The child is father of the man

Paediatricians should be more interested in adult disease

Lawrence T Weaver

Lawrence T Weaver
MD FRCP FRCPCH,
Samson Gemmell Professor of Child Health, University of Glasgow

Clin Med JRCPL 2001;**1**:38–43

ABSTRACT – We expect that most pregnancies will bear normal babies, which will grow up into healthy young adults free of the risk of serious disease. We also believe that many common diseases and causes of death in adulthood may be preventable through changes in living conditions, diet and lifestyle.

The 20th century saw a massive decline in childhood mortality and morbidity as well as improvements in child health. The relations between environmental influences and genetic endowment in the genesis of disease are ever clearer, and at their 'extremes' susceptible to interventions. The burden of infectious disease has been reduced to 5% of what it was a century ago, and many chromosomal and monogenic diseases can be avoided or their effects ameliorated before or soon after birth.

Nevertheless, there is strong evidence that poor environmental conditions are the principal determinants of ill health at all stages of life, and it follows that the optimal time to intervene to correct them is in early life. Moreover, we recognise the principal risk factors for chronic adult disease, and also have the tools to measure genetic susceptibility to them. There is, therefore, hope that as their natural history becomes better defined, they will be increasingly preventable or treatable.

The challenge to paediatricians now is to ensure that children are not only born healthy and remain healthy, but also grow up to be healthy adults. When it is increasingly clear that the origins of many adult diseases are in childhood or before, paediatricians should strive to work closely with their colleagues in primary care, public health, clinical genetics, education, government, housing, environmental and social services, toward the common goal of promoting optimum health throughout the fullness and completeness of life.

One of the forces that led to the foundation of the Royal College of Paediatrics and Child Health (RCPCH) was the belief that children are different from adults, and that the care of the sick child is based upon principles other than 'scaled down' adult medicine alone. Yet children are destined to become adults, and their health in adulthood has its roots in childhood. While paediatricians are organising themselves into a distinct professional group to promote and defend the interests of children, the links between child and adult health are becoming more apparent, and ways in which the early origins of adult disease can be investigated and modified are within closer reach.

Advances in child health

Paediatricians (literally 'child healers') see themselves as doctors who care for sick children. However, they owe their position largely to advances in public health. Until the 20th century, childhood mortality was dominated by acute, usually infectious, disease. At least one in four children died before the age of four, and those that survived often died prematurely from chronic bone, heart, lung or kidney disease. From around 1750 rising standards of living led to better housing and diet; then from 1850 advances in public health greatly improved sanitation, hygiene and housing; and during the last half century nutrition and immunisation programmes have added to the steady decline in the incidence of infectious disease[1,2]. Antimicrobials have made a relatively small and late contribution. The revolution in bacteriology and public health that began at the end of the 19th century had a great impact on children because they were so vulnerable.

The decline in childhood infectious disease has been followed by a rise in the early detection of congenital abnormalities and inherited diseases. Between 2% and 5% of all liveborn infants have genetic disorders or birth defects, and it is estimated that their prevalence is around 50 per 1000 of the population[3]. Antenatal and postnatal screening can identify many structural abnormalities *in utero* and after birth, and also an increasing number of chromosomal disorders, biochemical defects and inborn errors of metabolism, which include both single gene disorders and some polygenic diseases.

The effects of these achievements mean that the great majority of children can now expect to be born

free of congenital abnormalities or have them detected in early life, and to grow up free of the risk of serious infectious disease. Infections cause less than 5% of the disease they caused in 1900[1]. Childhood mortality rates have now fallen to less than 10 per 1000 live births and average life expectancy has increased by over 50%, from around 50 to 75 years. Survival curves have thereby assumed an increasingly rectangular shape, with a flattening of the rate of decline hitherto characteristic of early life[4]. 'Rectangularisation' of the survival curve (Fig 1) suggests that the limits of the reduction of premature mortality may be near, but hides the fact that for many adults considerable morbidity precedes mortality, and that current comparable morbidity curves are akin to the mortality curves typical of earlier periods of this century. Much adult disease is the end stage of lifelong processes which have their origin in early life.

