direct effect on renal tubular handling of calcium). The hypercalciuria may itself then lead to a compensatory intestinal over-absorption as follows:

These authors produce a good deal of evidence that this sequence of events may occur in other conditions, such as in the pharmacological state of vitamin-D overdosage.^{4, 5}

"Intestinal compensation" for high urinary-calcium loss must normally be occurring all the time, since different normal adults may have consistently different urinary calcium outputs, ranging from 50 mg. in some cases to 400 mg. per day in others. These great individual variations of urinary calcium in normal adults, the relative constancy of urinary-calcium excretion in each subject over long periods under normal conditions, and the extremely small changes produced in urinary calcium by great changes in calcium intake, have been fully attested on a large scale by Knapp,⁶ Nicolaysen *et al.*,⁷ and Hodgkinson and Pyrah.⁸ Yet, whatever the natural level of urinary calcium may be, each normal adult maintains a net bodily balance for calcium when considered over long periods. Thus his intestinal absorption must be naturally compensating and attuning itself to the level of urinary loss. The absorptive calcium "barrier" is therefore controlled by the urinary output.

However good or poor this general theory may turn out to be, it must surely be clear that over-absorption cannot be the primary lesion of calcium metabolism in sarcoidosis. We believe it to be a compensatory phenomenon.—We are, etc.,

W. P. U. JACKSON.
C. P. DANCASTER.

Department of Medicine,
Medical School,
Observatory, Cape Province,
South Africa.

REFERENCES

- Henneman, P. H., Carroll, E. L., and Dempsey, E. F., *J. clin. Invest.*, 1954, **33**, 941.
- Dempsey, E. F., Carroll, E. L., and Albright, F., *ibid.*, 1956, **35**, 1229.
- Anderson, J., Dent, C. E., Harper, C., and Philpot, G. R., *Lancet*, 1954, **2**, 720.
- Jackson, W. P. U., and Dancaister, C. P., *J. clin. Endocr.*, 1959, **19**, 658.
- ibid.*, 1962, **22**, 195.
- Knapp, E. L., *J. clin. Invest.*, 1947, **26**, 182.
- Nicolaysen, R., Eeg-Larsen, N., and Malm, O. J., *Physiol. Rev.*, 1953, **33**, 424.
- Hodgkinson, A., and Pyrah, L. N., *Brit. J. Surg.*, 1958, **46**, 10.

Health Centres

SIR,—Your leading article on health centres (29 May, p. 1394) is both timely and welcome. I hope you have started a debate which will arouse as much interest and controversy as "remuneration" usually does. General practitioners must stop looking over their shoulder, mourning the passing of their so called "independence," and we must bury

the hostility so often reserved for proposals to bring our work closer to that of the medical officer of health.

We must boldly recognize that improved hygiene and nutrition, advances in drug therapy, and immunization programmes have changed the pattern of community diseases. This, and our failure to organize to cope with the new situation and the new problems it has thrown up, is the root cause of our present discontent.

With so many problems arising from an individual's disturbed relationship with his environment, the good general practitioner needs to have at his disposal the means to operate in the environment, as well as the drugs or time to give to the patient. The environmental tools are the welfare services, and the general practitioner's frustration is the greater for being separated from them.

It has long seemed to me that to work in close co-operation with these and the paramedical services from a health centre must inevitably lead to a more rewarding professional life.—I am, etc.,

Liverpool 8.

C. TAYLOR.

SIR,—I was very pleased to read your leading article on "Impressions of Health Centres" (29 May, p. 1394) and a description of the Stranraer Health Centre (29 May, p. 1429). I feel very strongly that health centres would be the only solution for the

general practitioners in many areas. I have been a general practitioner for over 40 years and know all the difficulties the doctors encounter by carrying on their practices from their own houses. The expense of keeping the premises properly decorated and furnished is normally impossible for a general practitioner, as the cost of this is so very high nowadays. The employment of a receptionist and caretaker is beyond a general practitioner's salary, but at the same time a busy practitioner receives innumerable telephone calls on all sorts of problems, which must be answered. How conveniently this could be dealt with at a health centre, where a receptionist could take all the visits and with the help of a nurse could solve many minor medical problems.

