at a clinic or hospital, arrangements are made so that a chemist in the patient's area may supply him with the requisite drugs. Unfortunately, if the chemist is not open on a Sunday the addict receives a double supply on the Saturday and of course if the chemist is closed for Easter Monday or Christmas Day and Boxing Day following a weekend, then the drug addict is given a supply of drugs to carry him over this period.

This system may work well in many cases. As a police surgeon, I meet the cases where the system falls down and very real problems exist. These occur when, because the addict is so dependent on his drugs or for some other reason, he uses up his supply quickly, or when he sells them, and then is without drugs for the next day or so.

Another problem is that if a doctor wishes to confirm that a certain person is a drug addict, then facilities are available to obtain this information from the central register in London. This register is not manned outside normal working hours. Moreover, the information when obtainable is basically the fact that the patient is a drug addict; the name of the drug and the dose in use is not known, though the clinic that the patient is attending can usually be obtained. However, even if the clinic is known the records cannot be obtained outside normal hours.

My object in writing this letter is to stimulate some thought and, I hope, some appropriate action on these problems.—I am, etc.,

A. J. LAIDLAW

Worcester

Impaired Colour Vision in Diagnosis of Digitalis Intoxication

SIR,—I was interested in the letter from Dr. Vesa Manninen (14 December, p. 653) with regard to dyschromatopsia in early cases of digitalis intoxication. I have found similar early symptoms in suspected intoxication with digoxin, but I would suggest that the Ishihara plates are not really suitable since the early signs are usually on the blue/yellow axis, for which there are no plates in the Ishihara series. A more suitable test is the Farnsworth Munsell 100-hue test, which tests the whole range of colour hue and is, in addition, much more sensitive than the Ishihara test, which is primarily of value in the detection of the gross defects present in inherited colour blindness. Alternatively, and even better, is the use of the Pickford-Nicholson anomaloscope, but this requires a good deal of experience in a specialist clinic.—I am, etc.,

W. O. G. TAYLOR

Ophthalmic Unit,
Heathfield Hospital,
Ayr

Choice of Contraceptives

SIR,—Having just read the letter from Professor D. B. Jelliffe and E. F. Patrice Jelliffe (14 December, p. 658) I would like to make the following point before breast feeding is advocated instead of contraception.

About 12 years ago I practised in Manitoba and part of my work included 10 colonies of Hutterites. Every married woman in the colonies quite categorically stated that a woman could not become pregnant while

breast feeding. Yet I often saw a 2-year-old, 1-year-old, and 3-month-old child all feeding from the same mother. Certainly such feeding was unrestricted, on demand, and permissive. I have seen a 2-year-old run in from the garden, stand and feed beside its mother, and run out to play again.

I have not had the benefit of a personal communication from Rosa nor have I any knowledge of "curvilinear" compromises, but I would suggest that "linear" technology has a great deal more to offer than "curved" biotraditional contraception.—I am, etc.,

D. L. PRICE

Kingsclere,
Newbury, Berks

Distamine

SIR,—Some confusion has been caused by the presence on the pharmacists' shelves of three formulations of Distamine (D-penicillamine). The original capsule of penicillamine hydrochloride may be withdrawn in 1975. Its equivalent replacement is a tablet containing 125 mg of penicillamine free base, and this together with the standard 250-mg tablet of base is available now. Will prescribers please note that if a prescription for "Tab. Distamine" or "Tab. penicillamine" is made out without stating the strength required the smaller tablet must be dispensed.—I am, etc.,

W. H. LYLE

Medical Director,
Dista Products Ltd.

Liverpool

Treatment of Genital Herpes

SIR,—Dr. S. M. Laird and Mr. R. B. Roy (27 July, p. 255) reported the beneficial effect of co-trimoxazole in genital herpes, and Dr. Paula H. Gosling (17 August, p. 473), in support of similar findings, stated that trimethoprim inhibits the growth of the virus in tissue culture, though she did not give the data.

Co-trimoxazole depends for its antibacterial action on inhibition of bacterial purine synthesis, the sulphonamide component inhibiting dihydrofolate synthetase and trimethoprim dihydrofolate reductase, the bacterial dihydrofolate reductase being at least 10 000 times more depressed than the mammalian enzyme.¹ Suppression of herpes simplex growth would not be expected since these enzymes are not induced by herpes virus infections² and are probably not necessary for virus replication, the virus utilizing the pre-existing cellular pool of purines in the synthesis of its D.N.A.

