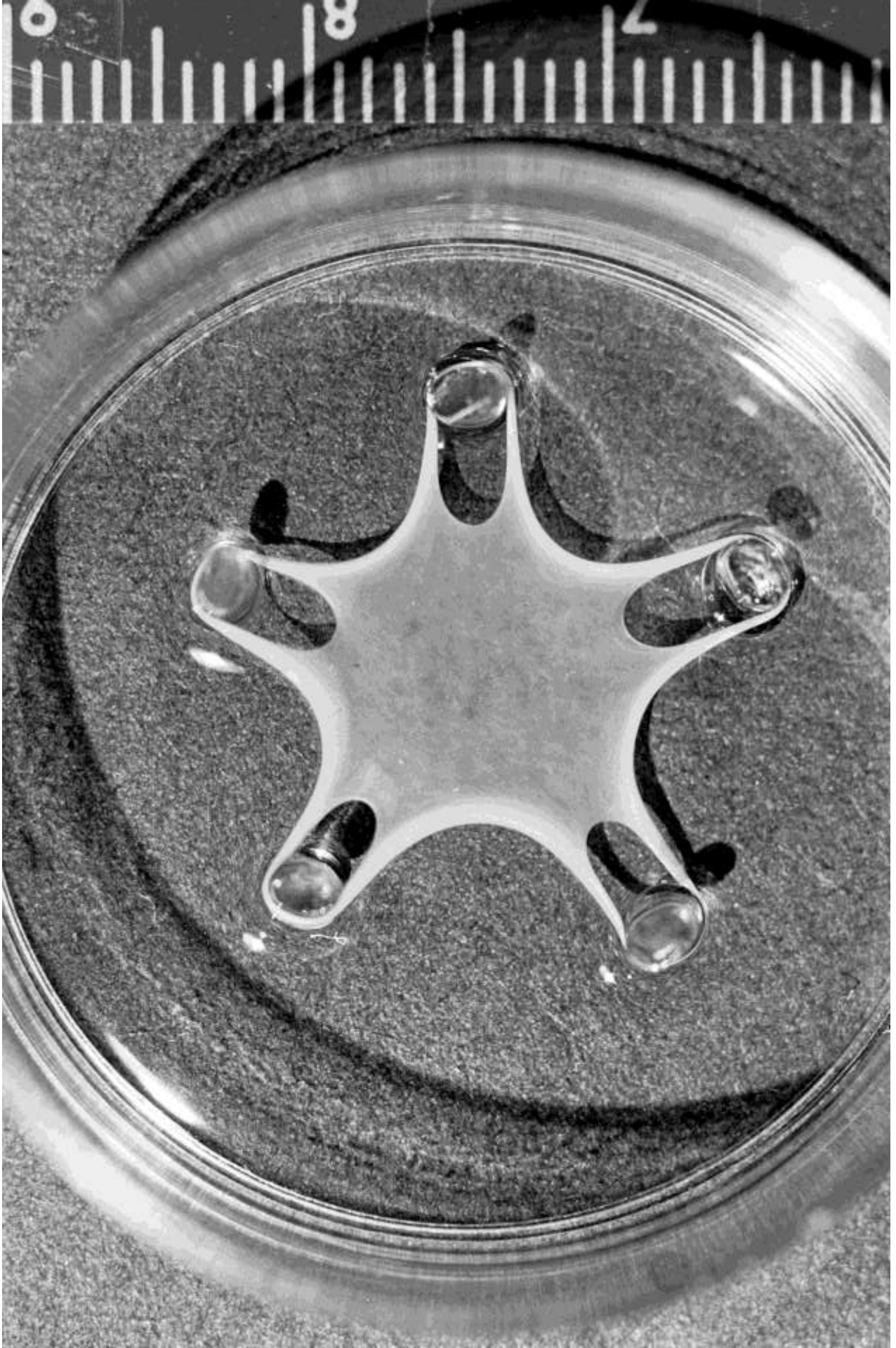
The Fifth Problem.

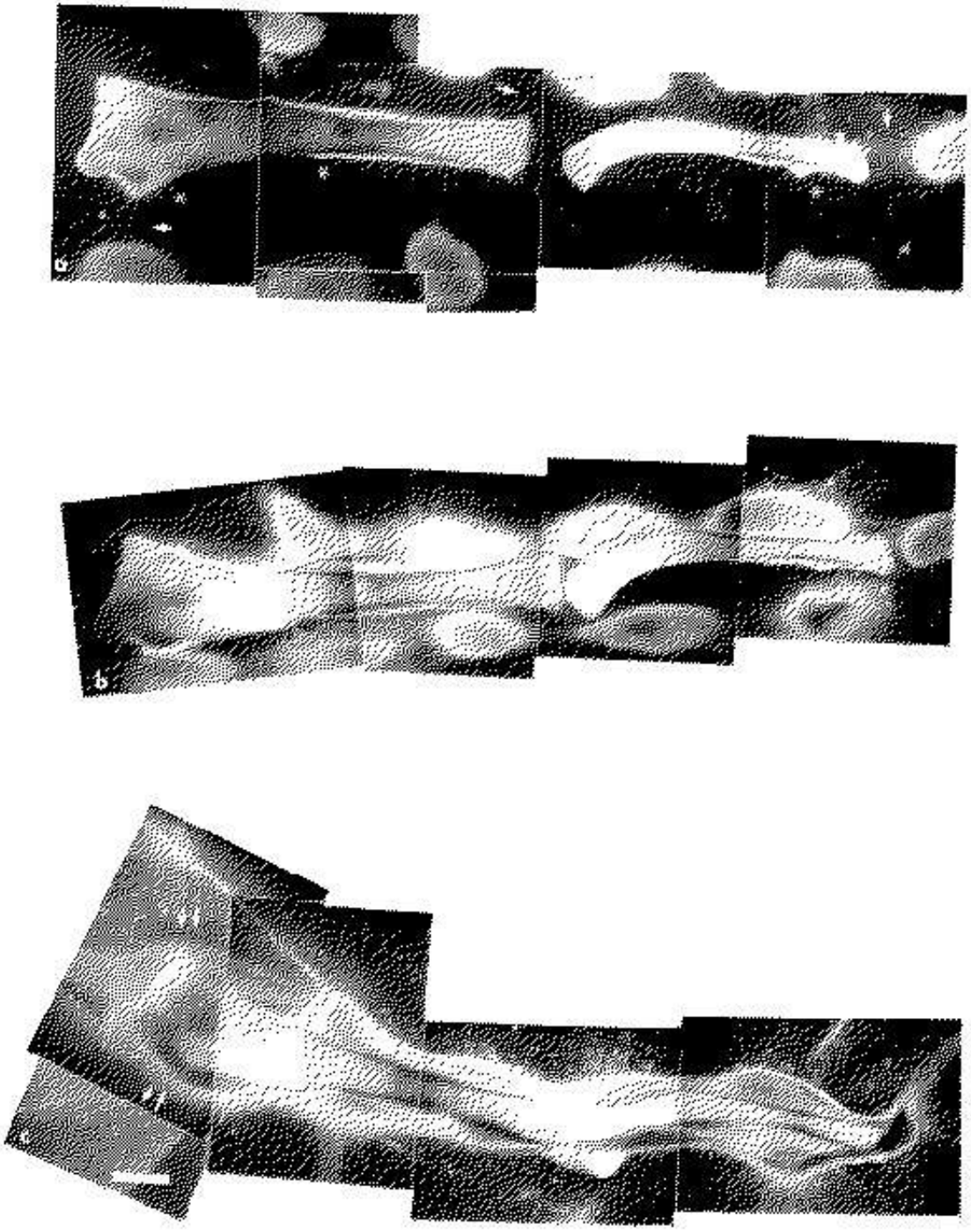
Does cell traction cause the alignment and packing of collagen?

