INDIANA UNIVERSITY
BLOOMINGTON, INDIANA

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Dr. Joshua Lederberg
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Dear Joshua:

Thanks for letting me see your "Genetics, Symbiosis and the Cell." There is much food for thought in it, though--as you imply--much of it is very familiar to me. I am sorry you had to cut so much, for I think the paper would be much more effective if you could have had space to develop your ideas more explicitly. The condensation, which is extreme in many parts, leaves some of your more important ideas hinted rather than explicitly and clearly exposed. My only other general complaint is your proclivity for making new words. I know this has psychological advantages, for it identifies the word-maker with the idea; but I wish this temptation could be resisted, for in the long run it adds to the confusion of terminology and distracts the time, thought and energy of many readers from the facts and their interpretation to a fruitless attempt to get clear on the fine distinctions believed to be associated with similar terms.

I shall not call your attention to the typographical errors in my copy, which I suppose you will catch; but there are several other points that should be mentioned.

Page 10, line 5. Don't you mean white x green instead of green x white? (I understand the female is listed first.)

Page 14, last line. Isn't something omitted here?

Page 19, paragraph 1, last sentence. If you refer here to Weisz's work (which I am very suspicious of), it should be made clear that it is not on Paramecium in which the form of the macronucleus differs importantly from the form in the organisms he studied. Nanney has some data which may be interpreted along similar (but not identical) lines. He believes the first formed "unit nuclei" in a developing macronucleus may differ in ploidy level and that this is the basis of selfers. Also, by fusing macronuclear anlagen that were destined to determine different mating types, he experimentally produced selfers and then separated the pure types out by macronuclear regeneration.

Page 19, paragraph 2. Your strong statement about the persisting macronucleus being the best case of a gene-initiated plasmagene seems to me readily translated into the idea that there are no good cases,--a view I have maintained. How you can confound a macronucleus with a cytoplasmic gene system is more than I can grasp. Regeneration from

fragments doesn't seem to me to justify this. The case is comparable to that of a polyploid somatic nucleus which is "reduced" and then again acquires a high polyploid level.

Page 19, last sentence. The differences between our group A and group B varieties seem to become less marked the more both groups are studied. The cytoplasmic component of the antigen system is evident in both, though perhaps less strikingly in group A. The same is true to a lesser extent for the cytoplasmic component in mating type determination. Killers have not yet been found in group A.

Page 21, line 7. Should not "kappa" be "paramecin"?

Page 21, 7th line from bottom. Our sera are good (usually perfect) reagents without absorption and we routinely never absorb. This is one of the most striking facts.

Page 21, paragraph beginning at bottom of page. Type C is often highly unstable. Your account here is based largely on the 1948 paper by myself and LeSuer. We now have 9 types in race 51 (more in other races). In any race, only some of the types can be maintained stable under our standard conditions of culture; some can be kept stable under other conditions; and some cannot regularly be stabilized under any conditions thus far tried. It would be better here if you limit yourself to A, B and D.

Skaar's work, to which you refer here, ignores--as I pointed out to him--the fact that exposures to dilutions of antiserum too low to affect growth rate appreciably can nevertheless increase the frequency of transformation.

Page 23. We use Arabic numerals for varieties, reserving Roman numerals for mating types.

Page 23, line 5. Our earlier statement about dominance of antigen genes was based on incomplete study. That is the way it looks when the sera used for diagnosis are against an entirely different type and work by cross-reaction only at high concentration. Dippell has extended her study now, using homologous antisera that act in high dilution. With these sera, the hybrids react as if both allelic antigens are present. The facts are much more difficult to demonstrate in variety 4, in which allelic antigens are always serologically similar, than in variety 1 in which allelic antigens are often so distinct as not to react at all to each other's antisera.

Page 23, end of paragraph 1. This statement about Beale gives the impression you think he maintains that the unexpressed genes as not doing anything. He does not say this. He merely says they are not expressed in this reaction, which is just what you imply by "indistinguishable." It seems to me unfair to give the impression, as you do,

that he interprets his observations differently from you.

Page 51, 6th line from bottom. "Absolute unit" of what? Units have no absolute meaning, do they? The vagueness with which this is expressed detracts from the argument.

Page 52. I have somewhat the same argument on self-reproduction in a manuscript written nearly a year ago which I have held up pending completion of additional experiments. We have in our system of mating type determination what seems to be a clear case of indirect "self" reproduction. The macronuclear constitution determines a cytoplasmic condition which in turn determines that new macronuclei arising in this cytoplasm will have the same constitution as the old macronuclei. This system even shows "mutability",--an appropriate change in either the cytoplasmic or nuclear component of the cycle resulting in perpetuated change in the whole cycle.

Page 53. The notion that mutability is simply an index of structural complexity seems to me an overstatement of the same kind as many of those you have rightly protested against in this paper. True, the classic cases of mutation are in structural complexes, but your "alkiligenic virus" shows how the essential feature of mutation could be extended to structurally simple ions. Mutability still seems to me to be conceptually independent of structural complexity.

I am still not entirely clear as to what you mean about the relationship of cytoplasmic states to gene reproduction unless you simply mean that the latter, like the former, may be reproduced by the cell instead of being strictly self-reproduced in the classic sense. If this is all you mean, I was looking for more than you intended. This I have also considered and mentioned in the paper referred to above.

I'm sorry I couldn't get to your paper any sooner, but I have had to devote every available minute during the last month to an extensive further test of Nanney's mating type hypothesis. This is the experiment I wanted to perform before sending off the paper I've already mentioned several times. The results were most surprising and leaves me with the conviction that the hypothesis needs fundamental revision; but I haven't yet had time to think through all the implications.

With best regards to you and Esther and the Skaars, and with much thanks for letting me see your provocative and stimulating paper.

Cordially,

Tracy

T. M. Sonneborn

TMS:jb