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

ROBERT BLOWERS

Chairman,
P.H.L.S. Quality-control Committee
Clinical Research Centre,
Harrow, Middlesex

E. JOAN STOKES

Department of Clinical Pathology,
University College Hospital,
London W.C.1

J. D. ABBOTT

Secretary,
P.H.L.S. Quality-control Committee
Public Health Laboratory,
Withington Hospital,
Manchester

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.,

H. PULLEN

Department of Infectious Diseases,
Seacroft Hospital,
Leeds

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 non-capsulated *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 pharyngitis³ but this is by no means proved.—I am, etc.,

D. C. TURK

Department of Bacteriology,
Radcliffe Infirmary,
Oxford

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. Dunnnett¹ 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-

fication on this point would be welcome, as well as how the actual trial tablets compare with the commercially available. Since comparative trials of different drugs are now more common it seems important to report not only the relative merits of various drugs tested but also the absolute merits in terms of the variables used, as well as to pay close attention to all aspects of methodology.—I am, etc.,

GUNNAR NYBERG

Medical Department I,
Sahlgrenska Hospital,
Göteborg, Sweden

1 Dunnett, C. W., in *Selected Pharmacological Testing Methods*, ed. A. Burger, New York, Marcel Dekker Inc., 1968.

2 Siegel, S., *Nonparametric Statistics for the Behavioral Sciences*. London, McGraw-Hill, 1956.

Potassium Deficiency during Treatment with Brinaldix K

SIR,—We wish to report four cases of severe potassium deficiency seen recently in this hospital in patients receiving Brinaldix K.

Case 1.—A 48-year-old woman was admitted to hospital with weakness, depression, and lassitude. For four months she had been known to be hypertensive, with an impaired creatinine clearance (12 ml/min), and had recently developed cardiac asthma. In addition to clonidine 0.1 mg four times daily for her hypertension she had been receiving digoxin 0.25 mg daily and Brinaldix K two tablets daily for three weeks. Severe hypokalaemia was found (see table) and treated by withdrawal of Brinaldix K and addition of Sando-K, with return to normal values over the following three days. In spite of the impaired renal function and hypokalaemia, no electrocardiographic features of digitalis toxicity were found.

Case 2.—A 69-year-old woman known to be hypertensive for six months was admitted to hospital with extreme weakness, nausea, and postural hypotension. Her hypertension was at the time being treated with clonidine 0.1 mg twice daily. She had been taking digoxin 0.25 mg daily for several months, and on admission showed gross electrocardiographic evidence of digitalis toxicity, with coupling and ST-segment depression. Electrolyte estimations confirmed marked hypokalaemia. For one month prior to admission she had been receiving Brinaldix K one tablet daily. This was discontinued after admission, and potassium supplements added, with return of serum potassium values to normal levels in seven days and disappearance of digitalis intoxication in three days.

Case 3.—A 79-year-old woman was admitted to hospital having been found on her kitchen floor, where she had presumably been for some hours. She was not hypothermic. Six weeks previously she had been discharged from hospital after treatment for congestive cardiac failure with frusemide. On return home her diuretic was changed to Brinaldix K two tablets daily. When readmitted asymptomatic hypokalaemia was found. Her diuretic was changed to frusemide and Slow-K added, with return to normal of plasma potassium levels in five days.

Case 4.—A 58-year-old woman was readmitted to hospital with congestive cardiac failure and chronic obstructive lung disease. She had been discharged one week previously following a period of treatment for the same condition. In hospital she had received frusemide and Slow-K, and this was replaced by Brinaldix K on her discharge. Electrolytes prior to discharge had been normal. When readmitted asymptomatic hypokalaemia was found

and reverted to normal values in three days upon withdrawal of Brinaldix K and administration of potassium supplements.

The use of potassium supplements together with diuretic therapy is widely accepted as necessary. It is perhaps less well appreciated that to be fully effective potassium should be given in the form of chloride. Potassium deficiency due to diuretics is often accompanied by hypochloreaemic alkalosis. Potassium in the form of bicarbonate may aggravate the alkalosis and thereby worsen the hypokalaemia in spite of the administration of potassium ions.¹

Each Brinaldix K tablet contains clopamide 20 mg and potassium 12 mEq but only 3.4 mEq of chloride ions. The remaining anion is present as bicarbonate. Clopamide 60 mg is more potent than bendroflumazide 7.5 mg², so that it is likely that the patient receiving Brinaldix K is receiving a greater effective amount of diuretic than with other combined diuretic and potassium preparations. We believe that this combination of a more potent diuretic dose together with inadequate chloride and significant bicarbonate content carries a risk of induced hypokalaemia. A striking feature in our patients was the short duration of treatment with Brinaldix K, and the knowledge from previous attendance that prior to receiving Brinaldix K hypokalaemia had not been present in spite of other diuretic and potassium therapy being administered.