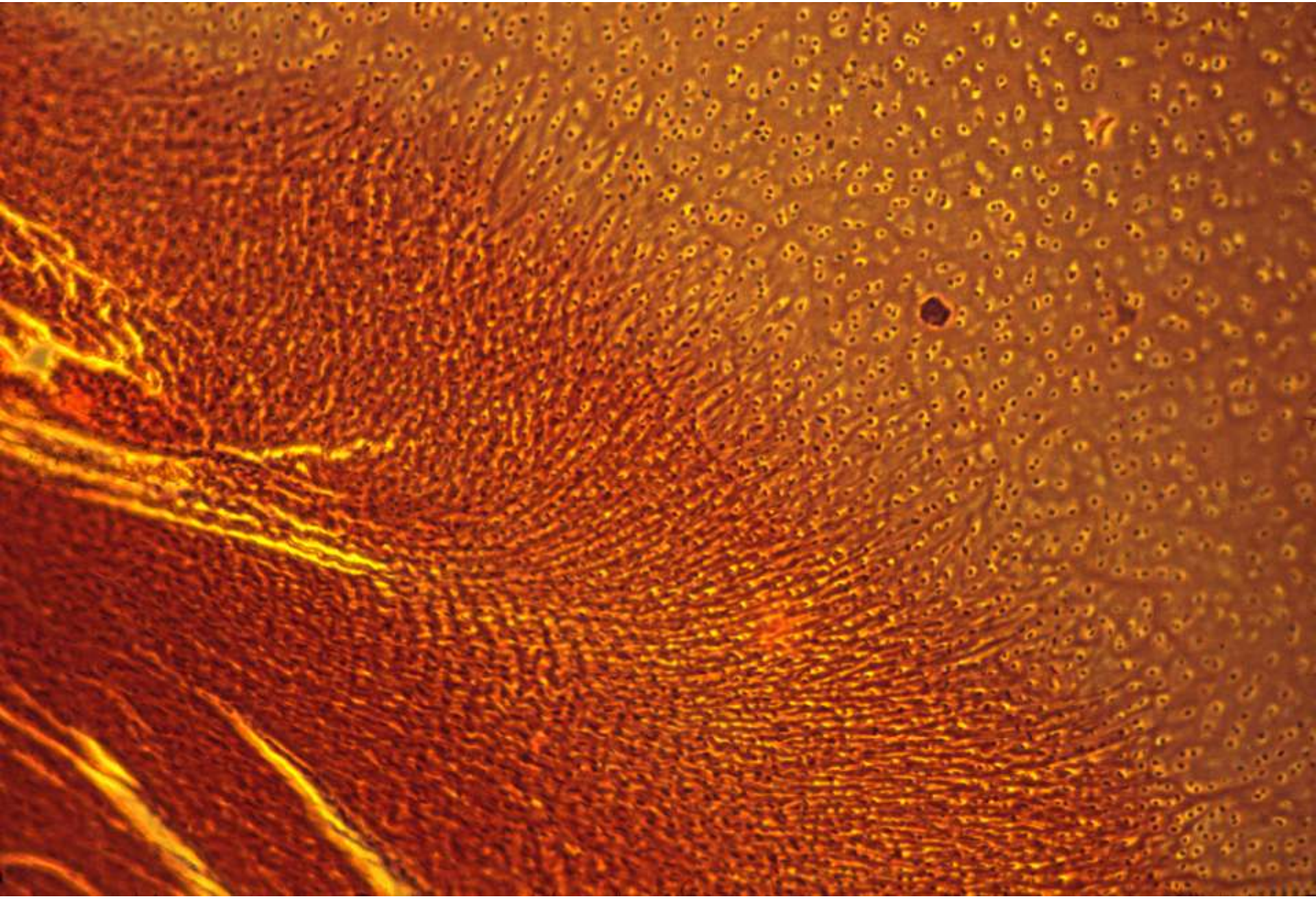






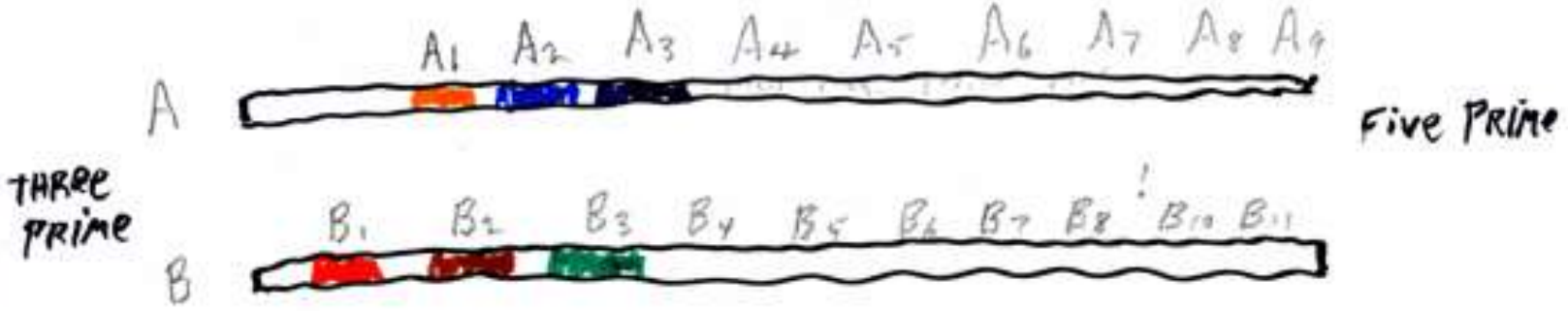


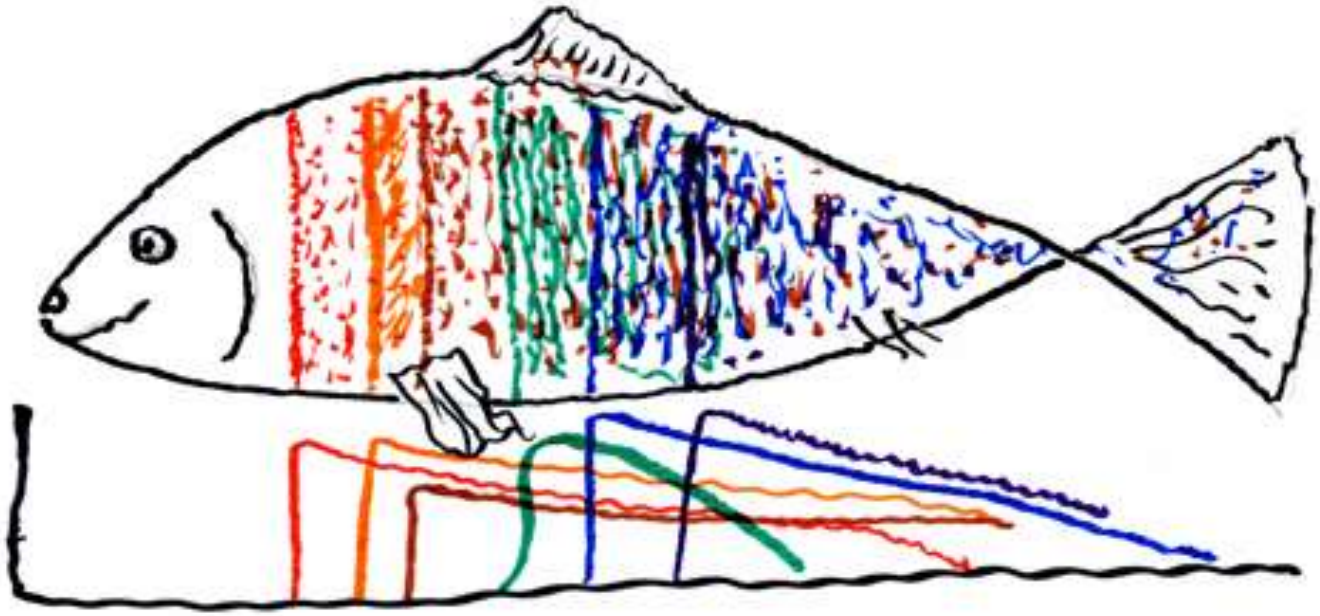




The Sixth Problem.

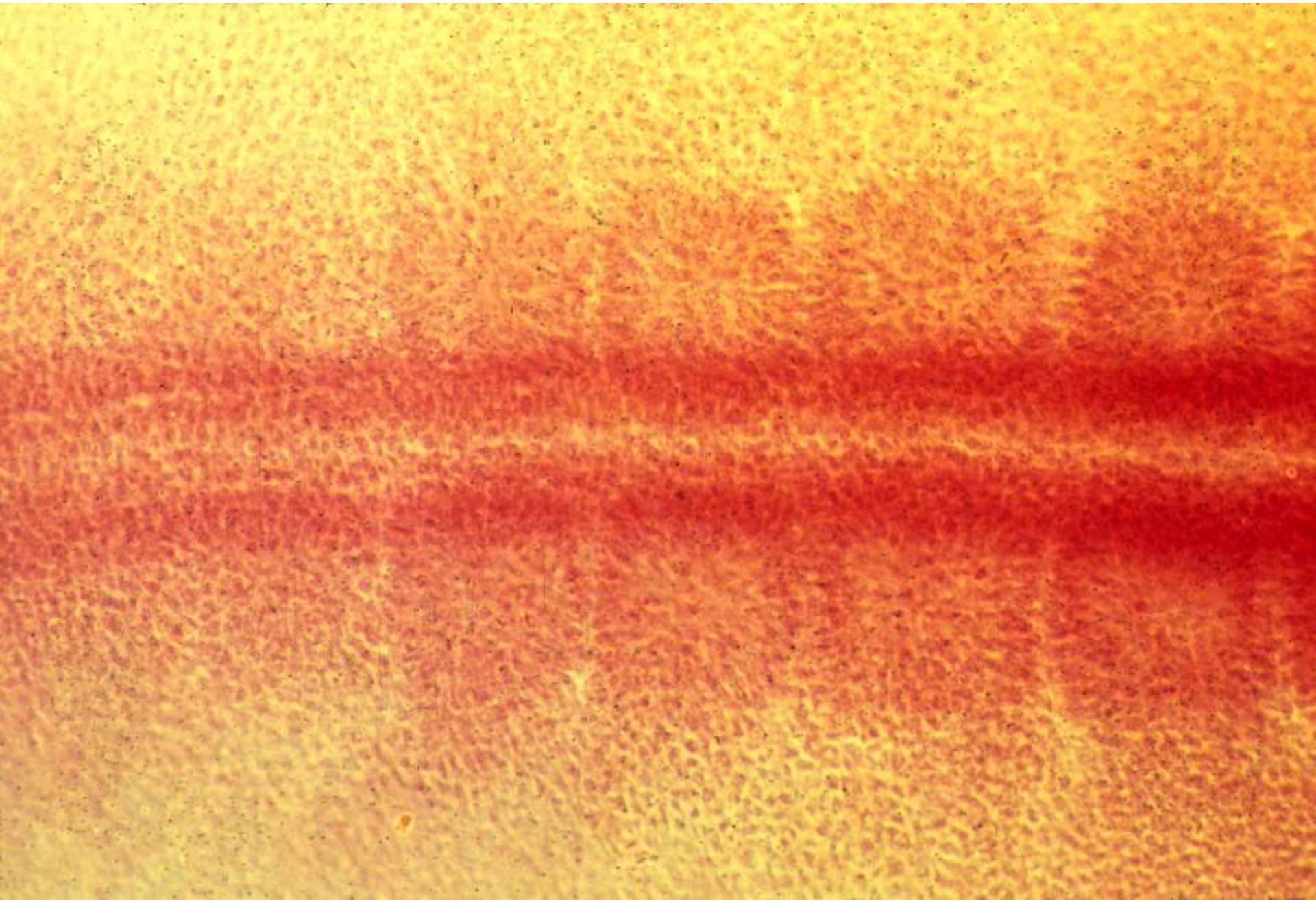
Hox gene expression patterns


A1 A2 A3 A4 A5 A6 A7 A8 A9
A
Five Prime
THREE PRIME
B1 B2 B3 B4 B5 B6 B7 B8 B10 B11
B



The Seventh Problem.

How are somites formed?



The Eighth Problem.

