Reviews in Medicine

Paediatrics – Part I

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Recent advances in neonatology

The single most important potentially correctable determinant of morbidity and mortality in babies is the inability to maintain spontaneous and adequate ventilation of the lungs. The more premature the baby the greater is the chance that some form of respiratory insufficiency will develop and respiratory support will be needed. In many babies this is due to an immaturity of the complex biochemical pathways by which pulmonary surfactant is produced and recycled. Until recently the only option available to the clinician caring for such a baby was to ventilate the baby's lungs mechanically and increase the ventilation pressures and inspired oxygen as dictated by the most easily measurable indices of pulmonary function, arterial pH and carbon dioxide and oxygen tensions. In a significant proportion of such babies mechanical ventilation could not produce the gas exchange required and periods of prolonged acidosis, hypoxia or hypercarbia resulted. If the baby did not die then the possibility of significant intracranial haemorrhage and chronic lung disease was high. In the last year an alternative approach to this problem has emerged as the first product specifically designed to correct the underlying surfactant deficiency has become commercially available.

Surfactant replacement therapy

The importance of surface tension in lung inflation was first proposed in 1929 and the relevance of this observation to newborn babies with respiratory distress proven by Avery and Mead in 1959¹. The first trials of surfactant replacement, using pure dipalmitoyl phosphatidyl choline (DPPC), followed shortly afterwards but were unsuccessful.^{2,3} In contrast a significant beneficial effect was seen in

animal studies using complete surfactant extract^{4,5} and the first successful trial of surfactant replacement in premature infants followed soon afterwards.⁶ This study heralded the onset of a period of intensive investigation of a number of surfactants which has led to the establishment of surfactant replacement as the most important advance in neonatology since the development of mechanical ventilation.

A number of different methods have been developed to obtain supplies of surfactant, the most logical being the concentration of human surfactant obtained from amniotic fluid.⁷ This material has most of the constituents of human surfactant including all the surfactant proteins and, being human in origin, should minimize problems of immunogenicity. Unfortunately supplies of this surfactant are severely limited. A number of groups have instead used techniques of solvent extraction and purification of animal surfactants which are obtained from calf lung lavage fluid or from a whole lung homogenate of bovine or porcine origin. Some of these extracts have been supplemented with additional lipids so that the composition of natural surfactant is more closely simulated. An alternative approach to these natural products has been the development of totally synthetic surfactants. Morley and colleagues⁸ have used a mixture of 70% DPPC and 30% phosphatidylglycerol and demonstrated efficacy in clinical trials,⁹ and Durand and coworkers¹⁰ combined DPPC with hexadecanol and tyloxapol to produce an artificial surfactant with similar spreading powers to natural surfactant. This product, now commercially available and marketed by Burroughs Wellcome under the tradename of Exosurf, is the most intensively investigated of all the available preparations.

Over the last 10 years more than 40 controlled trials involving more than 10,000 babies have been performed to evaluate the efficacy of surfactant replacement. All studies have shown a sustained reduction in the inspired oxygen concentration and ventilator pressures required after surfactant

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administration. Although reports differ in the populations studied, types of surfactant used and often to some extent in the definition of the treatment outcome being evaluated it is reasonable to consider all the trials together to give an overall impression of the impact of surfactant replacement. In the following tables (Tables I–III) all treated and control babies from the controlled studies have been combined and the difference in the incidence of a given outcome calculated by confidence interval analysis of the proportions in two unpaired groups. The estimated difference is expressed as a percentage reduction or increase in the incidence observed in the untreated group.

It is thus apparent that surfactant replacement therapy is associated with a highly significant reduction in mortality and in the incidence of pneumothorax and pulmonary interstitial emphysema. There is a surprisingly small reduction in the incidence of chronic lung disease, particularly considering the marked reduction in the magnitude of many factors known to contribute to the

development of this condition. The improvement in overall survival and reduction in respiratory complications does not appear to be accompanied by an increase in the incidence of other complications of neonatal intensive care, particularly intraventricular and intracerebral haemorrhage. Retinopathy of prematurity and necrotizing enterocolitis are rare, and reported incidence is extremely variable in the different studies, as it is for sepsis. For all these complications, therefore, although the average response implies an increase, the confidence intervals are such that no statistical significance can be conferred on the observations. It is not surprising therefore that this treatment has rapidly graduated from clinical trial to established clinical practice. This is not to suppose that there are no problems or unresolved questions.