Origins of adult disease

Disease is a maladaptation to the environment, and the extent to which the baby, child, adolescent or adult succeeds in achieving and maintaining health is a function of his or her genetic endowment and environment. There are clearly environmental factors in early life that can have lifelong adverse effects – exposure to rubella in the womb, iodine deficiency in infancy, polio in childhood all disrupt normal development and cause permanent damage. These diseases are primarily 'environmental'. At the other extreme are 'monogenic diseases', such as thalassaemia or cystic fibrosis (CF), due to a single gene defect, which can be detected and are manifest in early life. For many of these Mendelian disorders we now know the site of the genetic defect, the abnormal gene product, the pathophysiological consequence, and the clinical features of the disease.

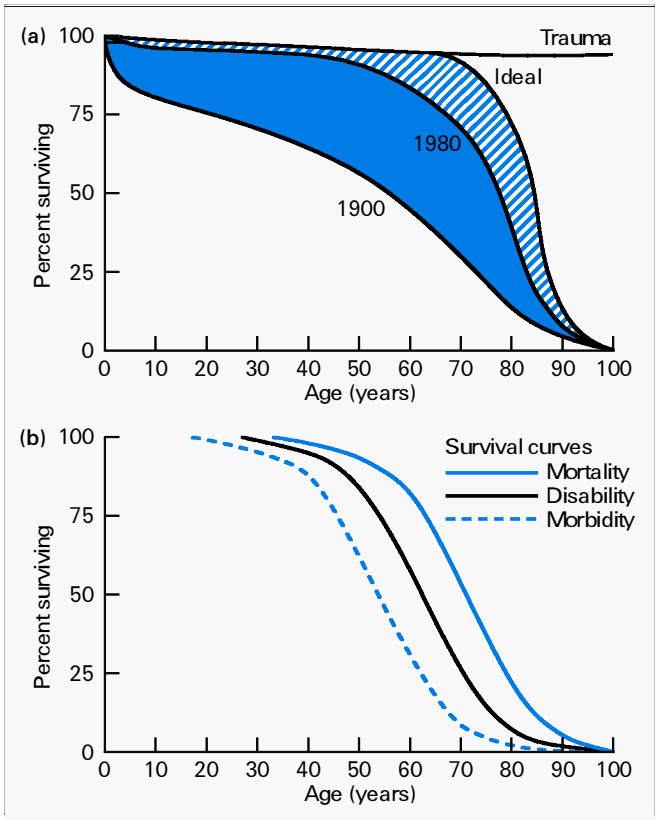


Fig 1. Rectangularisation of survival curves. (a) About 80% (tinted area) of the difference between the 1900 curve and the ideal curve (tinted plus hatched area) was eliminated by 1980. Trauma is now the principal cause of death in early postnatal life. (After Fries[4].) (b) Survival curves of mortality, disability and morbidity. (After Ebrahim[24].)

Key Points

Diseases are due to the interaction of genetic and environmental factors

Most acute childhood diseases are avoidable, controllable or treatable

Many adult diseases have their genesis in early life, and are due largely to sustained adverse environmental influences

Some monogenic diseases that are expressed in later life depend on an environmental factor: phenylketonuria (PKU) and galactosaemia are examples, both becoming manifest when feeding begins after birth as a result of a specific nutrient (protein containing phenylalanine, or milk containing galactose) in the diet. Control of diet means that many affected children enjoy normal growth and development to adulthood. Other monogenic diseases, such as certain hypercholesterolaemias and cancers, are not expressed until later life, by which time their harmful effects may be well advanced.

However, much chronic ill health is multifactorial, arising from disorders of more than one gene. It involves co-inheritance of several genetic determinants that usually have to interact with environmental factors before disease is manifest. These polygenic diseases are hard to detect in early life and treatment aims to control their expression and progression. They are thought to be responsible for up to 80% of all adult deaths, and as high a percentage of total disability. Arterial disease leading to stroke and coronary artery occlusion, arthritis, diabetes, chronic obstructive airways disease and cancers are the principal causes of chronic adult ill health and all develop insidiously, beginning in early life, and cross the symptom threshold in adulthood.

Environmental factors: childhood, poverty and adult disease

Many of the 'environmental' risk factors for these adult diseases are well recognised – smoking, obesity, hypertension, high-fat low-fibre diet, lack of exercise etc – and public health programmes, based on a 'lifestyle' model of the aetiology of disease, target them. The strong social class relation between these risk factors and chronic diseases has drawn attention to the connection between poverty and ill health. There is a four-year difference in the life expectancy of the citizens of Glasgow and Edinburgh, for instance. The mortality rates of both men and women of all ages from stroke, heart disease and cancers in these

two Scottish cities, which differ markedly in their levels of socioeconomic deprivation, have been apparent from late childhood in successive generations throughout the 20th century[5]. Many adult diseases are, therefore, often the end stage of a lifelong process of social, economic and environmental disadvantage whose origins and effects can be observed first in childhood.