Bone deposition and its response to different physical loads

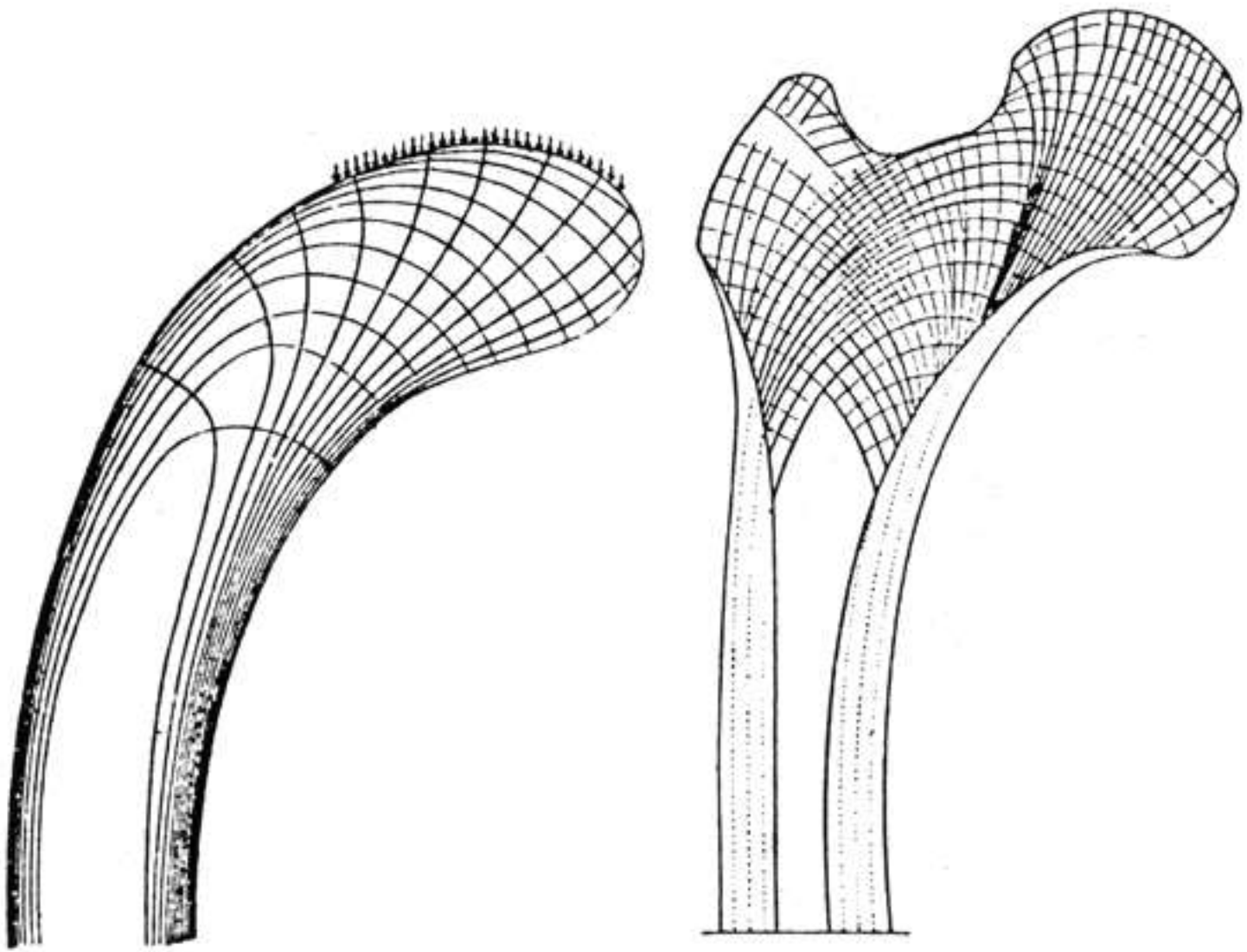
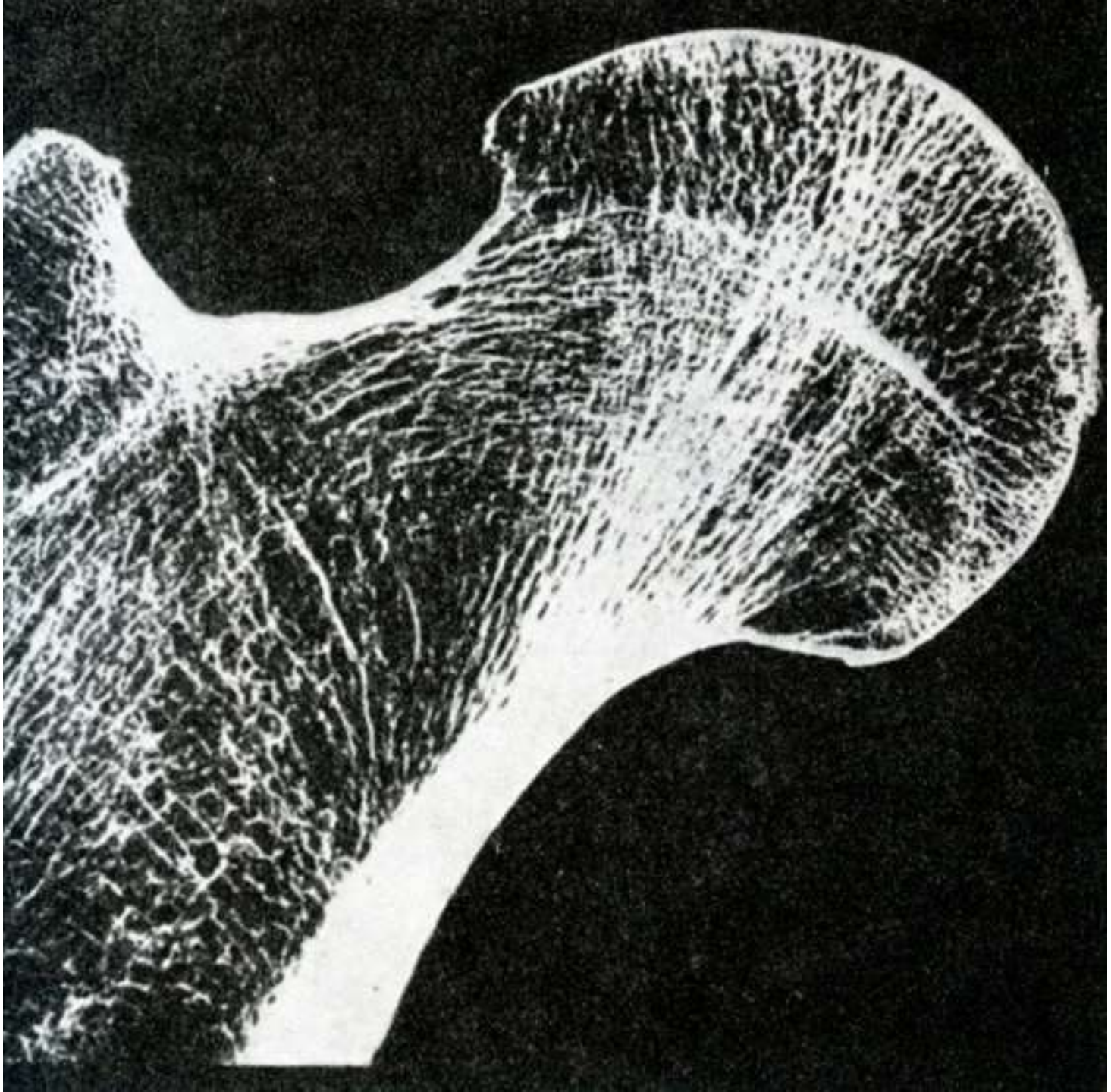


Fig. 463. Crane-head and femur. After Culmann and J. Wolff.



