

Discovering Mechanisms in Cell Biology

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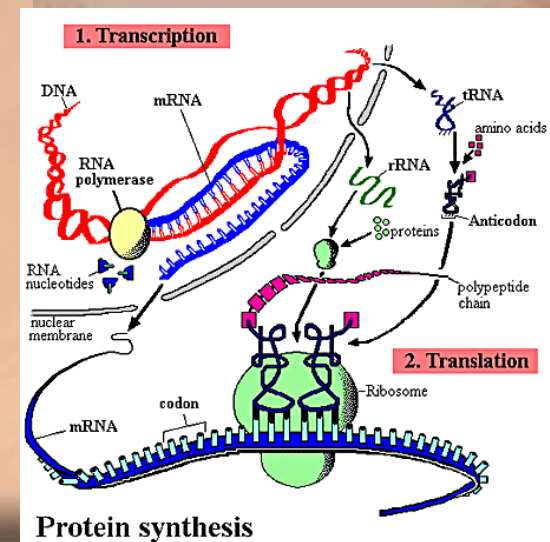
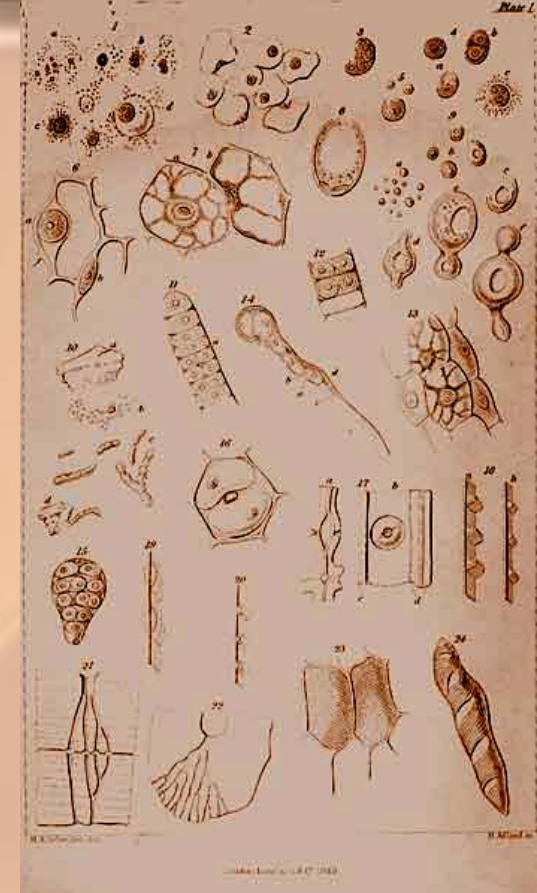
Outline



1. Mechanisms and mechanistic explanation
2. Case example: The discovery of the cell's respiratory mechanism
3. Reasoning about, discovering, and experimenting on mechanisms
4. Reduction, generalization, and idealization
5. Conclusions

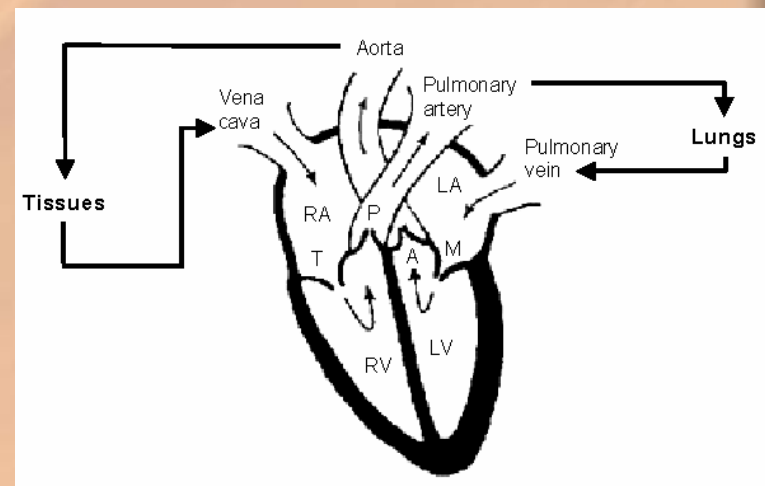
A long legacy of mechanistic thinking in biology

- Animal heat: Lavoisier and Laplace
- Schleiden and Schwann's cell theory
- Plant and animal chemistry: Wohler, Leibig, Berzelius
- Mechanisms of cell division
- Biochemical mechanisms (fatty acid metabolism, fermentation, respiration)
- Mechanisms of DNA replication and protein synthesis
- Mechanisms for active transport of ions across neural membranes



Mechanisms as Coordinated Causal Systems

- A mechanism is a structure performing a function in virtue of its **component parts**, **component operations**, and their **organization**. The orchestrated functioning of the mechanism is responsible for one or more phenomena (Bechtel, 2006, Bechtel & Abrahamsen, 2005; cf. Bechtel and Richardson, 1993, Glennan, 1996, 2002, Machamer, Darden, & Craver, 2000).
- Example: muscles in heart contract and relax while valves open and shut
 - Resulting in the phenomenon: circulation of the blood



Conception of Mechanism Is Not Static

- Descartes focused on size and shape of hypothetical corpuscles
 - All operations were action by direct contact
- Newton liberalized the characterization of operations
 - Allowed for forces operating at a distance
- 20th century theorists identified and emphasized dynamical interactions
 - Cyberneticists emphasized negative feedback as a regulatory mechanism
 - Biochemists recognized the widespread use of cycles
 - Self-organizing systems realized through autocatalysis
 - Small worlds and scale-free networks