The first problem is one of cost. An ampoule of the artificial surfactant Exosurf sufficient for a single dose in a baby of 1.6 kg or less costs £370. A vial of the porcine surfactant, Curosurf, sufficient for a single dose in a baby of 1.2 kg or less costs

Table I Results of surfactant replacement on major outcome events

<i>Treatment outcome</i>	<i>Difference as % incidence in control group</i>	<i>95% confidence intervals</i>
Death		
All	– 33.0%	– 24.2% to – 41.9%
By 10 days	– 40.6%	– 18.8% to – 62.5%
By 28 days	– 32.7%	– 21.0% to – 44.8%
Death or chronic lung disease	– 27.7%	– 20.3% to – 35.2%
Survival without chronic lung disease	+ 12.5%	+ 7.8% to + 16.6%

Table II Effect of surfactant replacement on respiratory morbidity

<i>Outcome</i>	<i>Difference as % incidence in control group</i>	<i>95% confidence intervals</i>
Pneumothorax	– 45.0%	– 35.5% to – 54.5%
Pulmonary interstitial emphysema	– 45.1%	– 37.6% to – 52.6%
Pneumonia	+ 9.3%	+ 38.8% to – 20.4%
Apnoea	+ 11.5%	+ 18.9% to + 3.91%
Pulmonary haemorrhage	+ 60.7%	+ 95.8% to – 12.5%
Duration of ventilation	– 3.4 days	– 18.5 to + 11.7 days
Chronic lung disease at 28 days after birth	– 11.84%	– 3.68% to – 20.0%
Chronic lung disease at 36 weeks gestation post-conception	– 16.5%	– 46.6% to + 13.6%

Table III Effect of surfactant replacement on non-respiratory morbidity

<i>Outcome</i>	<i>Difference as % incidence in control group</i>	<i>95% confidence intervals</i>
Intraventricular haemorrhage		
All grades	– 6.7%	– 0.2% to – 13.1%
Grades I & II	– 2.1%	– 26.3% to + 22.1%
Grades III & IV or cysts	0%	– 12.8% to + 12.8%
Patent ductus arteriosus	+ 1.2%	+ 6.2% to – 3.71%
Retinopathy of prematurity	+ 11.9%	+ 47.8% to – 22.4%
Necrotizing enterocolitis	+ 16.1%	+ 40.21% to – 8.0%
Sepsis	+ 27.9%	+ 42.1% to – 13.77%

£800. As anywhere between one and eight vials may be required depending on the size of the baby and the severity of disease it can be seen that the financial implications of a policy of surfactant replacement in all at-risk babies are considerable. In our neonatal unit treatment of 100 high-risk babies each year would cost anywhere between £75,000 and in excess of £200,000 – many orders of magnitude higher than our entire current drug budget. There have been few detailed studies of the cost benefit of this treatment but where reported there does appear to be a tangible benefit.^{11,12}

Survival alone is an inadequate assessment of the efficacy of this new treatment. It must be seen that if more babies of lower gestational ages are surviving then they should do so without an increase in the amount of neurological or respiratory handicap. Initial small studies suggested that there may be an increased risk of adverse neurodevelopmental outcome but this has not been confirmed by later studies.^{13,14} Results from more detailed long-term follow-up are essential.

The optimal treatment regime remains unclear. Current policies are to give a single dose as soon after birth as possible to all at-risk babies and repeat once after 12 hours if needed. An alternative policy is to give surfactant only after significant respiratory distress has developed and evidence of surfactant deficiency is apparent. The latter policy reduces the number of babies who receive this treatment by around 50%^{15,16} but opinion from the small number of studies comparing the two regimes is divided. In Europe two multicentre trials recruiting well over 5,000 babies have specifically considered this issue and their results are eagerly awaited.

