symptomless, and probably very frequent in the population. The body has a thrombolytic system. I believe therefore that clots in the vessels are fairly common and are dissolved again without always causing symptoms. I think that we now know that pulmonary emboli can occur without there being any good clinical evidence of a donor site, such as a thrombosed vein (13 December 1969, p. 676).

It is extremely difficult to know when the diagnosis of a pulmonary embolism should be made, and it may be that some of us who are aware of its frequency have a tendency to over-diagnose the condition. However, I believe that many cases of apparent neurotic dyspnoea—for which no cause can be found—are in fact due to multiple pulmonary embolism.¹ Fortunately, the majority of cases do not prove to be fatal, but I have reached the stage that I become immediately extremely worried whenever I hear of an individual who is short of breath with apparently no cause. I am sure that patients with genuine dyspnoea from pulmonary embolism are very likely to lose confidence in themselves, in their physicians, and in their treatment. I know of nothing so likely to relieve the breathlessness as anticoagulants, as I think that there can be a genuine physical basis for dyspnoea in pulmonary embolism which is difficult to diagnose.—I am, etc.,

H. J. TRENCHARD

Edgware Chest Clinic,
Edgware General Hospital,
Edgware, Middx

¹ Greenberg, H. G., *American Review of Respiratory Diseases*, 1965, **92**, 215.

Metastatic Calcification and Dialysis

SIR,—I read with great interest your leading article on "Metastatic Calcification and Dialysis" (25 March, p. 762). I would like to comment on the statement that inhibitors, such as those described by Yendt *et al.*,¹ are removed by haemodialysis. In a previous study² my colleagues and I confirmed Yendt's earlier observation that uraemic serum contains a factor that inhibits the calcification of ricketic rat cartilage in vitro. However, when we compared blood specimens obtained from patients on chronic treatment before and after haemodialysis and peritoneal dialysis, we found that, at the end of the procedure, the haemodialysis specimens still contained the inhibitor, whereas those obtained at the end of peritoneal dialysis did not. We concluded that peritoneal dialysis removes this inhibitor but haemodialysis does not.

The fact that pyrophosphate is removed by haemodialysis³ suggests that Yendt's inhibitor is not pyrophosphate, but rather a large molecule or a molecule bound to protein. It remains to be demonstrated whether there is a causal relationship between this finding (removal of the inhibitor by peritoneal dialysis but not by haemodialysis) and our observation that osteomalacia of renal osteodystrophy progresses in patients on chronic haemodialysis but not in those on chronic peritoneal dialysis.⁴ On the other hand, the observed persistence of Yendt's inhibitor in the blood of haemodialysed patients does not necessarily contradict the observation that soft-tissue calcification progresses in some haemodialysis patients.⁵ These two observations can be reconciled when one recalls that calcification is the end

result of a process involving, among others, calcifying solutions (CaXP), pH, and inhibitor(s) of calcification, some of which may be dialysable and some not.—I am, etc.,

D. G. OREOPOULOS

Toronto Western Hospital,
Toronto, Ontario,
Canada

- 1 Yendt, E. R., Connor, T. B., and Howard, J. E., *Bulletin of the Johns Hopkins Hospital*, 1955, **96**, 1.
- 2 Oreopoulos, D. G., Pitel, S., Husdan, H., deVeber, G. A., and Rapoport, A.; presented at the American Society of Nephrology, November, 1971.
- 3 Russell, R. G. G., Bisaz, S., and Fleisch, H., *Archives of Internal Medicine*, 1969, **124**, 571.
- 4 Oreopoulos, D. G., *et al.*, presented at the Henry Ford Hospital, International Symposium on Clinical Aspects of Metabolic Bone Disease, June, 1972.
- 5 Boner, G., Jacob, E. T., Pevzner, S., and Jungmann, A., *Israel Journal of Medical Sciences*, 1971, **7**, 1182.

