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T/22 July 7 talk at Arden House -- from Instruction to Selection, and back. May be ms. for Henry Vogel.

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From Instruction to Selection - (and back again)

Pleasure to be among such distinguished scientific colleagues; and old friends and coworkers. And to give tribute to Mac Burnet and Peter Medawar. Exactly same dedication in a memoir presented at the NYAS a year or so ago.

Unfortunately, I have very little to add to the precise subject of this symposium since the Spinozian exercise I published in Science 32 years ago -- I was naive enough to rely on Occam's razor, and "not multiply entities without cause". Well, now we know there is an enormous menagerie of cell types -- do we know all of them to this day? And may I venture it is still contro- versial whether cell ablation (the simplest model I could think of) or ANERGY, or both, and by what mechanisms are instrumental in autotolerance.

Purely personally, this meeting comes at a singular time for me. Just one week ago I concluded my 12 year term as the president of The Rockefeller University. So the published address is flawed
-- please address me at 400 Founder's Hall, not Office of the Presi- dent -- an experience that leaves me with limited credentials to contribute to your scientific discussions. It has also been a very busy time; and far from relaxing, I'm in the throes of setting up a new lab to look at some of the "back from selection to instruction" issues hinted in my title.

My work will be in the context of bacterial mutation and evolution, not immunogenesis. But I have no experimental data to report as yet. So, please relax, for your sake and mine. This is an after dinner, yet philosophical bemusement, not a carefully planned dissertation.

I will not bore you too long with much detail on old history - the reminiscence in Ann.NYAS will take care of that. I thought I'd say a few words about the historic setting of the revolution of immunological thinking of the mid 1950s for which "clonal selection" is the slogan.

Then say a little bit about whether we've been an iota too rigid in insisting that the only role of environmental stimuli -- like antigens -- is in ex past facto selection of mutations that occurred before, shorthand is "preadaptivity of mutation". I'll use "mutation" sensu latum, in its broadest sense, embracing nucleotide substitution, deletion and rearrangement and insertion.

Instructive ideas had seemed very natural in biology through the 19th and the early 20th century. Darwin notwithstanding -- and even he had very little to say about the origin of mutations. Closely tied in to specificity. And when we knew nothing of its origin, easy to impute that there could be massive information transfer from environmental substrates -- drugs, nutrients, antigens -- in evolving cellular responses.

The neo-Darwinian synthesis of the 1940s -- viz of Mendelizing genes; spontaneity of mutation; and Darwinian selection offered an alternative in the genetic realm. But we then had neither a microbial genetics nor a somatic cell genetics to bring these traditions into convergence or conflict.

My own involvement:
- following gene recombination in E coli 1946
- noting Mendelian inheritance of genes for B galactosidase 1948-50
drug resistance 1950
go back to questions of pre-adaptivity -- very much on Francis Ryan's mind at Columbia

Dealing with drug resistance -- in tradition started by Luria & Delbruck 1943 -- fluctuation test.
Constructive demonstration of preadaptivity using replica plating and indirect selection 1952.

When I turned to lactase, = B-galactosidase, induction -- instructive ideas were prevalent. No doubt influenced by Pauling and Campbell's claims 1942 in vitro ABF.

In my own work -- 1950 -- on sensitive chromogenic substrate ONPG -- on Lac....

Soon found
(1) baseline ~ 1% esp non glucose media
(2) constitutive mutants -- selected with a non-inducing substrates altrose -B-D-galactoside.
You should guess at analogies in immunogenesis -- the constitutive remind you of multiple myeloma)

Reported in 1951. Frankly, not much attended to. Henry Vogel can tell you a parallel story about repression.

I was very embroiled in mechanism of conjugation. Norton Zinder was discovering transduction; another postdoc Larry Morse -- the lambda- gal system. I had a very small group. Fireworks out of Paris were capturing world attention, including ours. So I threw that hat in the ring but didn't push it very aggressively.

November 55 symposium renewed the debate, largely between Jacques Monod and myself. Between the meeting and its publication, Monod was converted. (Jacob's first experiments.) Antibodies came up. I remarked that ABF looked different from enzyme induction. The latter looked like elective gene expression. (Try to save "selective" for proliferating systems with augumentation of progeny). ABF -- in effect that since AB came from "a common gamma-globulin", and there were so many of them, they wouldn't fit that paradigm : I balked at the idea of millions of preexisting genes waiting for selective expression; and my imagination had not yet reached the idea of somatic variability and I had exaggerated the scale needed. Based on Landsteiner, immunologists had taught o-o (inf)!