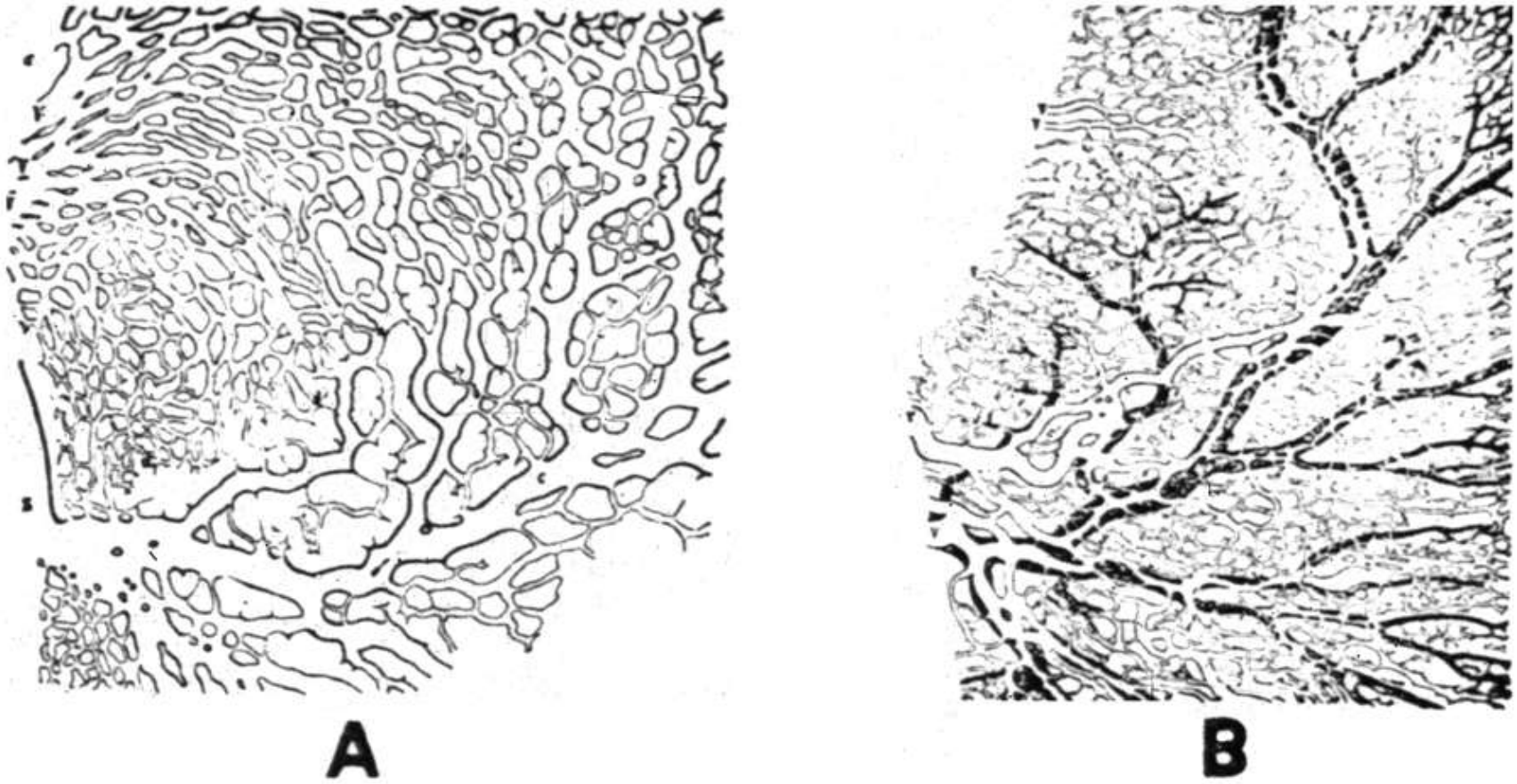


FIG. 9. The chance selection of pathways in the capillary plexus on the chick's blastoderm (*A*), and their conversion into artery or vein (*B*) depending on their relation to the aortas or to the venous end of the heart. Reproduced from Thoma, R. *Untersuchungen über die Histogenese und Histomechanik des Gefässsystems*. Stuttgart, F. Enke, 1893.

ZEN EMBRYOLOGY

MORPHOGENETIC OPTIMIZATION OF FUNCTION

A DESIGN PROBLEM: How To Carry a Given Traffic Load Using The Least Amount of Road

SOLUTIONS: Random Choice and Measurement

or Calculus of Variations

Write Equations For Length and Load

Take Partial Derivatives With Respect to Variables

Set Derivatives Equal to Zero & Solve For Minima

SOME ANALOG SOLUTIONS:

Model Traffic Load By Forces: Surface Tension or Weights

BLOOD VESSEL SOLUTIONS

Make Longitudinal Contractility of Vessels Approximately Proportional to Their Blood-Carrying Capacity

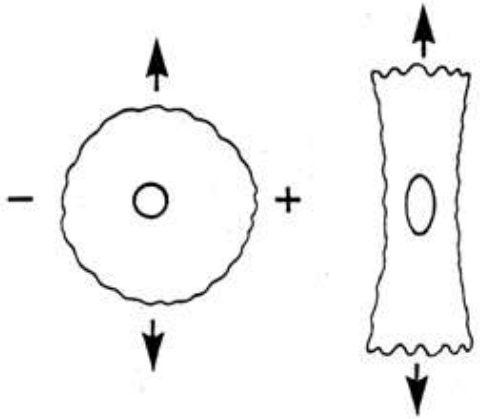
$\overleftrightarrow{T_L} = \frac{1}{2}\overrightarrow{T_c}$; $\frac{T_c}{R_c} = P$

Therefore, For Relatively Constant P Both T_L And T_c Will Vary In Direct Proportion to Vessel Diameter

The Ninth Problem.

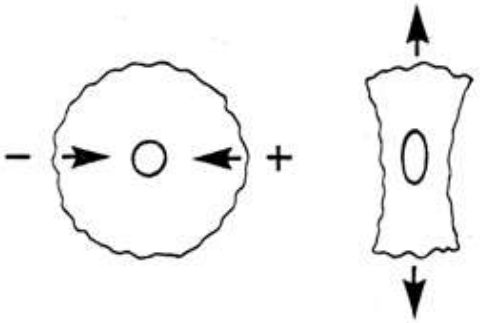
Galvanotaxis: electric field effects

1.