Although only one surfactant is licensed for use in the UK and one can be obtained on a named patient basis more surfactants will become available as research continues. Plans to start the

first comparative trial between different surfactants are being made at present but new developments will occur as such studies are performed. The genes for the key surfactant proteins have already been cloned and recombinant DNA technology employed. Method of combining surfactant proteins with lipids are largely developed and there is a real prospect of a laboratory engineered natural surfactant in the near future.

The relatively new field of surfactant replacement therapy has been of great importance to modern neonatology. In addition to the indisputable clinical impact it has also provided the stimulus to a large amount of detailed research which has greatly increased our understanding of the biochemistry, biophysics and immunology of pulmonary surfactant and the interaction with pulmonary function upon which the final effect depends. Much has been discovered but much is still to be learnt.

Steroids and chronic lung disease

Some babies who receive mechanical ventilation will develop chronic lung disease and require supplementary oxygen for many weeks, months or even years. The aetiology of this condition is multifactorial but the most important causative factors appear to be barotrauma from positive pressure ventilation and toxicity from high concentrations of inspired oxygen in lungs which are increasingly vulnerable as gestational age decreases. Despite the impressive effects of surfactant replacement on survival, ventilation and oxygen requirements and short-term respiratory morbidity there has not been a dramatic reduction in the incidence of chronic lung disease. In all the studies reviewed above the incidence in 2,978 babies who received surfactant was 24.4% compared to 27.7% in 2,813 controls. It is possible that

the incidence will be further reduced as treatment policies are refined but it seems unlikely that the problem will be reduced to a level that could be deemed acceptable. The sequelae of chronic lung disease have been well described and include persistent abnormalities of lung function, recurrent respiratory tract infection, repeated or prolonged hospital admission, growth retardation, increased risk of sudden infant death and others. Home oxygen administration may be required for a prolonged period and there is an immense toll on the families. The need for an effective means of treatment or prevention of this condition remains.

For the last decade the main treatment for chronic lung disease has been the use of short courses of high dose dexamethasone. During such courses lung function is frequently seen to improve but the improvement is often not sustained and there are doubts as to whether long-term outcome is affected. It was hoped that some of these points would be clarified by a large international controlled trial which reported recently.¹⁷ A total of 287 neonates was allocated to receive either dexamethasone (0.2 mg/kg three times a day) or placebo if they were static or deteriorating and still requiring supplementary oxygen at a mean post-natal age of 31 days. A first course of treatment was given for 7 days with the option of a second tapered course if required (0.2 mg/kg three times a day for 3 days, twice daily for 3 days, daily for 3 days). The clinician could give open steroids later if indicated by clinical deterioration.

Dexamethasone treatment significantly reduced ventilation requirements in those infants still ventilated at the time of trial (median 11 vs 17.5 days). There was no significant difference in the duration of supplemental oxygen or days in hospital, although the trend favoured the dexamethasone group. An equal number of babies died in the two groups and the incidence of infection was the same. There was no apparent increase in serious side effects as a result of treatment. Interpretation of these data is difficult, however, because the trial design allowed open treatment with steroids at a later date. Results were analysed according to the initial group designation yet 43% of the placebo group and 18% of the treatment group openly received steroids later. This degree of 'contamination' of the placebo group makes it very difficult to draw firm conclusions from the study.

In almost all studies performed so far, steroids have been given for short courses when the baby is 3 or more weeks old. Chronic lung disease starts as a severe inflammatory reaction and progresses to fibrosis and scarring. The inflammatory process almost certainly starts early in the postnatal period and may persist for some time. The use of a short steroid course after some delay has elapsed may thus be less logical than either early or prolonged

steroid courses. Cummings¹⁸ randomized 36 preterm infants to receive either a 42 day or an 18 day course of dexamethasone or a placebo at 2 weeks of age. Infants in the 42 day group were weaned from ventilation significantly faster than 18 day babies or controls (29 vs 73 vs 84 days) and required significantly less supplemental oxygen (65 vs 190 vs 136 days). In addition, follow-up at 6 and 15 months showed normal neurological and developmental progress in seven of the nine infants receiving a 42 day course compared to two of the nine babies with an 18 day course and two of five in the placebo group. The authors concluded that significant benefits were seen with prolonged steroid courses only.