Nils Jerne broke that intellectural impasse; but with a wildly implausible idea: that mutationally diversified globulin molecules might be self-reproducing. It was Mac Burnet who saw one could substitute the lymphocyte for the globulin molecule as the unit of

mutation and selection and spawned the clonal selection theory (=David Talmage).

I was lucky to arrive in Melbourne to visit Burnet's lab within a few weeks of his illumination; and my task was to translate it into the canons of molecular genetics, how the determination of globulin sequences, and their spontaneous assembly, coded by DNA sequence could be related to his magnificent intuitions. I was also lucky to meet Gus Nossal there and initiate some experiments on ABF by single cells I'll let him fill in that story.

Consider : What do we mean by selective vs. instructive?

We have to go back to the detail of the specificity of the situation -- say the antigen and how it relates to that of the response. And we may be surprised to discern our answer will depend on the resolution of our microscope. Still meaningful, even indispensable distinction.

The copying of sequence information, say DNA-->in--RNA is certainly instructive at the level of the ensemble, the genetic unit. The genomic message is faithfully copied. Yet each unit of assembly, picking out 1/4 nucleotides, is an election: 1/4 alternatives. The emergent is instructive -- transfer of 100s of bits of info and making an authentic copy. The ultimate unit process is an elective one. With rare exceptions, complex instructive transfer can be dissected into unit elections.

Borges' "Library" proves that all knowledge is there, but to be selected.

Epitope recognition we would say is elective. The primary act of binding offers but 2 alternatives (or a very limited range at most) = 1 bit of information). The specificity of the primitive act marks it as elective. The ABF system, if we enclose it in a black box, emerges with every appearance of massive instructive information transfer -- the evolution of high affinity complementary globulins.

Nothing mysterious about emergence -- a higher order of complexity that functions at its level as a quantum of a) our understanding b) physiological action c) evolutionary change.

Today we recognize -- our knowledge or our inspiration are limited to but 2 modes of instruction: primary to quaternary orders of structure in info storage [organelles/sequences].
1) assembly with sequence replication
2) polymer folding to match an - 3D conformation
2' sometime 4D.
I've discussed 1), will return to it.

2) Today's prevailing dogma is spontaneous assembly.. sequence predetermination of 3D protein structure. Proteins have perhaps been selected out of the universe of possible polypeptides for a predisposition to unimodal folding.

We scoff today at Pawling and Campbell 1942 (it certainly was flawed and I offer no place for it in ABF). It was a great impediment to the development of immunology theory. Nevertheless let us look more closely at the possibility that instructive information might be entailed in protein folding.

A) Molecule imprinting of polymers has been demonstrated!
G. Wulff/Dusseldorf
B. Ekbeng/Lund.
Not demonstrated in any biological system.

B) Spontaneous reassembly only works for fairly small proteins.

C) A variety of chaperonins and proline isomerases needed for
so called "correct assembly". (I am troubled by that projection

D)Allosterism...reversible
D') substrate stabilization of enzymes ?DATA
E) I venture we will find ambiguous folding... alternative functional states.

1) ? Environment => sequence modulation. ?
a) non specific mutagenesis. Of course nucleotide availability; base substitution; alkylation; polymerase defects; Anything.
b) no place for substrates directing how a gene should change!
DOES NOT EXHAUST POSSIBILITIES.
c) which genes are mutable -- terra incognita !
Here are most economical places to look -- all env. labile.
(DNA deformation in differential gene expression).
i)DBP's -ases (topisomases; nucleases; invertases)
ii) in pkg-DBP vs histone,
iii) in replication and cell cycle - leveler
iv) transcription :emphasis of my lab work; pervasive differentials and signalling systems.
v) others? contra Occam; was wrong before!

What if (it's so!): transcriptional activation plays a role in gene stability? Opens role of tissue specificity and env. substrates in mutational change, somatically, perhaps in germ. I am sure you have discussed all may play a role in immunogenesis, as well as clonal evolution, within bounds of standard model.

In fact most striking example of tissue specificity is with P- elements of Drosophila (a) unique to germ/line -- (except intron changed)
(b) prefer promoter ends of target genes.

SLIDES

Evolution of Individuality.
Phyla in which the germ line is not finely isolated from soma show greatest morphogenetic diversity e.g. Mollusca (squid-clams) vs. Rotifers
Separation enforces diversity in cell replicability without
importing somatic selection into germ line evolution.

Don't misunderstand me.

Power of Darwinian paradigm!

Not always the last word -- at least some fun to explore.