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December 30, 1980

Dr. Joshua Lederberg
President
The Rockefeller University
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Dear Dr. Lederberg,

Thank you for your note of December 19. Let me again state that it was a pleasure to visit with you and your colleagues. I apologize for not having provided you with copies of our two most recent submissions when I transmitted the PNAS manuscript. I am still in the embarrassing position of not having a preprint of the Archives manuscript to send you, however, I hope to correct that situation as soon as possible. I may have to send you a copy of the galley proof but have hesitated to do so because the first galley was in poor shape.

In specific reply to your question, the following concepts and findings are original to the PNAS manuscript and have not previously been published or submitted elsewhere:

- 1) That p-benzoquinone and 1,2,4-benzenetriol inhibit microtubule assembly.
- 2) That these same compounds inhibit lectin-induced blastogenesis and agglutination.
- 3) That the mechanism of action is through specific alkylation of critical sulfhydryl groups (Michael addition) and likely represents the mechanism of hydroquinone inhibition of microtubule assembly and lymphocyte suppression.
- 4) The direct comparison of sulfhydryl dependence and reactivity between the two systems.
- 5) The concept that differences in quinone chemistry may account for differences in the pattern of toxicity observed for hydroquinone and catechol.

The basic integrated mechanism has not been proposed in our previous papers nor has the chemistry been detailed before. We have published (in press) that hydroquinone inhibits microtubule assembly and accelerates

TCBA decay. This work is essentially descriptive and suggests that GTP-associated sulfhydryls are involved in the process but does not outline a molecular mechanism.

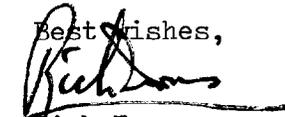
Similarly, we have submitted a work describing the effects of hydroquinone on lectin-induced blastogenesis and agglutination. This work does not present data on p-benzoquinone. A more detailed work is currently in preparation at this time. These manuscripts refer to the possible connection between sulfhydryl dependent sites and microtubule integrity, but present no data on the subject and go no further in outlining a proposed mechanism.

I should also add that the first "formal" exposition of the integrated mechanism will be at a symposium on "The genotoxic effects of airborne agents" to be held at Brookhaven National Laboratory in February. This will eventually be published in symposium format. I intend to present the subject in the form of a "mini-review".

I hope that I have satisfactorily answered your question and will endeavor to get copies of our previously submitted manuscripts to you.

On another subject: I think that I have a couple of examples of advances in basic understanding in biology that were preceded by a knowledge and understanding of the chemistry and effects of a chemical agent. Simply to outline my selection criteria I should state the well trodden view that advances in science occur in leaps coincident with the combination of conceptual integration with technical advances. The use of chemical "probes" provides a convenience in packaging both conceptual knowledge and technical understanding of chemical processes into a single focus. However biased I am with respect to the power of this approach, upon reflection I can think of precious few examples of its use in the past. As we said before, colchicine is obvious. Another is acetylcholine. Its synthesis and chemistry were detailed in the mid-1800's. Its effects on mammalian physiology led ultimately to the definition of the role of chemical transmitters in neurobiology.

Another thought I have not yet adequately formulated relates to the use of agents such as quabain, digitalis and others to characterize important aspects of both membrane conduction and energy metabolism. It seems to me that a number of agents were applied as tools in the elucidation of these cellular processes. I had hoped to research these better before writing you but thought I'd take this opportunity to suggest these examples.

Best wishes,

Rich Irons