Help Wanted: MD Physiologists/Pharmacologists needed in biomedical research?

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Overview of Talk

Disclaimer: this talk reflects my (extreme) biases stemming from personal experiences as a student and trainee and also as a mentor.
Recent Progress in Clinical Medicine Physiologically/pharmacologically Based.

- EDRF/NO
- $\beta$-blockers for CHF
- Mortality CAD vs Cancer
- Kinder gentler ventilation in ARDS
- Oral rehydration solutions
- Surfactant in preemies
EDRF/NO: Furchgott & Zwadecki’s Big Mistake

- Someone forgot the α-blockers
- Rumor has it that someone forgot to rub off the endothelium

Furchgott, JAMA 1996
Rhetorical Conclusions:

• Has Furchgott’s mistake contributed more insight to Biology & Medicine than the Genome (so far)?
• Would gas-transmitter signaling systems have been discovered by sequencing genes?
• What is the value of the lab as Montessori school?
• Make more mistakes?
β-Blockers for CHF

\[ p = 0.013 \text{ for Metoprolol vs standard therapy} \]

\[ p < 0.0001 \]

\[ p < 0.05 \]

A Tale of 2 Diseases
Heart Disease vs Cancer

Almost all of the decline in cancer deaths is attributable to reduced smoking rates…
O₂ Supply & Demand Narrative

Supply & Demand Narrative

Nelson et al: Circ, 1974

\[ \text{MVO}_2 \quad 0.37 \]
\[ \text{(HR)} \quad 26.91 \]
\[ r=0.80 \]

\[ \text{MBF} \quad 2.21 \]
\[ \text{(HR)} \quad 136.28 \]
\[ r=0.83 \]
Physiology & Progress Against CAD

- Oxygen supply vs demand and CAD
- Drugs that target many/most key sites
- Ecology of solid tumors & Mets prior to detection
- Swimming upstream against a tough narrative
- Mechanical therapy (surgery, stents)
- Public Health
- Lack of a parallel narrative for Cancer?
Recent Progress in Clinical Medicine Physiologically/pharmacologically Based.

Plenty of current opportunities:
- Obesity & related fall out
- Sarcopenia & aging
- Sepsis (~1% of GDP spent in ICUs?)
Struggles of “Omics” in a Physiological Vacuum?
"...because it been known all along that virtually every disease tends to track in families. What has changed is that.....we are now beginning to see possible therapeutic approaches based on gene discoveries that will change the way medicine is practiced." Collins 1999

Collins: Ann NY Acad Sci 1999
Risk Alleles & Cardiovascular Disease Event Status
10-Year Follow-Up for the Genetic Risk Score (GRS)
n=19,313

Paynter et al: JAMA, 2010
...phenotype based risk models provided greater discrimination for type 2 diabetes than did models based on 20 common independently inherited diabetes risk alleles.
STRESS BEATS OMICS:
Predictive power of the BP response to sympopathoexitatory stressors for future hypertension exceeds predictive power of any genetic test by multiple orders of magnitude……..

Matthews et al: Circ 2004
Is Systems Biology the Answer: Model of a Disease Gene Network

What is being regulated?
Death by PowerPoint
Systems Biology vs Afghanistan

Afghanistan Stability / COIN Dynamics

NYT 2010
Death by Abstract Expressionism: Jackson Pollock *Number 31*

www.ecole-art-aix.fr
Eric Berlow and the Way Out

1. **Most actionable items are non military**
2. **Fair distribution of resources**
3. **Address ethnic rivalries**
Parallels With Regulation?

Real world

Social stress, diet, exercise, obesity

ANS ↔ RAA

PSNS/SNS ↔ Local control

HR x SV x TPR

CO x TPR = MAP

Kidney

Baroreflex

BV

MAP
Where Does This Lead?

**Actionable Items = Therapeutic Targets**

- **Lifestyle Interventions**
- **“Druggable” Targets**
  - Every element of BP regulatory system
  - receptors, channels, transporters, 2\(^{nd}\) messengers
  - *Deep dives into cells are a real challenge!*
- **Devices**
  - Carotid Sinus Stimulators
  - Renal Nerve Ablation
What Can Physiology Do?

What's Missing With Systems Biology?

• Life is more than genes/proteins/cells.....
• Homeostasis
• Redundancy
• Feedback
• Adaptation/Acclimation

• Physiology: a bridge between reductionism and epidemiology?
Redundancy: ADO, K+ATP and NO Blockade NO Effect on Coronary Flow

- Block something “essential” to a critical response and other pathways/mechanisms compensate
- Why “we” yawn at most knockout models

Myocardial oxygen consumption (µl O₂ ⋅ min⁻¹ ⋅ g⁻¹)

Control-vehicle (n=10)
Emergent Properties: *It’s Complicated*.....

Roy Lichtenstein Fnd.
MD Trained “Real” Clinician Investigators Doing Physiology & Pharmacology?
Enrollment is Up

U.S. Medical School Graduates
1962 to 2009

Source: AAMC

MJ Perry’s Blog for Economics and Finance 2010
MD RO1 Applications Down & Funding Down

You do the Math:
• Mid 60s 7-8000 grads
• ~8-900 grant applications/yr
• ~ 40% hit rate

350 investigators “started”

• 2005 17,000 grads
• < 1000 applications (MD & MD/PhD)
• ~ 25% hit rate

250 investigators “started”

Dickler et al JAMA 2007
Are there solutions?

- Information smoothie needs to stop!
- Physicians as “Apex Technicians”?
- CTSA?
- MD/PhD programs?
- Back to the future with mentor based training?
• Time for rigorous Physiology and Pharmacology course and lab work needs to be protected in the curriculum.
• More focus on fundamental principles.
• Less focus on decision tree(s) de jour.
• Engage MD scientists if you can find them.
• Resist the urge to train Apex Technicians.
MD/PhD Programs & Late Bloomers

• Are MD/PhD programs generating basic scientists that happen to have clinical tickets?

• Are the CTSA education programs generating “outcomes lite” investigators?

• Has the extension of clinical training plus debt plus information smoothie limited the ability/desire of “late bloomers” to do targeted post-doctoral research training relevant to their field?
Back to the future: Change the Culture

• Revivify the scientific basis of medical education
• Reinstitute the research experience in many residency & specialty training tracks
• Ph.D. after M.D. programs with resources/financial incentives
• Recognize that a limited number of institutions and departments are capable of offering comprehensive research training and mentorship for emerging M.D. scientists
• Partnership with basic science departments critical
Physiologists as Yogis: Physiology Causes Nothing but Explains Everything
Carotid Stimulation in Resistant HTN

Mode: 100 Hz, continuous, bilateral

BP or HR

28 min Dose response testing
9 min Recovery
4 hrs Observation
3 d Continuous therapy

Mohaupt et al HTN 2007
This Was Tried In The 1960s!

MAP

BP mmHg

P<0.005

Control STIM

Epstein et al: Circ 1969
Renal Sympathetic Interactions

CNS Integration

- Smooth Muscle Migration
- Vasoconstriction
- Atherosclerosis

- Hypertrophy
- Arrhythmias
- Ischemia
- Heart Failure

- Renal Afferent Nerves
- Renal Efferent Nerves

Renal ischemia
- Stroke Volume
- Adenosine

- Renin Release
- RAAS
- Systemic Sym Gain
- Na⁺ Retention
- Hypervolemia
- Wall stiffness
- Decreased RBF
- Proteinuria
- BNP Resistance

Renal Denervation Suppresses Systemic Sympathetic Activation

Schlaich et al. NEJM 2009