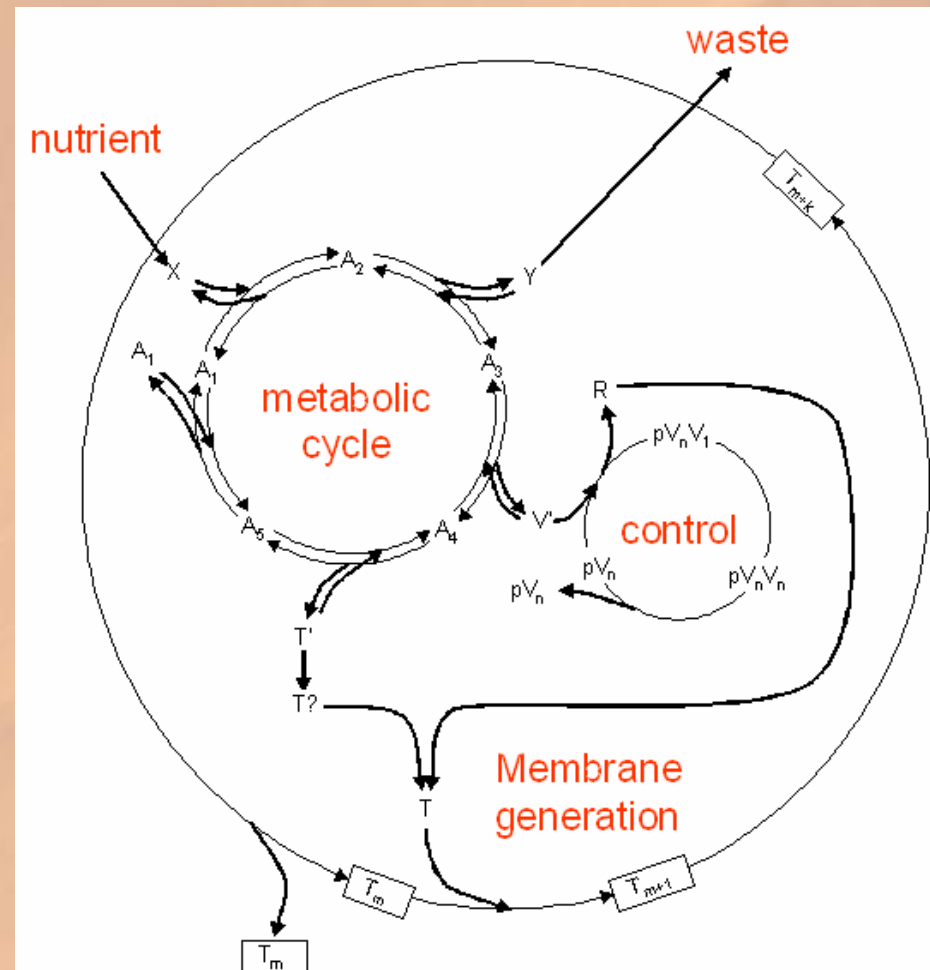
Autonomous Mechanisms

- Especially in biology, we are dealing with mechanisms (or systems of mechanisms) that are active
- Autonomous systems are ones that maintain themselves in a non-equilibrium state by controlling the flow of matter and energy through them



Tibor Gánti's Chemoton

- Gánti developed a hypothetical account of the simplest possible chemical system that would exhibit the characteristics of life
- Metabolic cycle: extracts matter and energy from nutrients
- Membrane system: generates membrane barrier that gives identity to the system
- Control system: stores and deploys information



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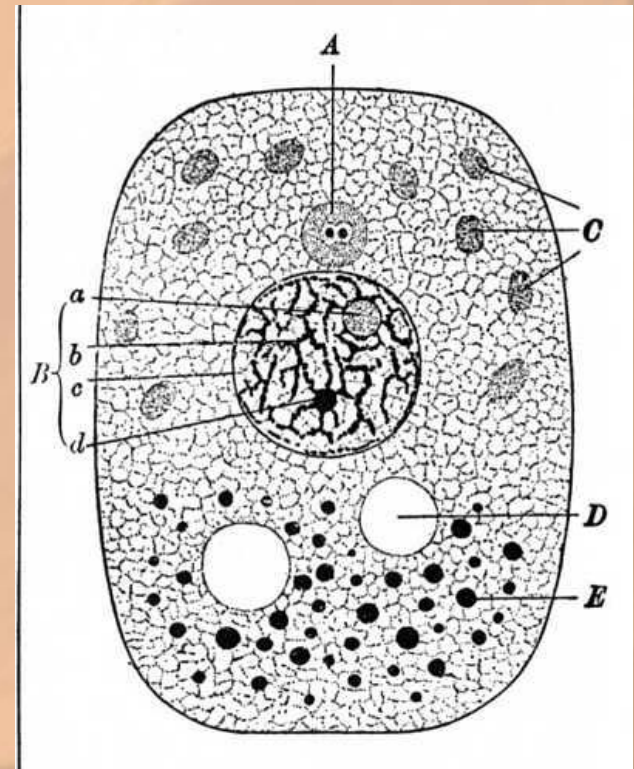
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Roots in Classical Cytology

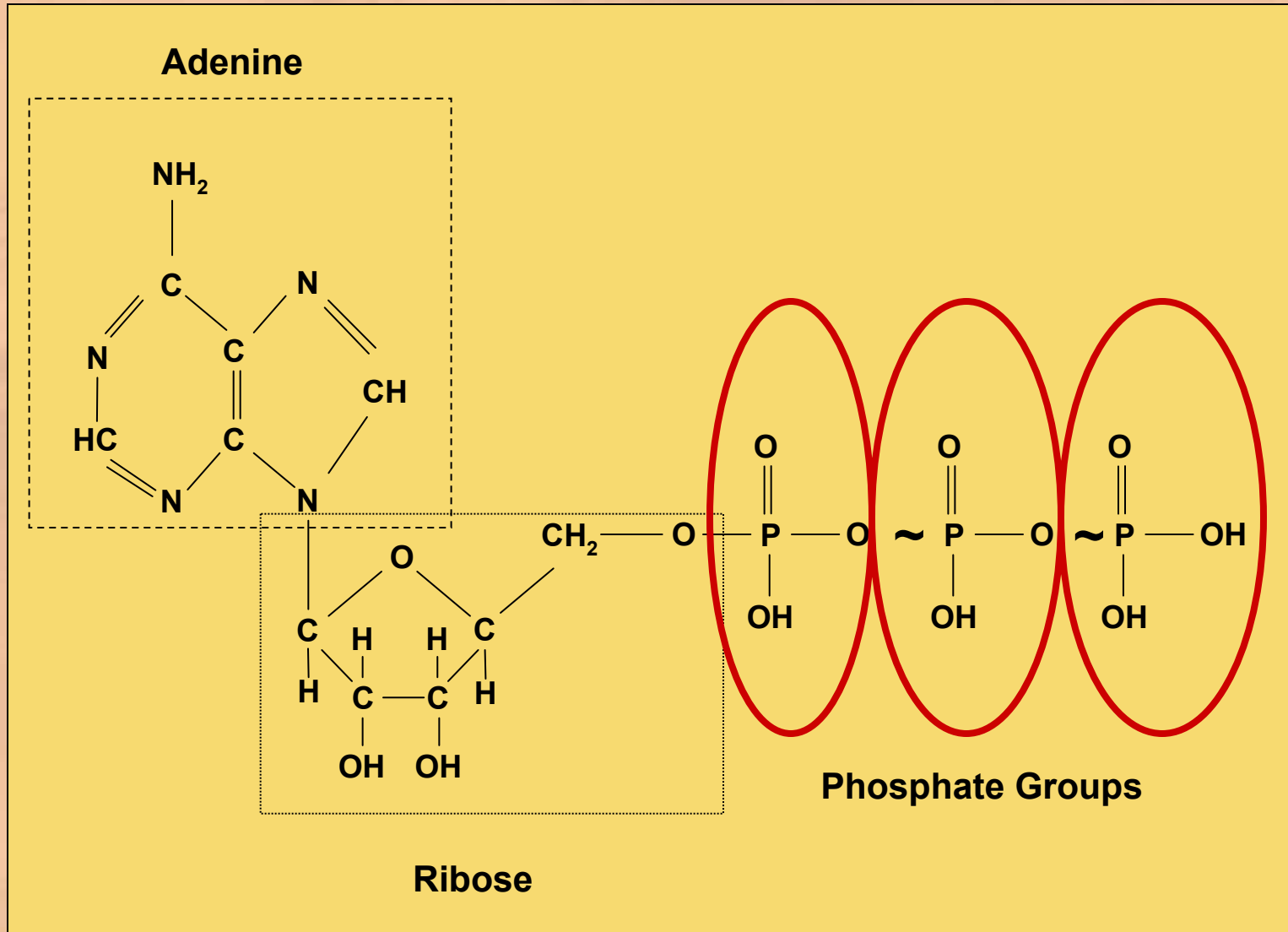
- With the advent of better microscopes, stains, and fixatives, cytologists identified not only cells but also some aspects of their internal structure
 - Nucleus
 - Chromosomes
 - Mitochondria
 - Golgi apparatus
- Ongoing disputes as to whether these were real or artifacts of stains and fixatives



