malabsorption of vitamin B₁₂ and four of these had abnormally low serum levels of the vitamin. We have data on 114 diabetic patients who have had at least 2 g of metformin daily for at least two years and of these no less than 17.5% had serum levels of vitamin B₁₂ at or below the lowest level of the normal range (160-900 µg/ml). The fact that this figure is considerably above the 5.6% of the Belfast workers may be owing to the relatively larger mean daily dose of metformin used in the Aberdeen series (3.3 g versus 1.8 g). Just under 10% of the Aberdeen series also had abnormally low levels of serum folate, but in all but one instance this occurred with normal serum vitamin B₁₂ levels. The mean duration of biguanide therapy was similar in both series (4.6 and 4.4 years for Belfast and Aberdeen respectively) but in Aberdeen most of the patients had had phenformin in preference to metformin before 1968. The change-over to metformin for those requiring more than 100 mg of phenformin a day was effected because of a few cases of serious lactic acidosis associated with the use of larger doses of phenformin, especially after an alcoholic spree. We have not seen lactic acidosis in patients taking up to 4.5 g of metformin a day.

We would like to support the recommendation of Dr. Tomkin and others that all patients on long-term therapy with metformin should have an annual estimation of serum vitamin B₁₂, for it is otherwise quite easy to miss cases of classical macrocytic anaemia and/or signs of subacute combined degeneration of the cord.

We would like to thank Dr. Audrey Dawson and her staff for undertaking the haematological investigations.

JOHN M. STOWERS
OLAJIDE A. O. SMITH

Diabetic Clinic,
Royal Infirmary,
Aberdeen

Vagotomy Diarrhoea

SIR,—There has been considerable debate concerning the incidence of incapacitating explosive diarrhoea after truncal vagotomy for peptic ulcer (1 February 1969, p. 302; and 14 February 1970, p. 412).

I would like to report the case of a 42-year-old man who was admitted to hospital in September 1970 with the clinical presentation of a perforated chronic duodenal ulcer. This was confirmed and treated at laparotomy by simple suture. Two months later, with no improvement in his symptoms, a truncal vagotomy and gastroenterostomy were performed. After this he immediately developed explosive incapacitating diarrhoea, up to 15 times daily, which failed to respond to any medical treatment. A diagnosis of vagotomy diarrhoea was made. Four months later it was clear that, from physical, occupational, and social aspects, the patient could not tolerate continuation of his symptoms. He was admitted to hospital for full reinvestigation. The further relevant findings were a history of intense hunger, not satisfied by any amount of food; the presence of undigested food in the stool; and on barium meal and follow through, the passage of barium from the hypopharynx to the caecum in 4½ minutes.

At laparotomy a terminal ileogastrostomy

was found. This was converted to a proximal jejunogastrostomy. The patient made an uninterrupted recovery, and is continuing to have a normal bowel action and to regain weight.

Mistakes are made. This is not a criticism but a cautionary tale. Diarrhoea does occur after truncal vagotomy, but, before it is given a diagnostic label of "vagotomy diarrhoea," the patient must be thoroughly reinvestigated.—I am, etc.,

ROSALIND M. MANCE

Queen Mary's Hospital,
London E.15

Genital Herpes Infection and Non-specific Urethritis

SIR,—Dr. C. S. Goodwin and others (28 November, 1970, p. 558) discussed the asymptomatic infection of the male urethra with herpes simplex virus (H.S.V.). H.S.V. was isolated from 2 out of 12 males with urethral discharge. The patients had no clinical signs or symptoms of herpes genitalis.

At Karolinska Sjukhuset since 1968 we have studied the incidence of genital H.S.V. infection in patients attending the V.D. clinic because of suspected venereal disease.¹ The specimens for virus isolation were taken from the urethra and collected on the patients' first visit to the clinic. Immediately after sampling the urethral swab was placed in a tissue culture tube with GMK-AH 1 cells (established line of Green monkey kidney cells).² In 29 out of 688 males H.S.V. was isolated. Seven of the males with verified H.S.V. infection had no clinical signs or symptoms of herpes genitalis. Their only symptom was urethral discharge. The Table indicates symptoms and histories in all our cases of virologically verified genital H.S.V. infection (figures in brackets give the number of patients with gonorrhoea in the respective groups).