At a health centre there should also be a link with the local authorities which many general practitioners miss so very much. The medical officer of health, the midwives, and health visitors would be close by, and that, believe me, would save a lot of work for the general practitioner.

It is also obvious that a health centre would provide a coverage in case of illness or holidays. I hope that each district will be surveyed for the possibility of health centres by the local authorities. For the sake of economy, when necessary, a health centre could be prefabricated. I hope we will read more about health centres in your esteemed journal.—I am, etc.,

London S.W.14.

H. W. SWANN.

Transferable Antibiotic Resistance

SIR,—Your leading article (22 May, p. 1325) draws timely attention to the possibility of a situation arising in which normal gut flora may possess multiple drug resistance transferable to intestinal pathogens by cell-to-cell contact, and to the subsequent problems of achieving successful therapy in intestinal infections.

In a survey at the Dysentery Reference Laboratory of the drug resistance patterns of all *Shigella* species (to be published elsewhere), 46 (1.5%) out of 3,051 shigellae showed multiple resistance to chloramphenicol, sulphonamides, streptomycin, and tetracycline. These multiply resistant strains included 13 out of 1,483 *Sh. sonnei* strains examined. It is interesting that, with the possible exception of one *Sh. sonnei* strain resistant also to neomycin (and kanamycin), all the multiply resistant strains came from patients who had acquired their infections outside Britain.

However, doubly and triply resistant strains, most of them resistant to sulphonamides and streptomycin, or to sulphonamides, streptomycin, and tetracycline, are by no means uncommon in patients infected in this country, and there is evidence that there has been a rise in the incidence particularly of triply resistant strains over the last few years. Indeed, of the *Sh. sonnei* strains tested, 84.8% were resistant to sulphonamides either alone or in combination with other drugs.

Twelve resistant *Shigella* strains were included in an investigation of R factors (to be published elsewhere) at the Lister Institute.

Of ten strains with the common pattern of resistance to chloramphenicol, sulphonamides,

streptomycin, and tetracycline, three (two *Sh. sonnei*, one *Sh. flexneri*) were resistant also to antibiotics of the penicillin and cephalosporin groups. The complete resistance pattern of four of these multiply resistant strains, including two of those resistant also to the penicillin group, of a *Sh. dysenteriae* 7 strain resistant to sulphonamides, streptomycin, and neomycin, and of a *Sh. sonnei* strain resistant only to neomycin was transmitted by a mixed culture to *Escherichia coli* K12, and from it to *Salmonella typhimurium* LT2. Thus the drug resistance of each of these *Shigella* strains resulted from possession of a transmissible drug-resistance factor.

Phage P22, grown on *S. typhimurium* LT2 given R factors derived from *Shigella* strains, transduced resistance traits to drug-sensitive LT2 lines. With two R factors conferring resistance to chloramphenicol, sulphonamides, streptomycin, and tetracycline the pattern of transduction was the same as that reported¹ for R factors in *Shigella* strains isolated in Japan. That is, some transductants acquired only tetracycline resistance and others became resistant to chloramphenicol, sulphonamides, and streptomycin but remained tetracycline-sensitive. Phage P22 was also grown on *S. typhimurium* given one of the R factors conferring resistance to these same four drugs and to the penicillin-cephalosporin groups; with this phage the same transductant classes were observed, and also a third class with only the penicillin-cephalosporin resistance of the donor strain. This R factor, derived from a *Sh. sonnei* strain isolated in Singapore, is transferred as a unit during conjugation but seems to separate into three fragments on transduction by phage P22, instead of into two as commonly observed.

These studies on the drug resistance of shigellae suggest that the situation here, despite the presence of strains carrying transmissible multiple resistance factors, is not as yet so formidable as that reported

from Japan,² where about 32% of all shigellae isolated have multiple drug resistance, but nevertheless serious thought should be given now to the measures which may prevent the present problems of the therapy of bacillary dysentery becoming even more difficult.—We are, etc.,

K. PATRICIA CARPENTER.

Dysentery Reference Laboratory,
London N.W.9.

W. T. DRABBLE.*

Guinness-Lister Research Unit,
Lister Institute of Preventive Medicine,
London S.W.1.