Carcinoma of the Cervix and Herpesvirus

SIR,—Some of the avenues of research recommended in your leading article (3 June, p. 548) concerning herpes simplex virus 2 (HSV-2) and cervical carcinoma are impractical. To monitor women who have been exposed to HSV-2 for many years would be difficult. The clinical diagnosis of herpes genitalis in high risk groups for development of cervical carcinoma is uncommon. Not one case has been confirmed during an on-going colposcopic and histological study of 700 such women confined to a penal institution, even though high prevalence rates of major cervical epithelial abnormalities and venereal disease exist.¹ These women are notoriously difficult to follow up because of their social environment and would respond poorly to epidemiological investigation. If women are included in such a study on serological rather than clinical evidence of infection then the high prevalence rate of HSV-2 antibody present in the general population would further complicate selection.²

Your suggestion that the recent studies recognizing incorporated viral DNA in tumour nuclei could profitably be extended to determine whether "malignancy arises from this integration of viral and cellular DNA," is not novel. Reid³ demonstrated histologically the uptake by cervical cells of fragments of human sperm (DNA) and their subsequent incorporation into the cells' genome. By chemical analysis he showed that the admixture of the nucleic acids of these genomes produced a possible mutation.⁴ If incorporated DNA be mutagenic as you imply, and remembering that cervical carcinoma is a coitally transmitted disease, the amount of DNA of spermatozoal origin normally in contact with the cervix far exceeds that derived from a viral source. Spermatozoal DNA would seem to be a more likely mutagen than HSV-2, as proposed by Reid and Coppleson.⁵

Recent evidence suggests that certain males are more likely than others to induce carcinoma in their female partners. In Puerto Rico cervical carcinoma developed in eight wives whose husbands had penile cancer.⁶ None arose in a matched control group. The evidence that one man had cohabited with a number of women who subsequently developed cervical premalignancy and malignancy in an Atlanta housing estate⁷ suggests that a high risk male as well as female exists in relation to the aetiology of this malignancy.

The increasingly liberal sexual behaviour of certain Jewish males could also account for the alteration in the traditional immunity of the Jewess to cervical cancer.⁸ Martin⁹ showed the increased incidence of venereal disease in husbands of American Jewesses with this malignancy. Ravich¹⁰ suggests that the increase in prostatic cancer in Jewish males, in whom it is still uncommon, may result from high rates of venereal infections and increased cohabitation inter-ethnically among these men. Israeli Jewish women with cervical cancer, interviewed by H. Pridham (personal communication), were more likely to have had coitus with a non-Jewish male and to have husbands who were more promiscuous than the ordinary population controls.

Although these data suggest that a venereally-transmitted mutagenic agent like HSV-2 is involved no direct evidence of this exists. Indeed, no elevation of viral antibody levels in husbands of women with cervical cancer is reported. However, an alternative explanation could be that some alteration has occurred in spermatozoal DNA which makes it highly mutagenic when incorporated into the cervical cell. B. L. Reid (personal communication) has recently demonstrated the complicated structure of DNA existing in the mucoid coat surrounding the sperm head. Changes in this structure, possibly as a result of promiscuity, may hold the key to an increased "neoplastic ability" of certain males. It is hoped that further research on this malignancy will tend to concentrate as much on the male as on the female.—We are, etc.,

ALBERT SINGER

Nuffield Department of Obstetrics and Gynaecology,
Oxford

MARGARITA STEVENSON

Medical Officer,
Home Office (Prison Department),
London W.C.1

- 1 Singer, A., and Stevenson, M., *Acta Cytologica*, 1972, in press.
- 2 Singer, A., *British Medical Journal*, 1971, **1**, 458.
- 3 Reid, B. L., *Lancet*, 1964, **1**, 21.
- 4 Reid, B. L., and Blackwell, P. M., *Australian Journal of Experimental Biology and Medical Science*, 1967, **45**, 323.
- 5 Reid, B. L., and Coppleson, M., in *Scientific Basis of Obstetrics and Gynaecology*, ed. R. M. McDonald. Oxford, Churchill, 1971.
- 6 Martinez, I., *Cancer*, 1969, **24**, 777.
- 7 Smith, D., and Jenkins, R. S., *American Journal of Obstetrics and Gynaecology*, 1969, **104**, 603.
- 8 Coppleson, M., and Reid, B. L., *Pre-clinical Carcinoma of the Cervix Uteri*, Oxford, Pergamon Press, 1967.
- 9 Martin, C. E., *American Journal of Public Health*, 1967, **57**, 803.
- 10 Ravich, A., *Cancer*, 1971, **27**, 1493.

