November 22, 1955

Dr. Clifford Grobstein
National Cancer Institute
Bethesda 14, Maryland

Dear Cliff:

It has taken me this long to get around to the Medical Library so that I could answer your letter of the 2d.

I must say I am not much impressed by Paschkis' arguments— they take no account of the possibility that the still viable cells are slightly altered in their physiological capabilities by the treatment, or by the residue of DNA with which they are mixed. Klein's argument is not irrefutable (as he himself was careful to point out) but it certainly seems to put Paschkis et al. under some burden of proof. I have talked this work over in some detail with Klein and Hauschka— perhaps it would help if I esimply enclose a short ms. that I wrote (as a so-called discussion of Klein's paper) for a NYAS conference on ascites tumors. Please send it back at your convenience, as I think this is my only copy.

To my mind there are two issues: the physical dimensions of the agent (particularly is it as big as a cell, nucleus, etc.), and its genetic scope. I think it would be very hard to get a convincing result on the former even by filtration/ methods, though this can well be worked up. I do think a very easy experiment would be to verify whether DNAase inactivated the chromatin (and(presumably ) not control cells; the same could be done with other enzymes or combinations of enzymes. Enzymatic treatments might also help to clear up the mess to tell whether there were actually some cells in the soup/

As to the second question, one should expect to find some separability of markers, if the transductive interpretation is correct. Novikoff is, I think, confused: the point is not that different markers are sometimes linked, but that they usually are not. Klein's experiment tried to demonstrate a separation of tumorigenesis from histocompatibility, and failed. Why not try other markers? Would not the lymphosarcoma be amenable to the use of drug-resistance as another marker?

If no separation of markers can be found in these supposed transductions, there is still the problem of identifying the agent. It would not have to be the intact cell— it might be a nucleus/ or large nuclear fragment. But I think the most conservative reaction now is that probably there are cells, perhaps damaged in some way, in the chromatin preparations.

Give my best to Lloyd Law...

Sincerely,

Joshua Lederberg