Last Lecture in Unsolved Problems *Mon. November 16, 2020*
Advice and suggestions for beginning a career in biological research:

 # ONE: ***Find solvable problems, that seem ripe, & that you have the equipment to study:***
This could be any phenomenon that puzzles you, and that are "studyable" in the sense of using methods that you know how to do, or have a realistic prospect of learning.

Likewise, phenomena that you can study using equipment that you can borrow, beg, or build.

Some examples from my own life: The summers of 1963 and 64 I spent at marine labs funded by an NSF grant, to study various salt water amoebae that kill oysters and sea grass. I thought the best way would to make tissue cultures of oysters and sea grass, and then use an electron microscope and time lapse movie camera to watch the infection process.

But I had never made tissue cultures, and had no time lapse camera.
So I discovered very little. Eventually professors at Harvard and LSU did most of what I wanted to do, making big discoveries.

So I then went to a different university that had the equipment I needed, and when some of it broke down, I succeeded in fixing it, although the manufacturer said it was beyond repair. Because I fixed it, I earned permission to use it much more than I would otherwise have been allowed. I also took courses in electron microscopy and "Optical Methods".

#TWO: Find important questions that not everyone has noticed.
An example.
Resting potentials and action potentials Sodium pumps are used for

1) nerve impulse
2) muscle depolarization, triggering contraction,
3) oocyte block to polyspermy
4) ciliate reversal

What else? **Why should we assume that there *are* any other functions of resting voltages**? Maybe there aren't any more? That is a possibility.

But all cell types maintain sodium gradients, which uses about ⅓ of their ATP energy, according to Efraim Racker. So much effort must be good for something.

There already exist techniques, chemical markers, concepts, criteria etc.
"Do it yourself kits" for solving problems about ion pumps, calcium concentrations.

Learn how to use as many techniques and equipment as you can. Take advantage of laboratory "rotations" - mutual exploitation between faculty and students.

I also used equipment intended for neurophysiology to map locations of cell glass adhesions. focal adhesions, which I thought at the time would be my most important discovery, but very few were interested.

#THREE) Paying attention to big gaps in knowledge. "Coley's toxins"

Bacterial infections that could cure cancer?!!

https://www.cancerresearch.org/blog/april-2015/what-ever-happened-to-coleys-toxins

Coley's toxins

"Alternative Medical Universes"
phages instead of antibiotics
and maybe some third category of method for selectively killing bacteria
origins of specificity cell wall synthesis
prokaryotic ribosome difference

Penicillin wasn't really discovered by accident
nor was streptomycin
what else do bacteria they die from - osmotic swelling

Imagine selective killing of cancer cells as some kind of side effect of bacterial or viral infections.

#FOUR) **Ignored phenomena** such as Warburg's anaerobic metabolism of cancer cells

The Warburg Effect: How Does it Benefit Cancer Cells?

www.ncbi.nlm.nih.gov › pmc › articles › PMC4783224

Jan 5, 2016 — The *Warburg Effect* is defined as an increase in the rate of glucose uptake and preferential production of lactate, even in the presence of oxygen.
by MV Liberti · 2016 · Cited by 1395 · Related articles
Warburg Effect and rapid ... · Warburg Effect and ... · The Warburg Effect and cell ...
(These are exact quotations from an NIH web site about the Warburg effect)

People also ask

What is the Warburg effect and why is it a cancer hallmark?

Why is the Warburg effect important?

Why do cancer cells use the Warburg effect?

Why do cancer cells prefer glycolysis?

(In my opinion the Warburg effect has a much better chance of leading to cures than Judah Folkman's angiogenesis)
Unwelcome phenomena.

#FIVE) lack of substratum adhesion under center of cell s and other mistaken explanations

Some figures from the following paper were shown:
Harris, A. K. (1973) Location of cellular adhesions to solid substrata. Dev. Biol. 35: 97-114. DOI: 10.1016/0012-1606(73)90009-2

These are now known as “focal adhesions.” See the lecture notes on retraction fibers for additional information. Keith Burridge in the UNC medical school department of Cell Biology and Physiology works on this problem.

Other topics, some of which were mentioned briefly:

See calcium bonds conformational changes
trypsinization cutting off parts of membrane proteins

or simply ignored such as how does penicillin work
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war gas skin damage reminded radiologists of radiation damage
radiation can fight cancer
side effects similar, therefore

#SIX)
Course in past discoveries what pattern to breakthroughs
OBSTACLES

#SEVEN) " Not Repeatable " shouldn't always be interpreted as "untrue"

Researchers run away from studying unstable phenomena
my own experience with some examples of galvanotaxis