* In receipt of a Junior Research Fellowship, Medical Research Council.

REFERENCES

- Watanabe, T., *Bact. Rev.*, 1963, 27, 87.
- Anzai, H., *Endem. Dis. Bull. Nagasaki Univ.*, 1964, 6, 158.

Treatment of the Climacteric Syndrome

SIR,—I was pleased to read the contents of the letter by Dr. F. Osmond-Clarke and Dr. M. Murray (8 May, p. 1249), and to note that their view is similar to my own, expressed on several occasions.^{1,2} I suggested that hormonal treatment should not only be given to relieve menopausal symptoms but to slow down the degenerative process of ageing. Vaginal cytology can assess the degree of oestrogen deficiency, and it is a useful guide for the dosage. In my experience, based on 700 cases, the best results are achieved by implants of oestrogen and testosterone pellets. There is no convincing proof that oestrogen is cancerogenic. Similar views have been expressed recently by Wilson^{3,4} and Davis.⁵—I am, etc.,

London W.1. E. SCHLEYER-SAUNDERS.

REFERENCES

- Schleyer-Saunders, E., *Med. Press*, 1960, 244, 337.
- , *Brit. med. J.*, 1960, 1, 1274.
- Wilson, R. A., *J. Amer. med. Ass.*, 1962, 182, 327.
- Brevetti, R. E., and Wilson, R. A., *West. J. Surg.*, 1963, 71, 110.
- Davis, M. E., *Year Book of Obstetrics and Gynaecology*, 1964/65, p. 339. Year Book Medical Publishers, Chicago. In press.

C.S.F. Protein in Multiple Sclerosis

SIR,—It is pleasant to learn that even one's occasional contributions to medical journalism are devoured with such avidity and scanned with such attention as is manifest in the critical letter from Dr. H. G. Garland and others (29 May, p. 1435) dealing with my review of the new book on multiple sclerosis by Dr. McAlpine and his collaborators. It would be ungracious to deny Dr. Garland the pleasure of the pedantic skirmish he so clearly invites. Alas, however, the "unfortunate mistake" in the review to which he refers is evidence of careless reading and not slipshod writing.

It did not escape me that on page 255 of the book Professor Lumsden "refers to" the Papadopoulos method of estimating spinal fluid proteins, but it remains true that, as I stated in the carefully phrased last paragraph of my review, he nowhere mentions its application. Even more remarkably he ignores an important and widely quoted study which validated the method of a routine diagnostic test in the columns of this journal¹ no less than three years ago.

Contrary to Dr. Garland's categorical statement a simple colorimetric test has been devised for the estimation of gamma-globulin. I and my biochemical colleagues fully appreciate that the zinc-sulphate-precipitation test measures other things as well as gamma-globulin, and yields values not entirely in agreement with those obtained by electrophoresis. However, at the protein concentrations with which we are dealing the results of the colorimetric and electrophoretic estimations show a degree of correlation which fully justifies the use of the former method as an empirical diagnostic test. The fact that the simpler estimation can be rapidly performed on large numbers of specimens by a relatively junior technician has led us in this context to discard the electrophoretic technique we previously employed.² The results of the application of the colorimetric method in a consecutive series of more than 2,000 consecutive spinal-fluid examinations will shortly be published.—I am, etc.,

The Royal Victoria Infirmary,
Newcastle upon Tyne 1. HENRY MILLER.

REFERENCES

- Foster, J. B., and Horn, D. B., *Brit. med. J.*, 1962, 2, 1527.
- Schapira, K., and Park, D. C., *J. Neurol. Neurosurg. Psychiat.*, 1961, 24, 121.

Fatal Reaction to Phenelzine

SIR,—Most of the reports of fatal reactions to monoamine oxidase inhibitors have concerned tranylcypromine.¹ There have been fewer reports of serious adverse reactions in patients taking phenelzine (Nardil). It may therefore be of interest to record the history of a patient treated with phenelzine who died after a short illness resembling the "cheese reaction," in whom the precipitating factor may have been alcohol.