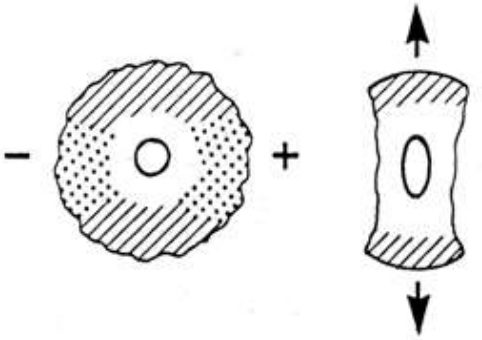
STIMULATION OF PROTRUSION
IN THE DIRECTION PERPENDICULAR
TO THE ELECTRIC FIELD

2.

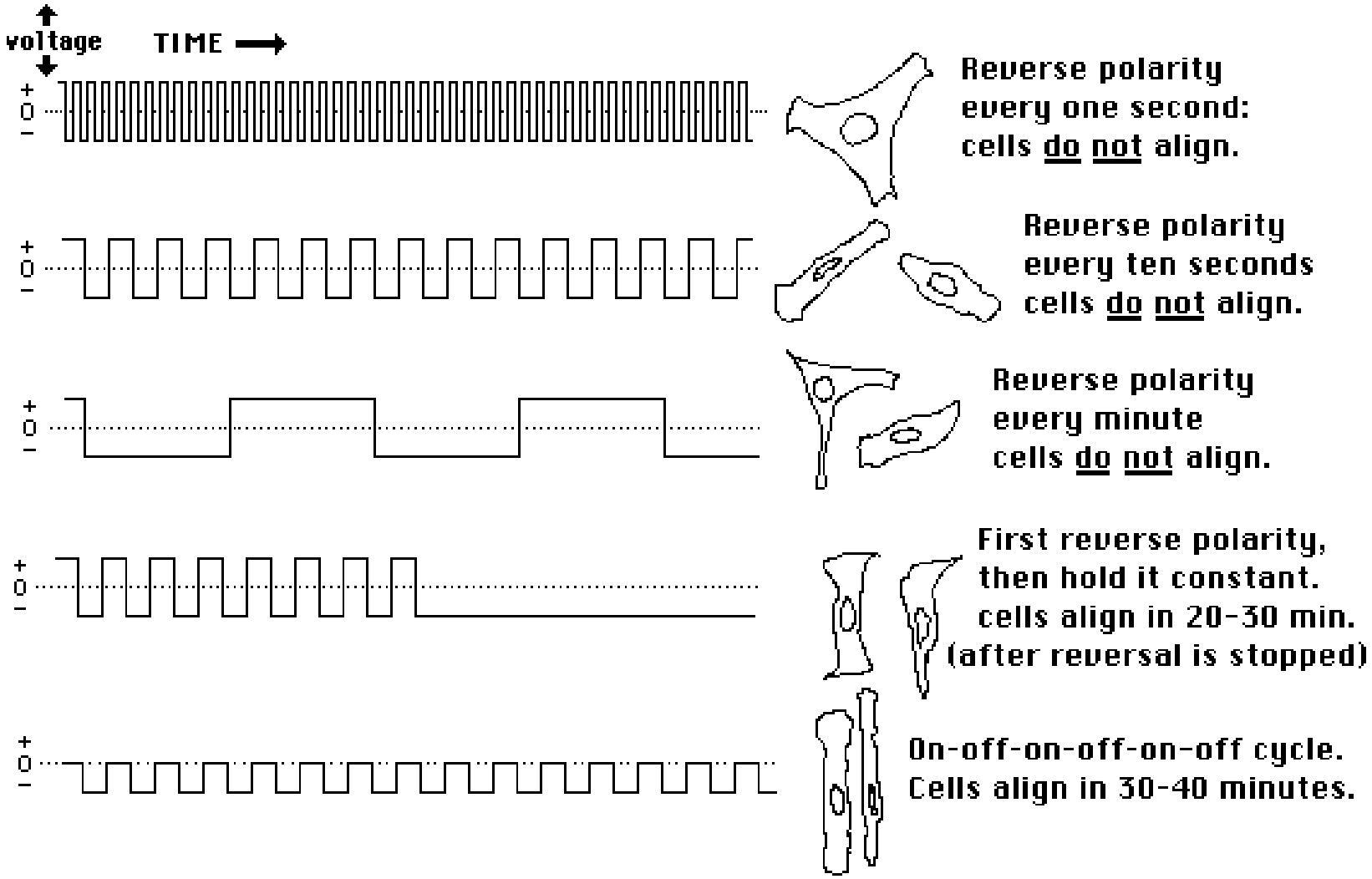


STIMULATION OF CONTRACTION
IN THE DIRECTION PARALLEL
TO THE ELECTRIC FIELD

3.



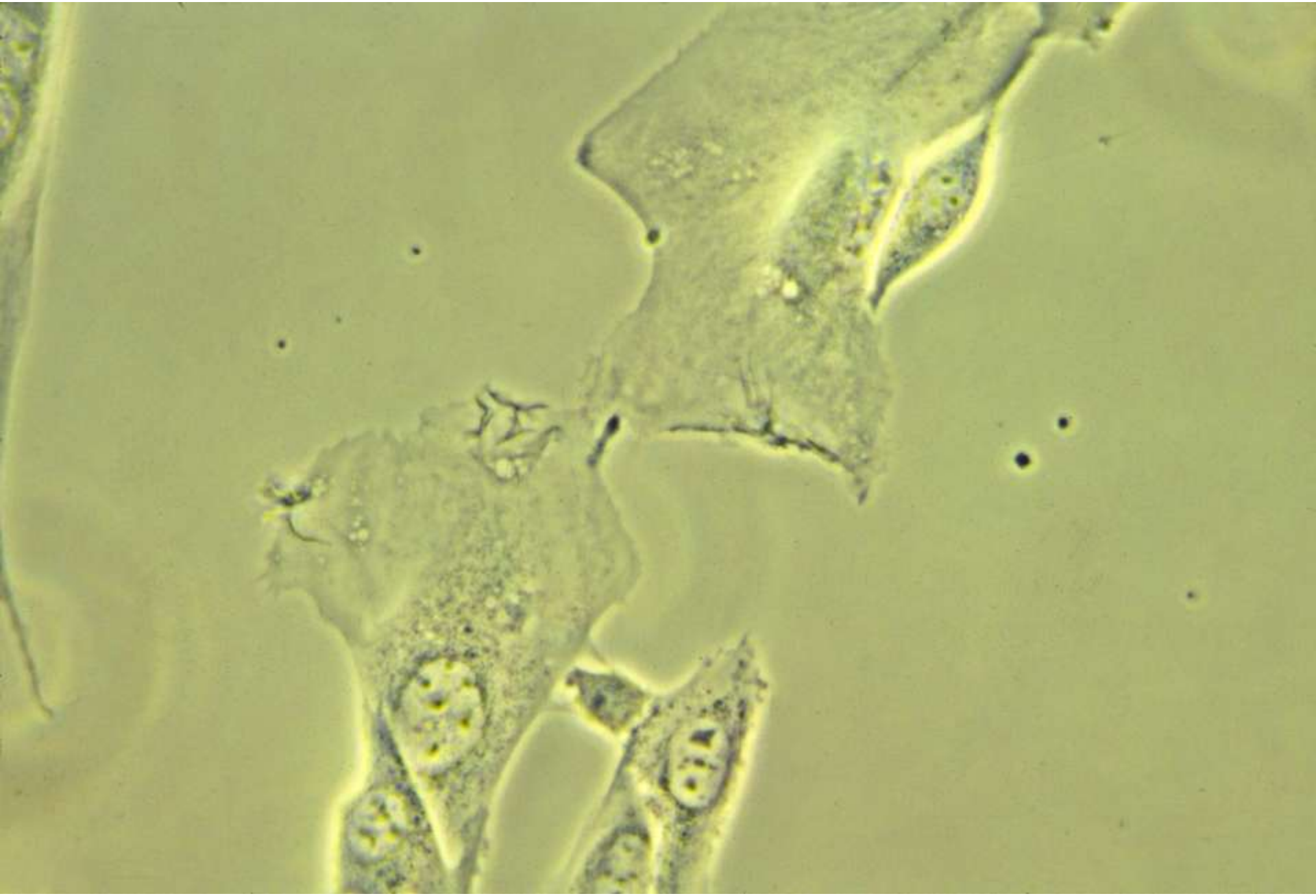
WEAKENING OF ADHESIONS
ALONG THE CELL MARGINS
MOST HYPERPOLARIZED AND
DEPOLARIZED BY THE
ELECTRIC FIELD


