CORRESPONDENCE

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Screening for Hyperlipidaemia in Childhood

SIR,—We wish to comment on two aspects of your leading article (16 November, p. 367). Firstly, you state that familial hyperlipidaemia in heterozygotes is readily corrected and imply that the outstanding problem is the age at which treatment should start. In our experience of treating children with the heterozygous form of familial hyperbetalipoproteinaemia (which is the only commonly encountered form of familial hyperlipidaemia in childhood) the abnormality is not always easily corrected, even in the short term, and long-term evaluation shows even poorer results. We have found that dietary measures alone achieve a mean reduction of serum cholesterol of about 20% of the pretreatment value,¹ and the addition of clofibrate to the diet achieves a further 10% reduction; cholestyramine resin (with or without dietary restriction) achieves a reduction of 36%.² The use of these treatments has not invariably been successful in lowering serum cholesterol to the generally accepted "normal" range even in the short term. Long-term evaluation of the three regimens³ has shown that two years after starting therapy the serum cholesterol level remains satisfactory in only 20% of children treated with diet alone and in none of a small group treated with the combination of diet and clofibrate. With cholestyramine, after three years adequate control was maintained in 57% of children. In our experience failure of long-term treatment is not due to loss of effectiveness of the agents prescribed but results from the inability of the children to follow the diet strictly over long periods or to take cholestyramine in sufficient amounts. Nearly all the children treated by us are from families in which premature coronary heart disease has already become manifest so that motivation towards treatment is likely to be high.

Secondly, you conclude by justifying extensive evaluation of cord blood lipoprotein assays for routine screening of babies born

to hyperlipidaemic parents and to families with a history of early-onset heart disease. While affected children may be identifiable by estimation of betalipoprotein cholesterol in cord blood serum,⁴ unless such diagnosis is to lead to the immediate institution of therapy it is probably better deferred. The need to treat such children in the first year is not proved; most paediatricians would be reluctant to use drug treatment at this age and evidence that infant formulae designed to lower serum cholesterol are always effective is lacking. Our own experience with two affected infants of heterozygous mothers has been disappointing; in neither case was adequate control of serum cholesterol achieved during the first year of life by dietary measures.

In view of the disappointing long-term results of available treatments, in our opinion screening entire populations of children for familial hyperbetalipoproteinaemia is not at present justified. We agree that screening of families in which early coronary heart disease has occurred should probably be undertaken but suggest that such screening be deferred until after the age of one year. Once treatment has been started it is important to supervise progress closely in order to assess adherence and to detect untoward side effects of the treatment(s).—We are, etc.,

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Medical Graduates in Clinical Chemistry

SIR,—I have spent three years as registrar and then lecturer in clinical chemistry. After considerable speculation I have decided to give up the study of the specialty and return to a career in clinical medicine. On the eve of my departure it may be worth while expressing a few of my thoughts on the present and likely future role of the medical graduate in clinical chemistry.

A perusal of publications in journals devoted to clinical chemistry and attendance at Association of Clinical Biochemistry and other meetings convince me that at present the accent is on the word "chemistry" rather than on the word "clinical." Indeed, the word "clinical" might almost be dropped and replaced by some more accurate description such as "medical." The present trends of laboratory centralization and increasing subspecialization are likely to remove the medical graduate further and further away from patient management and more towards an administrative and scientific role. The medically-qualified clinical chemist in these circumstances has very little more to offer the patient than a non-medical biochemist. Indeed, our clinical colleagues are now becoming so well informed on scientific matters that the advisory role the chemical pathologist once enjoyed is tending to disappear.

Dr. F. L. Mitchell states¹ that a possible solution to present-day problems of recruitment of medical graduates would be to suggest a laboratory career from the outset of medical training rather than on completion. Surely a more logical solution would be fundamentally to alter the role of the medical graduate in clinical chemistry, taking him more out of the laboratory and into the wards where he should have definite clinical responsibility. There are many areas such as endocrinology, intensive care, etc., in clinical medicine where an able clinical chemist would be of immense value. The other cogent reason for getting the medical clinical

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