

NOT FOR  
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See T&T/Cart \*

When I received this invitation, I leaped to reply, being entrained by a profound sense of returning to my intellectual and personal roots.

But

What does one say at alma mater, amidst professional colleagues still deeply immersed in own lab work, over 3 years after being seriously involved in own expt.

So

please forgive a somewhat personal statement in lieu of the latest intelligence from the lab. bench.

2 obsessional themes on my mind

1) goes back 35 years, yes when I was a second year medical student here July 1945, and began thinking about genetics in bacteria, largely in response to my instruction that bacteria were devoid of genetics in my introductory bact. course.

{show notes page}

2) second more recent vintage, perhaps about 1970, began to wonder whether the canonical model of medical science was correct. This model, as expressed in NIH planning documents, is the pyramidding of practical advance in orderly progression from the foundations of basic science.

The question was whether practical applications of biological science e.g. of molecular biology, were perhaps unduly delayed a/c flaws in this model, or of other structural features in the organization of medical research. Issues of the intercommunication of more basic disciplines with medical practice were at issue; and my ruminations were perhaps connected with my growing frustration about the development of medical genetics beyond the provision of counselling for a few moderately rare syndromes.

Hasten: I do not voice these concerns except in the intimacy of a closein family discourse like this, since they are subject to gross and mischievous misinterpretation at a time that the integrity of research efforts is threatened by budgetary and political pressures of the most alarming kind.

Not my style to maximize dramatic effect in lectures, so let me telegraph conclusions that there is some merit to each of these concerns; but that in large measure they reflect cyclical patterns in research in a changing environment. My main conclusion is that we should be preparing for revolutionary changes in human impact of medical science at a time when many others have become fainthearted; and hope this may be more credible as coming from more than an enthusiastic and uncritical devotion to my own guild.

REMINISCENCES: .....

recollections of microbiology in 1945  
relationships of Morningside Hts., P&S campuses  
origins of bacterial genetics and molecular biology  
Impact of Avery 1944-45. H Taylor; steps of  
Neuro Institute / H Waelsch lab

[Convergences of disciplines in own experience as medical  
student still doing genetics research with Ryan at M.H. campus]  
Diagram the strands.

Why wasn't bacterial genetics discovered in 1905?  
Blakeslee experience: no jobs in 1902  
Recall exponential growth of science: how few investigators were  
actually there. [« Rockefeller Institute]

SEMINAL PROBLEMS OF SCIENCE: analogs to icons of 1945?  
(bacteria asexual; gene sanctum sanctorum, and == protein)

obvious, and unachievable challenge to identify contemporary  
prospects. My reactions are surely idiosyncratic, probably  
even cantankerous.

[should be obvious how my own style of research would be  
influenced by that experience. Look for large leaps!]

Instances where main streams of current research seem unlikely  
to reach ultimate aims; happily science is more densely populated  
and almost always there are mavericks that are welcome exceptions  
to my chagrin. Will project review system -- that exacts approval  
of the proposal itself, not just tolerance for diversity of  
outlook on part of peers -- allow venturesome initiatives.  
What chance would my proposal in 1945 have had??

Scorn of so-called fishing expeditions illustrates this outlook.

... something here on clinical research paradigms; life cycle of the  
clinical investigator (the more successful, the less proportion  
of investigative time on human subjects; but need to remain in  
contact with clinical problems. {implications for stand-alone  
clinical research hospital like RU}...

Other difficulties include academic organizations wedded to existing  
disciplines and turfs; general slowdown of new entry; obsession with  
tenure, with perhaps excessive pressure on visible accomplishment  
in early years (esp. in clinically related disciplines); deflation  
of Ph.D., and prolonged infantilism of student status in combined  
multi-degree programs; Mexican jumping beans -- Ph.D., postdoc,  
tenure ladder in rapid succession, rather than longterm commitment to  
young investigator's own problem;

Impediments to real discourse in academic communities, besides structural barriers, our styles of presentation that proclaim what we know more than what we seek. (I try to set good example in seminars by not fearing to display ignorance in asking 'dumb' questions.)

#### LINKAGES OF BASIC SCIENCE TO MEDICAL PROGRESS

Slide of Health and expenditure statistics.

(Should put research and care on same scale)

#### PATTERNS OF EMPIRICAL PROGRESS

actual role of basic science since 1950, exc. vaccines and (??) almost irrelevant to NIH-supported research; new wave today. Tagamet; Captopril  
Medical Research training is clouded by rational reductionist model, and an abandonment to industry of the realities of new pharmaceutical development. But with the burgeoning of more rational opportunities in the current tide of scientific advance, the universities will play a larger role in practical development -- and in turn face many new dilemmas of relationship to profitable opportunity.

Evident problems of internal competition, freedom of publication, freedom of judgment. Fortunately, DNA bubble is largely a stockmarket phenomenon, and may be a passing transient in the extreme form of these difficulties.

Future prospects: threshold of revolution, from concept to technology  
DNA reductionism as analog to germ theory  
COMPLEXITY of human organism/ reflected in genome.  
SLIDE:: the reductionist agenda.

