Early origin of coronary heart disease

Maternal nutrition in early pregnancy may affect placental ratio

EDITOR,—In their editorial discussing the early origins of coronary heart disease Nigel Paneth and Mervyn Susser emphasise the importance of further investigation of the influences on the ratio of placental to fetal weight.¹ Godfrey *et al* have proposed that iron deficiency has a role since low maternal haemoglobin concentrations and a decrease in mean red cell volume during pregnancy are associated with an increase in the ratio.² In contrast, Perry *et al* found no relation between maternal haemoglobin concentrations in early pregnancy and placental ratio at delivery³ but confirmed the positive association between the ratio and maternal body mass index.²

Timing is another important consideration when the influence of the maternal environment on the developing fetus and placenta is studied. Many women start pregnancy with low iron stores, and we hypothesised that placental size would be increased by mid-pregnancy in those with low ferritin and haemoglobin concentrations. To investigate this we developed a method of measuring placental volume during the routine scan at around 18 weeks of pregnancy. In a study of 568 white women we found that low haemoglobin and ferritin concentrations at 14 weeks' gestation were associated with increased placental volume.⁴ Placental volume was also greater in taller women, in multiparous women, and in those who smoked heavily at the time of their last period. We found no relation between maternal weight or body mass index and placental volume.

We have since examined the factors affecting the ratio of placental to fetal size in mid-pregnancy by estimating fetal weight using Shepard *et al*'s algorithm.⁵ The relations between maternal characteristics and the ratio of placental volume to estimated fetal weight were examined by multiple regression analysis (table). The ratio was increased

Simultaneous effects of maternal characteristics on ratio of placental volume to estimated fetal weight (ml/g) at 18 weeks' gestation

Maternal factor	Regression coefficient (95% confidence interval)	P value
Gestation at which scan obtained (days)	-0.013 (-1.018 to -0.009)	<0.0001
Haemoglobin (g/l)	-0.002 (-0.0004 to 0.0)	0.05
Ferritin (square root µg/l)	-0.014 (-0.022 to -0.006)	0.001
Smoking at last menstrual period	0.027 (0.006 to 0.048)	0.012
Previous deliveries	0.007 (0.0004 to 0.014)	0.038

in scans obtained at earlier gestations, with lower maternal haemoglobin and ferritin concentrations, with increasing parity, and in mothers who smoked. None of these factors except gestation affected the estimated fetal weight, and the change in ratio was therefore principally due to changes in placental volume.

Perry *et al* concluded that their findings did not support a link between placental ratio and maternal nutrition at birth.³ In contrast, our study suggests that the ratio is affected early in pregnancy by the mother's nutrition as shown by the haemoglobin and ferritin concentrations. The evidence that maternal nutrition affects the placental ratio is further strengthened by experiments in sheep, which have shown that restricted maternal food intake results in an increase in placental size.⁶

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The influence of parental somatic features on childhood weight has been extensively studied

EDITOR,—In their editorial on the early origin of coronary heart disease (the "Barker hypothesis") Nigel Paneth and Mervyn Susser overlooked my contribution.¹ In 1982 I suggested that some heavier children were relatively immune to non-insulin dependent diabetes and coronary heart disease in adult life and that the decline in rates of coronary heart disease that was occurring in some communities was linked to the increasing average weight of children in those communities.² I was also the first to publish this hypothesis in major North American journals.^{3,4} In 1989 Barker and his colleagues put forward similar ideas.

I have had 11 contributions to the discussion on this subject published, including constructive appraisals of Barker *et al*'s early papers. For example, I advised against generalised postnatal nutritional intervention to promote heavier infants, suggested that the importance of placental weight was as a marker for maternal obesity, and warned that the prenatal nutrition theory was not consistent with the existing data on twins or on prenatal exposure to famine. To date, studies have vindicated these concerns.

There were differences in approach, whereas Barker *et al* focused on maternal nutrient intake during pregnancy I focused on the influence of parental somatic features on weight in childhood. For example, birth weight reflects both maternal adiposity and maternal muscle mass.⁵ Adult somatic features, in turn, are determined by both hereditary and environmental factors.

Primary care doctors do not have the resources of major research teams. Nevertheless, our contributions should be acknowledged. Thus it seems fairer to describe the Barker hypothesis as the "Barker-Bradley hypothesis."