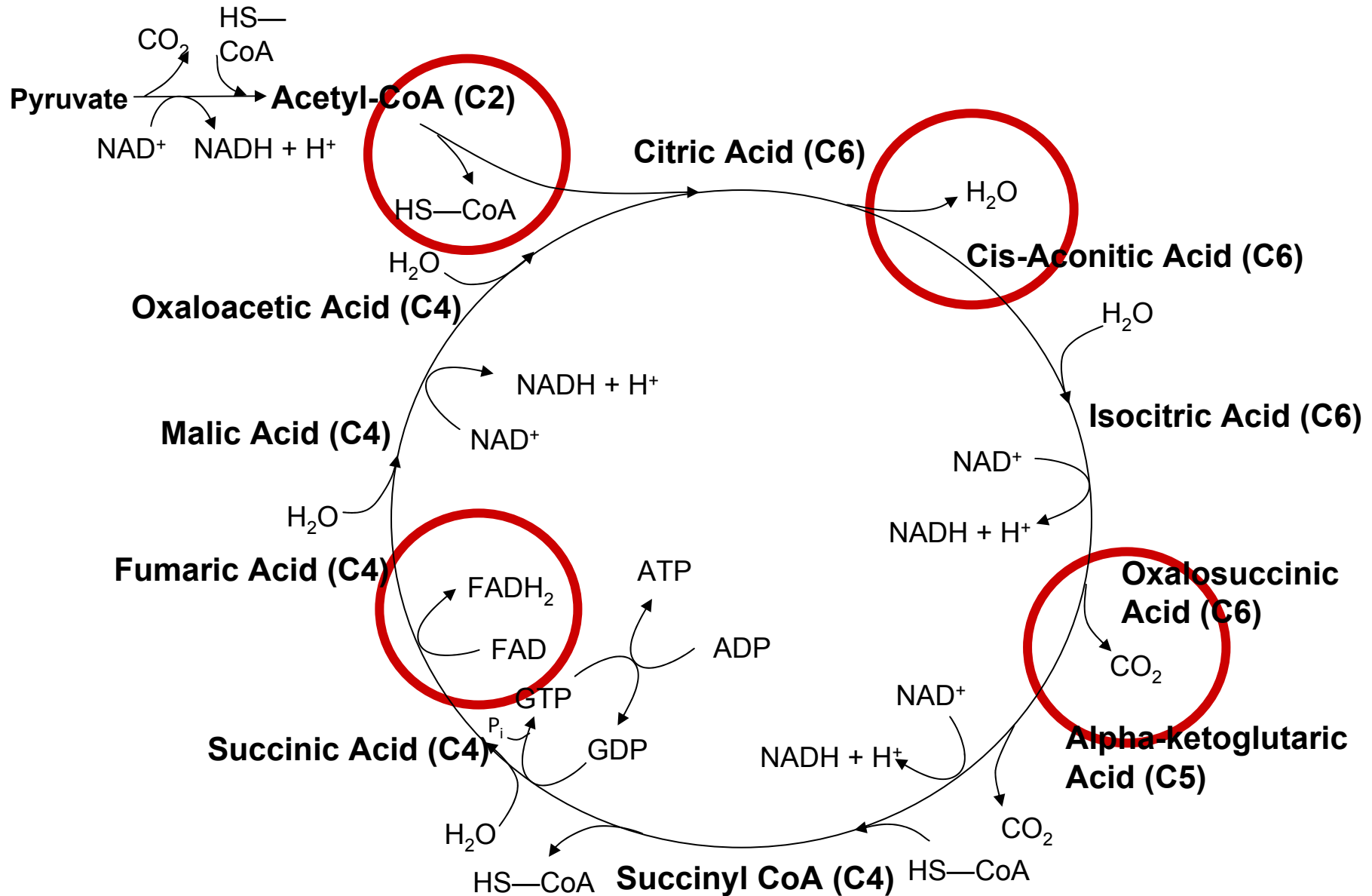
Roots in Physiological Chemistry

- By the early decades of the 19th century physiological changes could be described in terms of chemical elements
 - Fermentation: $C_6H_{12}O_6 \rightarrow 2 C_2H_5OH + 2CO_2$
 - Respiration: $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$
- Attempts to explain reactions as additions and deletions of atoms were underconstrained
- Discovery of chemical groups at end of 19th century made it possible to account for the reactions actually occurring in living systems
 - Oxidation and reduction—transfer of $2H$ or $2e^-$
 - Phosphorylation—adding a PO_4 group
 - Decarboxylation—removal of a CO_2 group

