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The relation between fetal malnutrition and chronic disease in later life

Good nutrition and lifestyle matter from womb to tomb

See p 837

David Barker's group has greatly increased our understanding of the factors contributing to chronic diseases in later life. In over 50 papers[1] the group has presented evidence from British populations that low birth weight at term and, in some cases, low weight at 1 year of age are associated with an increased adult risk of hypertension, coronary heart disease, non-insulin dependent diabetes, and autoimmune thyroid disease.[2] The importance of these findings is that they provide overwhelming evidence that malnutrition at a very early age (in utero and in infancy) in Britain this century resulted in earlier and more severe adult chronic disease. This week Barker and Finnish colleagues provide further data and offer an explanation for the epidemic of heart disease that accompanies Westernisation.[3]

The Barker group's initial observations were so surprising that they met considerable scepticism. Some suggested that birth weight was reflecting other socioeconomic factors, not just maternal malnutrition, while others doubted the generalisability of the findings. But, no matter what combination of poor nutrition and other environmental factors is responsible for fetal growth retardation, the concept of fetal origins of adult disease is still valid, and the associations have been found in other populations wherever investigated. For blood pressure alone a recent review clearly showed that at all ages and in all populations examined, blood pressure tends to increase as birth weight falls.[4] Confounding socioeconomic factors do not provide an adequate explanation for this association. For coronary heart disease, the early findings in Sheffield, England,[5] have been have corroborated in Caerphilly, Wales[6]; Uppsala, Sweden[7]; the nurses health study in the United States[8]; and now in Helsinki, Finland.[3] A study in Mysore, India, provided the first confirmatory evidence from a contemporary developing country.[9] In the Gambia the blood pressure of children at 8 years was inversely proportional to their mothers' weight gain in the last trimester of pregnancy.[10] The earlier and more frequent death from heart disease among veterans of the American civil war who were shorter at recruitment also suggests the lasting effects of early malnutrition.[11]

Concurrent with the Barker group's studies are others in several countries showing that iodine deficiency during pregnancy affects fetal brain development at a critical stage and can permanently affect cognitive performance.[12] In populations with endemic goitre the distribution of IQ can be depressed by as much as 10 points.[13] Convincing evidence also exists that iron deficiency during infancy has the same kind of lasting effect on cognitive performance.[14 15] Low weight for age of preschool children was reflected in poorer neurointegration in lower socioeconomic groups in Mexico but not in middle and upper socioeconomic groups.[16] In Guatemala nutritional supplementation during pregnancy and of the child up to 2 years was reflected 15 years later in better scholastic achievement and cognitive performance than in a control group.[17] To these examples of ways in which malnutrition can permanently damage the expression of the genetic potential of the fetus and young child can be added the adverse effects of drugs, alcohol, and smoking during this critical development period.

Thus we must conclude that fetal malnutrition can lead to structural or functional changes in utero that permanently increase susceptibility to chronic diseases. Describing this as "programming, however, is misleading: rather, it is an increased propensity to develop these diseases when adult diet and lifestyle are conducive to them. For atherosclerosis overwhelming evidence has accumulated on the importance of controlling diet, exercise, smoking, and other risk factors at any age. Regardless of susceptibility, some populations are essentially free from mortality from heart attacks. In the 1960s serial necropsies were obtained from eight public hospitals in Latin America and Charity Hospital in New Orleans. The aortas and coronary vessels were dissected out, stained for fat, and evaluated blindly for the degree of atherosclerosis. In some Latin American populations there was almost no clinical disease, even in people aged over 60.[18] In New Orleans, however, atherosclerosis increased sharply after the age of 20 and some men in their 30s and 40s were at risk of myocardial infarction. Thus, although the prevalence of low birth weight was relatively high in the Latin American populations, the low proportion of dietary energy from fat and other lifestyle factors made the "Barker effect" irrelevant to ischaemic heart disease.