We have studied the effect of trimethoprim on the growth of herpes simplex types

TABLE I—Plaque Assay of Herpes Simplex Virus Types 1 and 2

Drugs Added*	Virus	
	Type 1	Type 2
None	37	82
TMP 1 µg/ml	42	94
TMP 10 µg/ml	46	110
TMP 100 µg/ml	36	106
P and S	41	74
TMP 1 µg/ml + P and S	43	100
TMP 10 µg/ml + P and S	35	82
TMP 100 µg/ml + P and S	39	72

*TMP = Trimethoprim. P and S = Penicillin and streptomycin (100 U/ml and 100 µg/ml respectively).

1 and 2 in B.H.K.21 cells using plaque assays (see table I) and one step growth curves (tables II and III) as indices of virus growth. The growth curves were carried out in the absence of penicillin and streptomycin and both dividing and resting cells were studied, the growth in resting cells being more closely analogous to infection in the intact host. Levels of trimethoprim up to 100 µg/ml, alone or in combination with sulphamethoxazole, produced no more than 50% reduction in virus growth, a value insignificant in comparison with other antiviral agents. This level of trimethoprim is some 30 to 50 times that achieved in serum after a 240-mg oral dose,³ reduces mammalian dihydrofolate reductase activity by 50%¹ and is toxic to B.H.K. cells (personal observations). Patients receiving trimethoprim in a daily dose of 1 g have been shown to have significant bone marrow depression.⁴

TABLE II—Virus Growth at 18 Hours after Infection in Absence of and in Presence of Trimethoprim

Virus	Plaque-forming Units per Cell		
	No Trimethoprim	30 µg/ml Trimethoprim	100 µg/ml Trimethoprim
Type 1 ..	10		10.1
Type 2 ..	15	13.3	12.6

TABLE III—Virus Growth at 18 Hours after Infection in Absence of and in Presence of Co-trimoxazole

Virus	Plaque-forming Units per Cell		
	No Co-trimoxazole	Co-trimoxazole (= 30 µg/ml TMP*)	Co-trimoxazole (= 100 µg/ml TMP)
Type 1 in dividing cells	40 54 38	27	23 28 28
Type 2 in resting cells	141		67

*TMP = Trimethoprim.

Our studies failed to show significant inhibition of the growth of herpes simplex in tissue culture. The reported effect of co-trimoxazole in the clinical situation is unexplained.—We are, etc.,

DAVID H. WATSON

DAVID HAIGH

Department of Microbiology,
School of Medicine,
Leeds

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Screening for Gynaecological Abnormalities

SIR,—In her interesting survey of gynaecological abnormalities found at a cytology screening clinic Miss Diana Edwards (26 October, p. 218) makes the important point that abdominal and pelvic examinations should always be carried out at such clinics. However, I would contest her statement that this assessment should be done only by doctors with gynaecological experience. This is an ideal arrangement in countries with a high doctor-patient ratio but not in the under-doctored areas of the world where "well-women" screening services are at present inadequate or totally absent.

The increasing numbers of family planning clinics in the developing areas of the world provide an ideal setting for a screening programme. This is an important part of the service in my family planning clinics for Black Africans in Johannesburg. All our patients have a medical and gynaecological examination and a Pap smear if indicated. As I am the only doctor supervising four busy clinics most of the responsibility for the screening falls on my nurses. Initially, they performed many bimanual examinations under my supervision and all abnormalities were demonstrated. They were soon able to recognize quite minor deviations from the normal—for example, early pregnancy, adnexial masses, pelvic infection, prolapse, and vulval lesions—and they have also identified other abnormalities such as thyroid disease and breast lumps. Patients with pathological findings are then referred for a medical opinion.

My findings with respect to the use of paramedical personnel in health screening are confirmed by many more experienced authors—for example, by Ostergard *et al.*¹ in the U.S.A., where the cost of medical care rather than shortage of doctors is encouraging the use of medical auxiliaries.—I am, etc.,

SUSAN M. HALL

Johannesburg,
S. Africa

¹ Ostergard, D. R., Broen, E. M., and Marshall, J. R., *Advances in Planned Parenthood*, 1972, 7, 59.

endogenous creatinine clearance and during the experiment he continued working as a medical registrar. The isocaloric diets contained 40 g (0.57 g/kg), 70 g (1 g/kg), and 120 g (1.7 g/kg) of protein respectively. An interval of one week elapsed between each day of study. Blood samples were saved and all were estimated in a Technicon-Auto-Analyzer on the same occasion.

The figure shows that fasting plasma urea levels were very comparable, but after a large breakfast (26 g protein) the level increased to the upper limit of normal. Following lunch containing 36 g of protein urea production exceeded the maximum rate of clearance and the plasma concentration became abnormal. Plasma creatinine concentrations remained essentially constant in the 16 samples taken in each experimental day.