ATP



Krebs (Cytric Acid) Cycle

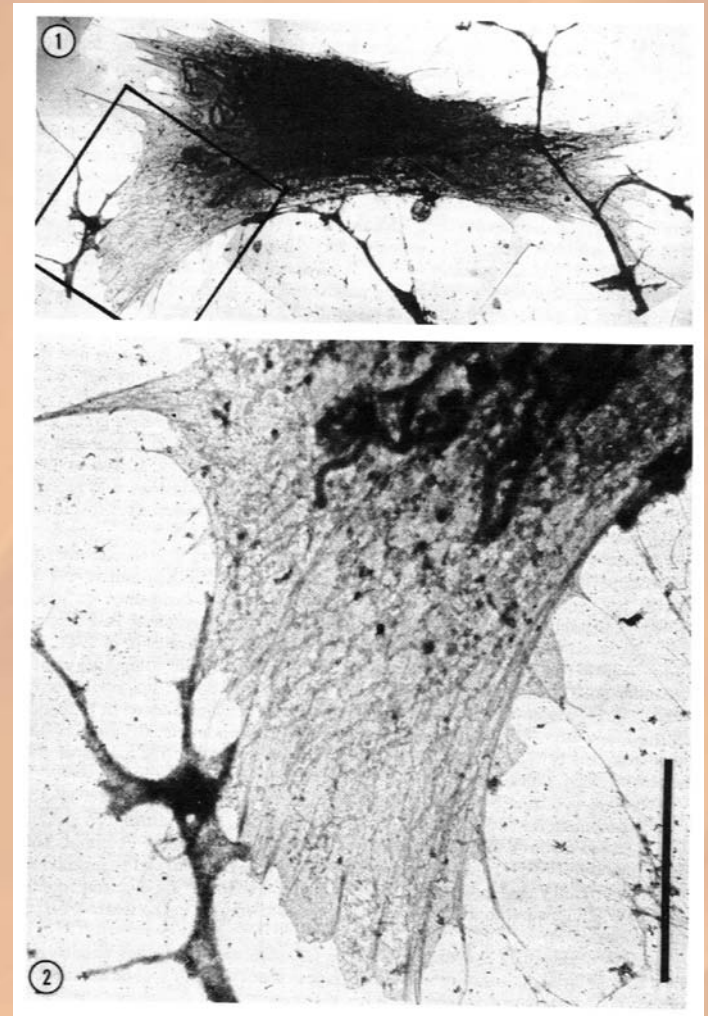
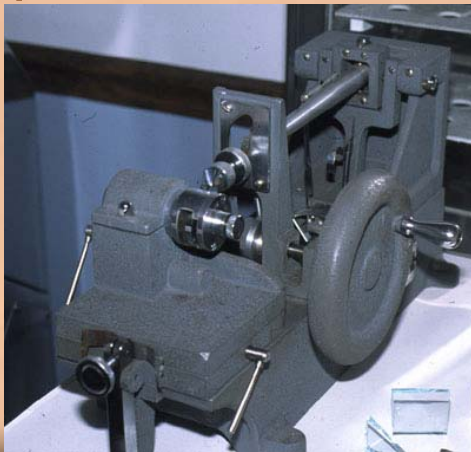


The No Man's Land Between Cells and Macromolecules

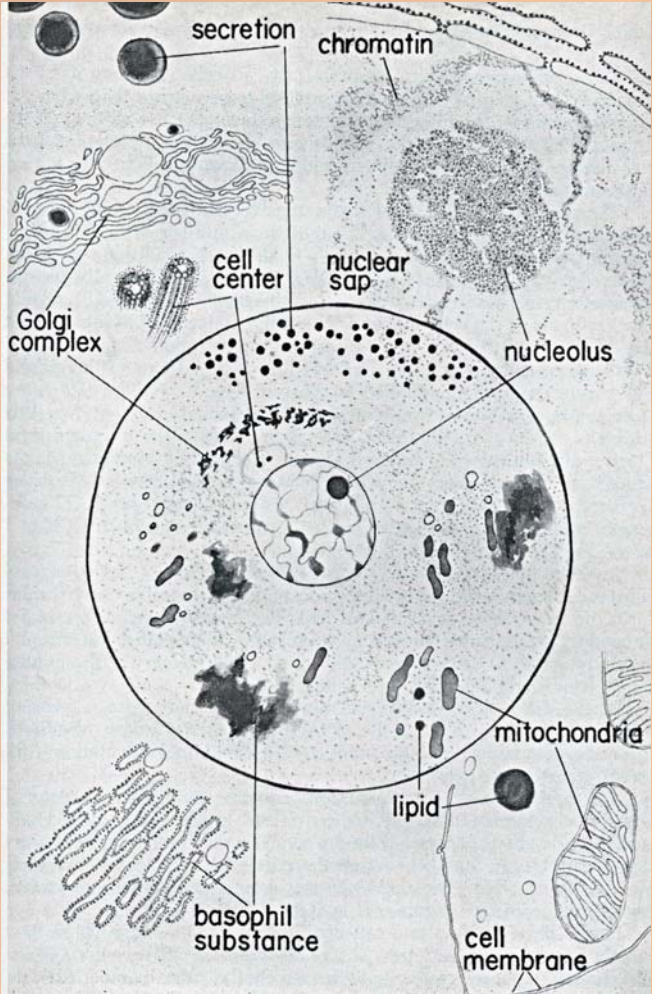
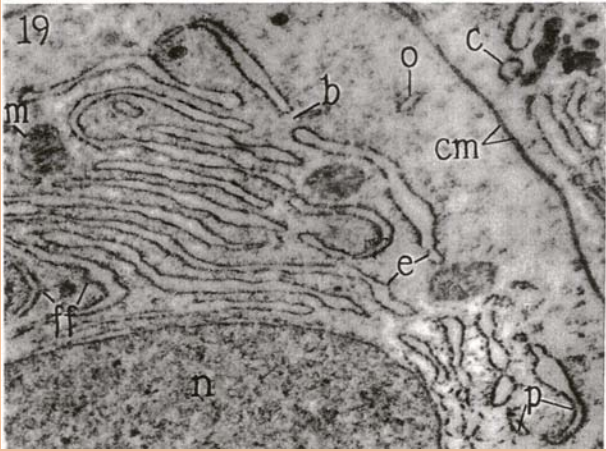
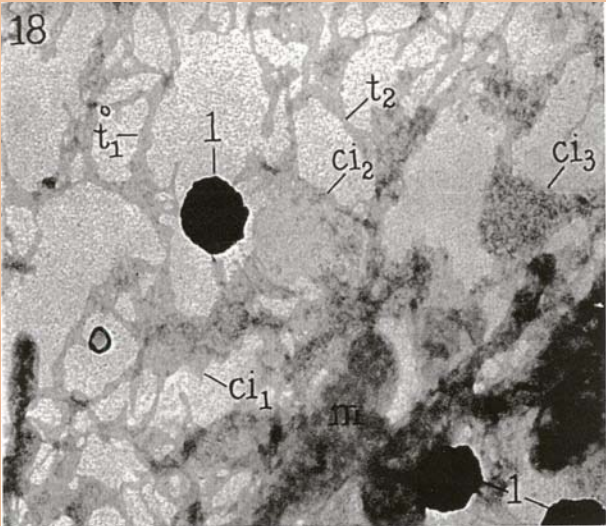
- The light microscope and its variants could not resolve most structures at the level of cell organelles
- Biochemists focused only on enzymes as they operated in an aqueous milieu (sacs of enzymes)
 - Succeeded with glycolysis, Krebs cycle, and electron transport, but not with oxidative phosphorylation
 - Oxidative phosphorylation occurred only in preparations that included membrane fragments
 - And the membranes were a nuisance (Lehninger)

Entering No Man's Land from Above

- Use of the new electron microscope in mid-1940s
 - First micrographs of cells used whole cells prepared through tissue culture (Porter, Claude, & Fullam)
- Techniques for thin sectioning developed in 1950s