The falling death rates from heart disease in countries that have aggressively promoted healthier diets and lifestyles confirm the importance of paying attention to disease prevention at later stages of life. It does

not detract from the seminal contributions of the Barker group to suggest that a broader paradigm is emerging that extends the concept of the fetal origins of adult disease. This recognises that most human embryos have the potential for a long and healthy life. From the moment of conception, however, adverse environmental forces limit this potential. Intrauterine growth retardation due to poor maternal malnutrition is an important factor; but so are diet at all ages, cigarette smoking, a sedentary lifestyle, the use of drugs, and others.

The Barker group's findings have made it clear that preventive measures should begin with improving the nutrition and health of women to prevent damage to their fetuses. This will require attention to the risk factors for low birth weight before pregnancy since nutritional supplements during pregnancy are inadequate.[19] Moreover, for a long and healthy life good nutrition and lifestyle are necessary throughout the entire life span. While not all individuals have the same genetic potential for avoiding premature degenerative disease, their chances of doing so can be dramatically improved by good nutrition and health practices from womb to tomb.

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The use of statins: a case of misleading priorities?

National guidance that does not link costs and benefits is worthless

Last month the NHS Executive distributed to health authorities and general practitioners a statement from the Standing Medical Advisory Committee on the use of lipid lowering drugs.[1] This argues for a strategy of treatment on the basis of underlying risk, but it adopts a level that is probably unachievable, fails to present the evidence, and ignores cost effectiveness. In so doing it jeopardises the objective of targeting high risk patients, but it also raises questions about the worth of guidance that does not link benefits and costs.

The statement recommends that, having considered other methods of reducing the risk of coronary heart disease, clinicians should give statins to the following three groups of patients. The first priority are patients who have had a myocardial infarction and have low density lipoprotein values of 3.2 mmol/l or more; second are those with angina or other clinically overt atherosclerotic disease with low density lipoprotein values of 3.7 mmol/l or more; and third come those with a high risk of developing coronary heart disease according to the revised Sheffield tables[2] and a low density lipoprotein value of 3.7 mmol/l or more. The statement estimates that meeting all three priorities will mean treating 8.2% of the population aged 35-69. No recommendations are made for patients aged over 70, although there is no evidence that benefits are limited to younger patients. The statement was sent to all general practitioners and health authorities and trusts with a commendation from the chief medical officer[3] or the NHS Executive.[4]

In Warwickshire Health Authority full implementation of these recommendations will involve treating about 17 000 patients, some 10 000 for secondary prevention and 7000 for primary prevention. The cost of the statins (using the cheaper evaluated agent) with doses reflecting those in major trials will be about £8m for the authority, representing 20% of the drugs budget, at an average cost of about £100 000 per practice. These costs do not include diagnostic tests and the time required to identify, counsel, and treat patients. The statement gives no indication of the likely benefits if the recommendations are followed, although three large randomised trials,[5-7] and an epidemiological study[2 8] are cited. No additional resources have been made available, and the statement gives no indication of where savings should be made to pay for the proposed changes in practice.

Number of patients randomised in three major trials of statins and the numbers who died or suffered myocardial infarction

	Treatment with statins			Placebo			Absolute risk reduction % (95% CI)	
Trial	Mortality	Myocardial infarction	Total	Mortality	Myocardial infarction	Total	Myocardial infarction	Mortality
Secondary prevention								
4S[5]	182	164	2221	256	270	2223	4.8 (3.0 to 6.5)	3.3 (1.6 to 5.1)
CARE[6]	180	135	2081	196	173	2078	1.8 (0.25 to 3.4)	0.8 (–1.0 to 2.5)
Primary prevention								
WOSCOPS[7]	106	143	3302	135	204	3293	1.9 (0.8 to 3.0)	0.9 (–0.02 to 1.8)

