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Annotations

Early growth and cardiovascular disease

Ten years ago studies in Britain showed for the first time that people who had low birth weight were at increased risk of coronary heart disease and the disorders related to it: stroke, non-insulin dependent diabetes, raised blood pressure, and the metabolic syndrome.[1–3] In a study of 16 000 men and women born in Hertfordshire death rates from coronary heart disease fell twofold between those at the lower and upper ends of the birth weight distribution. In groups investigated clinically the prevalence of non-insulin dependent diabetes and impaired glucose tolerance fell threefold. Such findings led to the "fetal origins hypothesis", which states that cardiovascular disease and non-insulin dependent diabetes originate through adaptations that the fetus makes when it is undernourished.[4] These adaptations, which include slowing of growth, permanently change the structure and function of the body.

Recently, associations between low birth weight and later disease have been widely replicated in studies in Europe and the USA.[5–7] These studies have also confirmed that the associations are not the result of confounding variables, such as low socioeconomic status and smoking, which act in postnatal life. Influences that act in postnatal life do, however, add to the effects of low birth weight. For example, the highest prevalence of non-insulin dependent diabetes is found in people who had low birth weight but were obese as adults.[2] Replication of the associations between low birth weight and later disease in large studies such as the American nurses' study has been possible because most adults are able to discover their birth weights from parents or other relatives.[6] However, while birth weight serves as a marker of fetal growth it is a crude one. The same birth weight may be the outcome of many different paths of growth.[8] Furthermore, findings among people who were in utero during the Dutch famine show that the fetus' metabolism may be permanently changed by levels of undernutrition that do not affect fetal growth.[9] This finding has important public health implications as it suggests that associations with body size at birth underestimate the contribution of intrauterine development to later disease.

Body proportions at birth and adult disease

Further insight into fetal responses to undernutrition and their long term consequences has come from studies where detailed measurements of size at birth, including length, head circumference, and placental weight, were available. Four birth phenotypes associated with later disease have been identified.[10]

THIN

Babies that are thin tend to be insulin resistant as children and adults, and are therefore liable to develop the insulin resistance syndrome.[11] One interpretation of this is that the thin baby has adapted to undernutrition through endocrine and metabolic changes.

SHORT

Babies that are short in relation to their head circumference, and have a reduced abdominal circumference, tend to have persisting abnormalities of liver function, including raised serum LDL cholesterol and plasma fibrinogen concentrations.[12 13] Replication of these observations has, however, been limited because few datasets include abdominal circumference at birth. Babies that have a small abdominal circumference in relation to their head circumference can result from "brain sparing" circulatory adaptations by which cardiac output is diverted to the brain at the expense of the trunk.[14]

SHORT AND FAT

Studies in southern India have shown that babies who are short and fat tend to become insulin deficient and have high rates of non-insulin dependent diabetes.[15] This is consistent with findings in Pima Indians and with observations in Sheffield that showed a U-shaped association between abdominal circumference at birth and death from coronary heart disease.[16 17] Babies that are short and fat are thought to be the result of maternal hyperglycaemia, with consequent imbalance in the supply of glucose and other nutrients to the fetus.

LARGE PLACENTA

Studies in Preston showed that babies whose placentas are disproportionately large in relation to their own weight tend to have raised blood pressure.[18] While this has been replicated in other studies it has not been found consistently; in a study in Aberdeen, raised blood pressure was associated with small placental size.[19] Animal studies offer a possible explanation. In sheep the placenta enlarges in response to moderate undernutrition in mid-pregnancy. This is thought to be an adaptive response to extract more nutrients from the mother. It is not, however, a consistent

response but occurs only in ewes that were well nourished before pregnancy.