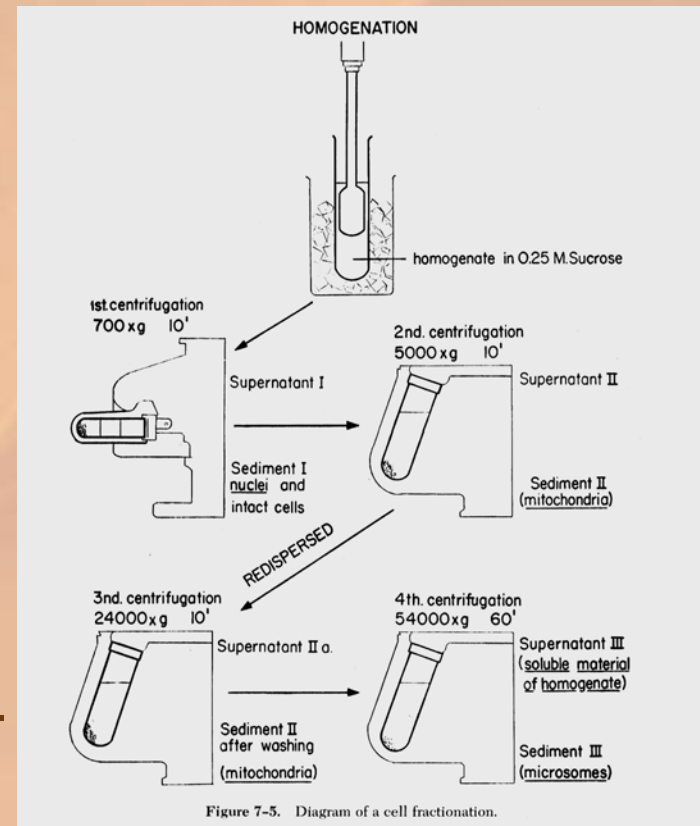


Discovering New Cell Organelles



Entering No Man's Land from Below

- Introduction of cell fractionation by Claude and colleagues
- By repeatedly centrifuging cell preparation, could separate different constituents and assay their reactivity
 - Mitochondria contain major oxidative enzymes—power plant of the cell
- Result: Localization of biochemical functions in cell organelles



Developing a Productive Bridge Between Cytology and Biochemistry

- In 1950s, George Palade discovered cristae (infoldings of the inner membrane of the mitochondria)
- Cristae quickly became candidate locus for ATP formation and began to explain membrane nuisance

