for pathogens isolated from sites other than the urinary tracts.—We are, etc.,

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Ampicillin for Sore Throat

SIR,—Dr. A. A. Robertson's conclusion (9 June, p. 614) that the use of ampicillin must be considered in the treatment of acute sore throats is based on the following premises: (1)—that *Haemophilus influenzae* is frequently isolated from the throats of patients with acute sore throats; (2)—that where this organism is isolated it is responsible for the acute sore throat; and (3)—that ampicillin is the antibiotic of choice in *H. influenzae* infections.

The first premise is true, but it is also true that *H. influenzae* is frequently isolated from the throats of normal people,[1 2] so that the truth of the second premise is to be questioned. With regard to the third premise it is true that on average ampicillin is about twice as active as penicillin against *H. influenzae*[3] and this "resistance" of *H. influenzae* to penicillin and "sensitivity" to ampicillin is frequently stressed (especially in advertisements for ampicillin). However, it should be remembered that many strains of *H. influenzae* are as sensitive to penicillin as to ampicillin, and most *H. influenzae* will have their growth at least inhibited by levels of penicillin which should readily be achieved by correctly given oral phenoxymethylpenicillin.

In life-threatening infections with *H. influenzae* such as acute epiglottitis, septicaemia, and meningitis, it would, of course, be imperative to give the most active antibiotic, and ampicillin would be more appropriate than penicillin in these situations. However, in relatively trivial infections such as acute sore throats, which will almost invariably settle spontaneously within a few days (unless due to infectious mononucleosis) other factors, such as the cost of the drug and the risk of adverse factors such as monilial superinfection and drug rash, have to be taken into account.

If one considers all the factors mentioned above, it is doubtful if ampicillin is ever indicated in the treatment of acute sore throat, even if *H. influenzae* has been isolated. When one considers also the predominance of haemolytic streptococci in bacterial sore throats, surely the routine use of ampicillin in preference to penicillin in acute sore throats is never justified.—I am, etc.,

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1 Wilson, G. S., and Miles, A. A., eds., *Topley and Wilson's Principles of Bacteriology and Immunity*, 5th edn., vol. 2, p. 2473. London, Arnold, 1964.
2 Turk, D. C., and May, J. R., *Haemophilus Influenzae: Its Clinical Importance*, p. 13. London, English Universities Press, 1967.
3 Ibid, p. 73.

SIR,—Dr. A. A. Robertson (9 June, p. 164) states that "penicillin was not the antibiotic of choice in over one-third" of 143 patients with sore throat. He apparently bases this statement, and his preference for ampicillin as the drug for treating sore throats, on the fact that 49 of the patients "yielded swabs positive for *Haemophilus* species." Failure to find a penicillin-sensitive potential pathogen may constitute an adequate reason for regarding penicillin as inappropriate; but the findings of *Haemophilus* species in the throats of one-third of the patients is irrelevant to the issue. It is not uncommon to find *H. influenzae* in the throats of 50% or more of the members of a healthy population.[1] I know of no evidence that the ordinary noncapsulated *H. influenzae* strains of the upper respiratory tract cause sore throats (though capsulated type b strains can occasionally cause tonsillitis—and also, of course, epiglottitis, which is hardly to be included under the term "sore throat").[2] There is some circumstantial evidence that *haemolytic* haemophili (which are mostly of the species *H. parahaemolyticus*) may cause pharyngitis[3 4] but this is by no means proved.—I am, etc.,

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1 Turk, D. C., and May, J. R., *Haemophilus influenzae: Its Clinical Importance*, pp. 13-23. London, English Universities Press, 1967.
2 Addy, M. G., Ellis, P. D. M., and Turk, D. C., *British Medical Journal*, 1972, 1, 40.
3 Salgado Correia, M. J., and Torres Pereira, A., *Arquivos do Instituto Bacteriológico Câmara Pestana*, 1966, 11, 87.
4 Branson, D., *Applied Microbiology*, 1968, 16, 256.