Wine and Migrainous Neuralgia

SIR,—Migraine is probably related to ingestion of food. Fothergill blamed malt liquors and other food in sensitive individuals as causal.¹ Wilks recognized migraine, as did many before him, as a spasm of vessels from vasomotor phenomena, sympathetic stimulation, and vasodilatation.² Other work^{3,4} confirms the food relationship. Hanington⁵ related the vasomotor phenomena to tyramine in the food.

We have assayed the histamine, tyramine, bradykinin, and "other" amine content of red and white Australian wines, the former of which precipitate migrainous neuralgia in a migraine subject and the latter of which do not. This subject suffered severe attacks at least once every four weeks for many years, but was symptom free for 18 months after avoiding cheese, chocolate, strong beer, red

wine, and oranges. Strong beer and red wine regularly produced attacks.

The assay on the isolated jejunum showed a content of 2-3 µg histamine/ml in the red wine confirmed on the chromatogram, while the white wines were free of histamine, but contained large amounts of bradykinin. Many amines other than tyramine or histamine are found in the wine precipitating migraine and in these wines tyramine was conspicuously absent. Antihistamine preparations do not relieve migrainous headache or migrainous neuralgia. The presumed kinin SRS is present in large quantity in the wines not precipitating migraine. Youdim *et al.*⁶ have shown a deficiency of conjugation of tyramine in migraine subjects. We suggest deficiency of conjugation of substances other than tyramine or histamine may account for the migrainous headache, and is probably related to a genetic deficiency since the condition is familial. Conjugation (acetylation) of the amine histamine occurs in the normal liver⁷ and very rapidly in one to two minutes

logical importance in the production of cirrhosis.—We are, etc.,

E. R. TRETHEWIE

Department of Physiology,
University of Melbourne,
Victoria, Australia

LAILA KHALED

University of Cairo,
Cairo, U.A.R.

- 1 Fothergill, J., 1778, quoted in *On Megrin, Sick-Headache, and Some Allied Disorders*, p. 8. Liveing, E., London, Churchill, 1873.
- 2 Wilks, S., *British Medical Journal*, 1872, 1, 8.
- 3 Alvarez, W. C., *Proceedings of the Staff Meeting of the Mayo Clinic*, 1932, 7, 443.
- 4 Rowe, A. H., *California and Western Medicine*, 1930, 33, 785.
- 5 Hanington, E., *British Medical Journal*, 1967, 2, 550.
- 6 Youdim, M. B. H., Carter, S. B., Sandler, M. I., Hanington, E., and Wilkinson, M., *Nature*, 1971, 230, 127.
- 7 Trethewie, E. R., and Gaffney, F. M., *Australian Journal of Experimental Biology and Medical Science*, 1951, 29, 67.
- 8 Trethewie, E. R., *Medical Journal of Australia*, 1970, 1, 67.

Lignocaine Overdose and Ampoule Labelling

SIR,—I am reporting the survival of a 70-year-old man following the accidental administration of 1 g of intravenous lignocaine, given over a period of three minutes. My aim in doing so is to decry the lack of relevant labelling on some commonly prescribed drugs.

The patient was admitted in ventricular fibrillation which was immediately converted electrically to sinus rhythm. One hundred mEq of sodium bicarbonate were given. Ventricular tachycardia supervened, and lignocaine as a 1% solution was given with an immediate return of sinus rhythm. A dose of 100 mg had been asked for and unfortunately 1% was interpreted as 1 mg/ml so that 10 times the dose was given.

Blood pressure remained stable and pulse rate was steady at 82 per minute. Respiratory arrest occurred immediately but spontaneous respiration returned after five minutes artificial ventilation. Grand mal convulsions lasted 30 minutes and generalized rigidity one hour. Initial treatment consisted of 250 mg thiopentone intravenously, positive pressure ventilation for five minutes via an endotracheal tube, and intermittent doses of intravenous diazepam to control the convulsions and following restlessness. The patient remained stuporose and restless for 12 hours and he remained disorientated for three days. After this till discharge he was intermittently depressed and euphoric and was amnesic for the 24 hours following his cardiac arrest.

The electrocardiograph showed an antero-septal myocardial infarction. The only other abnormality which developed was a rise in blood urea from 38 mg 15 hours after admission to 134 mg/100 ml on the 15th day. When see two months later it was 28 mg/100 ml. Urine output remained above 800 ml in 24 hours after the first day.