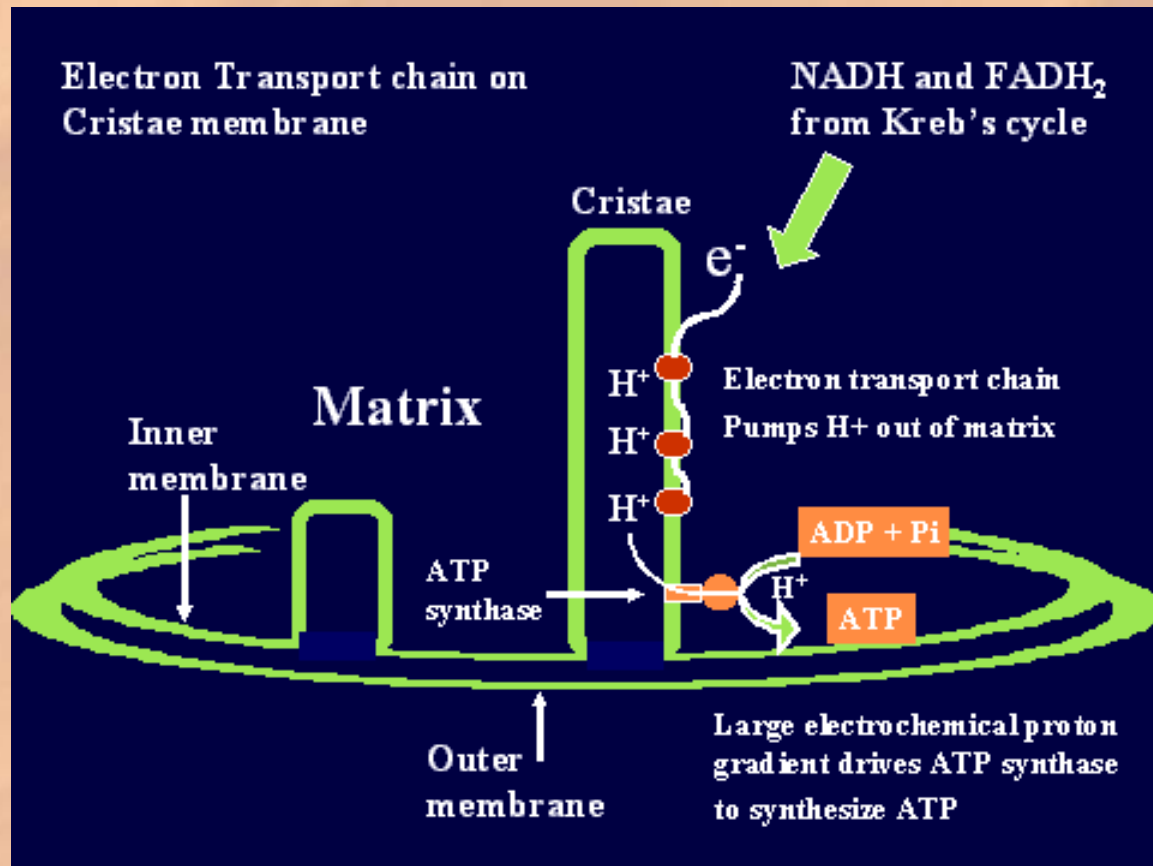


Even More Structure and Function

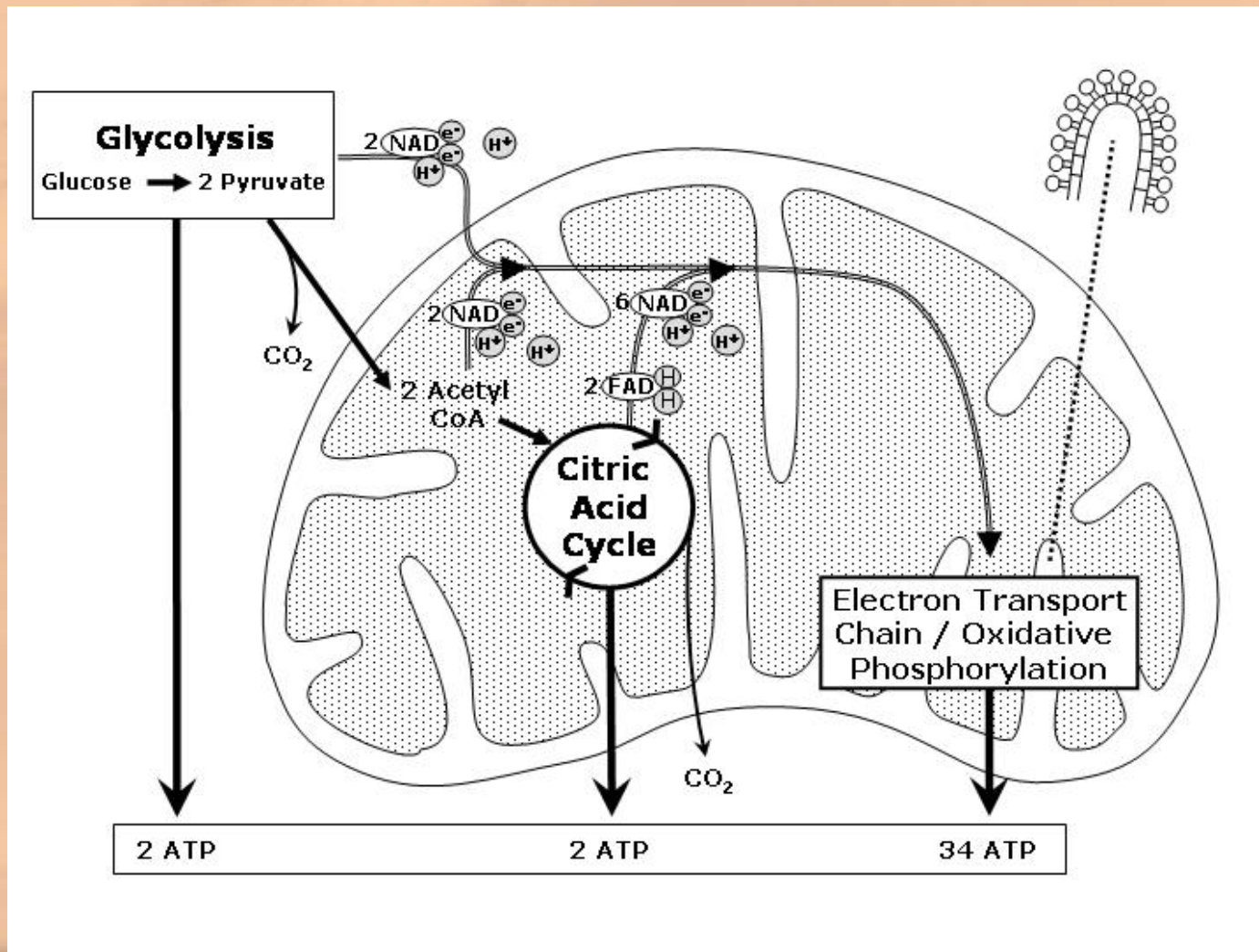
- Fernández-Morán developed reverse staining which revealed particles on mitochondrial membrane
- Racker et al. identified these as the locus of the ATPase
- Mitchell proposed that proton gradient over membrane provided energy for ATP synthesis



Localizing Electron Transport and Oxidative Phosphorylation in Cristae



Localization: Linking Structure and Function



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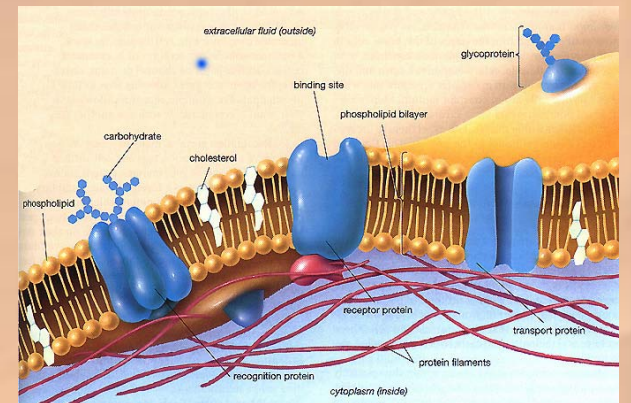
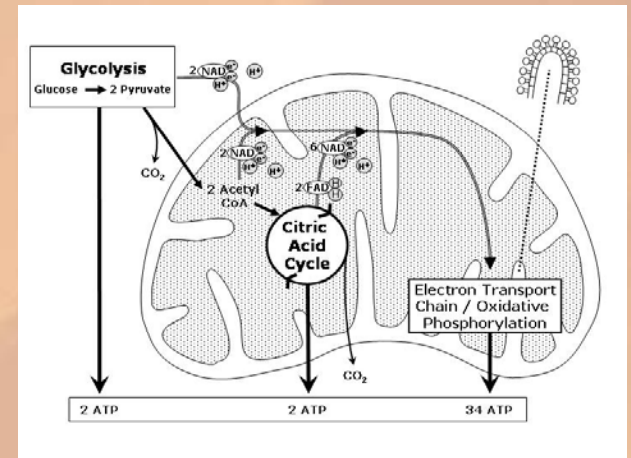


Reasoning About Mechanisms

- In a mechanism, different sorts of parts perform different operations
 - These are related to each other in complex ways
- To understand how the parts and operations of the mechanism are orchestrated so as to realize the phenomenon of interest requires representing and simulating these parts and operations
 - And keeping track of how they affect each other
- Linguistic representations certainly play a role
 - Often take the form of a narrative or story