How should health authorities and clinicians respond to the statement? The first issue is to identify the number of patients likely to benefit. The numbers randomised in the major trials and reductions in deaths or myocardial infarctions are described in the table. In the secondary prevention trials, which included mainly patients with previous myocardial infarctions and a few with angina, the cholesterol concentration required for inclusion differs. A total plasma cholesterol value of less than 6.2 mmol/l and low density lipoprotein of 3-4.5 mmol/l was required in the CARE trial[6] and a total serum cholesterol value of 5.5-8.0 mmol/l in the 4S trial (the Scandinavian Simvastatin Survival Study)[5] (average low density lipoprotein at baseline was 4.87 mmol/l). In both trials patients were treated for about five years. The 4S trial included higher risk patients, which probably explains the larger estimated benefit, but was also stopped early on the basis of a data driven criterion and thus may overestimate the effects of treatment. The Sheffield tables are derived from epidemiological data from the Framingham population[2 8] and may not adequately take into account benefits from alternative recently introduced treatments.

The absolute risk reduction in the 4S trial was 3.3% over the five years of treatment (see table). In other words, about 30 patients will require treatment for five years to avoid a death (or 150 for one year). If, in line with the medical advisory committee statement, treatment is broadened to patients in the lower risk band evaluated by the CARE study,[6] 128 patients will require treatment for five years to avoid a death (or 640 for one year). The authors of the revised Sheffield tables argue that targeting treatment at patients at a 3% annual risk of a major coronary event,[8] twice that in the WOSCOPS study,[7] will lead to twice the benefits. This implies that about 55 patients will require treatment for five years to avoid a death (or 275 for one year). Even using "time to event data"[9] in the original trial reports, only the 4S trial achieved narrow confidence intervals in the estimated reduction in overall mortality.[5] The benefits in primary prevention depend on strong assumptions and are somewhat speculative.

Achieving desired change in the NHS is a difficult process that requires planning resources. The Faculty of Public Health Medicine, which also issued advice to directors of public health in August,[10] recommends an approach based on locally developed guidelines that target high risk patients and consider issues of cost effectiveness. However, the faculty does not provide examples of the likely benefits for a range of risks for secondary and primary prevention patients. A first step in planning local implementation may be to ensure that patients meeting the inclusion criteria in the 4S trial are targeted for treatment as the benefits for these patients are substantial.

Neither the faculty advice nor the Standing Medical Advisory Committee statement refer to cost effectiveness, although the statement notes that such studies are being commissioned. If NHS resources are to be used efficiently policies have to be based on information on costs as well as benefits. Failure to do this can lead to the sort of inefficient practices apparently advocated by the Standing Medical Advisory Committee and supported by the Department of Health. There are also competing demands such as ensuring that patients with heart failure get angiotensin converting enzyme inhibitors.[11 12]

Cynics may see in the release of the statement and instruction from the NHS Executive in August an element of "passing the buck." Enthusiasts for cholesterol lowering drugs may adopt the priorities but unless they curtail prescribing in other areas they will soon run into financial difficulties. Given the absence of information on cost effectiveness, they may do more harm than good through making savings in more cost effective areas to pay for statins. Most practitioners will probably be overwhelmed by the size of the proposed changes and do little, which may mean that high risk patients likely to benefit substantially from treatment will remain untreated.

National evidence based guidelines in which recommendations are linked explicitly with evidence on benefits and costs and which provide decision makers with the information they need to determine local priorities are necessary to support strategic change. The four page statement from the Standing Medical Advisory Committee, which describes neither the likely benefits and associated costs nor a realistic range of options, is simply inadequate.

