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Dear Joe:

I suspect you may regard this as an untranquilizing regression, but I had a thought for a possible approach to a rational chemotherapeutic that may still be of interest. Lately, I've been following up studies on penicillin action, in relation to protoplasts, and more recently to cultivating protoplasts, in fact the L-form problem. The osmolality of the medium is the key to the situation.

Now one of the theoretical difficulties with rational chemotherapy is finding a reaction which is unique to the parasite, so the antagonist does not either damage the host also, or is not already reversed by the presence of the principal metabolite in the host tissues. Penicillin seems to be affecting such a reaction in wall synthesis: we don't yet know just what it is, though the condensation of sugar residues from uridine-diphospho-conjugated monomers seems a likely bet. Now there is one metabolite which has been unique in bacterial walls, namely diaminopimelic acid, and there are some preliminary indications (from some work and conversation between Bernie Davis and myself) that auxotrophs for this compound are defective in wall synthesis, though I've just started to play with this, and don't have it very clear yet at all. If this reasoning is correct, analogues of DAP should be especially effective chemotherapeutic agents, analogous in their effect to penicillin.

I haven't seen any mention of trials of such analogues, though the interest of Work in DAP would seem to make this an unavoidable thought. (The most recent studies on DAP are in J. Gen Microbiol. 9:394, 12/53; and 14:583, 7/56). I won't offer any suggestions as to which analogues would be profitable to look for. If I can cooperate [illegible] ing compounds as "protoplastogens", let me [illegible] rogram. At least the sulfonic analogues

[illegible]urs sincerely,

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