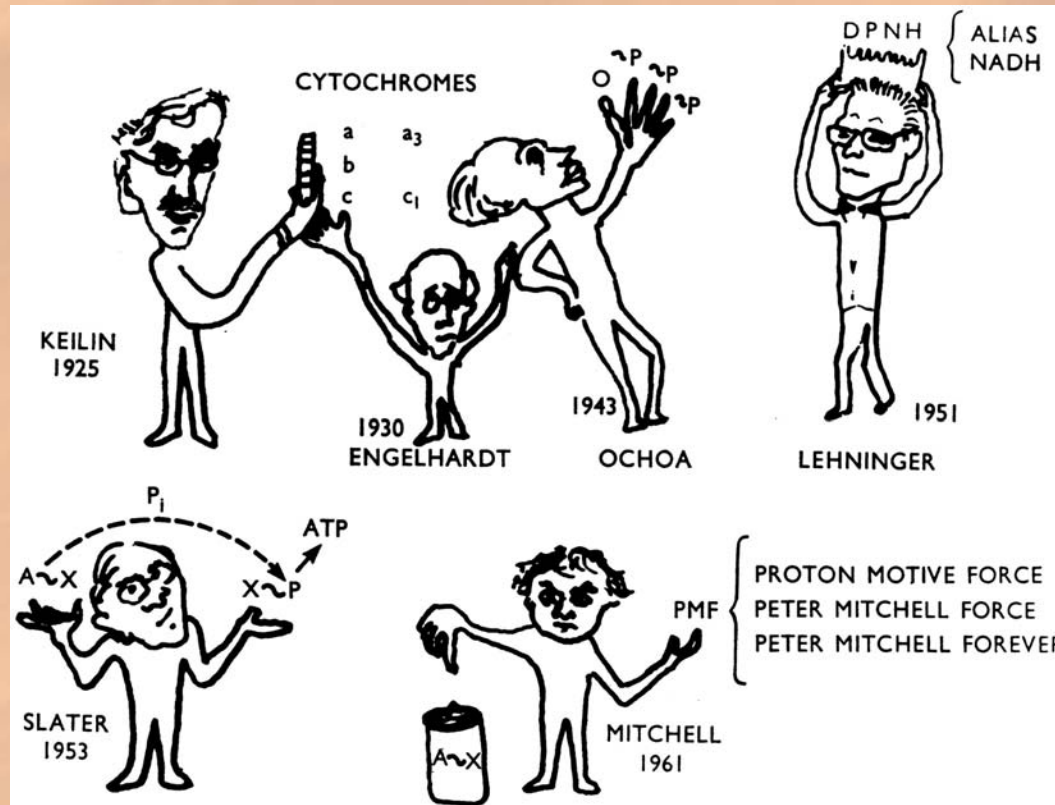
Centrality of Diagrams

- Often researchers find it more useful to represent a mechanism diagrammatically
 - Use the resources of space to represent spatial relations between parts (or less often, to represent time)
 - Use arrows to represent time, transformation, or causation
 - Use color and shape to help distinguish parts (and focus attention)



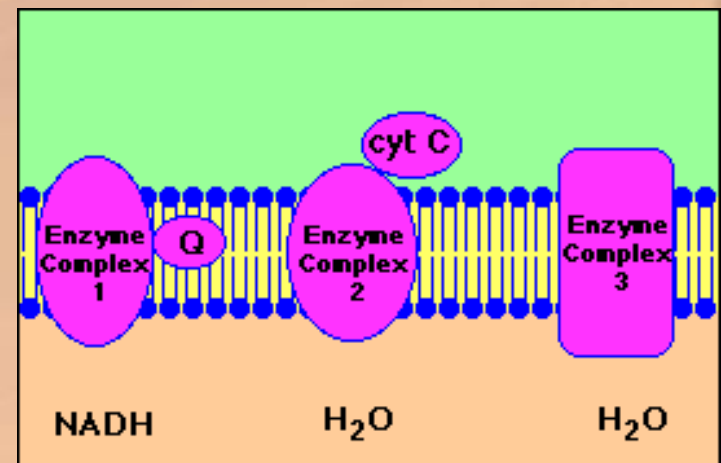
Diagrams

- And sometimes used to keep track of the scientists themselves and their positions



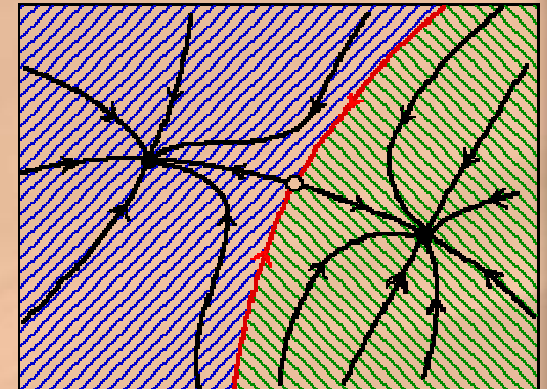
Simulating Mechanisms

- To understand a mechanism, one needs to capture dynamical processes
 - The execution of the individual operations
 - The relations between the operations
- This requires simulating the running of the mechanism
 - With static diagrams, the user must imagine the execution of the operations
 - Animated diagrams often make these relations clearer



Mathematical Modeling

- Our imagination breaks down with complex mechanisms
 - Especially when many operations are occurring simultaneously and each affects the others
- If we can write and solve equations to describe various operations, this is a more reliable way of assessing how multiple operations affect each other
 - For complex systems, may run computer simulations to explore these interactions
- Often it improves understanding to use visual displays



Discovering Mechanisms

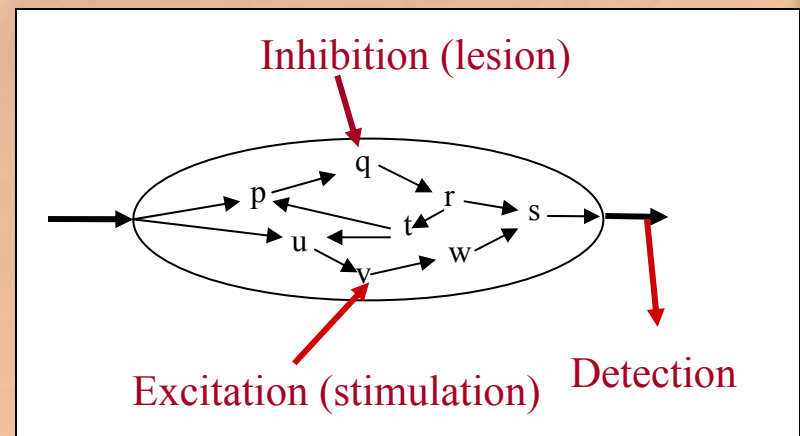
- The “context of discovery” was long dismissed as a topic for philosophy
 - But discovery of mechanisms is a tractable philosophical topic
- Mechanisms do not
 - Come predelineated
 - Wear their parts and operations on their sleeves
 - Reveal the mode and consequences of their organization
- Discovering mechanisms requires both creative ideas and techniques for experimenting on mechanisms themselves

Decomposition, Localization and Organization

- Central to the understanding of a mechanism is identifying the parts and operations within it
 - To identify these, it is necessary to **decompose** the mechanism, literally or metaphorically
- Different techniques are required to decompose into parts and decompose into operations, but the operations involve the parts
 - Need to **localize** (situate) the operations in the parts
- The interaction of component parts and operations is affected by how they are **organized**

Intrusive Observation and Experimentation

- Observation often requires altering the components in order to detect them
 - Hacking and the microscope
 - Cell fractionation
- Experimentation often involves forcing the mechanism to operate abnormally so as to reveal the operations that occur when it is functioning normally
 - Inhibition or lesion experiments
 - Excitation or stimulation experiments
 - Recording experiments



Artifact!?

- The nature of the manipulations employed raises the prospect that the results are due to the manipulation itself, not to characteristics of the original mechanism
- Often there is not detailed knowledge of the consequences of the manipulation
 - So one cannot assess the manipulation theoretically
- Resort to indirect evaluations
 - Are the results distinct and robust?
 - Do they cohere with other results?
 - Although this often serves principally for calibration
 - Do they support theoretical hypotheses about the phenomena?

