respectively. Thus it would seem that the mortality following transplantation is grossly underestimated on the basis of the Edinburgh data (however, other transplant survival data are available).

Secondly, there are several minor errors in the text and Tables. For example, in Figure 3 the numbers of patients surviving in the first five months bears little relation to the percentage survival graph. Also, in the paragraph on dialysis survival, it is stated that a survival of 0.98 has been used in states 7, 15, 23, and 25; this is not true of state 25.

Finally, it would seem that some explanation of the derivation of the 95% confidence limit is necessary. As I understand forecasting by a Markov process a 95% confidence limit is calculable on the basis that each parameter behaves as a random variable subject to predetermined probabilities. However, each probability, based on observation of past data, is subject to error and an estimation of these errors is desirable before confidence limits are applied to a forecast. As indicated above, I consider that several of the more important probabilities have been assigned values in error.—I am, etc.,

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¹ Woodruff, M. F. A., Nolan, B., Robson, J. S., and McDonald, M. K., *Lancet*, 1969, 1, 6.

Long-acting Phenothiazines in Schizophrenia

SIR,—I have belatedly received the 23 January issue of the *British Medical Journal* and was most interested in your leading article on "Long-acting Phenothiazines" (p. 189).

This article mentions "no double-blind controlled investigations of long-acting fluphenazines have been reported." At least six are known to me, of which three compare an active oral phenothiazine with fluphenazine enanthate.¹⁻³

Despite this oversight the writer rightly interprets the remaining data as indicative of their usefulness. This is important since we should not make a mystique out of the controlled trial. The necessity for their use in certain areas should not blind us to the information available from other approaches, particularly in this type of patient.

In the first study of fluphenazine decanoate in man we concluded that it was a most useful potent agent, longer acting, and with fewer side effects than fluphenazine enanthate; this in an open-study of 12 patients.⁴ No evidence has appeared to contradict the above statements, and indeed in two controlled studies of fluphenazine enanthate versus fluphenazine decanoate both concluded that fewer extrapyramidal side effects are produced with the decanoate, although the results were less conclusive about the greater length of activity.^{5,6}

The incidence and control of side effects has been detailed elsewhere, but are not necessarily as frightening as has been suggested.⁷

The range of improvement which appears greater than with oral preparations may be related to bypassing the gut and the liver therefore avoiding absorption and possibly early metabolic breakdown. Finally, the

question of depression may be related to the more rapid improvement noted with this drug. As the article states, depression is a common feature of schizophrenia, but an alternative explanation is the "depression with insight" which often occurs with the rapid removal of symptoms.—I am, etc.,

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- ¹ Ravaris, C. L., Weaver, L. A., and Brooks, G. W., *Diseases of the Nervous System*, 1965, 26, 33.
- ² Kinross-Wright, J., and Charalampous, K. D., *International Journal of Neuropsychiatry*, 1965, 1, 66.
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- ⁴ Simpson, G. M., Amin, M., Kunz, E., and McCafferty, F. V., *American Journal of Psychiatry*, 1965, 121, No. 8, 784.
- ⁵ Kurland, A. A., and Richardson, J. H., *Psychopharmacologia*, 1966, 9, 320.
- ⁶ Neal, C. D., and Imlah, N. W., *Diseases of the Nervous System*, 1970, 31, No. 9, Suppl. p. 24.
- ⁷ Simpson, G. M., *Diseases of the Nervous System*, 1970, 31, No. 9, Suppl., p. 12.

Antibiotic Sensitivity Testing

SIR,—Your recent leading article (22 May, p. 416) drew attention to the difficulties and lack of agreement in the interpretation of antibiotic sensitivity tests. This is hardly surprising considering that in any one organism each type of drug resistance shows different characteristics and that the level of resistance detected by standard dilution methods or inferred from zone diameters in diffusion tests depends on such a variety of factors peculiar to the organism.

Very little decisive information has been collected on the significance—in terms of interference with therapeutic response—of several of the commoner types of drug resistance seen in hospital strains of *Staph. aureus*. In trying to simplify the situation we probably err on the side of over-caution in some of our assessments of resistance—in particular with the penicillins—and may consequently not benefit to the full from some of our basic antibiotics.

At the present time the emergence in hospitals of new types of *Staph. aureus* showing a temperature-dependent tolerance to all penicillins and cephalosporins—usually referred to as methicillin resistance—has added to the difficulties in sensitivity testing. The distinction between cultures of full sensitivity and those showing this, the only type of naturally occurring resistance, is clear-cut in disc diffusion tests with methicillin carried out at 30°C. In similar tests at 37°C no clear picture emerges, there being a continuous range of zone sizes from apparently "sensitive" to apparently "resistant" in tests on nutrient agar media without added salt.¹ It may well be, however, that there is a better correlation between response to therapy and apparent sensitivity in disc diffusion tests at 37°C—particularly in those patients with otherwise unimpaired resistance to infection. Benner and Kayser have used the term "basal resistance" in an attempt to relate levels of methicillin resistance to in vivo therapeutic response.²

In the absence of comparative clinical trials it seems that there are two ways in which clinically relevant information on this and similar difficulties could be obtained. Firstly, for clinicians in hospital or general

practice and pathologists advising on chemotherapy to attempt an unbiased retrospective analysis—from patient records—of the outcome of chemotherapy in patients where the infecting microbe was subsequently demonstrated to harbour a specific type of resistance to the drug used. Secondly, for a central laboratory to examine in detail collections of cultures from specific types of infections where the outcome of single course antibiotic therapy is known—whether successful or not—irrespective of what previous interpretation had been made of sensitivity tests.

Studies of this type might help in our understanding of which levels of resistance are likely to compromise successful therapy in particular categories of infection. In the case of methicillin resistance in staphylococci, for example, they might help to tell us which types of infection are amenable to treatment with penicillins (for example, cloxacillin) alone, and which require supplementary or other therapy. A similar study would be useful in the case of outpatients in whom infections are often caused by *Staph. aureus* strains producing small amounts of penicillinase. Many of these infections are still amenable to treatment with penicillinase-labile penicillins.^{3,4}

In a subject where there is little factual information to rely on it would seem prudent to make use of all possible sources of information. It would be of interest to hear if anyone has access to material that might be of value in the types of assessment described.—I am, etc.,

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Cyclophosphamide and the Bladder

SIR,—A point referred to in your leading article (26 June, p. 726) merits amplification. It relates to the distinction between cyclophosphamide-induced cystitis and bladder malignancy.

Your leading article reinforces the manufacturer's recently circularized note about haemorrhagic cystitis, drawing attention to the occurrence of this side effect of the drug in some 10 to 20% of patients receiving large amounts of cyclophosphamide. Increased awareness will reduce the possibility of misinterpretation of the cause of haematuria when this is not accompanied by the more usual dysuria or increased frequency of micturition. Even cystoscopy, biopsy, and cytology can be misleading. Liedberg *et al.*¹ say "The cytologist and the clinician should be aware of the fact that pictures suggesting malignancy may appear during treatment with cyclophosphamide. The polymorphous, tumour-like granulation tissue sometimes seen on cystoscopy may be mistaken for metastases or primary bladder tumour both macroscopically and microscopically, particularly in very small biopsy specimens." Goldman and Warner² also emphasized the importance of recognizing the atypical