There has long been an intuitive sense that sound child health is the foundation of sound adult health. Recruitment to the armed forces during the Boer and First World Wars revealed alarming levels of poor health and nutrition in young men, and in the first half of the 20th century the dominant public health view, based on demographic changes in age-related death rates and actuarial analyses, was that factors acting in childhood determined the risk of mortality in adulthood[6]. This view declined after the Second World War, in part due to a rise in the prevalence of smoking-related heart and lung diseases in middle-aged men, which focused preventative programmes on adult lifestyle. However, we are now seeing a re-emergence of theories relating early life events with the risk of adult disease[3].

The relative risk of death from stroke and gastric cancer is strongly related to poor socioeconomic conditions in childhood, and mortality from coronary heart disease and respiratory diseases is dependent on poor social circumstances in both childhood and adulthood, while death from accidents, violence and lung cancers is mainly related to factors in adulthood[7].

Children are particularly vulnerable to poverty and the number living in very poor socioeconomic circumstances has grown in Britain from around 10% in the late 1970s to more than 30% (over 4 million) now. Two in every five children are born into poverty which, measured by social class, is associated with increased perinatal, infant and child mortality, low birthweight and high hospital admission rates in the first year of life. Parental smoking, drinking and substance abuse are all more common in the poor and socially disadvantaged. Poverty is associated with less uptake of immunisation, low uptake of health surveillance and antenatal and postnatal screening, higher incidence of childhood accidents, greater frequency of infectious disease and teenage pregnancies[8]. Poverty is also associated with poor maternal diet before and during pregnancy, low breastfeeding rates, inappropriate weaning foods, poor dental health and inadequate diet during the pre-school period[9]. Dietary surveys of pre-school children, adolescents and adults in Scotland show that poor diet is established at an early age, and unhealthy childhood eating patterns not only persist into adulthood, but are also imprinted onto succeeding generations[10].

Early life is clearly a critical period for adult health, but the major chronic diseases of adulthood may be a consequence of more than simply the effects of 'poor' genes or an adverse environment. The expression of some adult diseases appears to be 'programmed' during the 'critical period' of early life. There is evidence, mostly from retrospective epidemiological studies, of a prenatal or perinatal contribution to the aetiology of cardiovascular disease, hypertension, type 2 diabetes, certain hyperlipidaemias and coagulopathies[11]. There are at least three hypotheses that can explain the connection between early life 'experience' and adult ill health (Table 1).

Table 1. Hypotheses that can explain the connection between early life 'experience' and adult ill health.

- Clustering of populations with genetically determined risk factors associated with adult disease in poor socioeconomic groups.
- Continuing, sustained adverse effects of poverty operating throughout life (in both childhood and adulthood).
- Exposure to events in early life that increase the risk of adult disease (programming).

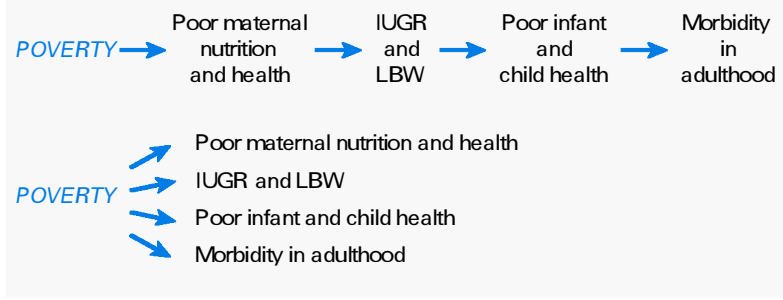
Associations between poor growth and nutrition in early life and adult disease suggest that perinatal malnutrition may permanently affect metabolism in some way. Low birthweight may be both a marker and determinant of later ill health (Fig 2). Somatic growth, neurodevelopment, bone density, cardiovascular function, energy metabolism, blood pressure and body composition may all be in part determined by 'experience' in early life[12,13]. But the magnitude of this 'programming effect' is unclear: there are difficulties in knowing to what degree environmental factors in adult life are also responsible, and in identifying mechanisms to account for it[14,15].