An alternative approach has been to give steroids very early.¹⁹ A total of 57 babies were randomized to receive steroids or placebo within 12 hours of birth and continued for 15 days. Infants receiving steroids demonstrated improved lung function compared to controls and required a lower mean airway pressure during ventilation. Of the treated babies, 57% were extubated within 2 weeks compared to 28% of controls; 39% of treated babies developed 'lung injuries' compared to 65% of controls.

The use of prolonged or early steroid regimes as an alternative to standard therapy is interesting and warrants further assessment. There is, however, an impressive list of both theoretical and actual side effects of steroid administration.²⁰ Although no trial has shown a significant increase in adverse events arising from steroid treatment it appears prudent to give steroids only to those babies where risk of chronic lung disease is high. The ability to identify these babies at an early stage remains a challenge.

Neonatal extracorporeal membrane oxygenation

In a small proportion of babies, conventional ventilation is unable to provide adequate life support. For some of these infants it is now possible to provide additional aid in the form of extracorporeal membrane oxygenation (ECMO) or, as is preferred in some American centres, extracorporeal life support (ECLS). This technique, utilizing modified heart/lung bypass equipment, was first described in neonates by Bartlett in 1976²¹ and has steadily but slowly become more widespread with more than 80 centres currently registered worldwide. Until very recently there has been only one ECMO centre in the United Kingdom.

ECMO most commonly provides cardiopulmonary support by veno-arterial perfusion requiring cannulation of the internal jugular vein and common carotid artery. Provision of pulmonary support alone is possible by veno-venous perfusion through a double lumen venous catheter.

Blood is circulated by a roller pump to a membrane oxygenator in which carefully selected gas mixtures allow adequate oxygenation and carbon dioxide clearance. Blood is returned to the body through a heat exchanger.

ECMO has considerable potential for reversing hypoxia which appears irreversible using standard treatment, particularly when the clinical picture is complicated by persistence of the fetal circulation where pulmonary vascular resistance is high and there is substantial right to left shunting at ductal and atrial levels. To a large extent the reported success of ECMO has been due to careful selection of appropriate patients. Selection criteria are continually evolving as experience grows but a number of generally accepted exclusion criteria are shown in Table IV.

Different methods of determining the point at which ECMO should be commenced have been derived by evaluation of historical controls. Those most commonly used are the oxygenation index or alveolar to arterial oxygen difference which would predict an 80% mortality. The validity of such retrospective indicators has been questioned but an approximate index of disease severity is given to allow survivors of ECMO to be compared with other groups. The use of ECMO worldwide has been accompanied by the provision of a central data registry – The Extracorporeal Life Support Organisation (ECLO). Data from all babies receiving ECMO are recorded here and a recent review of their data provided the survival data given in Table V.²²

Despite these impressive survival data, scepticism exists over the potential role of ECMO. This is largely due to the absence of any controlled trials

comparing ECMO to conventional treatment. Two trials have been performed but pressure from the media and health care professionals led to an adaptive study design being adopted with very few babies assigned to conventional treatment. In the first study²³ the first baby received conventional treatment and died, the next 11 received ECMO and survived. In the second, four of 10 babies who received conventional treatment died compared to one of the 29 who received ECMO.²⁴ Although the statistical basis for such studies is said to be sound, they have failed to convince many practitioners.

A major deficiency of these trials is the inability to compare like with like in studies of long-term morbidity. The cannulation methods completely interrupt the blood supply to one side of the brain and, although there may be good collateral flow at the Circle of Willis, immediate changes in cerebral blood flow have been documented.²⁵ Positron emission tomography has failed to show any asymmetry in the hemispheric blood flow 6 days after decannulation whether the carotid artery had been repaired or remained ligated.²⁶ Neuro-developmental assessment of 67 children who had received ECMO in Pittsburgh between 1979 and 1989 showed that 90% of school age children, 70% of preschool children and 57% of infants were neurologically and cognitively normal. The lower incidence of abnormality in the older children may either reflect increased mortality in the early years of this treatment, or disappearance of milder abnormalities as the child grows older. A total of 21% of children tested had previously undetected moderately severe high-frequency sensorineural hearing loss.²⁷ All these figures are worse than would be anticipated in the general population but probably no worse than expected in a group of babies who had experienced illness of equal severity.^{28,29} Further comment is impossible in the absence of controlled trial data.