voltage
TIME
+
0
−
Reverse polarity
every one second:
cells do not align.
Reverse polarity
every ten seconds
cells do not align.
Reverse polarity
every minute
cells do not align.
First reverse polarity,
then hold it constant.
cells align in 20-30 min.
(after reversal is stopped)
On-off-on-off-on-off cycle.
Cells align in 30-40 minutes.

The Tenth Problem.

Force transmission tangentially through fluid-mosaic membranes

1) The locomotion of fibroblasts and other tissue cells is achieved, not by a simple cycle of protrusion, adhesion and contraction, but rather by means of shearing forces (traction) exerted tangentially through broad areas of the plasma membrane.



A Dozen Questions About How (and Why!) Tissue Cells Crawl:

1) Self-perpetuation of the many special properties of "front" ends.
(Ruffling, actin assembly, adhesion initiation, rearward force exertion)

2) Microtubule control of cell polarity and actin distribution.
(Why/how MT poisons broaden "fronts" and strengthen contraction)

3) What is the molecular basis of contact inhibition?
(Is actin assembly locally inhibited near cell-cell adhesions?)

4) What (which?) abnormality of invasive cells escapes C.I.?
(Why can sarcoma cells & macrophages continue actin assembly?)

5) How (& why?) do crawling cells let go adhesion under their middle?
(What is the mechanism of "letting go"; and why do it beneath center?)

6) Are focal adhesion plaques crystallizations or aggregations?

7) Formation of "stress fibers" *(Nucleation from adhesion plaques or gathering-together of already fibrous actin from cortical meshworks?)*

8) What functions are served by different myosins? *(Do conventional myosins pull the actin rearward? Other myosins control assembly?)*

9) Contact guidance = Topographic responses to substratum shape.
(Actin assembly favored parallel to sharp kinks; inhibited perpendicular?)

10) Which anatomy-generating functions does traction serve?
(Tendon formation? Organ capsule formation? or just cell mov't?)

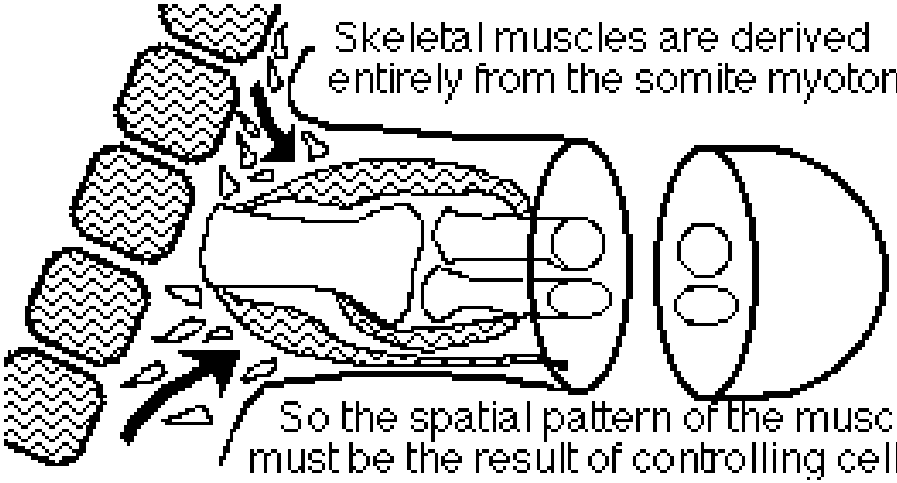
11) Why do cell aggregates round up, engulf & sort out?
(Maximization of cell-cell adhesion? Or cortical contraction?)

12) Cells rounding up, in mitosis, high hydrostatic pressure, EDTA?
(Does membrane let go of glass? Or cytoskeleton let go of membrane?)

Harris, A.K. (1998). A dozen questions about how tissue cells crawl. In: *Cell Behavior: Control and Mechanism, Biochemical Society Symposium No. 65*, edited by J.M. Lackie; Portland Press Inc., London. pp. 315-341. PMID: 10320947

