(En Route, San Francisco to Madison)

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Dear Joe: Lein

As you can now gather, I'm just on my way home from my long trip, and it will be good to get there. You will also see from the letterhead that my formal affiliation has changed (a couple of weeks ago) but my lab and mailing address will be as before for the time being.

I'm sorry that it was quite impossible for me to visit along with Bernie. I saw him in Britain, and he told me of your interest in adding him to your panel of consultants, which is of course a first-class idea. I gather he also backed the kind of empirical search for accumulators of useful metabolites thatwe havebeen batting back and forth: of course this doesn't have to be just mutants of E. coli: in fact I would be willing to bet that some Streptomycetes would be even better as metabolic excretors: if you'd care tobeat Pfizer's at their own game, it wouldn't be too hard to find even a lysine- or rather dap-accumulating mutant to do the same job better. However, it seems to me a more imaginative tack would be to specify other useful products. After all, it was the realization that lysine was worth making even by this round-about route that (to me) seems the main coup from Casida-Pfizer. So, you tell us what kinds of compounds you're after!

At Berkeley, I saw Ben Volcani again-- he'sactually been working, and successfully it turns out, on the isolation of organisms that split TMV. If you had spare time in an antiviral program, I would again recommend this approach to you. Ben's interests are in the finding of enzymes that mightbe useful in elucidating virus structure, but it would be hard to believe that the therapeutic possibilities would escape the notice of all his colleagues at the Virus Laboratory.

The London-Ciba meetings were not remarkably interesting, except for the personalities: Hinshelwood, two Russians, a Hungarian and a Pole included. My own summing up there was a) the mutation-selection theory of resistance was pretty well nailed down, b) one could try to get around the problem either by preventing the mutations (which seems hopeless) or getting at the resistants. For the latter, one observes that (by definition)the original wild types are sensitive, andthis trait must therefore have some specific selective advantage. The best I can recommend, beyond further routine screening, to get to the problem is to screen in addition for adjuvants which will have a particular effect on the <u>resistant</u> varieties, preferably in the presence of the primary drug. Beyond doubt, streptomycin-Tbc, and penicillin-staph are the two immediate targets. I think I've proposed this to you already.

All thisaside, however, the 'substitive chemotherapy' proposal still remains in my own mind as the most promising novel theoretical approach, andnot just for antibacterial action, butalso in re tumors and viruses. I hope this is getting a hard push! There's been a meeting in N.Y. on biological actions of alkylating agents, mainly oriented to tumors, which may give some more fuel to this fire? Were any of your people there? But you must know the list of reagent types the Sloan-Kettering and Chester Beatty crowd is involved with.

A final note: there has been a scattering of promising results in the use of marrow and spleen implants as an adjunct to experimental tumor therapy, based on the protective effects of these cells for radiation injury (i.e. the replace-

of the lymphogenic system which has been damaged along with the tumor in the treated animals. The chief snag to practical application is histo-incompatibility between non-isogenic individuals. A practical regime that would induce tolerance to transplants would start a revolution in surgery as well as chemotherapy,

With best regards,

Joshua Lederberg