The malnourished fetus

The weight of evidence from studies of the birth weights of relatives has led geneticists to conclude that, although the growth of a fetus is influenced by its genes, it is usually limited by the nutrient and oxygen supply it receives.[10 20] Constraint of fetal growth by the mother has been shown in embryo transfer and cross breeding experiments; a fetus transferred to a larger uterus will achieve a larger birth size. A study of babies born after ovum donation showed that while their birth weights were strongly related to the weight of the recipient mother, they were unrelated to the weight of the woman who donated the egg.[21] It has been suggested that the associations with low birth weight reflect genes that determine both reduced fetal growth and later disease. The known plasticity of fetal growth and its control by the mother makes this speculation improbable. Rather there is a clear need to study interactions between genes and nutrient supply in utero. This focus on the nutrient supply to the fetus is supported by numerous animal experiments showing that poor nutrition may permanently affect the structure and physiology of the fetus in ways that can be related to disease in humans, including life long elevations of blood pressure and altered glucose–insulin metabolism in the offspring.[22]

Mother's body composition and diet

The availability of nutrients to the fetus is determined by the mother's body composition at conception and her diet in pregnancy. In early studies in Britain there were few data on mothers. Cohorts that include this information as well as having detailed measurements of body size at birth have now been identified in Europe as well as in the developing world, and include mothers who are chronically malnourished. Preliminary findings suggest that many babies today may be malnourished and at increased risk of coronary heart disease and non-insulin dependent diabetes either because their mothers are too thin, or too fat, or eat unbalanced diets. The offspring of women who are thin, as measured by skinfold thickness, tend to have raised blood pressure,[23] while the offspring of mothers with a high body mass index have increased rates of coronary heart disease and non-insulin dependent diabetes.[15 24] Imbalance in the mother's protein and carbohydrate intake is associated with raised blood pressure in the offspring.[19]

Childhood growth

Studies in Helsinki have shown that the path of growth through childhood modifies the risk of disease associated with size at birth.[25] The highest death rates from coronary heart disease occurred in men who were thin at birth but had accelerated weight gain in childhood. We do not yet know whether this association is because of the pathological effects of a high fat mass persisting into adult life, deleterious effects of catch up growth, or the intrauterine resetting of endocrine axes that control growth. It suggests that while the primary prevention of coronary heart disease and non-insulin dependent diabetes may ultimately depend on changing the body composition and diets of young women, more immediate benefit may come from preventing imbalances between prenatal and postnatal growth among children.

Primary prevention

To reduce chronic disease we need to understand how the human fetus is nourished and how malnutrition changes its physiology and metabolism. Fetal development is governed by complex, non-linear systems. Components of these systems interact, and the systems will have generic properties that do not depend on the details of their components.[26] We cannot solve our problems by reductionist science alone, but need to combine this with further clinical and epidemiological research.

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Evidence for using nebulised antibiotics in cystic fibrosis

Standards of care for patients with cystic fibrosis (CF) have been defined largely on the basis of "best practice", an accolade awarded to treatment regimens showing low chronic pulmonary infection rates, greatest patient longevity, and least patient morbidity. While acknowledging the wisdom accrued through clinical experience, paediatricians caring for children with CF are fighting for limited resources and must convince purchasers, who stroll the fashionable catwalk of evidence based medicine, of the scientific basis of our demands. They ask, "Where's the beef?" For the use of nebulised antibiotics in CF care we can reply only that we have a lot of "topside" but few "prime cuts".

Clinical trials, the results of which affect all of our prescription practices, have been generally parochial in conception, bedevilled by small patient numbers, and underpowered, partly reflecting patient recruitment problems for research into an illness that affects only a small minority of the population and, until recently, a lack of multicentre trials. In his meta-analysis of the benefits and risks of nebulised antibiotic treatment in CF, Mukhopadhyay *et al* suggested that a definitive study would need 500 patients, the minimum that would allow for imbalances in patient characteristics that are not amenable to adjustments in the analysis.[1] In Ramsey's study of TOBI, a preservative free preparation designed for nebulisation, over 80% of almost 500 patients completed the trial,[2] but the most comprehensive published multicentre study at the time of writing has only 71 patients.[3] The antibiotics studied (gentamicin, tobramycin, colistin, ceftazidime), the antibiotic dose (20 mg to 600 mg of aminoglycoside), the type of nebuliser used, and the length of treatment have varied, making comparison between trials difficult.

