

August 23, 1974

Dr. Philip E. Hartman
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Dear Phil,

Thank you for sending me the preprint of your review on antischistosomal compounds, which I read with great interest.

To respond first of all to your cover comment, I do not recall ever having said in public or in private that I approved of the use of hycanthone in man. Enough questions have been raised about its efficacy and about other kinds of side-effects that its use is certainly subject to question quite apart from genetic problems. Privately I have said that I needed to see a more detailed account of the costs and benefits of the genetic hazard on one hand and its utilities for dealing with one of mankind's most serious diseases on the other before I could reach a definitive conclusion. I would still defend that general position, but it seems to me that your own article goes a long way to providing critical information for policy - the references to carcinogenesis and perhaps most important the optimistic outlook for a more precise design of safer compounds. That is certainly one of the most striking and important facets of your review.

I was, of course, also impressed by the negative results of tests directly in mammals as mitigating some of the prior suspicions that had been appropriately directed to these compounds. I accept your own further comments on that point.

I am, however, rather distressed about the paragraph, page 2B, quoting number like 10^{16} . That, of course, is one of those ultimate absurdities that might have been used as an argument against any such analyses. I would hope that you had rather attempted to make a calculation of the possible bounds of the number of mutations that present knowledge permits one to infer have been induced in the human population through the past use of hycanthone, and of course to compare this with the spontaneous mutation rate during the same interval. Then one needs to do a cost analysis about the actual expected health consequences of such shifts in rate. As you may know, people like Howard Newcombe have been taking a rather strong line that even a doubling of the mutation rate would have rather small health consequences over a reasonable period of time. I think he takes too sanguine a view but I think his arguments will have to be answered by more explicit calculations about health consequences. And, of course, this is what then must be balanced against the presumed advantages of these compounds. However, I fully agree that if there are substitutes that are totally free of this stigma, that

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there is little justification for continuing with suspicious compounds. Of course, one trouble is that with our system of drug regulation it will be another 5 or 10 years of testing before the new derivatives will then be allowed on the market.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr