chemist into the wards is to maintain the sometimes tenuous link between the patient and the laboratory—a link which often seems to be in danger of breaking down. It may be argued that there is nothing to stop any medical graduate from going on ward rounds, etc., but I feel that this clinical role must be “part of the job” and not an occasional exercise.

I realize that implementation of my suggestions would mean complete reappraisal of an area of medical establishment, involving other specialties as well as clinical chemists. However, one could point out that this reappraisal appears to be taking place in haematology, and there seems no particular reason why it should not take place in clinical chemistry. If it did recruitment of doctors into this fascinating branch of medicine would greatly increase, to the mutual benefit of patient and clinical chemistry alike.—I am, etc.,

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¹ Mitchell, F. L., *Annals of Clinical Biochemistry*, 1974, 11, Part 5, 149.

Chronic Diuretic Therapy and Potassium

SIR,—Though there are a number of clinical conditions—cirrhosis of the liver and nephrotic syndrome, for example—in which potassium supplements are important when diuretics are given the common problem is to decide how necessary supplements are in patients given diuretics as part of therapy for hypertension. Dr. H. J. Dargie and others (9 November, p. 316) rightly emphasize that potassium supplements need not always be given during chronic diuretic therapy. It is important, however, that a false extrapolation should not be made from a restricted study. Their patients with essential hypertension and normal renal function took only a single dose of frusemide daily. Such a regimen would be less likely to produce much potassium loss than one using a longer-acting thiazide diuretic. Incidentally it is also less effective in hypertension therapy.¹ Frusemide has a rapid, short action so that with a single dose it would not be acting over much of the 24 hours, so allowing possible retention of potassium to compensate for the excess lost. Not surprisingly, therefore, the reduction in plasma potassium values they observed were small, the mean values were within the normal range, and total body potassium (T.B.K.) remained normal.

Our experience, gathered from the study of patients receiving thiazide diuretics over some years at University College Hospital, London, is in general agreement in that when plasma potassium is maintained within the normal range then, in the absence of significant acid-base disturbances, T.B.K. remains normal. Here potassium supplements are obviously unnecessary. In a considerable proportion (more than 60% in our current studies) of younger patients, well apart from mild or moderate hypertension, plasma potassium has remained within the normal range without potassium supplement. Some patients, however, have developed persistent hypokalaemia (plasma potassium <3.4 mEq/l); these patients tend to be older and to have more severe hypertension, but there is

unfortunately no certain way of prediction. In our first report of T.B.K. changes measured by ⁴⁰K-counting² we were particularly interested in this type of response and we found that persistent hypokalaemia was usually associated with some reduction, usually modest, of T.B.K. In the patients of Dr. Dargie and his colleagues hypokalaemia was infrequent but in two with plasma potassium of 3.2 mEq/l (shown in table IV of their paper) T.B.K. appeared to be reduced by about 10%, which is the sort of change we have observed.

The control of intracellular potassium is complex, dependent on the activity of ionic pumps and not simply on extracellular potassium concentration. It is not really surprising, therefore, that mild hypokalaemia is not necessarily associated with reduction of T.B.K. It is important not to think of potassium deficiency in terms of T.B.K. alone. The plasma potassium level itself may be of more clinical significance, since the cellular transmembrane potentials depend on the ratio of extracellular to intracellular potassium.

In practice, plasma potassium is usually all that is available and so has to be the basis of monitoring. We suggested² that patients on chronic thiazide diuretics should begin with a potassium supplement (20–30 mEq/day) with plasma monitoring at one- to two-monthly intervals at first and the supplement stopped if plasma potassium remained in the normal range. It is probably better to start with a supplement to reduce the initial, often transient, potassium deficiency that often occurs on starting diuretics. Plasma potassium should be monitored for a further few months after stopping the potassium supplement but subsequently only infrequent monitoring (4–6 monthly) is needed. What level of hypokalaemia should be treated is more difficult to say for certain. With a plasma potassium of 3.0–3.4 mEq/l E.C.G. abnormalities are infrequent and T.B.K. reduction is small. There is, however, a case to be made for correcting even this deficiency by giving potassium supplements or, if these fail, a potassium-sparing diuretic, especially to older patients. It is most important that the work of Dr. Dargie and his associates should not be generalized to imply that potassium supplements (or potassium-sparing diuretics) are unnecessary in prolonged diuretic therapy except in certain particular conditions such as cirrhosis of the liver. The need for potassium correction must in all cases be decided by monitoring of the individual patient.—I am, etc.,

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¹ Anderson, J., et al., *Quarterly Journal of Medicine*, 1971, 40, 541.

² Edmonds, C. J., and Jasani, B., *Lancet*, 1972, 2, 8.

Maternal HL-A Antibodies and Fetal Sex

SIR,—With reference to the report by Mr. K. Johansen and Dr. H. Festenstein (26 October, p. 202) some unpublished data from a survey of cytotoxic antibodies in first pregnancies are of interest. In each instance the pregnancy was the first term pregnancy. A sample of serum was obtained when the patient booked in and a second sample was

taken at delivery. The sera were tested for cytotoxic antibodies against a pool of 20 random lymphocytes.

Of the 279 pregnancies studied in this way the infant was male in 126 and female in 153. Forty-five women had cytotoxic antibodies at some time in the pregnancy and in 23 instances the infant was male and in 22 female. In 34 pregnancies the first sample of serum was negative and the delivery sample positive for antibodies. Of these, 15 produced a male and 19 a female infant. There was thus no evidence from this study that a first pregnancy in which the fetus was male was more likely to be associated with antibodies in the mother than one in which the fetus was female. Though these data do not support those of the above report they are not statistically different from them (uncorr. $\chi^2=1.75$). The HL-A specificities of the antibodies were not determined.

The reason for giving attention to the sex of the fetus in this survey was the evidence that where an Rh-positive fetus is male the Rh-negative mother is more likely to produce anti-D than where it is female. It has previously been shown in retrospective studies¹ that the male:female ratios of immunized fetuses in two different series were 1.44:1 and 1.74:1 respectively. In a prospective survey of Rh antibody formation in the months subsequent to delivery of first Rh-positive ABO-compatible infants in Rh-negative mothers, of 72 instances where anti-D appeared the infant was male in 37 and female in 25—a ratio of 1.5:1.² Though this figure was not significantly different from that for pregnancies not associated with the appearance of anti-D, the data supported the findings of the previous report. Studies of the count of fetal cells after delivery in these mothers showed no evidence that a greater volume of cells entered the mother's circulation when the fetus was male.

If there are unidentified sex-specific histocompatibility systems influencing the antibody responses to HL-A antigens they are most probably also involved in the response to red cell antigens.—I am, etc.,

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¹ Renkonen, K. O., and Timonen, S., *Journal of Medical Genetics*, 1967, 4, 166.

² Woodrow, J. C., and Donohoe, W. T. A., *British Medical Journal*, 1968, 4, 139.

New Causes of Malignant Hyperpyrexia

SIR,—I was disturbed to find that in your leading article (30 November, p. 488) you accept the conclusions of Ellis *et al.*¹ without further question.

The most obvious question is—what precautions had these workers taken to eliminate halothane from the anaesthetic machine used? Titel and Lowe² found the rubber-gas partition coefficient for halothane to be 120, which means that a single rubber breathing tube in equilibrium with 1% halothane will hold about 700 ml of vapour. Assuming half of this to diffuse inwards (the other half diffusing to the outside air)—this is the equivalent of giving the patient 1% halothane in 5 litres gas flow for seven minutes. If a circle absorber has been used the time is nearly 20 minutes. Neither flushing the system with oxygen nor washing

the tubes out significantly reduces the transfer problem, helped only by using non-absorptive material such as polyethylene, polyolein, or polyurethane. Polyvinyl chloride is worse than rubber in this respect.³

While Ellis *et al.* may have taken the necessary precautions, unfortunately we cannot know this unless they are reported. Since we do not know the triggering dosage of halothane or any other substance in humans we must assume that these quantities are significant until proved otherwise.—I am, etc.,

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¹ Ellis, F. R., *et al.*, *British Medical Journal*, 1974, 4, 270.

² Titel, J. H., and Lowe, H. J., *Anaesthesiology*, 1968, 29, 1215.

³ Lowe, H. J., *Dose-regulated Penthrane Anaesthesia*, p. 79. Queenborough, Abbott Laboratories, 1972.

Geriatric Policies

SIR,—The recent tragedy in a Nottingham old people's home raises not only the issue of safety in these homes but also that of the suitability of some of these old people to be admitted to these homes.

In most areas of this country there are active old people occupying hospital beds, while some of the residents of old people's homes are bedfast. This can lead on occasion to acrimony between the hospital service (usually, but by no means exclusively, the department of geriatric medicine) and the social services, neither of which is able to fulfil its obligations to the community because of its limited resources.

There is a tendency for social services departments when assessing clients for part 3 accommodation to say to themselves, "This individual cannot manage in this environment, we must change the environment" without considering sufficiently, since they do not have the training, to what extent the individual can be changed—that is, habilitated so that he can remain in his home environment.

In the main the primary health care physician and his team do not have the facilities or expertise adequately to carry out this function. I would therefore suggest that assessment of suitability for part 3 accommodation should be a joint undertaking between social services and departments of geriatric medicine so that correct placement and maximum habilitation can be achieved.—I am, etc.,

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SIR,—While I take issue with Professor G. F. Adams over his paper "Eld Health" (28 September, p. 789), I do not feel as strongly as Dr. H. M. Hodgkinson that he is guilty of denigrating his colleagues (2 November, p. 290). If those of us who claim the advantages of high turnover and low waiting list wish to be taken seriously we must take care to show beyond reasonable doubt, firstly, that the advantages we claim for our approach are shared by the community. Secondly, we must show that we can contain the difficult geriatric case load from our district and have taken account of any help

received from other hospital departments, neighbouring geriatric departments, the social services department, and institutions run by sympathetic religious bodies. It is important to appreciate that this help may be given to the geriatric department directly by transfer to these institutions or indirectly by admission from the community to these institutions. Hospital activity analysis is probably the best method of demonstrating the extent and significance of such invisible exports. Finally, we must show that our approach has worked for a minimum of 10 years. I would suggest that the paper by O'Brien *et al.*¹ satisfies these criteria.