Genetic basis of adult disease: promise of 'new genetics'

Diseases are largely defined by their clinical expression, using terms that describe symptoms, signs or pathophysiology (eg diabetes mellitus, cirrhosis, hypertension). Molecular genetics increasingly allows us to define them by their mechanisms and to move from a phenotypic to a genotypic classification of disease. This change in focus, from the manifestations of disease to the mechanisms involved in their pathogenesis, is transforming our understanding of the natural history of disease (in particular gene–environment interactions) and could generate more rational treatments aimed at the fundamental defect[16].

Hitherto molecular genetics has been used to identify single

Fig 2. Suggested alternative relations between poverty, low birthweight, maternal, childhood and adult ill health. IUGR, intrauterine growth retardation; LBW, low birthweight.



gene disorders, but its focus is now shifting to multifactorial, polygenic common diseases (Fig 3), and the genes and DNA variants associated with them. Some chronic adult diseases, such as diabetes mellitus, hypertension and vascular disease, can be divided into genetically defined subgroups (patients with variants in insulin receptors, ACE genes and LDL receptors, for instance), and genetic linkage analysis is leading us to the site of new genes for common diseases. Genetic markers are allelic variants at a particular locus that have strong disease associations, and in the future many of these are likely to be defined. As the technology becomes more rapid, reliable and cheap, DNA analysis could play a growing part not just in diagnosis, but also in determining disease progression, prognosis, and choice of treatment, as well as complications and response to treatment[17].

There remains a gap between our understanding of the molecular mechanisms of disease and its expression. Even the first step between gene and gene product is far from clear and predictable, and the rise of 'translational research', 'structural biology' and 'integrative physiology' is driven by our need to make clinical sense of the human genome[18].

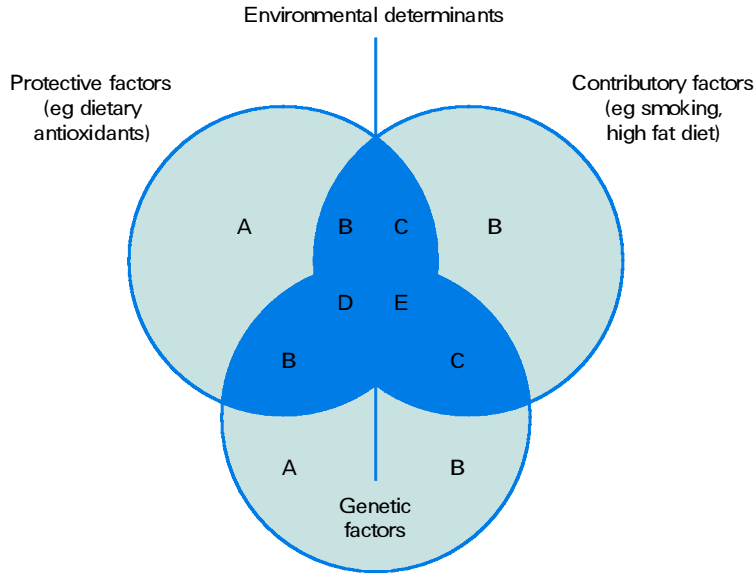


Fig 3. Interactions of environmental factors and gene expression contributing to multifactorial polygenic diseases. The circles represent different genetic factors, with overlapping areas corresponding to increased genetic susceptibility due to multiple gene effects. The background represents the environmental contribution, which may be protective or deleterious. The letters relate to the risk of disease: A, low risk unless monogenic disease; B, medium risk; C, moderate to high risk; D, high genetic susceptibility; E, disease phenotype. (After Galton and Ferns[25].)

Mother and child in the third millennium: what should we do?

With the massive decline in infant and child mortality during the 20th century and control of many infectious diseases that killed adults or led to premature death, the practice of paediatrics has changed fundamentally. Paediatricians should turn their attention to ensuring that the children they look after not only grow up to be adults, but also enjoy an adult life free of chronic disease.

Strategies for the management of chronic adult diseases used to concentrate on the prevention or avoidance of factors that lead to them, aimed at changing diet and lifestyle in adult life rather than before, postponement of their rate of progression, or treatments that increase the threshold of symptom expression. However, we now have the conceptual framework and, to some degree, a practical understanding of the connections between genotype and phenotype in the genesis of many diseases to tackle them much earlier in their development. So what should we do?