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Genetic diagnosis before implantation

Applications of the technique are growing

Research on the feasibility of preimplantation genetic diagnosis began in the 1980s as a result of pressure from patients. The couples concerned had experienced repeated termination of pregnancy, had moral objections to abortion, or were at risk of transmitting an X linked disorder for which the only available option was termination of all male pregnancies (of which half would be unaffected). These couples wanted to start a pregnancy with reasonable certainty that their child would be free of the familial inherited disorder. The first couples were treated in 1990 at Hammersmith Hospital and 55 couples have now been treated in Britain. This slow rate of application is about to change with the recent granting of two further treatment licences to University College London and Guy's/St Thomas's Hospital. Over the next year this will open up the opportunity for treatment to a far greater number of patients. So what can we offer in the way of genetic testing before implantation?

Early research showed that it was possible at three days after fertilisation to remove one or two cells from an 8-10 celled embryo without detriment to its further development.[1] Embryos were sexed on the basis of the presence or absence of a DNA fragment specific for the Y chromosome; in 1990 two sets of twin girls were born to five couples at risk of passing on an X linked disorder.[2] Alarmed at the rapid progress of embryo research, the British government permitted research only up to 14 days after in vitro fertilisation. Centres performing research (or diagnosis) on preimplantation embryos had to be licensed, and until recently the Hammersmith Hospital was the only licensed centre in Britain.

Sexing the embryo to avoid X linked disease remains the commonest reason for preimplantation diagnosis, now optimally carried out by the molecular cytogenetic technique of FISH (fluorescent in situ hybridisation) with DNA probes derived from the X and Y chromosomes.[3 4] This approach allows chromosome copy number to be determined and avoids the transfer of embryos with a single X chromosome (potential Turner syndrome and at high risk of the X linked disorder). Of the autosomal recessive disorders, cystic fibrosis was the first to be successfully managed by preimplantation diagnosis[5] and remains the most common application worldwide.[6] Success has also been achieved with Tay Sachs disease, Rh D blood typing, and X linked disorders such as Duchenne muscular dystrophy and Lesch Nyhan syndrome. Worldwide, almost 100 babies have been born after preimplantation genetic diagnosis, with no reported increase in congenital anomalies.

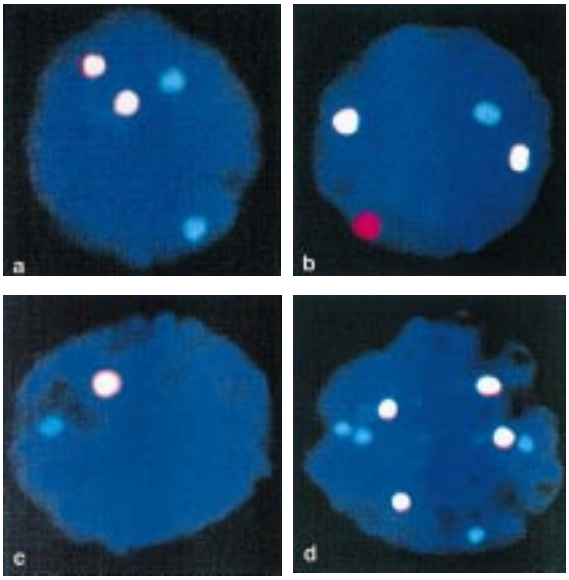

Fig 1 Nuclei of single cells from human cleavage embryos (8 cell stage) to show the copy number of chrmosomes X (blue), Y (red), and 1 (white). (a) normal female, XX;11; (b) normal male, XY;11; (c) haploid, X;1; (d) tetraploid, 4×X; 4×1

Protocols have been developed for the various mutations causing β thalassemia and for sickle cell disease, and both the new centres will offer treatment for these disorders. In principle, providing the molecular basis of a disorder is known, mutation detection is possible at the single cell level which can then be applied to the one or two blastomeres available from the cleavage stage embryos—for example, chronic granulomatous disease (currently under research at University College).