In the UK, because of the lack of ECMO facilities, a trial remains a feasible proposition though the period for which this will remain true is probably very short. It has been estimated that less than 5% of suitable candidates in the UK are referred for treatment.³⁰ For this to alter

Table IV Major exclusion criteria for ECMO

Birthweight below 2 kg
Gestational age below 35 weeks
More than 10 days of maximal ventilation
Intraventricular haemorrhage
Irreversible abnormality in any organ system

Table V Survival data of babies receiving ECMO

Condition	Total	Survivors	Survival (%)
Meconium aspiration syndrome	2,328	2,170	93
Respiratory distress syndrome	831	705	85
Congenital diaphragmatic hernia	1,151	696	60
Pneumonia or sepsis	844	651	77
Air leak syndrome	26	16	62
Persistent fetal circulation	775	668	86

significantly some form of evaluation within the framework of the neonatal services in this country is essential.

Outcome and extreme prematurity

With the advances of the last decade, survival of babies who have received neonatal intensive care has steadily increased. In recent years this has been most marked in extremely low birthweight babies. Combined results from several centres in the USA have given the following estimates of survival from 1,765 babies born between November 1987 and October 1988 (Table VI).³¹

If increasing proportions of such small babies are to survive it is to be hoped that survival will be accompanied by a good neurodevelopmental outcome. A recent article has reviewed nine studies of babies <1,000 g and 16 studies <1,500 g reported before the end of 1989.³² Attention is drawn to the difficulty of an overview when studies report follow-up at variable intervals and using differing assessment techniques. The overall conclusion from this review is that the majority of these children have an age-specific IQ which is lower than that in age-matched controls. Most of the children are within the normal school system but 10–71% are reported as needing special education or remedial therapy. Inattention and behavioural problems occur in 30–50% and language delay or articulation deficit in 14–55%. Major motor impairment is uncommon and apparent early whereas mild motor deficit or visual-motor integration deficit are likely to be much commoner and present much later.

An assessment of the incidence of major handicap is provided by the Victorian Collaborative Study Group³³ who reviewed 88 survivors, born with a birthweight of 500–999 g, at a mean age of 8.2 years (Table VII). Less severe disability has been assessed at 8 years of age in 129 babies with a birthweight of 501–1,000 g and compared with 143

Table VII Incidence of major handicap in 88 survivors 500–999 g birthweight

Handicap	Incidence (%)
Cerebral palsy	9
Bilateral blindness	6.7
Bilateral deafness	5.6
Epilepsy	2.2
Low IQ (<71)	6.5
Borderline IQ	11.7
Severe handicap – any reason	18.0

age, sex and social class matched term controls.³⁴ The authors of this study concluded that, although more than two-thirds of these extremely low birthweight babies functioned within the normal range, as a group they were significantly disadvantaged in every measure tested (Table VIII).

All these studies, by virtue of the age at which the children are assessed, are reporting babies who were cared for several years ago. Neonatal care has evolved rapidly in that time and some improvement in outcome is to be expected. A comparison of outcome of babies of 500–999 g born between 1977 and 1982 and 1985–1987 has shown an increase in survival rate from 33.6% to 45.9% associated with an increase in the proportion free of disability at 2 years from 59.3% to 68.5% and an increase in the Bayley scales Mental Development Index from 90 to 98.³⁵

From the information presented in this review it is apparent that the outlook for a baby born prematurely is steadily improving. There is a good chance of normal outcome in even the highest risk babies and a very high chance of a good quality of life. Despite this there is still a significant proportion of premature babies who will die or develop severe neurological, developmental or respiratory handicap. Although many risk factors which predispose to an adverse outcome are known there remains some idiosyncratic factor which allows two seemingly identical babies to progress by very different routes. It is the identification of the basis of this idiosyncrasy which will allow us to improve further the outlook for this high-risk population.