Act upon the evidence that environmental factors are the principal determinants of both childhood and adult disease

Whatever the connection between early life 'experience' and adult ill health, the evidence is sufficient to justify concentration of resources and implementation of interventions during fetal life and early childhood. Getting rid of child poverty requires no scientific justification, and is likely to have a positive effect on child health. The evidence for the adverse effects of poverty on child health is overwhelming, and many evidence-based interventions designed to reduce inequalities in health are aimed at mothers and children. Provision of social, financial and psychological support during pregnancy and childbirth, smoking cessation programmes for pregnant women, folic acid supplementation before and around the time of conception, neonatal biochemical screening, personal support for breast-feeding, free school milk and meals, fluoridation of water supplies, interventions to reduce accidents in children of deprived communities, provision of sex education and services to reduce teenage pregnancies, improving oral hygiene, reducing sugar and saturated fat intake, and promoting healthy eating have a positive effect on the health of children[8].

Acheson, referring to many of the studies cited before[19], recommended that a 'high priority is given to policies aimed at improving health and reducing inequalities in women of childbearing age, expectant mothers and young children'. He also suggested that policies that reduce early adverse influences are likely to have multiple benefits throughout the life of children and even into the next generation.

Seek to be involved in studies aimed at testing the value of genetic markers of adult disease

Prevention can target adverse environmental factors, but to know where best to concentrate it we need to learn much more about the relation between genetic susceptibility and the natural history of the corresponding disease phenotypes. Screening in

early life (both ante- and postnatally) for several 'childhood' diseases is well established and effective, but should be undertaken only if effective treatment of the disease is available[20].

In some monogenic and polygenic diseases where no effective treatment is available (such as neural tube defects), antenatal detection can be followed by termination of pregnancy, but in diseases that have later expression it is essential to be sure of the reliability of genetic markers to predict later outcome. However, for both PKU and CF the relations between genotype and phenotype are far from simple. As a 'classic' monogenic autosomal recessive disease in which a single mutation (genotype) seemed sufficient to explain the impaired function of phenylalanine hydroxylase, the clinical expression (phenotype) of PKU is very variable[21].

In CF, where at present supportive means is the best we have to offer, the debate about the pros and cons of screening remains unresolved. More than 850 'abnormal' genes can cause CF, and even children with the commonest (homozygous for Δ*F508*) can range in the severity of their disease from severe pancreatic insufficiency to near normal pancreatic function, and it is unproven whether early detection improves long-term outcome[22]. Clearly there are genes other than those recognised at the primary loci that are responsible for the clinical manifestations and natural histories of these 'monogenic' diseases[23].

For multifactorial adult diseases there is, therefore, a need to develop ways of properly measuring the effects of early detection and intervention in early life on later outcome. This will become increasingly pressing as population studies identify genetic markers that predict high risk of particular diseases to individuals and families. Paediatricians must be aware of the implications of these findings to their practice, and take part in studies aimed at linking genomic research with pathophysiology and clinical epidemiology. Moreover, the training of paediatricians must not be isolated from that of other major medical specialties, and in particular should interface with clinical genetics, public health and primary care.

Recognise the relative and complementary importance of primary, secondary and tertiary health care

Polarisation of theories of the origins of ill health between environmental and genetic extremes is reflected in the spectrum of approaches to the treatment of disease, from primary through secondary to tertiary care. Primary care focuses upon children at home, outside hospital, and embraces community paediatrics as well as general practice. Much of the thinking that informs the planning and delivery of primary care is based on a social model of health and disease. Secondary care covers the treatment of patients in hospital, and a medical model of disease is the dominant framework in which it is practised. Tertiary care, located mostly in major medical centres, encompasses specialist services, intensive care and biotechnology, and a scientific model is shared by its practitioners. It is the job of the NHS to co-ordinate all three levels of care, and the holy grail of paediatricians is to integrate them into a single service for children.

With rectangularisation of the survival curve, and increasingly the morbidity curve[24] (Fig 1), paediatric medical centres have become the place for the care of a small number of children with life-threatening injury or disease, infants born prematurely, planned surgery and the management of chronic diseases that require continuous or regular multidiciplinary care. Paediatricians must recognise the relative and complementary contributions of primary, secondary and tertiary medical care, and work towards a seamless, integrated health service for children that recognises the childhood origins of many adult diseases.

Conclusions

The care of children with acute and chronic disease remains a fundamental job of paediatricians. But they must also take responsibility for the long-term health of all children, by recognising how susceptible and vulnerable they are to malign environmental influences (eg poor diet, parents and parenting, child abuse, smoking, alcohol, accidents, drugs etc). Paediatricians, in partnership with those who care for adults, need to test properly ways in which the effects of interventions in early life can be measured. It must be at least as worthwhile to do this as to mount large and expensive studies aimed at testing the efficacy of cholesterol-reducing agents or anti-hypertensive drugs in adults.

