

STANFORD UNIVERSITY

MEDICAL CENTER
PALO ALTO, CALIFORNIA

DEPARTMENT OF GENETICS
School of Medicine

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Cables STANMED

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Dear Luca:

There are so many details of things to talk about that I am not sure we are going to get them all done, but I would rather not have them pile up too far. I was happy to see Giovanni at Princeton and we did have a good chance to talk over a great many issues. To answer one of your main questions, we can certainly wait until February for you to come to a definite conclusion. The first consideration is perhaps that you should be able to put your own mind at ease and we can just hope that this will be forthcoming as soon as possible for your sake as much as ours.

Through Giovanni and in your letter, you indicated a definite interest in coming to Stanford at least for the spring quarter which begins about the first of April. We will be very happy to have you here at that time, in particular as this is when we will be giving the regular course to the medical students. This is only one hour a week, on Saturday morning at 11 o'clock, so it is really not too strenuous a program. However, as probably the first and second year class will be enrolled in it, it will be rather a large group and it may be profitable for at least part of the course to divide it into two sections and this would be a logical point of division of labor between us.

Paradoxically enough, I may have to be away for one or two weeks in April and quite possibly this will be in Milan. In that case, for that interval, you would be very helpful indeed by taking over the two courses. I have no plans, hopefully, other than this one of being away for any appreciable time during the spring quarter. For the three months of April, May and June - but this is subject to some official verification which I can hardly doubt - we can offer you a stipend of \$4,000. I trust you will have some other help in obtaining your travel expenses. Likewise, I would still hope that I could do some interest business with Giovanni and your associates in April and that this could help subsidize the trip in which Esther could also take some part. If you could manage to be here by the first of April, this would give us several days for planning discussions before I had to go myself. I hope

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that you can manage such a schedule. Please let me know whenever you can as to your final plans on this so that we can make any necessary arrangements. This time, I will try to see if we can manage to have a car leased on your behalf rather than put you to all the trouble you went through. Also, please let us know if Alba will be able to come with you, as we very much hope but have to doubt as a practicality; we will also have to make a start again on the simple visa arrangements. In this connection, I hope that you can have some forethought by way of a tentative application, if this is possible, if this would simplify your obtaining a regular visa later on should this be indicated.

Giovanni has the Subtilis strain that you asked for - this is a histidine tryptophan mutant. However, as I discussed with him, I am not sure this is the most appropriate system in which to look for a specific pattern of resistance to related antibiotics, since you would probably be dealing with a polygenic system I would think that you would have better hope of unraveling it with sexual recombination analysis than with DNA transfer in which only one element at a time could be transferred. In fact, it is not impossible that he would have some luck in finding such specific phenotypes among the diverse recombinants of crosses between highly selected resistant and sensitive strains. The types you are looking for may, after all, be relatively poorly adapted combinations of genes which could defeat your finding them by simple progressive selection.

You and Alba were very kind to be so thoughtful in sending the several gifts through the mail and with Giovanni. Thank you so much for them. Giovanni will have to tell you about the straw slippers.

As I should have mentioned in my last letter which crossed yours of the tenth, Norman and I have listened carefully to your suggestions about the consanguinity questionnaire and we are going ahead on a tentative basis. I think we are in good agreement as to the desirability of what is to be done and in general, how to go about it. At the very least, Norman has laid the ground work for the accumulation of data during the next months or year or two by his discussion at the meeting of the Academy of Pediatrics. I did have a chance to talk about this with Jim Neel and he had another very useful suggestion, namely that Newcombe's record linkage system might present another very useful approach. I have written to Howard to ask whether he would be able to obtain the necessary linkages from the accumulated cases of childhood deaths attributable to drug reactions.

At the Macy Meeting in Princeton, as Giovanni will tell you, we discussed not only chemical mutagenesis, for example, by caffeine, but also a possible chemical basis for chromosome nondisjunction. The only reasonable suggestion how to verify a caffeine effect in man was your own, namely, to classify the grandparents with respect to their beverage habits and determine whether there was a significant difference in the slope of sex ratio with respect to grandparental age. You certainly should get every encouragement for this type of study. As to nondisjunction, in view of the obvious effect that compounds like Colchicine would have, I am beginning to wonder whether there may not be a

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chemically induced component in mongolism. This was the first thought to cross my mind when I first heard of the trisomic story, but like most people, I did not see how this could relate to the major fact of the dependence on maternal age. However, I think it is at least intuitively obvious that the consumption of drugs also has a strong age dependence. In fact, Luca, this is a set of statistics that ought to be carefully collected and tabulated as a background for all such discussions. I do not know which drugs one might point to but at least such compounds as ethyl ether, chloral hydrate, and barbiturates are already known to have spindle-inhibitory effects. Perhaps there are others that are not so obvious. To test this proposition, one should have the statistics on different populations with different habits of drug consumption. Perhaps you would already be able to quote me some data, for example, on rural Italian populations, that would refute the proposition that say, one-half the incidence of mongolism was induced by chemicals. Are there any hints at all as to the etiology of mongolism from its geographic distribution? The age effect may well have obscured this problem from several standpoints.

If indeed there are any significantly controllable populations which have distinctive habits of drug consumption, they might be most valuable in several similar connections. Do you think the Christian Scientists fall in this category? If so, on the other hand, would it be possible to obtain reliable diagnoses bearing on the distribution of causes of death?

In connection with the Kefauver investigations and some similar reactions to the over-aggressive distribution of drugs by some companies, there is going to be more than a little political interest in drug-induced disease. While some of the hysteria is exaggerated, there is no question that this is an extremely important problem and we ought to be on the lookout for ways of investigating it.

That's all for now. Our best to Alba and the children.

Yours sincerely,

Joshua Lederberg
Professor of Genetics

JL/jh

P.S. I have in mind your request for Volume II of Supey's Geometry when it is published. Also, I am enclosing two references to papers on the medical use of computers by Ledley. I am also trying to find other sources for you. By separate mail you should get a copy of a book called "The National Purpose" that Alba should be very much interested in. Please let us know if there is anything else along these lines that we could get for you. Has she had time to look at Lear?

Ledley, Robert S., 1959. Digital electronic computers in biomedical science. *Science* 130: 1225-1234.

Ledley, Robert S. and Lee B. Lusted, 1959. Reasoning foundations of medical diagnosis. *Science* 130: 9-19.