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Generalizing

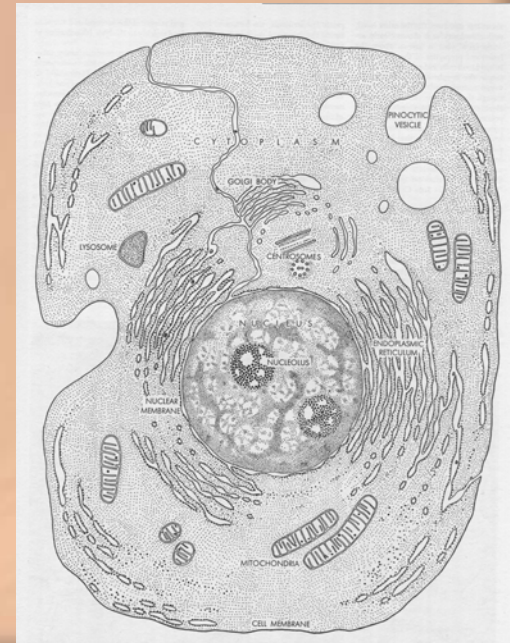
- Research on mechanisms commonly begins with a particular experimental system
 - Liver and heart in the case of oxidative phosphorylation in mitochondria
 - Giant squid axon in the case of the action potential
 - Macaque and cat brains in the case of visual processing
 - Fruit flies in the case of classical genetics
- Interest is not limited to the experimental system
 - How far one can generalize to other systems and related phenomena is an open question
 - To be established experimentally

Conserved Mechanisms

- Descent with modification ensures that many biological mechanisms will be highly similar
 - But with some modifications (which may or may not be adaptive)
- Allows research on mechanisms in one species to be informative about mechanisms in other species
 - Although there will be differences which may or may not alter the functioning of the mechanism

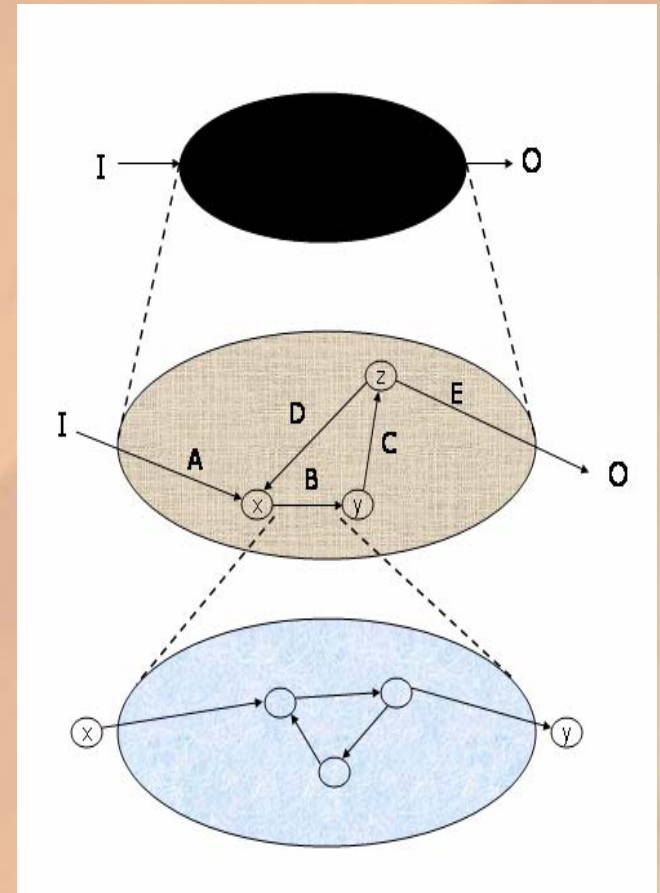
Idealizing

- Except in fields such as pathology, the interest is not in the individual case, but rather in the idealized accounts that can be obtained
 - For example, idealized account of oxidative phosphorylation as it occurs in all cells
- Formulating an idealized account requires
 - Abstracting from differences
 - Selectively emphasizing some common elements



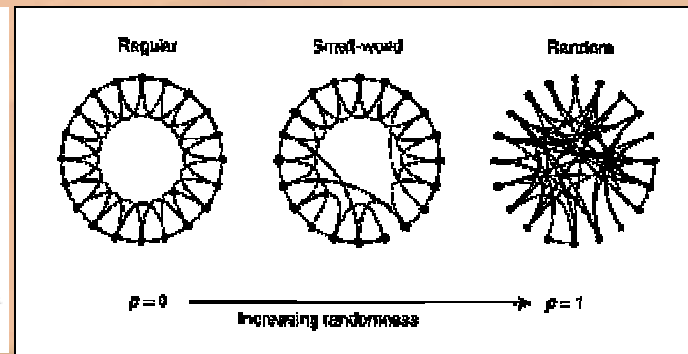
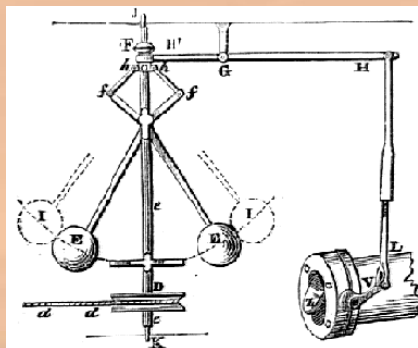
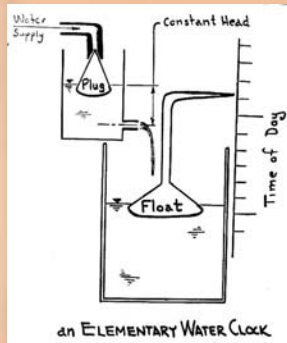
Mechanistic Explanation is Reductive

- Concerned with component parts and operations within mechanism
 - In a natural sense, these are at a lower level than the mechanism
 - Moreover, the kinds of operations performed are different than what the whole mechanism does
- Many of the components may themselves be mechanisms that can be decomposed into their parts and operations



But not just reductive!

- In order for the mechanism to do more than what an individual component does, the components must be organized
 - The way in which the components are organized must be discovered
 - It does not follow from facts elicited about parts and operations studied in isolation
 - There are important regularities about different modes of organization



Causal Processes at Multiple Levels

- Mechanisms are always situated and what they do is affected by their environment
 - Often there are regularities in the interactions of a mechanism with its environment that can be identified at that level
 - It is the whole mechanism, not the parts on their own, that engages objects in the environment
 - But not top-down causation
 - Causation at multiple levels
 - Constitutive relations between levels

Conclusions

- Mechanistic explanation involves showing how organized parts and operations are able to produce a phenomenon of interest
- Discovery of mechanisms of cell respiration involved identification of mitochondria and their structure and linking these parts with biochemical reactions
- To understand mechanisms it is often useful to represent them diagrammatically and simulate their functioning
- Discovery employs techniques to differentiate parts and operations and modes of organization

Conclusions

- Generalizing accounts of mechanisms involves tracing both similarities and differences (often in the context of evolutionarily conserved mechanisms)
- Mechanistic accounts involve both a reductionistic focus on parts and operations and a recognition of causality at different levels of organization (but not between levels)