Rationale for nebulised antibiotics

CF is a multisystem disease but morbidity and mortality closely correlate with progressive pulmonary damage, most often caused by chronic *Pseudomonas aeruginosa* endobronchial infection. Persisting infection promotes chronic airway inflammation and progressive lung destruction. While intravenous antipseudomonal aminoglycoside antibiotics are fundamental to the treatment of this infection, decreasing the pulmonary bacterial load and improving lung function,[4] they do not penetrate well into sputum, peak levels approximating to 12% of the serum concentration.[5] Aminoglycoside activity is further compromised by biological antagonism in sputum. Half of a gentamicin dose added to CF sputum may be bound by extracellular neutrophil DNA and the altered ionic environment interferes with drug accumulation by the bacteria, significantly decreasing its bactericidal activity.[6] In vitro, an aminoglycoside bactericidal effect can only be reliably produced with concentrations 25 times the minimum inhibitory concentration (MIC).[5] To achieve such high drug concentrations in sputum in vivo by intravenous antibiotic delivery would increase unacceptably the potential for nephrotoxicity and ototoxicity. Aerosol delivery could provide a high concentration at the desired site with minimal absorption and therefore low risk of toxicity.[7 8]

The widespread use of nebulised antibiotics in the management of patients with CF has evolved from three landmark publications; Hodson *et al* in 1981, Littlewood *et al* in 1985, and Valerius *et al* in 1991.[9–11] These studies showed that twice daily inhalations improved respiratory function and decreased hospital admissions,[9] decreased the frequency of positive *P aeruginosa* cultures in recently colonised patients,[10] and increased the chances of eradicating this organism when used to treat early infection in combination with oral ciprofloxacin.[11]

Aerosol delivery of antipseudomonal antibiotics has been widely used in Europe for over a decade, and is becoming increasingly popular in the USA where significant results have been obtained in trials of preservative free tobramycin (TOBI). It is a good time to look at the available evidence for its efficacy in maintaining respiratory function, treating acute exacerbations, and eradicating early *P aeruginosa* colonisation.

Treatment of patients with chronic *P aeruginosa* infection

In 1981 Hodson *et al* compared nebulised gentamicin 80 mg and carbenicillin 1 g (both bid) with placebo in a double blind crossover trial in 20 adult patients over a one year period.[9] During active treatment patients showed improved respiratory function, felt better, and were hospitalised less frequently. Subsequent studies emphasised these positive findings: enhanced lung function tests,[3 12–14] slower decline in respiratory function,[13 15–18] decreased hospital admission rates,[3 12 15 18] improved clinical score,[17 18] better weight profile,[12 14 15 18] and decreased *P aeruginosa* density,[3 14] exotoxin A or elastase.[18] Patient numbers in these studies were small (nine to 41) and treatment length varied from three to over 32 months. Antibiotics used were ceftazidime, gentamicin and carbenicillin, colistin and tobramycin. Study designs were crossover, placebo controlled, and open label.

Only Ramsey *et al*'s paper[3] can stand alone as evidence based research. Otherwise we need to turn to Mukhopadhyay *et al*'s meta-analysis to distil the evidence that confirms the benefit of nebulised antibiotics in CF care.[1] Nine of 14 clinical trials were rejected because they lacked appropriate randomisation or failed to describe adequately outcome measures. These were defined in the meta-analysis as the number of acute pulmonary exacerbations, alterations in lung function, the number of patients with an altered pseudomonas respiratory load, alterations in the number of patients with resistant *P aeruginosa*, and the incidence of auditory, renal or respiratory side effects. The analysis of the five qualifying papers concluded that nebulised antibiotics significantly reduced respiratory *P aeruginosa* load and the frequency of respiratory exacerbations requiring systemic antibiotic treatment, and significantly increased lung function. The only adverse finding was a possible increase in in vitro bacterial resistance.

Ramsey *et al*'s studies of aerosolised tobramycin allow us to make evidence based decisions about clinical and bacteriological efficacy.[2 3] In a multicentre, double blind, placebo controlled trial, 71 patients received half strength physiological saline or 600 mg TOBI in 30 ml half strength saline delivered by ultrasonic nebuliser.[3] The drug dose was chosen to attain a sputum concentration of at least 400 μg/g—that is, 10-fold the MIC of tobramycin susceptible *P aeruginosa.* This sputum concentration is necessary to prevent bacterial growth.[5] Group 1 received tobramycin for 28 days and placebo for 56 days, and group 2 received tobramycin for 56 days followed by placebo for 28 days. Quinine was added to placebo and drug to mask differences in taste. Nephrotoxicity was monitored by serum creatinine concentrations and urine analysis, ototoxicity by auditory acuity and vestibular function tests, and adherence by urine quinine concentrations. Sixty six patients completed the trial.