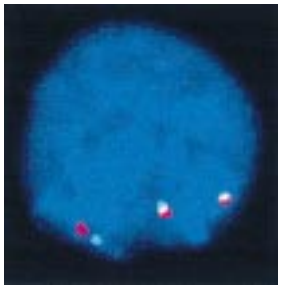

Fig 2 Nucleus from embryo with trisomy 21. Two DNA probes for chromosome 21 have been used, red and blue (white is produced where they overlap)

The growing number of diseases caused

by the expansion of triplet repeats in the DNA within or close to the gene, such as fragile X syndrome and Huntington's disease, are best diagnosed embryologically by making use of closely linked genetic markers. Technical problems involving the necessary amplification of DNA from single cells also make the preimplantation diagnosis of dominant disorders difficult. Nevertheless, diagnosis has been achieved for Marfan's syndrome[7] and recently for the inherited cancer syndrome familial adenomatous polyposis coli.[8] Diagnosis before implantation seems particularly appropriate for the inherited cancer syndromes. Despite the fact that the molecular basis has been understood for several years, families at risk of familial adenomatous polyposis coli have shown little interest in prenatal diagnosis. Couples who are reluctant to terminate an established and otherwise normal pregnancy in the case of a late onset disorder are, however, showing an interest in preimplantation diagnosis as a means of reducing the risk of passing on the disease.

Rather unexpectedly, one of the commonest reasons for requesting preimplantation diagnosis is because one partner is at high risk of transmitting a chromosome anomaly. This is usually due to chromosomal translocation but can be caused by gonadal mosaicism for trisomy 21 for example. Such couples have suffered repeated spontaneous or induced abortions and often also periods of infertility requiring assisted conception.[9] The fact that routine prenatal diagnosis has not been effective in helping these couples achieve a normal pregnancy suggests that particular adverse factors are operating, and research on the untransferred embryos after preimplantation diagnosis is beginning to reveal the nature of these factors.[9]

In fact, it is the application of the FISH technique to spare, untransferred embryos after in vitro fertilisation cycles that has led to the most interesting finding: that 30% of normally developing cleavage stage embryos are chromosomally mosaic.[10 11] This may provide one explanation for the low success rate of in vitro fertilisation, the poor fecundity of humans, and the origin of confined placental mosaicism that plagues chromosomal prenatal diagnosis by chorionic villus sampling.

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Hunger strikes

Understanding the underlying physiology will help doctors provide proper advice

Hunger strikes in different parts of the world are regularly in the news. Doctors with an interest in human rights may be asked to give independent medical advice to an asylum seeker intending to start a hunger strike. Several recent articles have addressed the ethics of treating hunger strikers,[1 2] but there is less information available on the physiological issues. It is essential to understand both these issues to be able to advise the individual appropriately.

There have been several studies of fasting for a few days, but in the past 15 years only three studies have described voluntary total fasting for prolonged periods. The first was of a monk who tried to fast for 40 days for religious reasons but was forced to stop on day 36 because of unacceptable symptoms.[3] The second was of four adults who were planning to fast indefinitely. One became very unwell on day 38, and the others ceased fasting on day 40.[4] The third was a retrospective study of 33 South African political prisoners on hunger strike for up to 28 days.[5]

Hunger strikes have been around since Roman times, and the suffragettes brought the tactic to public awareness in Britain earlier this century. Gandhi fasted at least 14 times but never for more than 21 days. After the second world war Ancel Keys published an extensive review of people subjected to prolonged starvation and a study replicating these conditions in the laboratory.[6] The hunger strikers of the Maze Prison in Belfast in the early 1980s died after 45-61 days, but no results have been published.

For the first few days of starvation the body uses its stores of glycogen in liver and muscle.[7] This is accompanied by glucagon induced naturesis, with substantial weight loss. The next phase lasts up to day 10-14, during which time glycogen stores are exhausted and cer-

tain amino acids take over as the substrate for gluconeogenesis. This is associated with a loss of muscle, including heart muscle. In the final phase protein is protected, so that it forms only about 10% of energy source. Most energy comes from ketones produced by the breakdown of fatty acids. When fat stores are used up there is catastrophic protein catabolism, but generally other complications arise first.

