protracted and symptoms are relieved within half an hour of receiving glucose.² On the other hand, in a study of normal children (5 to 15 years of age) as little as 2.5 mg of glibenclamide produced a marked decrease in blood sugar with lower than normal blood sugar values persisting for more than six hours (six hours being the total investigation time).³ In our patient there appeared to be a prolonged hypoglycaemic effect lasting 48-72 hours. Moreover, we can only conclude that the hypoglycaemia has caused permanent cerebral damage with epilepsy. Mental retardation cannot be excluded.—We are, etc.,

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¹ Kullavanijaya, P., *British Medical Journal*, 1970, **4**, 53.

² Davidson, M., et al., *Lancet*, 1970, **1**, 57.

³ Weber, B., and Hahn, W., *Zeitschrift für Kinderheilkunde*, 1970, **108**, 32.

Potentialiation of Warfarin by Co-trimoxazole

SIR,—I was interested to note the observations of Dr. J. M. Hansen and others (21 June, p. 684) on their finding of co-trimoxazole "as an inhibitor of drug metabolism in man." Their remarks were prompted by previous correspondence discussing potentiation of the action of warfarin by co-trimoxazole and consequent increased hypoprothrombinaemia.

In several years' experience in supervising a long-term anticoagulant clinic now comprising about 1000 patients, about 95% of whom are treated with phenindione, I cannot recollect a case of potentiation of hypoprothrombinaemia to untoward levels (less than 5% thrombotest control) whenever co-trimoxazole was added for intercurrent infection. I would, therefore, recommend the use of this drug whenever an oral broad spectrum antibiotic is needed in patients with phenindione—especially since the latter group of anti-infective agents usually does cause troublesome hypoprothrombinaemia with warfarin or phenindione. This clinical advantage in using phenindione rather than warfarin is, in my experience, one reason for preferring the former anticoagulant for routine use.—I am, etc.,

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Clomiphene in Investigation of Ovulatory Failure

SIR,—I cannot accept as reasonable the conclusion of Dr. Jean Ginsburg and others (19 July, p. 130) that "clomiphene's failure to evoke a response when there was a positive response to LH/FSH-RH suggests a functional defect at hypothalamic level or above." They state correctly that "clomiphene is thought to act essentially through competition with oestrogen at hypothalamic receptor sites," but are incorrect in adding: "stimulating release of LH/FSH-RH and gonadotrophins by negative feedback."

A negative feedback is, by definition, inhibitory, and clomiphene exhibits a positive feedback by blocking without stimu-

lating the hypothalamic receptors that would otherwise transmit to the anterior pituitary the negative feedback effect of oestrogens. When the ovaries are producing no oestrogens the negative feedback is already virtually nil, and clomiphene cannot be expected to have an effect. Hence a failure of gonadotrophins to rise in response to clomiphene can reasonably be ascribed to a hypothalamic defect only if levels of oestrogen sufficient to produce a negative feedback have been demonstrated before the administration of clomiphene (given also, of course, that a functional anterior pituitary has been demonstrated by a response to LHRH).

No data about oestrogens are given in the paper, but support for my argument is provided by the finding that among the abnormal women all the five who were menstruating, and who must therefore have been producing substantial amounts of ovarian oestrogens, responded to clomiphene with a rise in LH.—I am, etc.,

P. BYE

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Serum α -Fetoprotein in Cystic Fibrosis

SIR,—Paediatricians and geneticists have been looking forward to a reliable method of diagnosing cystic fibrosis in children and also in identifying clinically unaffected heterozygote carriers. Professor R. K. Chandra and others (29 March, p. 714) suggest that estimation of serum α -fetoprotein (AFP) might help in detecting carriers in families at risk. Their patients with cystic fibrosis had significantly raised levels of serum AFP, and the patients' parents and some siblings, presumed to be heterozygotes, also had moderately but significantly raised levels. Observers in the U.K. (17 May, p. 392) have been unable to confirm these findings, whereas Dr. J. A. Smith of New York (17 May, p. 392) supports them. More reports may be on the way. Perhaps the crux of the matter lies in the technique of estimating serum AFP.

Professor Chandra and others state that "In autosomal recessive traits the proportion of carriers to normal subjects in a sibship should theoretically be 2:1, whereas this ratio was 1:1 in our study." Their patients numbered 18, parents 16, and siblings 14, with seven presumed heterozygotes and seven presumed normal. Presuming that all the parents and all the siblings were studied, there were a total of eight families and 32 children, with an average of four children per family. Theoretically, an average of about eight affected children, eight normal children, and 16 heterozygote carriers could have been expected, but this was not so. Theoretically, 1 in 4 of the siblings is affected if a large number of families are analysed.¹

If a small number of families is analysed the proportion of affected individuals may differ from the expected. By chance some families may have all normal children whereas some may have all affected children. For example, nowadays, since families tend to be small, the appearance of an autosomal recessive condition is often sporadic with only one affected person in the family.² This could well apply to cystic fibrosis.

There are about 1 in 25 heterozygote carriers of cystic fibrosis among Europeans and North American Whites.³ Perhaps the time will come when these heterozygotes will be identified as part of their routine medical care. When two heterozygotes married each other the risk would be known in advance.—I am, etc.,

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¹ Danks, D. M., Allan, J., and Anderson, C. M., *Annals of Human Genetics*, 1965, **28**, 323.

² Emery, A. E. H., in *Textbook of Paediatrics*, ed. J. O. Forfar and G. C. Arneil, p. 66. Edinburgh and London, Churchill Livingstone, 1973.

³ Carter, C. O., *Fogarty International Centre Proceedings No. 6*, ed. M. Harris, p. 22. Bethesda, Maryland, National Institute of Health, 1970.

Junior Hospital Staff Contract

SIR,—We, the undersigned junior hospital staff at the Aberdeen teaching hospitals, agree with the views expressed by the junior staff at the National Hospitals for Nervous Diseases, Queen Square and Maida Vale (5 July, p. 43).

We are opposed in principle to the proposed junior contract and support the call for a halt to the present negotiations; it is our opinion that the views of all the junior staff in the country should be sought by a national postal ballot before such ill-advised arrangements are finalized.—We are, etc.,

C. J. ALLISON

Aberdeen Royal Infirmary,
Aberdeen

. This letter had 62 signatures appended to it in addition to that of Dr. Allison.—ED., *B.M.J.*

SIR,—As a "flying doctor" from the outback of Western Australia, I am appalled at the conditions of service that the junior hospital doctors have obtained in Britain. The rate of emigration of junior doctors from this country speaks for itself—there is only one way to reverse this trend and that is to obtain better working conditions for junior doctors. Fortunately there is one way of obtaining this and that is by pressing for a 40-hour contract.

Mrs. Barbara Castle promised us the 40-hour contract in January of this year. Even the Review Body in its Fifth Report pointed out (para. 15) that the work load on junior staff will continue to increase. Since the G.M.C. has at last tightened up the regulations there will be fewer overseas doctors available to staff the hospitals in Britain. The crunch of the matter is that the peripheral hospitals will be the first affected and hence they will need to lead the rest of the junior hospital doctors in their fight to secure better working conditions.

As I said at the Annual Representative Meeting you obtain from the Government what you think that you are worth—and I sincerely believe that a houseman who works well in excess of 80 hours (many of these being unsocial hours) is worth £6000 per year. However, you can only achieve this figure if you can obtain a solid basic 40-hour contract. For comparison, just look at