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Madison, Wisconsin

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Dear Joe:

From time to time I try to reflect over the broader aims of the screening programs to see whether I can think of any objectives that might be overlooked from day to day.

It has been quite some time now since substitution chemotherapy came up and I must confess that I have still been unable to think of a sounder basic approach that has not yet been well worked over. Expensive as the screening for antimicrobial agents is, it is, of course, a basically simpler proposition than the search for other pharmacological agents, and I see no help for it but to contemplate the expenditure of larger amounts of money to make further progress in other fields where the assay systems are more complex.

A propros antimicrobial chemotherapy, I wonder if you still have great difficulty in translating the production of a promising compound from your flask scale cultures to larger scale. If this is still a significant problem, as of course it has been in the past, I wonder whether the sound approach is to continue to try to use optimum conditions in the preliminary screening or whether it would not be better to set up a preliminary screening regime that from the start would more nearly reflect the technical procedures that you would have to use later on. This supposes that you know something of the variables which are responsible for the difficulty in translating from laboratory to pilot scale operations. Since you are often unable to give full attention except to those compounds that can be handled on a larger scale, it would be better to limit your screening to those compounds which were, in a sense, preadapted for it. If, as one suspects, oxygen limitation is the chief factor limiting production in larger scale cultures, then one might try to find methods of laboratory handling which would more nearly simulate the pilot plant and production plant situation. I am sure your engineers have gone as far as they are likely to in the near future in the direction of optimizing the production facility itself. So at this point, it would seem to me to make good sense to try to match your production conditions in your small scale screening experiments insofar as possible. It is just conceivable that the very vigorous aeration that one customarily uses may help to defeat this purpose.

I know that you must be mainly preoccupied with setting up the tumor screening program that you have been telling me about during the past several months. It is very difficult for me to comment on such a program in the abstract without knowing the general organization and limitations of this operation. Once you have shaken-down its initial organization, along what must be fairly self-evident lines, I would very much like to have an abstract of your procedure and will see if I can offer any useful comment at that time. Also, if there have been any inovations in the antimicrobial screening program or if there are any

aspects of it that might be worthwhile going over once again, I would be happy to hear from you about it.

It is hard to think of any fundamental approach to the tumor problem that has not already been worked over quite a few times before. Obviously the empirical search while it has no particular rational basis is something that must go on and must be pushed with great vigor. I myself believe that transplantable tumors in the host strain of origin, provided they had not been selected too far for further anaplasia by repeated transplantation, are the most suitable material. A trouble with something like HeLa cells in tissue culture is that they are so far removed from their cells of origin, and there is no possibility of retesting them as such in vivo under suitable conditions that they represent only one step more than a microorganism in screening programs. That does not, of course, mean that they are without value. However your substitution chemotherapy program for coli works out I hope you will also give it a try in the tumor program. It is reasonably obvious that compounds like fluorouracil should have been picked up by such a regime.

There is one problem in medicine that is going to be of huge dimensions once the appropriate technical tools have been devised. This is the capacity to conduct homotransplantation in the replacement of diseased or damaged organs from one individual to another. At the present time, there is no practical way to get around the homograft destruction response that follows transplantation of tissues from any individual to any other. Eventually, it may be possible to stimulate the conditions of prenatally-acquired tolerance in adult life, but at the present time this is somewhat visionary. X-radiation has been used but this has such a non discriminate effect on a variety of cell types that it represents a cure hardly better than the disease in most instances. What we are obviously looking for would be an agent which could selectively inhibit the homograft response without too badly imparing other vital functions. While one can argue that this might mean interrupting the entire defense mechanisms of the host, this is not necessarily so. There is good evidence that humoral antibodies play a very small role, if any, in homograft destruction. It looks as if it requires the specific activity of a certain type of cell, presumably the lymphocyte, to destroy homograft cells. It might be possible, therefore, to find an agent which would selectively destroy this aspect of the hosts immune mechanisms without preventing the formation of soluble antibodies and without imparing the overall blood forming ability. It is in this respect that a specific agent would be far superior to X-rays.

How then would you go about screening for such effects? Historically, the easiest technique for testing histocompatability has been the use of tumor cells derived from genetically different strains. When transplanted into incompatable mice such tumors will ordinarily regress after a short period required for the development of the immune reaction. Anomalously then, you would be looking for a reagent that would modify this reaction in such a way that the graft implant would then grow progressively and kill the host.

The most promising agent that one should screen in such a program, are those which appear to have some effect against cells of the lymphocytic series, and there are bound to be some clues in the course of routine tumor screening. Since it is conceivable, however, that the desired agent would have a blocking effect without necessarily destroying the lymphocytic cells it would probably be worthwhile considering an extended program of blind screening as well. And, of course, the possibility of developing a reagent through the principles of substitutional chemotherapy, that is, by chemical modification of products from lymphocytes, should not be neglected. Since a screening program along these lines could be integrated without great difficulty into your program already in progress for screening antitumor agents, it may deserve particular consideration.

Sometime ago we touched on the question of antibiotic screening for contraceptive purposes. I am told that such an agent has in fact been found having been developed by Warner Chilcott, which has the effect of causing the lysis of spermatozoa. If the rumor is correct, the lysis will take place whether the material is injected by either the male or the female.

Well, that's about all for now.

Yours,

Joshua Lederberg

JL:ac