UNIVERSITY OF CALIFORNIA

DEPARTMENT OF ZOOLOGY
BERKELEY 4, CALIFORNIA

October 23, 1953

Dr. Joshua Lederberg
Department of Genetics
University of Wisconsin
Madison 6, Wisconsin

Dear Dr. Lederberg:

I truly appreciate your letter of October 19. The ideas that one admires most are those that he would never have created himself, and this applies to your comments on the reversibility of transduction effects in the cell that is the primary receptor. If the externally introduced agent acts by some sort of competition with its counterpart that is already present, then it could only be fixed by being trapped by cell division in a cell that has lost the normal counterpart. Do I understand correctly that this is your picture of what happens? Regardless of mechanism, those experiments on Salmonella that you describe are most elegant.

The experiments on embryos were carried out at my suggestion by a graduate student of mine, Ruth Neff. While I find that graduate students perform best in experimental work requiring strong motivation, I feel that they earn proprietary rights to the problem in doing so. In this case, the work has been delayed by the wanderings of Ruth Neff, and I have done nothing myself until she could complete as much of her plan as possible. She is now at Vanderbilt, where her husband is teaching in the Zoology Department and has carried the work further. You will recall that Brachet reported that he was unable to confirm our experiments. On returning to the work, Ruth too began to encounter inconsistencies in her results. After a great deal of work, the reason finally was discovered. It appears that the active agent, although insensitive to many other treatments, is extremely sensitive to conditions of low pH. In ordinary work on the isolation of DNA, insufficient precautions are taken to prevent this. Zamenhof tells me that the same situation holds for "transforming principles" that he has studied. He finds that they are extremely insensitive to heat, compared to most proteins, but, unlike many proteins quickly lose their biological activity at pH levels not too far below neutrality.

Mrs. Neff still finds that the species-specific embryo-blocking activity does not depend on a high polymer state of DNA. In fact, her best method of preparation involves extraction with the aid of desoxy-

ribonuclease. We have found that DNAase ordinarily liberates very little material other than DNA fragments. If the currently fashionable hypothesis assigning the specificity of DNA to nucleotide sequences is true, I don't see why the specific units need be very large. Whether a piece of DNA retained its specificity or not would, it seems to me, depend less on the size of the fragment than on the use of a technique that would prevent uncoiling or separation of chains. The work that James and I did on surface films of DNA indicated that a lowered pH did bring about an irreversible decrease in the thickness of the molecule that could easily be interpreted as an unravelling of chains.

If you do not mind, I would like to tell you about some other work I am doing that relates to your interests. As you may know, I had worked for a long time on the factors responsible for chromosome continuity, and had been forced to the conclusion that we were dealing with a protein continuum because the only means that was found for "dissolving" the chromosome involved splitting of peptide bonds. Recently, some work done by Bernstein in this lab, working with sperm heads, showed that the chromosomal material could be dispersed into a solution of macromolecules containing DNA and protein by the following sequence of operations. The material was exposed to citrate, which presumably removed some divalent cation, then to a medium containing no ions at all. If citrate was omitted, the material hydrated but the particles could not come apart. We interpreted the citrate effect as being possibly an effect on the membrane. But, now I personally have done a series of experiments at the cytological level, using interphase, mitotic, and meiotic chromosomes from a variety of sources. I find consistently that I can literally dissolve the chromosomes by application of citrate and water, but not by either of them alone nor by the reverse sequence.

This may seem like a pedestrian sort of experiment, but if one thinks about it, it seems to mean that the chromosome is after all a fundamentally particulate structure, with the particles being bonded by electrical and ionic forces alone. (The ionic factor being intermolecular bridging by divalent cations). The existence of identifiable chemical discontinuities bears on a number of questions, including the ideas of my colleague Goldschmidt with whom I have not yet had the opportunity to discuss the matter. It is conceivable that a point of attack for the mechanism of crossing over or recombination phenomena can be found. It is even conceivable that some sense could be made of the distinction between "point mutation" and "rearrangements." At any rate, I am still doing the pedestrian part, trying to identify the discontinuities, and would be interested in your reaction to this development.

It is incredible that we are not better acquainted, considering our common body of friends, and I hope that we can correct this before too long.

With many thanks and best wishes,

Cordially yours,

Daniel Mazia

DM:th