Old people, particularly if they are sick, are in danger of institutionalization in the community just as they are in hospital or old people's homes. Such people generally come for the first time to the notice of the local authority or hospital services when the community finally rejects them. The difficulty of their subsequent rehabilitation and return to the community is far greater if seen at this stage of their illness than if seen earlier, before their rejection and before their institutionalization. Destruction of this vicious circle is surely the nub of geriatric medicine. A hospital geriatric service, if it is to be adequate, must take on the task of cultivating the community. This cannot be achieved without high turnover or low waiting list.

Sir Heneage Ogilvie² also said, "We must seek truth, remembering that when we meet her it may be in a guise we do not expect and coming from a quarter we have despised, and when we have found her we must follow her."—I am, etc.,

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¹ O'Brien, T. D., Joshi, D. M., and Warren, E. W., *British Medical Journal*, 1973, 4, 277.

² Ogilvie, H., *British Medical Journal*, 1949, 2, 663.

Oral Contraceptives and the Liver

SIR,—In your leading article on this subject (23 November, p. 430) no mention was made of porphyria cutanea tarda symptomatica (P.C.T.S.). This form of porphyria is now well recognized as a rare complication of oral contraceptive medication¹ and as a reliable cutaneous marker of liver cell damage.

In the past four years we have encountered five patients, aged 20–31, who have developed P.C.T.S. while taking oral contraceptives and in three of these the aspartate aminotransferase level was moderately raised, though other conventional tests of liver function were normal. In none of the patients was there any history of previous liver disease, porphyria in other members of the family, or more than infrequent social drinking. In three of our patients the porphyria appeared within six months of starting oral contraceptives. In some patients it may disappear when oral contraceptives are stopped, but in others treatment by repeated venesection is necessary. Persistence of the porphyria during subsequent pregnancy has been reported.² Though there have been a few reports of P.C.T.S. occurring in more than one member of a family, we are not aware that a familial basis of this reaction to oral contraceptives has been demonstrated.

It is probable that the oestrogenic component precipitates P.C.T.S. in these patients

since the syndrome also occurs in patients treated with natural and synthetic oestrogens for carcinoma of the prostate or menopausal symptoms.³ Though the mechanism of this action of oestrogen in, presumably, susceptible patients is not understood, it is clear that it is a reaction distinct from the precipitation of acute attacks of porphyria by oestrogens or progestogens in patients with acute intermittent⁴ or variegate porphyria.⁵ Rarely, oral contraceptives may exacerbate the cutaneous manifestations of variegate porphyria, but this effect appears to be secondary to their cholestatic action and is associated with jaundice and diversion of porphyrins from the biliary route of excretion.⁶

It is important to ensure that P.C.T.S. and variegate porphyria are not confused when a young woman presents with the characteristic skin lesions of the cutaneous hepatic porphyrias. This can be achieved only by appropriate laboratory investigation of samples of urine and faeces from the patient and, if necessary, other members of her family.⁷—We are, etc.,—

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¹ Baker, H., *British Journal of Dermatology*, 1969, 81, 946.

² Borrie, P. F., Case 41, British Association of Dermatology, 52nd Annual Summer Meeting, July 1972.

³ Roenigk, H. H., and Gottlob, M. E., *Archives of Dermatology*, 1970, 102, 260.

⁴ Zimmerman, T. S., McMillin, J. M., and Watson, C. J., *Archives of Internal Medicine*, 1966, 118, 229.

⁵ McKenzie, A. W., and Acharya, U., *British Journal of Dermatology*, 1972, 86, 453.

⁶ Goldswain, P. R., and Eales, L., *South African Journal of Laboratory and Clinical Medicine*, 1971, 17, 111.

⁷ Elder, G. H., Gray, C. H., and Nicholson, D. C., *Journal of Clinical Pathology*, 1972, 25, 1013.

Combination Chemotherapy for Breast Cancer

SIR,—We recently (9 February 1974, p. 218) reported our initial experience in 25 cases with a combination chemotherapy regimen for metastatic breast cancer which included cyclophosphamide, methotrexate, and fluorouracil in addition to prednisone. At the present time we have achieved a complete or partial response in 26 out of 38 cases (68%), which lasted for a median duration of eight months (range 6–34+). Eight of these patients achieved a complete disappearance of all measurable disease. The median survival for the responding group is 20 months and for the non-responding group five months. The haematological toxicity was greatest in those patients with hepatic functional impairment and extensive bone or bone marrow replacement by tumour. In these cases we recommend that the initial doses of cytotoxic drugs be reduced by 50%, with modification of subsequent cycles according to haematological tolerance.—We are, etc.,

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