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Earlier published work supports the "Barker hypothesis"

EDITOR,—Nigel Paneth and Mervyn Susser discuss the fetal and early life origin of coronary heart disease, referring to the "Barker hypothesis."¹ We acknowledge the important contributions of Barker and his coworkers. More strongly than previous authors, they have pinpointed the rele-

vance of fetal nourishment to later coronary risk. Readers of the *BMJ* should also be aware, however, of the earlier publications by Anders Forsdahl of the University of Tromsø. In 1973, in a paper published in Norwegian with an English summary, he advanced "the theory that extremely poor social conditions during childhood and adolescence can be considered as risk factors for cardiovascular diseases."² This was more than 10 years before the paper by Barker and Osmond in 1986.³ Since 1977 Forsdahl has published several studies supporting his hypothesis in international journals.^{4,5}

Thus we believe that if one person alone is to be given the honour for the theory that experiences in early life are of major importance for the risk of cardiovascular diseases several decades later it should probably be Anders Forsdahl.

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A definition of sexual health

EDITOR,—No seminar or conference on the subject of sexual health seems complete without a presentation or debate rhetorically titled "What is sexual health?" Those who have discovered the subject since the launch of *Health of the Nation* face a daunting choice of definitions. Most definitions, coming from a political¹ or health promotion² background, extol in lengthy prose the positive personal benefits of sexual relationships for self esteem and fulfilment, apparently ignoring the medical perspective; the medical perspective appears as a more or less comprehensive list of serious health problems associated with sexual activity, giving an entirely negative impression.

A concise definition of sexual health that unites both benefits and deficits in one sentence of plain English is clearly needed. It must be simple enough to be understood and remembered easily; applicable to a wide range of social, religious, and sexual cultures; yet be robust enough to stand critical analysis and sufficiently unambiguous to be capable of expansion without significant distortion. Such a sentence is: Sexual health is the enjoyment of sexual activity of one's choice, without causing or suffering physical or mental harm.³

This definition allows the term "enjoyment," in its widest interpretation, to be expanded to the lengths of previous statements without prescribing the type of sexual relationship—be it heterosexual, gay or lesbian, monogamous, or otherwise—provided it is by mutual consent without coercion or damage. It can also promote two of the safest options, masturbation and abstinence, as positively healthy choices. It is consistent with the traditional humanist medical principle of first do

no harm and John Stuart Mill's libertarian philosophy of individual sovereignty and responsibility,⁴ so that sexual health is regarded as a basic human right. It emphasises the inseparability of physical and mental health in any holistic consideration of a person's sexual wellbeing.

In this form it could be construed that the goal of sexual health is difficult or impossible to attain, given human fallibility. Previous definitions have been criticised as being applicable only to Western or European societies. Yet whenever choice is limited—be it by economic necessity (market forces), personal threat, societal norm, government legislation, religious edict, or other cultural pressures—both physical and mental aspects of sexual health suffer greatly because people are coerced into sex against their will. Indeed, the highest rates of sexually transmissible diseases and other reproductive morbidity occur where women and their rights are least valued or respected.

The need for an integrated approach to sexual health and its medical care is not a sudden, recent development but one that has been obvious to a minority of concerned clinicians and educators for at least a generation. This definition further strengthens the philosophical basis of destigmatised, holistic sexual health care, which integrates the promotion of sexual health with the provision of services for its maintenance.⁵

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Electronic diaries for asthma

EDITOR,—Hyland and coworkers have reported the successful use of hand held computers as electronic diary cards in asthma.¹ Such devices greatly simplify data handling, and they record the time at which each entry was made. However, the use of a conventional type of computer may present problems for some patients. Pen based devices (Personal Digital Assistants, PDAs) provide an alternative that may be easier for many patients to use.

We have developed an electronic asthma diary on the Apple Newton. Entries are made by tapping choices with a stylus on the screen. Handwriting recognition is not used. We evaluated it in 13 men and nine women aged 18-70 who completed paper and electronic diaries morning and evening for four weeks each in randomised order. Peak flow (Vitalograph peak flow meter), symptoms, bronchodilator use, and night time awakenings were recorded. All patients completed a survey questionnaire at the end.

