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A Case History in Biological Research

In casting around in search of a new approach as a basis for this lecture, considering that ~~various of the obvious possibilities~~ most of this area ~~have~~ has been, and will be, covered, by Prof Beadle and Prof Lederberg in their lectures, in Symposia and in ~~by~~ many reviews and discussions, in which ~~the basis of~~ all aspects of the area of chemical genetics have been, and will be, considered in greater detail and with greater competence than ~~possibly~~ I can hope to do here, it occurred to me that perhaps it might be valuable, instructive, and interesting to use the approach which I have attempted to define by the title "A Case History in Biological Research".

In the development of this case history I would hope to ~~pr~~ point out ~~[illegible]~~ and ~~perhaps~~ ~~[illegible]~~ ~~[illegible]~~ some of the factors involved in all research, ~~[illegible]~~ specifically, the ~~inter~~dependence of scientific progress on the past knowledge and concepts, provided by investigators all over the

past and present (2)

world, on the free interchange of ideas

~~between these &~~ within this international

Scientific community, on ~~the~~ the hybrid vigor resulting from cross-fertilization

between disciplines, and last but not least also dependence

on chance; geographical proximity, and

opportunity. I would like finally to

complete this case history with a brief ~~description~~ discussion

from a variety of viewpoints

of the present status of the patient, and

a prognosis ~~for~~ of his future development.

Under the circumstances, I hope I will be forgiven if this presentation is given from a personal viewpoint. After graduating from the Univ. of Wisconsin, ~~with the M.S.~~ in chemistry, I ~~was~~ fortunate to have in biochemistry and microbiology the opportunity of doing graduate work at this University under the direction and leadership of ~~Dr. E. B. Fred~~ Prof. W. H. Peterson and Prof. E. B. Fred. ~~During this period~~ At this time, in the early 30's, one of the expanding areas of development was concerned the study of the so called "growth-factors" for microorganisms, as yet for the most part mysterious and unidentified. I became deeply involved in this field, and was fortunate to have been able, in collaboration with Prof. H. G. Wood, then visiting at Wisconsin, to identify one of the required growth-factors for propionic acid bacteria, as the recently synthesized vitamin B_1 or thiamine.

this was in the time before the universality of
need for, and the basis of, vitamins, had
been clearly defined. Although the vision
of Barry A. Knopf and Prof B C J G Knight had
indicated the correlation of the need of microorganisms
for "growth-factors" with failure of synthesis, and
correlated this failure with evolution, particularly
in relation to the complex environment of
"fastidious" pathogenic microorganisms, the tendency
at this time was to consider "growth-factors" as
highly individual requirements, peculiar to particular
strains or species of microorganisms, and
their variation in these respects
was not generally considered
similar to (variation and mutation in gene)
higher organisms. Actually, my ignorance and
naivete of genetics was probably typical of
that of most biochemists and microbiologists
of the time, with my only contact with
genetic concepts being a course, primarily on vertebrate
evolution.

After completing graduate work at Wisconsin I was fortunate to be able to spend a year studying at the University of Utrecht with Prof. F. Kögl, the discoverer of the growth factor biotin, and to work in the same laboratory with Prof. Nils Fries, who already had contributed significantly in the field of nutrition and growth of fungi.

At this time, Prof. Beadle was just moving to Stanford University, and invited me as a biochemist to join him in the further study of the eye-color hormones of Drosophila, which he and Prof. B. Ephrussi in their work at Cal Tech and in Paris

Stanford had so brilliantly established as diffusible of gene-controlled reactions. During this, my first contact with modern genetic concepts, as a consequence of a number of factors — the observation of Khouvine, Ephrussi and Chevais in Paris that dietary tryptophane was concerned with Drosophila eye-color hormone production; our studies on the nutrition of Drosophila in aseptic culture; and the chance contamination of one of our cultures of Drosophila with a particular bacterium — we were

able to isolate the 1st hormone in
bacteria
crystalline state from a culture
with Prof. A. J. Haagen-Smit
supplied with tryptophane, and to identify
originally
it as tryptamine; isolated by Kotaké, and
correctly
later structurally identified by Butenandt. It might
be pointed out here that tryptamine has since been
recognized to occupy a central position in
wide phylogenetic
tryptophane metabolism in many organisms, including
mammals and fungi.

Dr Prof Beadle has pointed out,
at about this time, out of many discussions
and considerations of the general biological applicability
of chemical genetic concepts, stimulated by
the wealth of potentialities among the
microorganisms and their variation in nature
in regard to their nutritional requirements,
we began our work with the mold Neurospora
crassa.

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I shall not reenumerate the factors involved [nor the details of the experimental production of chemical mutants] [or nutritionally deficient] in our selection of this organism, ~~since Beadle has already done so~~; but must take this opportunity of ~~pointing out the importance of~~ [reiterating our indebtedness] to the [pioneering] findings of a number of ~~previous~~ investigators. ~~and have much~~ ~~foremost~~ ~~first~~ among these, [to] the ~~gentle in~~ [for his] [Prof. B.O. Dodge] establishment of this ascomycete as a most suitable organism for genetic studies; ~~and then with the encouragement~~ ~~to Prof. C.C. Lindegren, who the~~ ~~of Prof. T.H. Morgan at Columbia University became acquainted with Neurospora from Prof Dodge,~~

and to Prof C.C. Lindegren, who became interested in Neurospora ~~and the work of Prof. Dodge~~ through Prof. T.H. Morgan, a close friend of Prof. Dodge. ~~contacts with Prof Dodge~~

Our use of Neurospora for chemical genetic studies ~~would also have been~~ would also have been much more difficult, if not impossible, without the availability of synthetic ~~synthetic~~ biotin as the result of the work of Kögl and of its du Vigneaud. In addition, the investigations of Prof. N. Fries on the nutrition of ascomycetes

were most helpful, as shown by the
fact that the ~~original~~ synthetic medium
used with Neurospora was that described by
Fries, but only supplemented with biotin, and referred
to as Fries medium". ~~It should also be~~
~~pointed out that the~~ It should also be
pointed out that the feasibility of producing
the desired nutritionally deficient mutant strains
~~could not~~ depended on the early work of
Roentgen, and on that of Prof H. J. Muller,
on the mutagenic activity of X-rays on Drosophila
All that was needed was to put these
facts and findings together ~~to~~ producing
with irradiation, nutritionally deficient
(auxotrophic) mutant strains of Neurospora
and to show that ~~the~~ each single deficiency produced
was associated with a mutation of a single
gene.