Fetal and childhood origins of adult disease

An adverse environment during early childhood and specifically factors that impair growth and development in early life have been advanced as risk factors for later ischaemic heart disease (IHD). These postulates have important implications for preventive medicine and the evidence warrants close examination.

The geographical association between current

Table VI Estimates of survival from 1,765 babies born between November 1987 and October 1988

Birthweight (g)	Survival (%)
<750	34
751–1,000	66
1,001–1,250	87
1,251–1,500	93

Gestational age (weeks)	Survival (%)
23	23
24	34
25	54

Table VIII Disability in 129 survivors 501–1,000 g birthweight compared with 143 term controls

Assessment	501–1,000 g	Term
Mean full scale IQ	91 ± 16	104 ± 12
Abnormal IQ result	8–12%	1–2%
Reading, spelling, mathematics assessment ≤ 2 s.d. from mean	20–28%	3–10%
Motor performance assessment ≤ 2 s.d. from mean	3–10%	1%
Visual-motor integration assessment ≤ 2 s.d. from mean	21%	6%

areas of high mortality from cardiovascular disease and high neonatal and maternal mortality in the past, led Forsdahl³⁶ to postulate that nutritional deprivation in childhood followed by relative affluence in later life increased the risk of IHD in adult life. Associations between fetal, early infant, childhood and maternal health and markers for IHD such as blood pressure, heart rate, ischaemia on exercise testing and mortality from IHD, have been explored largely retrospectively. These studies have been critically reviewed.³⁷

It has been postulated³⁸ that processes linked to growth and acting in prenatal life or early postnatal life were strongly influencing the risks of IHD. Among a study population comprising 5,654 men born in Hertfordshire, England during 1911–1930, those with the lowest weights at birth and one year had the highest death rates from cardiovascular and chronic obstructive airways disease. Death rates from cardiovascular disease were three times higher among men whose weights were 18 lb or less at one year, than among those who had attained 27 lb or more. The standardized mortality rate for IHD was also inversely related to birthweight, although this relationship was weaker than that with weight at one year.³⁹ Those who had the lowest birthweight, however, had the highest mortality from all causes, not just IHD or chronic obstructive airways disease, and there did not seem to be any significant downward trend in mortality with increasing birthweight. Although there was no association with social class at death, it is not possible to exclude the action of environmental factors operating throughout life.⁴⁰ Little intergenerational class mobility occurred in males born in the first half of the 20th century, and those born of low birthweight were likely to retain their poor social rating into adulthood. Re-examination of the association between birthweight, weight at one year, and adult mortality, confirmed the correlation between mortality rates from IHD, bronchitis, stroke, carcinoma of the stomach, cervix and lung (men), with infant mortality rates. However, when adjusted for indices of the socio-economic

conditions prevalent at the time when the cohort was dying, the correlation between infant mortality rate and adult mortality rate for IHD, stroke and carcinoma was greatly attenuated or abolished. Correlations for chronic bronchitis persisted suggesting that repeated childhood infections led to adult respiratory morbidity. The strong correlation between early environment and adult morbidity and mortality may simply be an effect of continued deprivation throughout life leading to a number of detrimental health effects.⁴¹

A low socio-economic state in childhood was significantly associated with ischaemia on exercise testing in a study of 2,679 middle-aged Finnish men, and led to the proposal⁴² that IHD develops earlier in those circumstances. Adjusting for adult social status, however, reduced the excess risk due to low socio-economic status in childhood by more than half and removed any statistical significance.³⁷

Birthweight has been inversely associated with the risk of raised diastolic pressure in early adult males.⁴³ The systolic and diastolic blood pressure of 449 men and women around 50 years of age, born during 1935–1943 in Preston, were inversely related to birthweight and positively related to placental weight. Systolic pressure fell by 11 mmHg as birthweight increased from 5.5 lb to over 7.7 lb, and rose by 15 mmHg as placental weight increased from 1 lb or less to over 1.5 lb. This association was stronger than that with current factors such as alcohol consumption or body mass. The systolic blood pressure (BP) for 3,259 36 year old men and 9,921 10 year olds from the National British Birth Cohort study, was also inversely associated with birthweight and directly related to current weight and height.⁴⁴ Diastolic pressure showed no trend but measurements were only to the nearest 10 mmHg. Familial hypertensive disorders were not excluded and might also lower birthweight. In stepwise multiple regression analysis, it was shown that blood pressure for 4,500 persons under 20 years, was largely determined by height and weight of the subject, and parental blood pressure, with only a very small additional