Patients found both diaries easy to use. Most preferred the electronic diary (electronic, 13; paper, 4; no preference, 5). A similar pattern was found when data were broken down by age, sex, and reported comfort with technology. Thus there is no evidence for any subgroup for which the Newton diary presents any special difficulty.

Chowienzyk *et al* have recently shown that a substantial proportion of conventional diary data may be invented.² Two lines of evidence from our study suggest a similar conclusion. Firstly, the proportion of missing data was higher for the electronic than for the paper diary (electronics, 8.9%; papers, 0.16%), raising the suspicion that

some paper entries were initially missed and then completed later. Such retrospective entry was not permitted by the Newton software. Secondly, inspection of the data suggests serious problems with paper entries for some patients. In the most extreme case, over half the peak flow values recorded on paper were the same, 35 out of 61 entries being 150 l/min—but the corresponding electronic entries were nearly complete (94%) and showed the kind of distribution expected for valid readings (figure).

Peak flow values recorded by one patient (a) on paper; (b) electronically

Pen based electronic diaries are highly acceptable to patients. As well as simplifying and speeding up data handling, they bring substantial improvements in the trustworthiness of the data obtained.

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Events per person year

A decrease in multiple events may be missed

EDITOR,—Jürgen Windeler and Stefan Lange describe the "new measure" invented in 1982 to describe osteoporotic fractures in the context of clinical trials—namely, the frequency of vertebral fracture.¹ They suggest that the number of patients developing vertebral fractures is a more appropriate end point. In their review they neglect to mention that the problems with this approach are well recognised,^{2,3} though perhaps not universally applied. Nor is the fallacy ignored by some registration authorities, and in some countries the test agents to which they refer have been refused licences for these reasons. Though we do not wish to defend the use of fractures/100 patient years, the event rate is relatively low in the context of vertebral osteoporosis. Thus few individuals will have repeated events, so that the number of patients with a fracture is proportional to the number of patients experiencing an event.² As confidence increases that changes in bone mineral density can be equated with changes in the fracture rate, at least with some therapeutic agents,⁴ the

need to study fracture end points will probably decrease.

The situation is more problematic in the bone disease of malignancy, in which event rates are much higher and the number of patients experiencing an event may not be proportional to the number of events.⁵ In our studies of 171 women we showed that the number of patients with metastatic breast cancer who developed vertebral fractures was decreased by 15% (44 v 52; NS) in those exposed to a bisphosphonate.⁵ The number of fractures observed, however, was decreased by 32% (58 v 90, respectively; $P < 0.025$). We reported both approaches (patients and events), since we thought that an intervention that decreased the total number of events was clinically worth while. The expression of only the number of patients who developed a vertebral fracture hides some aspect of the benefits of the intervention.

Discussions with statisticians have been of little help in advising us how to report clinically beneficial effects in a manner that is statistically acceptable. One approach has been to use expert systems that iterate the likelihood of an observed outcome arising by chance. When we applied this to our own data the probability of a difference between no treatment and treatment arising by chance was similar ($P < 0.07$) to that obtained with the less purist method that we reported. Though we agree with criticisms raised by the authors, it would be a pity if in the future the clinical importance of a decrease in multiple events was not also appreciated.

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Use individual event rate adjustment for follow up time

EDITOR,—We agree with Jürgen Windeler and Stefan Lange about the importance of correct analysis of data on fractures and that the widely used sample statistic events per person year may lead to flawed results.¹ The reason is, as the authors point out, that the data may include more than one event (fracture) in the same patient and these events do not fulfil the criteria of independence, which is the basic assumption for the usual statistical tests of rates. The idea that statistical analyses can be performed when the statistical assumptions are not met is incorrect.

Windeler and Lange suggest three methods for proper analysis of data on fractures. The first is comparison of the proportions of patients with at least one fracture. This approach, however, requires often unrealistically large sample sizes. For the second approach—use of the mean number of fractures per patient in the study period—the follow up time must be taken into account. New variables thus created can be called the individual event rate (used when the follow up time is similar, at least approximately) or the individual event rate adjusted for the follow up time (number of fractures per patient divided by follow up time). The latter is especially useful when the drop out rate is