While in general deprecating the use of combined diuretic and potassium preparations, we accept that there are some indications for their use, but we feel that in its present form Brinaldix K should not be used in preference to the non-effervescent preparations containing a thiazide with potassium as chloride in a slow-release form. As Brinaldix K is an effective diuretic and pleasant to take, we feel that the chloride content should be increased and the bicarbonate reduced or omitted.—We are, etc.,

RICHARD T. TAYLOR
M. JOHN T. PEASTON

Kidderminster District General Hospital,
Kidderminster, Worcs

1 Welt, L. G., in *Pharmacological Basis of Therapeutics*, ed. L. S. Goodman and A. Gilman, 4th edn., p. 794. New York, MacMillan, 1970.

2 Briggs, J. D., McSweeney, R. N., and Kennedy, A. C., *Postgraduate Medical Journal*, 1965, 41, 193.

Fenfluramine and Growth Hormone Release

SIR,—Mr. W. R. Sulaiman and Dr. R. H. Johnson (12 May, p. 329) describe the effect of a single intravenous injection of 20 mg of fenfluramine on the metabolic response to exercise lasting 20 minutes and report a suppressive effect of this drug on the secretion of growth hormone normally encountered in response to exercise. They then suggest a hypothalamic site of action for the drug and draw inferences for clinical practice.

We would remind them of almost completely contrary evidence¹ presented in a

symposium report from which they quote two references. This other study involved obese patients—to whom fenfluramine is commonly administered. The dose was 40 mg orally four times daily for one week before repeating the exercise study. Plasma growth hormone concentrations showed striking increments with exercise, and these were even greater on the drug—"the differences between the mean values . . . when fenfluramine was added were statistically significant at 1½, 2½, and 4½ hours after the start of the period of exercise." Again contrary to Mr. Sulaiman's and Dr. Johnson's findings, changes in blood glucose and the plasma concentration of insulin were not found during periods of exercise more prolonged than those they used.

Furthermore, the most vigorous and consistent secretion of growth hormone occurs during natural sleep. Having previously mentioned that chronic intake of fenfluramine, far from suppressing growth hormone secretion during sleep, may lead to increased plasma levels,² we now show in the accompanying figure an example where plasma levels (in ng/ml) were consistently higher throughout a night, in the case of a man who had received oral fenfluramine for over two months, than was the case six weeks later when he had been off fenfluramine for a month. Blood was withdrawn without disturbing sleep, using a venous catheter technique.³

In studying the mode of action of a drug such as fenfluramine it would seem important that the conditions of administration should resemble as nearly as possible those in which it is commonly used.—We are, etc.,

D. L. F. DUNLEAVY

University Department of Psychiatry,
Nottingham General Hospital,
Nottingham

IAN OSWALD

University Department of Psychiatry,
Royal Edinburgh Hospital

J. A. STRONG

University Department of Medicine,
Western General Hospital,
Edinburgh

1 Brockie, B. K., Brown, P., Ahmed, N. E. L., Shirling, D., and Strong, J. A., *South African Medical Journal*, 1971, 45, Suppl. (June), p. 26.

2 Lewis, S. A., Oswald, I., and Dunleavy, D. L. F., *British Medical Journal*, 1971, 3, 67.

3 Ogunremi, O. O., et al., *British Medical Journal*, 1973, 2, 202.

Transmission of *Trichuris trichiura*

SIR,—Dr. D. M. Lynch and others (14 October 1972, p. 73) described the incidence

Case	Serum Electrolytes (mEq/l.)			Blood mg/100ml Urea	Dose of Clopamide (mg/day)	Duration of Treatment with Brinaldix K (weeks)	Reversal Time of Hypokalaemia (days)
	Na	K	Cl				
1	140	1.6	85	75	40	3	3
2	136	1.8	85	67	20	4	7
3	139	2.6	93	31	40	6	5
4	140	2.6	94	42	20	1	3