Some notesk on proposal 11/29/56
and other topics

1. I had some suggestions of other target compounds besides DAP, that might be unique to bacteria. I think I've already mentioned "phragmose" ar carboxy-ethyl-glucosamine. In TBc there are a kitkk lot of difficult lipids, and also methyl-cytosine, and there are some heptoses in cell walls of different bacteria. But I think these are superseded by the general proposal.
(at least consciously, afterthoughts)

2. Precedents:/ The main one is iodination of casein to get thyroxin-like activity. You are well aware of metabolic substitutions (e.g. phenylacetic / penicillin fermentation). There are some reviews on substituting reagents that would give some provocative suggestions: see Haddow in Physiopathology of Cancer; Ross in Adv Canc Res. Vol 1; Fraenkel-Conrat in Chem Rev 41:151; Herriott Adv Prot Chem 3:169. For R-ylation of bacteria see Cohen, J.Exp.Med. 82:133; Puck,Arch Biochem Bioph 51:229 and even Lederberg, Cold Spr Harb Symp 16:429-430. But none of these reach the application suggested. However a literature and patent search would be indicated.

Tactics and implications: I hope I have made clear the generality of this approach. Because of assay problems, antibacterial activity is the first thing to look for, but there is an obvious extension to search for this key to specificity in viruses and tumor cells— even in hormone and enzyme gemisch-- indeed anywhere that the concept of metabolic antagonism would be relevant, and that covers almost all of biology & medicine. If the idea is justified, don't think too narrowly about application.

The advantages of this approach are too succinctly stated in the pepposal. The principal practical advance is that the empirical testing precedes the science, but still has a rational basis, at least more so than random screening for actinomycete products. By using the same organism, as the source of the metabolites for structural modification, you increase the likelihood of hitting a target unique to that organism. Etc. Scientifically, this is a way to find new kinds of targets(including genetic ones!)
There is an embarrassment of riches: where to begin? Well just use the easiest reagents: you can grow a batch of coli cells and sulfonate, chlorinate, nitrate, formylate, etc. etc. The first runs should be a lot of fun; I wish I could be around for them.

This is an approach both to discovery and preparation, though probably organic synthesis will cover some of the latter. [I can conceive, however, of growing E. coli on a commercial scale as the cheapest raw material for some substitution-reactant! But yeast might be cheaper to start with some!]

What do your lawyers think of the patent situation here? Can you tie up the a technique for discovery? In any case, it might be advantageous to get an even trivial but tangible success with the approach, if only to establish ypur leadership.

3. Some further extensions. On the organic chemical side, it may be harder to get C-linked substitutions than on more reactive H's. But there are lots of standard tricks: e.g., covering the more reactive groups with acetyl, so you can use more intensive conditions of halogenation, etc. Now you once argued that microorganisms were a method of random screening for new organic structures. Why not use an even more direct bludgeon-approach: a pyrolysis of your waste mycelium ought to generate 100 new compounds for every old one that was there! This is getting away from the more rational procedures above, but you certainly would have a mess of new compounds.

*2 also remotely connected: esp. the toxic agent in NCl_3-treated gluten; the peroxylated-broth effects of Stone-Wyss-Haas; see also Markham's review on uptake of purine-pyrimidine analogues, Adv Virus Research 3 (or 2).