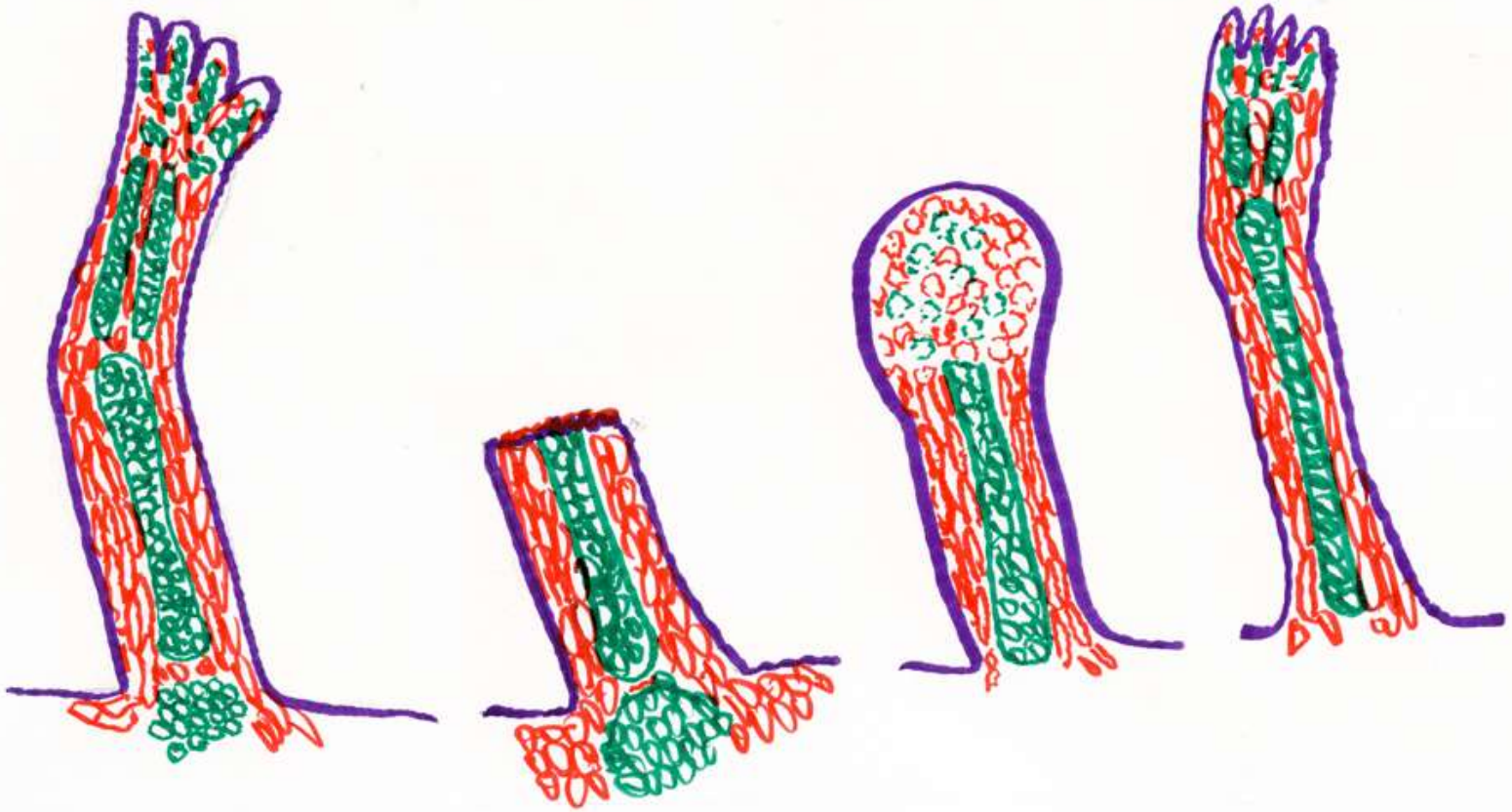
The Eleventh Problem.

Limb regeneration in salamanders:
Why not in people too?



Some cells are already determined and migrate to their eventual anatomical position

Limb regeneration in salamanders



The Twelfth Problem.

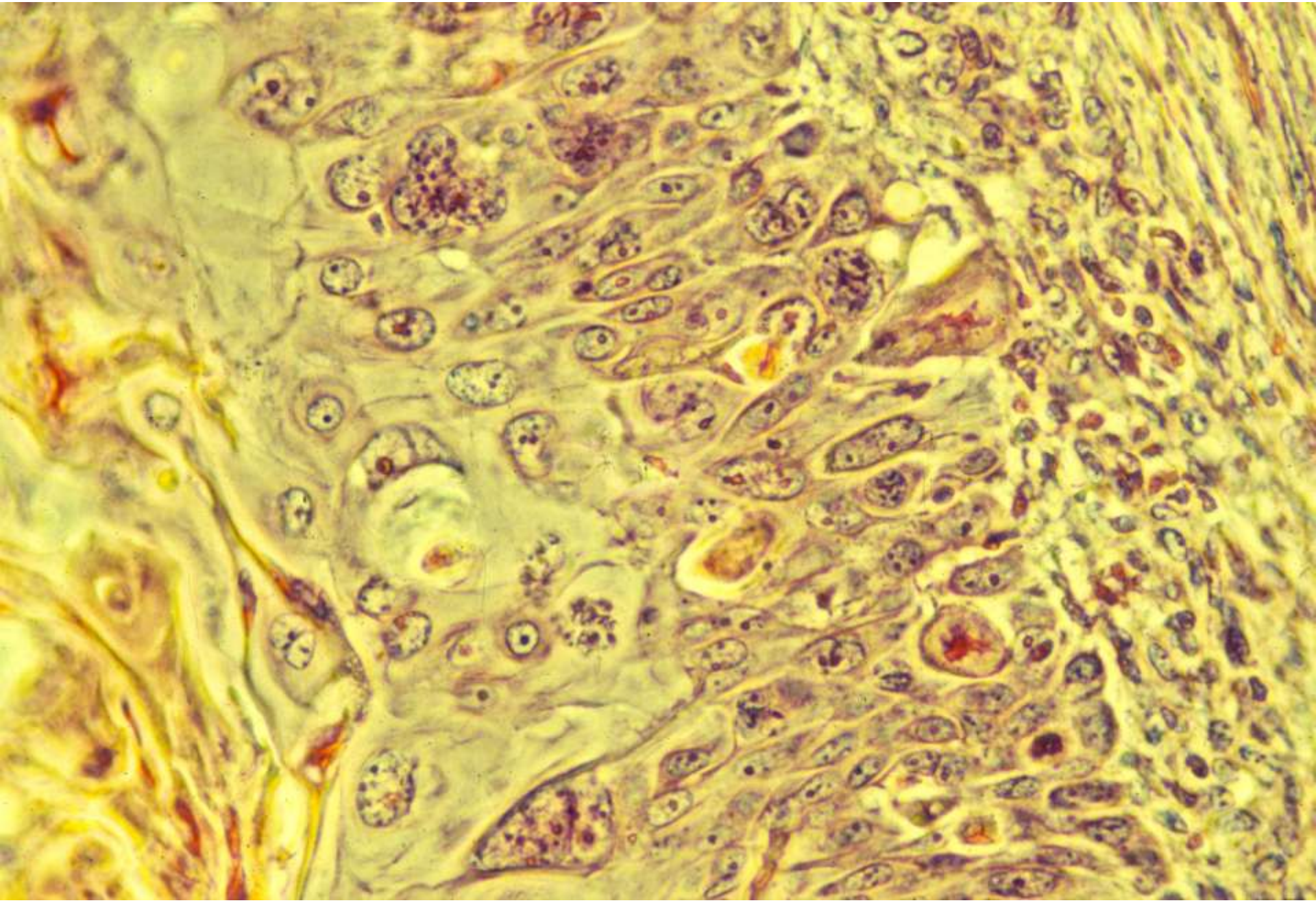
Explanation and cure of autoimmunity

Immunology, Allergies, and Autoimmune Diseases in Relation to Embryology

http://www.albertkharris.com/2012_immunology.html

The Thirteenth Problem.

Why cancer chemotherapy drugs work as well as they do, considering that cancer cells don't really grow faster



Cancer, from an Embryological Point of View

http://www.albertkharris.com/2012_cancer.html