Dilemmas of success looming, e.g. in aging of population.

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#### SOME MORE SPECIFIC EXAMPLES WHERE CANONS SHOULD BE QUESTIONED?

(If even one of these stands up, worthwhile exercise):

{reconsider order of presentation}

Intelligence -- human

{Need developmental plasticity}

Do we need a revolutionary successor to the prewired switchboard model? Certainly abundant evidence for abundant cell migration, replacement in vertebrate brain; deterministic networks in simple invertebrates may be lacking in some elements of complexity, however suitable they may be for primary device analysis.

-- machine (theory of highly parallel computation)  
computer scientists locked into linear, von Neumann model.

**Eobiology** (origin of life)

We should acknowledge how unsatisfactory our current theories are. But there remain unexplored experimental opportunities, especially the more concerted search for missing links: e.g. organisms much simpler than bacteria, requiring specialized habitats.

**Exobiology** ("are we alone in universe")

exptl. harassment; skepticism of astrochemists

But odd, large molecules are being found in space!

**Ontogeny**

dogma of genetic uniformity of somatic cells. Overthrown with theory of antibody formation. (Own experience, having mastered problem of elective enzyme induction, misread the data on antibody diversity -- or is that yet the final story?)

still many problems related to preexisting cytoarchitecture; will there be self-assembly in face of [Bloebel] zipcode sequences

model of phase variation in Salmonella. Exciting culmination, but still not environmentally induced

Surprised more attention not given to grossly obvious histological differentiation of nuclear and chromosomal structures -- the bands in polymorphs, the dimples in monocytes .... must be epiphenomena of underlying chemical differentiation; and I will be rather surprised if they are not associated with fairly specific segments of DNA information and their current expression.

**Aging**

not yet a clearly consensual phenomenon, to use as a standard model clearly differences between mouse and elephant; which are diagnosable in isolated cells, and to what extent do they reflect populational distribution among samples. field needs a Delbruck/ his discipline on phage studies.

**Cancer**

under enormous pressure; everything tried.

finally have some satisfaction in most fundamental approaches, namely DNA differences amongst tumor cell lines .... Too hot to comment

**Heart Disease**

Clumsy delays in exploitation of HDL/LDL polymorphism

Is exercise best inducer we can find?

(12/81: norbutaline induces HDL !! -- see NEJM)

Moralistic lifestyle movement may be having effects comparable to doctrinal pressures on treatment of venereal disease.

**Psychosomatics**

really not controversial (recall my lectures from Wolf??)

but methodology today still grossly deficient

-- training of psychologists still grossly deficient; human biology curriculum as intended experiment -- yes pre-Meds, but education, law, social sciences, psychology even more welcomed

## Psychiatric disease

ONLY leads are a) psychotropic drugs

b) genetic influences in disease

Almost none looking at polymorphism in drug metabolism, which would reflect compounds of undoubted influence.

May need deeper grounding in DNA probes for polymorphisms linked to psychiatric diseases susceptibility

## Physiology, Anatomy -- orphaned founders.

who looks at nicotine addiction?

how exercise influences muscle hypertrophy

organ size regulation: problem I worked on as medical student

(liver regeneration after partial hepatectomy is till

unsolved. Paradigm: look for a regulating substance and

a receptor!! has never failed when tried hard)

skin --e.g. corns.

nerve root distributions. Fluctuating back syndromes attributed to hysteria: 3 rediscoveries of dural anastomoses between roots.

Some stupidities: too close demands for relevance, e.g. rejecting birds for reproductive physiology

## Public Health. Orphans: scientifically informed epidemiology

Tyranny of blind clinical trials (narrowness of hypoth.)

## Parasitology

Happily are seeing rapid renaissance of interest in problems like malaria, tryps. and recruitment of young mol. biologists through programs like the summer workshops at Woods Hole.

Toxicology; may be most visible application of fundamental mol. biol categorical need to develop predictive theory, not clinical trials, to assess environmental hazards. Must be elevated from stepchild of pharmacology to a central responsibility in health sciences, against all obstacles of funding, political turmoil.....

Comparative toxicology must face up to growing public unrest about ethics of animal rights (esp. in re higher primates!!). Quite apart from these issues, untold waste in routine testing for regulatory purposes that adds nothing to our scientific knowledge of biological mechanism.

Historically, toxic substances (metabolic inhibitors) had been central to unravelling of metabolism -- and colchicine / tubulin neurotoxins/synaptic mechanisms more modern examples -- but displaced by more sophisticated tools of microanalysis, tracer methodology, genetic lesions for pathway analysis, and direct isolation of enzymes, has left a generation only dimly aware of that history.

vacuum of policy analysis (Harvard/MIT main exception)

## METHOD OF SCIENCE

AGNOSTICISM s/ self-foolishness. Display ignorance.  
Project (not peer) system problems  
Dilemma of Big Science; equipment vs. ideas (unenviable)  
cf Thackray. use quote

Philosophy of science -- descriptive, almost never captures conviction  
of practitioners.  
-- normative, since Leibniz' dream, has never succeeded  
in providing formal notation and logistical criticism.  
(Smullyan?, Woodger)