Conclusions from studies recommend independent medical monitoring after a weight loss of 10% in lean healthy individuals.[7] If the pre-hunger strike weight is unknown, a maximum of 10 days' hunger strike, or a body mass index of less than 16.5 kg/m^2, should be the trigger. Major problems arise at a weight loss of about 18%.

The main disabling symptom is feeling faint and dizzy. Hunger strikers learn to stand up very slowly and may become almost bed bound. This may affect their ability to state their case. Bradycardia and drop in blood pressure are well recognised as effects of even relatively short fasting and were seen in all the individuals studied closely.[4 5] Orthostatic hypotension was present by about day 20 in all cases in which it was recorded and in at least one case was almost disabling. Weakness and lightheadedness was common. The cause of this is not clear, but could be partly due to electrolyte imbalance. Although thyroxine concentrations are maintained in fasting, tri-iodothyronine is converted rapidly to an inactive metabolite, thus reducing effective thyroid function. This is an important physiological protective function but will lead to weakness and a sensation of feeling cold. Abdominal pain was described by around three quarters of those studied, even in the early stages.[5]

Dehydration is a risk in voluntary total fasting, as individuals may lose their feelings of thirst and hunger.[1] This is in complete contrast to prolonged severe undernutrition, where people may drink to relieve feelings of hunger.[6] Average fluid intake needs to be maintained at around 1.5 l/day. Ideally water should be supplemented with up to 1.5 g sodium chloride (half a teaspoon of salt) per day. More than this may precipitate hypokalaemia, and monitoring of potassium concentrations may be helpful where possible.

Of the five individuals monitored closely, one developed symptomatic hypokalaemia, which eventually needed intravenous rectification. This individual went on to develop acute Werneke's encephalopathy. The risk is increased by ingested glucose; some hunger strikers eat small amounts of chocolate that are brought in by friends trying to help.

The study of detainees showed 77% of hunger strikers to be clinically depressed at the time of admission to hospital, measured by an independent psychiatrist, although they also demonstrated features similar to those of the post-traumatic stress syndrome.[5] Emotional lability is a later feature of voluntary total fasting.

Once a hunger strike of more than three weeks is over, re-alimentation is potentially dangerous. Werneke's encephalopathy has been recorded in patients taking inappropriate food after fasting. Ingesting carbohydrate after fasting will also cause a reverse of the initial naturesis, causing measurable weight gain and potentially acute oedema. In South Africa, diluted proprietary lactose free balanced feed was used until a light diet was tolerated.[5] Elsewhere, boiled vegetables have been the nutrients taken in the initial period. The patient needs to consume small amounts of food which are high in neither processed sugars nor protein. Hospital monitoring needs to be continued for several days after eating has restarted.

Cardiac problems are potential hazards of refeeding. Hypokalaemia is a risk, and a sudden increase in fluid volume can precipitate cardiac failure as the physiological load is increased. The bradycardia and hypotension of starvation resolve and often overshoot.[6] The exact cause is unclear. These fatalities may be related to loss of cardiac muscle in parallel to skeletal muscle loss. The deaths were also associated with prolonged QT intervals on electrocardiographic monitoring. Laboratory studies showed that the QT interval was one of the variables that took the longest to recover on refeeding.[6]

Hunger strikers are not aware of the complex physiological processes that they are disrupting or the risks on restarting eating. Doctors working with hunger strikers must be aware of the processes and potential problems so that they can advise them fully.

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Correction

Young adults with arthritic hips

An editorial error occurred in this editorial by M D Northmore-Ball (2 August, p 266). At the end of the fourth paragraph the statement, "a recent case series has shown maintenance of symptomatic improvements, with no development of osteoarthritis in about 80% of patients treated by acetabular redirection at an average age of 10 years" should have read "at an average follow up of 10 years."