It is the responsibility of paediatricians, therefore, to look beyond the immediate needs of children and to work with adult physicians, epidemiologists, general practitioners, clinical scientists, policy makers, politicians and public health doctors to identify the mechanisms, to establish a proper framework for further exploration of the relations between childhood events and the development of adult diseases, and interventions to prevent them. Good medicine cares for the whole person; good paediatrics must care for the whole life.

Acknowledgements

I thank Allan Colver, Forrester Cockburn, David Stone, Morgan Jamieson, John Evans, Mike Connor, Edna Robertson, Graham Watt and Al Aynsley-Green for their helpful comments.

References

1 McKeown T. *The role of medicine: dream, mirage or nemesis?* Princeton: Princeton University Press, 1988.
2 Szreter S. The importance of social intervention in Britain's mortality decline c. 1850–1914: a reinterpretation of the role of public health. *Soc Hist Med* 1988;**1**:1–37.
3 Yates JRW. Medical genetics. *Br Med J* 1996;**312**:1021–4.
4 Fries JF. Aging, natural death, and the compression of morbidity. *N Engl J Med* 1980;**303**:130–5.
5 Watt G, Ecob R. Mortality in Glasgow and Edinburgh: a paradigm of inequality in health. *J Epidemiol Community Health* 1992;**46**:498–505.
6 Kermack WO, McKendrick AG, McKinley PL. Death rates in Great Britain and Sweden: some general regularities and their significance. *Lancet* 1934;**226**:698–703.
7 Davey Smith G, Hart C, Blane D, Hole D. Adverse socioeconomic

conditions in childhood and cause of adult mortality: prospective observational study. *Br Med J* 1998;**316**:1631–5.
8 Reading R. Poverty and health of children and adolescents. *Arch Dis Child* 1997;**76**:463–7.
9 BMA. *Growing up in Britain.* London: BMJ Books, 1999.
10 Scottish Office. *The Scottish diet.* Edinburgh: HMSO, 1994.
11 Barker DJP. *Mothers, babies and disease in later life*. London: BMJ Publishing Group, 1994.
12 Marmot M, Wadsworth MEJ (eds). *Fetal and early childhood environment: long-term health implications. Br Med Bull* 1997;53.
13 Boulton J, Laron Z, Rey J. *Long-term consequences of early feeding*. New York: Raven, 1996.
14 Joseph KS, Kramer MS. Review of the evidence on fetal and early childhood antecedents of adult chronic disease. *Epidemiol Rev* 1996;**18**: 158–74.
15 Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am J Clin Nutr* 1999;**69**:179–97.
16 Cox TM. Molecular biology and the future of medicine. In: Cox TM, Sinclair J (eds). *Molecular biology in medicine*. Oxford: Blackwell Science, 1998:311–21.
17 Bell J. The new genetics in clinical practice. *Br Med J* 1998;**316**:618–20.
18 Wetherall D. The relative roles of nature and nurture in common diseases. In: Cartledge B (ed). *Health and the environment*. Oxford: Oxford University Press, 1994:172–98.
19 Acheson D. *Inequalities in health*. Department of Health. The Stationery Office: London, 1999.
20 Wilson JMC, Junger G. *Principles and practice of screening for disease*. Geneva: WHO, 1968.
21 Scriver CR, Waters PJ. Monogenic traits are not simple: lessons from phenylketonuria. *Trend Genet* 1999;**15**:267–72.
22 Farrell PM, Kosorok MR, Laxova A, Shen G, *et al*. Nutritional benefits of neonatal screening for cystic fibrosis. *N Engl J Med* 1997;**337**:963–9.
23 Hull J, Thomson AH. Contribution of genetic factors other than CFCP to disease severity in cystic fibrosis. *Thorax* 1998;**53**:1018–61.
24 Ebrahim S. The public health implications of ageing. *J R Coll Physicians Lond* 1995;**29**:207–15.
25 Galton DJ, Ferns GAA. Genetic markers to predict polygenic disease: a new problem for social genetics. *Q J Med* 1999;**92**:223–32.

Address for correspondence: Professor L T Weaver, Department of Child Health, University of Glasgow, Yorkhill Hospitals, Glasgow G3 8SJ.
E-mail: lweaver@clinmed.gla.ac.uk