These findings indicate that for accuracy blood urea should be sampled only shortly after breakfast and that specimens taken during afternoon clinics may prove misleading. Measurement of the plasma creatinine level avoids this problem. This work is being extended to include patients of varying ages and to include other biochemical variables.—I am, etc.,

ROGER GABRIEL

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Royal Infirmary,
Hull

¹ Addis, T., *Glomerular Nephritis*. New York, Macmillan, 1948.

she opened her eyes and appeared to be waking. She soon relapsed into coma. A second dose of levodopa was given 12 hours later. After 50-60 minutes the patient opened her eyes and started to talk, though still slightly confused. By the end of the day she regained full consciousness.

Case 2.—This was a 30-year-old woman who had been in coma for three days. She did not respond to an initial dose of levodopa 6 g, but there was rapid improvement 30 minutes after a second dose 12 hours later. After an hour she was able to talk and obey commands. She regained full consciousness some 48 hours after the first dose of levodopa.

Case 3.—This was a 19-year-old man in his third day of coma. He was given 6 g of levodopa with no success but a second dose 18 hours later produced a rapid and spectacular response. The patient opened his eyes, moved his hands, and answered questions. A few hours after that he regained full consciousness and eventually recovered.

The other eight patients treated with levodopa showed no improvement and they died.

The mechanism of the metabolic disturbances leading to coma in cases of acute hepatic failure is not known with certainty. A disorder of neurotransmission at the neural synapses of the reticular formation has been incriminated, and perhaps levodopa acts as a neurotransmitter. The rapid improvement in the clinical condition in the cases described and the favourable outcome seemed to be due to levodopa.—We are, etc.,

P. A. CONTOYIANNIS

E. DRAGINIS

D. A. ADAMOPOULOS

G. TRIANTAFYLLOU

Athens

Endotoxaemia

SIR,—As your leading article (28 December, p. 730) so succinctly states, whether endotoxin is detectable or not in endotoxic shock depends on the functional capacity of the liver and its degree of perfusion. The limulus material used in 1970 was not as sensitive as that now available. The statement that some patients with Gram-negative shock then had negative assays does not refute the role of endotoxin but serves to emphasize that even now the test has to be refined and that some thought should be given to the tissue used for assay (for example, better results can be obtained from platelets or liver).

Endotoxin is not only a powerful vasoconstrictor but it is difficult, and somewhat academic, to dissociate among the causes of impaired tissue perfusion the associated disseminated intravascular coagulation, the release of lysosomal proteases, the kinin activation, the possible role of complement, and the metabolic effects. Since staphylococcal alpha-toxin has some similar actions; this explains the discrepancy which you appear to use as an argument against a definitive role of Gram-negative endotoxins.

The work of Cuevas *et al.*¹ in relation to burns is of interest, but should not be taken out of context to detract from previous work of the same group, and that of others, which suggests that a period of bowel ischaemia induced by poor perfusion in certain species during shock gives rise to portal endotoxaemia. The crucial question is whether this applies to man.—I am, etc.,

NIGEL WARDLE

St. Peter's Hospital,
Chertsey, Surrey

¹ Cuevas, P., *et al.*, *Surgery, Gynecology and Obstetrics*, 1974, 138, 725.

Variations in Plasma Urea and Creatinine

SIR,—Estimation of the blood urea concentration is widely used as a screening test of renal function. Addis¹ compared the serum concentrations of creatinine and urea in normal men eating diets containing 0.5-2.5 g of protein/kg body weight and showed that the creatinine concentrations varied less than those of urea.

A comparison has been made between plasma urea and creatinine sampled hourly in a 30-year-old male weighing 70 kg while on three different protein diets. The subject had normal renal function as judged by

Levodopa in Coma Due to Fulminant Hepatitis

SIR,—So far we have used levodopa together with conventional therapy in 11 cases of hepatic coma due to fulminant hepatitis. The drug dissolved in water is easily administered to a comatose patient through a gastric tube. Three of our 11 patients recovered with this treatment.

Case 1.—This was a 23-year-old woman who had been in grade 4 coma for three days. Routine treatment was ineffectual. Exchange blood transfusion was not attempted. Levodopa 5 g was given through a gastric tube. After 15-20 minutes the patient moved her hands and after 45-50 minutes

Variations in Plasma Urea and Creatinine Concentrations over 24-hour Periods on Diets of Different Protein Content.

Conversion: SI to Traditional Units. Urea: 1 mmol/l $\approx$ 6 mg/100 ml. Creatinine 1 μ mol/l $\approx$ 0.01 mg/100 ml.