The pharmacology and the toxic effects of lignocaine have been well described since the first report of its use in ventricular fibrillation in 1950.¹ Binnion *et al.*² have reported myocardial failure in dogs following 400 mg of lignocaine. Crampton and Oriscello³ describe a fatal toxic reaction following an infusion of 4.56 g of lignocaine over 24 hours terminating in respiratory and cardiac arrest.

Thiopentone is a controversial drug to use

in treatment. Steinhaus *et al.*⁴ suggested barbiturates have an additive effect on medullary depression. Possibly paralysing the patient and maintaining him by artificial ventilation may be more effective.

Although reporting the above misadventure is embarrassing I feel that it underlines the need for all drugs to be labelled clearly with the units usually needed in clinical practice. Astra have overcome this problem for lignocaine with disposable syringes containing a fixed amount of lignocaine, but other drugs such as calcium and potassium are still often dispensed in inadequately labelled ampoules.—I am, etc.,

P. P. MAYER

Birmingham

- 1 Southworth, J. L., McKusick, V. A., Peirce, E. C., and Rawson, F. L., *Journal of the American Medical Association*, 1950, 143, 717.
- 2 Binnion, P. F., Murtagh, G., Pollock, A. M., and Fletcher, E., *British Medical Journal*, 1969, 3, 390.
- 3 Crampton, R. S., and Oriscello, R. G., *Journal of the American Medical Association*, 1968, 204, 201.
- 4 Steinhaus, J. E., *Anesthesiology*, 1957, 18, 275.

Malignant Lymphoma and Acute S.L.E.

SIR,—A number of reports of acute systemic lupus erythematosus (S.L.E.) and reticulosis have been recorded, mainly by authors in the U.S.A.¹ We should like to report a further case.

The patient, a 79-year-old spinster, was admitted with a short history of increasing lethargy, weakness, febrile symptoms, diarrhoea, abdominal pains, and a generalized rash. Her previous health had been unremarkable and she denied being on any medication. On examination she exhibited a generalized maculopapular rash, lymphadenopathy, hepatomegaly (spleen not palpable), and pitting oedema of both feet.

The abnormal investigations were as follows: Hb. 6.9 g/100 ml; W.B.C. 10,400/mm³ (eosinophils 8%); E.S.R. 83 mm/hr; serum bilirubin 1.6 mg/100 ml; direct Coombs test positive; latex L.E. and R.A. slide test strongly positive; L.E. cells in peripheral blood; plasma proteins albumin 2.8 g/100 ml, globulin 4.9 g/100 ml (gamma globulin 2.9 g/100 ml). Chest radiograph—bilateral pleural effusions. The patient refused a lymph node biopsy but a skin biopsy showed changes compatible with lupus erythematosus. Treatment with prednisolone produced a dramatic improvement in her general well being, disappearance of the rash and lymphadenopathy, and suppression of the autoimmune haemolytic phenomenon. A few weeks later she exhibited return of the lymphadenopathy, now very gross and extensive, enlargement of the spleen and palpable abdominal masses. She rapidly deteriorated and died. A necropsy confirmed widespread lymphoma (Hodgkin's type).

The concurrence of malignancy with dermatomyositis,² the occurrence of lymphoma in Sjögren's syndrome,³ and a similar case report of S.L.E. with lymphoma associated with a high titre of IgM antinuclear antibody⁴ suggest a potential relationship between the autoimmune connective tissue diseases and neoplasia, in particular reticulosis. This type of association is possibly more common than suspected and a careful look for underlying lymphoma is worthwhile in patients presenting with S.L.E. or other connective tissue disease states, particularly

FIG.—Chromatogram run for one hour (a) and for four hours (b) in butanol acetic-water. Stained with ninhydrin. At W white wine spot, R red wine spot, T tyramine, H histamine, CR concentrated red. Note tyramine is absent in red wine, but histamine and a particular amine spot with 2½ times mobility of histamine present.

for the amount present in wine. This principle will explain the long duration of migraine headaches and the fact that the substance or substances precipitating migraine do not produce migraine in "normal" subjects.

A further point of interest is that the histamine content of the red wine is comparable to the output of histamine from dog liver by alcohol.⁸ It has already been pointed out that thioacetamide intoxication in rats no longer produces cirrhosis of the liver in the presence of antihistamine and histamine stimulates fibroblasts to activity. It is not inconceivable, remembering the relatively low histamine content in human liver, that the histamine content of the red wine (and also strong beer) might be of aetio-