Drugs for Angina Pectoris

SIR,—Dr. Brian Livesley and others (17 February, p. 375) recently reported a five-drug trial in angina pectoris, comparing verapamil in two dose levels, propranolol, and isosorbide dinitrate. I find it pertinent to make a few methodological observations on this study.

The order of treatment was always the same, though different patients started at different parts of the drug cycle. This meant that drug E, which was isosorbide dinitrate, in 80% of the patients came after at least one other drug. Consequently, all possible carry-over effects of this drug longer than one month will be reflected in the results ascribed to isosorbide dinitrate. The same consequence is true for all the other drugs. A complete randomization of the order of these five treatments would have obviated this difficulty. The authors state that only the last two weeks of each four-week period were analysed in order to avoid carry-over effects. They have missed the point, however, of analysing whether there were any carry-over effects at all. If the analysis of all four weeks yields the same results as for only the last two weeks there are either carry-over effects longer than four weeks or none at all.

The authors give significance limits for differences between various treatments using the non-parametric Wilcoxon signed ranks test, which no doubt is a relevant test since nothing is known about the distribution of data. However, no average or median values are given to show how large these differences were. Moreover, six comparisons are presented. Dunnett[1] thinks that if repeated paired testing is performed in a multi-treatment system like the one reported not more than N−1 comparisons are allowed, where N = no. of treatments, and furthermore, that one of the treatments is not to be used more than twice. If all treatments are to be compared an analysis of variance should be performed. Assuming that the recorded variables are not normally distributed, an assumption with which I would agree, the type of test that should be used is the Friedman two-way analysis of variance.[2] This involves ranking of the different treatments for each patient. In doing so, propranolol comes out with the lowest rank sum (= best results) in the 16 patients having all five treatments. The control or placebo values come out with the highest rank sum. However, a Friedman analysis of variance does not yield any statistical significance—that is, the results of these five treatments differ with a confidence limit higher than 5%. If the average values of the work done for these 16 patients are calculated it will be seen that verapamil 120 mg three times daily increases the work (compared with the average control value) by about 33%, verapamil 80 mg three times daily by about 14%, propranolol 100 mg three times daily by about 21%, and isosorbide dinitrate 20 mg three times daily by about 49%. It is readily seen that the high value for isosorbide dinitrate is due to one patient having a tremendous increase of work on this drug, and the results just reported bear out another point worth mentioning: the characterization of a sample which is not normally distributed is better done by the median rather than the mean. The median values of the work done (in kg/sec) for these 16 patients are respectively (approximately) 9,500 for control, 12,500 for verapamil 120 (+32% compared with the median control value), 9,500 for verapamil 80 (±0%), 13,000 for propranolol (+37%), and 11,000 for isosorbide dinitrate (+21%).

Maybe the best and most relevant way of expressing the results is to state which drug was the best for each patient. It is then seen in the 16 patients mentioned that verapamil 120 was best in four patients, verapamil 80 in three patients, and verapamil 120 *and* 80 was equally good and the best drug in one patient. Propranolol was the best drug in one patient and isosorbide dinitrate in one patient. In one of the patients best on verapamil 120 the result was equal with isosorbide dinitrate. Six patients showed practically no difference between any of the drugs. All these values are with reference to the control values. This analysis would indicate that in the 16 patients going through all five treatments the best drug was in the majority of cases verapamil, whereas propranolol and isosorbide dinitrate were equal in terms of "best drug." On the average, however, there was no significant difference between any of the drugs in terms of increased work done, and the results do not point to very important differences between the drugs. At all events, it seems unwarranted to state specifically for isosorbide dinitrate that it is as ineffective as placebo.

It seems as if the original proprietary tablets were not used in this trial. Nevertheless, the authors state in the summary that Cordilox, Inderal, and Vascardin were used. A clari-