No typical herpes symptoms No anamnesis of herpes	6 (1)
No typical herpes symptoms • Anamnesis of herpes	1 (1)
† Suspect herpes symptoms No anamnesis of herpes	12 (2)
Suspect herpes symptoms • Anamnesis of herpes	2 (1)
*† Typical herpes symptoms No anamnesis of herpes	5 (1)
*† Typical herpes symptoms • Anamnesis of herpes	3 (0)
Total	29 (6)

- History of clinical H.S.V. infection in the genital region
- † A few minor lesions, similar to H.S.V. infection, in the genital region
- *† Grouped vesicles or grouped shallow ulcerations in the genital region

The same technique for virus isolation has been used in a control group.¹ One hundred and thirty three young males without venereal disease and without history or clinical signs of genital H.S.V. infection were investigated. The rate of genital H.S.V. infection in the control group was none (no virus isolated).

From the Table it is obvious that in five patients without typical symptoms and history of genital H.S.V. infection, all with urethral discharge, H.S.V. was the only agent that could be isolated. If virus isolation had not been performed these patients might well have been classified as suffering from non-specific urethritis.

To our knowledge none of the authors who previously have reported negative virus isolations from males with non-specific urethritis^{2,3} have used a comparable technique. Nahmias *et al.*⁴ have reported a prevalence of 0.3% genital H.S.V. infection in males attending a venereal disease clinic. Virus isolation was done only from genital lesions in males with clinical symptoms of genital H.S.V., and the swabs were placed into Hank's buffered salt solution before inoculation of the specimens into tissue culture tubes. Considering the relative lability of H.S.V. Type 2⁵ it is to be expected that a method with direct inoculation of the specimen into the tissue culture tube will be a more sensitive method of detecting the virus.—We are, etc.,

S. JEANSSON
L. MOLIN

Department of Clinical Bacteriology,
Section of Virology, and
Department of Dermatology,
Karolinska Sjukhuset,
Stockholm, Sweden

- 1 Jeansson, S., and Molin, L., *Lancet*, 1970, 1, 1064.
- 2 Ford, D. K., *Canadian Medical Association Journal*, 1968, 99, 900.
- 3 Günalp, A., *Proceedings of the Society for Experimental Biology and Medicine*, 1965, 118, 85.
- 4 Nahmias, A. J., *et al.*, *British Journal of Venereal Diseases*, 1969, 45, 294.
- 5 Plummer, G., Waner, J. L., Phuangsab, A., and Goodheart, C. R., *Journal of Virology*, 1970, 5, 51.

Haemodialysis/Transplantation Programme

SIR,—I have been interested in the logistics of renal dialysis units and I should like to raise a few points regarding the paper by Dr. S. C. Farrow and others on a statistical approach to planning an integrated haemodialysis-transplantation programme (19 June, p. 671).

Firstly, certain important probabilities used in the matrix do not appear to fit the data from which they were derived. The Table giving survival figures should be corrected in the columns given below. It is appreciated that a monthly survival greater than 1.00 is unreal, but such parameters are meaningful when the average "matrix survival" for months 7 to 30 is calculated; this is 0.9897 (or 0.99) not 0.98 as given in the Table. (A simple graph of the survivals for these months illustrates that 0.99 gives a closer fit than does 0.98). It should be noted that this is the monthly survival for all states, and includes poorer survivals from states with poorer prognoses, such as the months following transplantation.

Table Corrections

Months	10	16	19	21	22	24	26
Patients surviving	38	25	19	17	15	12	9
Patients observed	47	36	29	25	23	18	12
Overall survival	0.81	0.69	0.66	0.68	0.65	0.67	0.75
Monthly survival	1.01	0.99	0.98	1.04	0.96	1.03	1.13
Matrix survival	← 0.99 →						

The probabilities inserted in the matrix for the survival of patients following transplantation do not agree with those obtained from the Edinburgh data.¹ The Edinburgh data (for 35 patients) indicate survival at 1, 2, and 3 months of 86%, 70%, and 64% respectively. However, in the matrix higher probabilities lead from states 8, 9, and 10 to rejection (state 11) than to death (state 0). Analysis of the matrix in this region leads to survival at 1, 2, and 3 months following transplantation of 97%, 94%, and 90%

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.,

R. R. WEST

Department of Mathematical Statistics and Operational Research,
University College,
Cardiff

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.,

GEORGE M. SIMPSON

Department of Mental Hygiene,
Rockland State Hospital,
Orangeburg, New York, U.S.A.

- ¹ Ravaris, C. L., Weaver, L. A., and Brooks, G. W., *Diseases of the Nervous System*, 1965, 26, 33.
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- 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.
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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.,

J. H. HEWITT

Clinical Research Centre,
Watford Road,
Harrow

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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