Correspondence

Letters to the Editor should not exceed 500 words.

New Penicillins

SIR,—In your leading article on new penicillins (8 August, p. 323) you refer to quinacillin, "the least familiar of these substances." The recent publication by Smith *et al.*¹ which has confirmed some of our own laboratory findings and the interest shown in this antibiotic by several groups of workers prompt us to outline our results to date and views regarding the possible therapeutic value of quinacillin.

In vivo laboratory tests and preliminary clinical studies indicate that quinacillin may be of more practical value in the treatment of infections with penicillin-resistant staphylococci than the *in vitro* studies described by Barber and Waterworth² might suggest. In *in vitro* tests in simple media quinacillin is active against recently isolated strains of *Staphylococcus aureus* at levels similar to those of other penicillinase-resistant penicillins. Our own results, given in Table I,

with activity *in vivo* in animal experiments or with clinical efficacy. Many tests have been carried out in mice infected intraperitoneally with various strains of *Staph. aureus* and dosed with penicillins one hour later. In Table II results are given for the minimal inhibitory concentration (M.I.C.) in $\mu\text{g./ml.}$ in nutrient agar and the approximate curative dose₅₀ (CD₅₀) in mg./kg. for penicillins given subcutaneously in mice. It seems obvious that there is little correlation between *in vitro* activity and ability to protect mice from a lethal staphylococcal infection. Fuller details of these and other findings are being prepared for publication.

Our suggestion that *in vivo* results with quinacillin may give a more accurate picture of its clinical usefulness is supported by results of preliminary trials in man. So far a number of patients treated with quinacillin, all suffering from significant infections with

tainly call for some comments. In particular, the leading article shows a surprising unfamiliarity with the already extensive *in vivo* studies and clinical data reported for nafcillin.

Studies carried out in our laboratory¹⁻⁴ with more than 20,000 mice demonstrated that nafcillin, administered intramuscularly or orally, was considerably more active than methicillin, oxacillin, and cloxacillin when the animals were experimentally infected with penicillin-sensitive and penicillin-resistant staphylococci, streptococci, and pneumococci. Interestingly enough, recent studies⁵⁻⁷ have shown that subinhibitory concentrations of nafcillin are far superior to those of oxacillin and cloxacillin, both for inhibiting the cell-wall synthesis of staphylococci and for increasing cellular lysis following exposure to the stress of heat or enzymes (e.g., lysozyme and/or trypsin). However, the exact interpretation and application of these data in the management of clinical problems remain to be determined.

Though wisdom would decree caution in extrapolating data from *in vitro* studies to the situation found in the host-parasite relationship, your leading article directly implies that because of high protein-binding nafcillin is not as effective as some of the other penicillins. In the same article, however, you point out that nafcillin and cloxacillin are bound to serum proteins to the same extent, and yet conclude "... cloxacillin seems to be the antibiotic of choice for resistant staphylococcal infections. . . ." Considering the point that nafcillin, administered either parenterally or orally in man, has already proved its worth in the treatment of staphylococcal, streptococcal, and pneumococcal infections,⁸⁻¹³ the protein-binding is presumably reversible and apparently does not significantly alter the therapeutic index of this drug.

I think it unwise to allude to the entirely misleading title of the clinical paper by Breese and his colleagues (i.e., "Comparative Ineffectiveness of Nafcillin Against Hemolytic Streptococcal Infections in Children")¹⁴ and to judge the efficacy of a drug from implications in that title. In the body of their paper the authors actually showed a 75% cure rate for nafcillin against streptococcal disease in children. Moreover, the authors compared unbuffered nafcillin with buffered benzylpenicillin; had they compared buffered agents, their study (as they themselves admitted) would have had greater validity.

This correspondent wholeheartedly agrees with your leader writer that more information is needed concerning the therapeutic efficacy of the newer penicillins. It was not his intention to argue that any particular penicillin has been proved superior in the clinic. Rather, the present comments are intended to emphasize that too literal extrapolation of laboratory data from *in vitro* studies to therapeutic efficacy in man is at best a matter of guesswork. The ultimate criterion of efficacy of any penicillin is its usefulness in the treatment of well-defined infections. Therefore one must analyse the host-parasite-drug interrelationship rather than any combination of two of these variables. Although the bacteriologist experiments in

TABLE I

No. of Strains of <i>Staph. aureus</i>	Penicillin	Minimal Inhibitory Concentration $\mu\text{g./ml.}$ in Nutrient Agar and Number of Strains Sensitive								
		<0.07	0.07	0.15	0.31	0.62	1.2	2.5	5	50 or > 50
50	Benzyl	6	0	0	0	0	1	0	0	43
50	Quinacillin	0	0	7	26	17	0	0	0	0
50	Methicillin	0	0	0	0	0	25	24	1	0
25	Cloxacillin	0	0	0	15	10	0	0	0	0

resemble those obtained in several other laboratories. The values vary, of course, not only with the strains of staphylococcus but also with the techniques used for determining them.

The degree of protein-binding is low, and the resistance of quinacillin to staphylococcal penicillinase is high; also, unlike other penicillinase-resistant penicillins, quinacillin is a poor inducer of staphylococcal penicillinase.¹ For these and possibly other reasons the end-point with quinacillin is relatively little changed in the presence of blood or serum or with large inocula of organisms.³

From the results given by Barber and Waterworth² it seems that quinacillin is less effective *in vitro* against some methicillin-resistant staphylococci than are other penicillinase-resistant penicillins, but Smith *et al.* report quite opposite findings and state, "... there is cross-resistance between cloxacillin, methicillin, and quinacillin, but it appears that resistant strains are slightly more susceptible to quinacillin than to the other two, at least using large inocula." This point is still under investigation in our laboratories.

The point of major interest, however, is that activity *in vitro* may not run parallel

benzylpenicillin-resistant staphylococci, have made a good recovery. Of these, several have failed to respond to other penicillinase-resistant penicillins. In particular, one patient with staphylococcal meningitis recovered dramatically from a moribund state following intramuscular treatment with quinacillin, having already been treated unsuccessfully with cloxacillin, methicillin, and chloramphenicol.

Full details of these and other trials will be published in due course. At the moment, however, there seems a reasonable possibility that quinacillin may be of practical value as an antibiotic for specific use in the treatment of resistant staphylococcal infections and may in certain circumstances have advantages over other penicillins.—We are, etc.,

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TABLE II

Strain of <i>Staph. aureus</i>	Quinacillin		Methicillin		Cloxacillin	
	MIC	CD ₅₀	MIC	CD ₅₀	MIC	CD ₅₀
8452	0.31	3	2.5	7	0.62	18
231	0.62	8	2.5	15	0.31	31
Dakin	0.31	11	1.2	11	0.31	39
Smith	0.31	8	—	—	0.31	16

SIR,—The recent paper by Professor Mary Barber and Miss Pamela M. Waterworth and the opinions expressed in your leading article (8 August, pp. 323 and 344) on the relative therapeutic efficacy of new penicillins cer-