results of the acute infarction ramipril evaluation study, however, suggest that patients who develop heart failure after infarction should also be considered for treatment.³ A large proportion of patients in the acute infarction ramipril evaluation study had an ejection fraction greater than 40%.

Finally, Darbar and colleagues may have underestimated the incidence of heart failure after myocardial infarction since it was sought only once, on day 2. In the acute infarction ramipril evaluation study patients could be enrolled if they had clinical or radiographic signs of heart failure at any time up to 10 days after myocardial infarction.

We conclude that Darbar and colleagues have misinterpreted the aims of the algorithm and in doing so have underestimated both its sensitivity and its specificity in identifying patients who should be treated with angiotensin converting enzyme inhibitors after myocardial infarction. Two of us (JB, HD) have tested the algorithm in 133 patients with acute myocardial infarction and found a sensitivity of 88% and a specificity of 81% for important left ventricular dysfunction or heart failure.

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Predictors of neonatal encephalopathy in full term infants

More information needed about possible role of thyroxine

EDITOR,—Stuart J Adamson and colleagues suggest that maternal thyroxine treatment increases the risk of neonatal encephalopathy, with an odds ratio of between 1.2 and infinity (the mothers of six of the affected babies were taking thyroxine, compared with none of the mothers of the control babies).¹ They also claim that this is biologically plausible. These statements need further qualification in view of the large numbers of women who take thyroxine in pregnancy (approaching 1% in our population).

Do the authors claim that the maternal thyroxine treatment itself is dangerous? The fetal thyroid begins to function independently of the maternal hypopituitary-thyroid axis late in the first trimester and is not affected by either maternal thyroxine or thyroid stimulating hormone.² More importantly, little if any maternal thyroxine is able to cross the placenta.³ Even large doses of thyroxine taken to suppress thyroid cancer do not adversely affect the fetus.

Or do the authors consider that the underlying maternal condition necessitating thyroxine treatment causes neonatal encephalopathy? Under-treated maternal hypothyroidism is associated with fetal distress in labour and a reduced IQ in the child at age 7, neither outcome occurring in women taking sufficient doses of thyroxine. De Escobar

et al concluded that low maternal thyroxine concentrations are associated with poor neurological outcome.⁴ This is distinct from the problem in areas of endemic iodine deficiency, where children born to iodine deficient mothers with reduced total thyroxine concentration have a reduced intellectual capacity and motor competence.⁵ This suggests that iodine deficiency in the absence of frank hypothyroidism itself is detrimental—a concept different from that proposed by Adamson and colleagues.

Before we can accept that maternal thyroxine is harmful to the fetus we must know the circumstances of the study, including the indications for thyroxine treatment and the maternal thyroid status. Until these data are available, the relevance of this observation cannot be assessed.

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Measures used in study are hard to interpret

EDITOR,—Stuart J Adamson and colleagues' study of the predictors of neonatal encephalopathy in full term infants¹ is timely in view of changes and practices in Britain and trends in litigation. It is worrying, however, that serious problems with interpretation are known to arise with several of the measures of intrapartum events used in the study to indicate birth asphyxia and subsequent neonatal encephalopathy.

Cardiotocographic appearances are poorly correlated with asphyxia, and serious acidosis can occasionally be present with "normal" tracings.² Likewise, meconium staining has an imprecise correlation with outcome.

The Apgar score can be normal at delivery despite the presence of severe fetal acidosis,³ and there is documented evidence that babies with "normal" Apgar scores have collapsed hours after delivery and developed neonatal encephalopathy.

It is imprecise to use cord pH without specifying whether the blood is of arterial or venous origin. Cord gas analysis of the umbilical artery and vein is an objective measure of neonatal status at delivery provided that both vessels are reliably sampled. Unintentional double sampling of a single vessel occurs in up to 30% of cases and can be overcome by the use of computer software for interpreting blood gas values. Thus in the authors' study some of the infants with neonatal encephalopathy that was not thought to be due to intrapartum events might have been found to be profoundly acidotic at delivery had routine cord gas sampling been available.

The Royal College of Obstetricians and Gynaecologists recommends that the cord artery and vein should be sampled immediately after all deliveries to determine the "fetal response to labour in terms of fetal placental respiratory function" and to obtain a consensus of normal ranges for the partial pressure of oxygen and base deficit.⁴ Data are now

being collected in several centres in Britain,⁵ and it is hoped that they will clarify the relation between intrapartum events—in particular, asphyxia—and a range of neurodevelopmental disabilities.

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Authors' reply

EDITOR,—We agree with J Girling and M de Swiet that our pilot study did not establish a causal link between use of thyroxine and subsequent neonatal encephalopathy. The study was intended to generate a hypothesis, which we are testing in a further study. Preliminary data from this study (excluding data from the pilot study) show that the range of thyroid disease in the women includes Graves' disease, primary hypothyroidism, and hypothyroidism after medical or surgical treatment. The unadjusted odds ratio is 4.8 (95% confidence interval 1.22 to 18.8), which suggests that women with thyroid disease are nearly five times more likely to have an infant with neonatal encephalopathy than are euthyroid women.

Our observations tell us nothing about the potential mechanisms by which maternal thyroid dysfunction and subsequent treatment increase the risk of neonatal encephalopathy. The fetal thyroid gland does not function until late in the first trimester.¹ Current evidence suggests that small but important amounts of maternal thyroid hormone cross the placenta and have a role in the maturation of the fetal brain.² Thus maternal thyroid dysfunction may adversely affect the development of the brain in the early stages of pregnancy. We hypothesise that as fetal thyroid hormone requirements have not been established we cannot be certain that what is assumed to be adequate maternal treatment results in appropriate fetal thyroid hormone concentrations.

We agree with A M Mander and S C Leeson that serious problems with interpretation arise with several of the measures of intrapartum events used to indicate birth asphyxia in our study. Any case-control study of either neonatal encephalopathy or cerebral palsy depends on retrospective ascertainment of exposure (for example, intrapartum asphyxia) and has the added challenge of the absence of diagnostic tests. Cardiotocograms are hard to interpret and have an extremely low positive predictive value.³ Apgar scoring varies among observers and is affected by prematurity, drugs, maternal anaesthesia, and neuromuscular conditions as well as intrapartum hypoxia.

It would have been useful if cord pH had been measured in more of our study infants, but this reflects clinical practice. Furthermore, cord pH values do not correlate well with other measures of birth asphyxia and are not predictive of an adverse neurological outcome. In fact, neonates with a low Apgar score and a normal cord pH at birth may fare worse than those with a low Apgar score and a low cord pH as they may be unable to mount an appropriate biochemical response to hypoxia.⁴

Most other studies of neonatal encephalopathy have been confined to infants presumed to have been asphyxiated at birth. Our study included