A man of 44 years with previous good health presented with anxiety and depression. He had been treated with sodium amylal, imipramine, and promazine without noticeable improvement. Four weeks before death phenelzine (15 mg. three times a day) was prescribed, and taken regularly until the day before death. Apart from 3 gr. (195 mg.) of sodium amylal at night as a sedative, all other drug treatment was discontinued.

Two days before death his wife thought his behaviour uncharacteristic but not abnormal, in that he was more active and helpful about the house than usual. On the day before death he complained of severe headache and later became confused, talking in a rambling and incoherent way, at which his wife, with ample justification from past experience, assumed that he was drunk and helped him to bed. Next morning he seemed well at first, but at 10.30 a.m. he was again confused and incoherent. He may have had some alcoholic drink in the interval. He tried to get out of bed but was unable to stand, and fell to the floor clutching his stomach, retching, and sweating profusely. On arrival at hospital he was in coma, had a temperature of 104° F. (40° C.), stertorous respiration, fixed dilated pupils, exaggerated tendon reflexes, and extensor plantar responses. There was a regular tachycardia of 120 per minute, the blood-pressure was 150/90 mm. Hg; the blood-sugar and urea concentrations were normal. Rapid deterioration continued and he died two hours after admission.

At necropsy the abnormal findings were as follows. The brain (1,580 g.) showed severe vascular congestion and oedema, with swelling of the cerebrum and bilateral tentorial compres-

sion marks in the uncus region indicating distortion of the brain-stem and accounting for the terminal clinical picture. There was no gross subarachnoid or intracerebral haemorrhage, and the cerebral arteries showed only mild atheroma. Histology confirmed the naked-eye diagnosis. The lungs also showed intense congestion and alveolar oedema (right 870 g., left 570 g.). Such appearances are commonly seen after a fatal rise in intracranial pressure, and since there were no respiratory symptoms until the end of the illness the lung changes may have been entirely a consequence of the cerebral swelling. Analysis of blood, urine, and stomach contents for phenelzine, aspirin, and barbiturates were negative.

This case showed most of the features of the "cheese reaction" type of adverse response to monoamine-oxidase inhibitors and considerable resemblance clinically and at post-mortem to two fatal reactions to tranylcypromine, one of which was precipitated by eating cheese² and the other spontaneous.³ Unfortunately the blood-pressure was not measured during the early phase of headache and confusion, and the only available reading (150/90) was taken about one hour before death, when the patient was comatose and with severe cerebral and pulmonary oedema.

Alcohol has been incriminated as a precipitating factor of these attacks and possibly was in this case, on circumstantial evidence; however, the possibility that it was a spontaneous reaction produced by the drug alone cannot be ruled out.—I am, etc.,

Department of Pathology, IAN MACLEOD.
Newcastle General Hospital,
Newcastle upon Tyne.

REFERENCES

- Brit. med. J.*, 1964, 1, 578.
- Cuthill, J. M., Griffiths, A. B., and Powell, D. E. B., *Lancet*, 1964, 1, 1076.
- Womack, A. M., *Brit. med. J.*, 1963, 2, 366.

Studies with Complamin

SIR,—We have read with interest the article by Dr. G. P. McNicol and Dr. A. S. Douglas, "Studies with Complamin, a Nicotinic-acid-Theophylline Ester, as a Fibrinolytic Agent" (1 May, p. 1149). As Complamin is much used in Sweden as well, we should like to comment on some details.

The article gives the impression that Complamin appeared as the result of a search for a fibrinolytic agent superior to nicotinic acid. We do not know the background of the synthesis, but we doubt that the fibrinolytic activity was the main purpose for the preparation. In any case we are of the opinion that the essential action of Complamin in experiments of the type described is to cause an improved peripheral blood-flow. This effect is even more pronounced in experiments ranging over a long period. The observed transient fibrinolytic effect, which has also been detected through angiography by several other investigators, can then be regarded as a positive side-effect of minor importance not comparable to the well-established effect of streptokinase and similar enzyme preparations.

According to our experience careful intravenous injections of Complamin 150 mg. will cause a distinct flush, but in general leave pulse and blood-pressure little affected. The reported fall in blood-pressure from 118/72 to 65/40 in 10 minutes in one subject and similar results in two other cases is remark-