effect—seen only in boys—from complications of pregnancy, such as toxæmia.⁴⁵ In studies of 405 4 year old children and 216 7 year olds, born to mothers who had been hypertensive in pregnancy, associations were found between blood pressure and maternal weight, maternal blood pressure and duration of anti-hypertensive therapy in pregnancy. However, the strongest statistically significant association was with current weight and weight for height ratio.^{46,47} In contrast, systolic and diastolic blood pressure in a population of 32,580 Israeli subjects being screened for military service aged 17 years, were directly but only weakly related to birthweight. The contribution of birthweight to variation in blood pressure was small and low birthweight (<2,500 g) was not associated with significantly higher systolic or diastolic pressure. The association was greater with body weight and body mass index at age 17 years. Overweight adolescents rather than low birthweight infants seem to be at risk of increased BP in adulthood.⁴⁸ Furthermore, no relation was found between blood pressure and birthweight for 249 very low birthweight (VLBW) infants followed from birth to 8 years compared with 363 normal birthweight infants. Blood pressure was if anything lower in the VLBW group at follow-up.⁴⁹

Although geographical variation in blood pressure distribution seen in adults was also matched by variation in blood pressure in children aged 5–6 years, this association was strongly influenced by the lowest BP areas and overall was not strong.⁵⁰

Blood pressure tracking establishes in the second 6 months of life. Although BP changes little between 6 months and 10 years, the tracking correlation increases as does the correlation between maternal and child BP, and the child's weight becomes a stronger predictor of BP.⁵¹ Unfortunately, tracking only accounts for 35% of BP variability in children aged 10 years; the rest is between occasion variability, which precludes screening children at 10 years of age for risks of later hypertension.

Short stature has been used as a marker of deprivation in early life and has been associated with increased blood pressure, but is also independently related to lower socio-economic status in adult life. Inverse relationships have been described between height and mortality from all causes, including coronary heart disease.

Overall, these studies do not provide strong support for the hypothesis that early life experiences determine the subsequent risks of cardiovascular disease. If the relative importance of risk factors acting throughout life in the aetiology of adult disease is to be unravelled, it is important that prospective cohort studies should obtain data on early childhood factors and factors in later life. These studies will need to be large to disentangle

the confounding effects of these two highly correlated features.

Patterns of adult lifestyle begin to be established in childhood and adolescence. Increased awareness in childhood of the known risk factors for IHD in adult life and screening for these may be one way of preventing adult disease, and children may be more easily influenced than adults to adopt healthy habits that last a lifetime. This approach has been enthusiastically adopted in the USA and elsewhere, where education and intervention programs have targeted children and adolescents through school programmes.^{52–55}

Demonstration that the extent of aortic and coronary artery fatty streaks was associated with total cholesterol and LDL-cholesterol levels has led to targeted screening being recommended by the Nutrition Committee of the American Academy of Pediatrics. The aim is to detect hypercholesterolaemia in children over 2 years, where there is a positive family history of hyperlipidaemia or premature myocardial infarction under the age of 50 years for males and 60 years for females).⁵⁶ No similar recommendations exist for the United Kingdom. There is continuing debate in the USA over whether screening should be targeted to high-risk groups or whole population strategies.^{57,58} Cholesterol screening of children is only worthwhile if levels are predictive of adult values and therefore of risk for later cardiovascular disease, if intervention is more effective if begun in childhood and if screening and intervention can be accomplished with little risk to the child. Longitudinal studies of cohorts of children have examined the correlation of total cholesterol and lipoprotein levels for up to 16 years, between childhood and age 30, and long-term tracking has been confirmed.^{56,59}

The Bogalusa Heart Study,⁵⁶ a long-term epidemiological study of cardiovascular disease risk factor variables in 1,586 children and young adults, found that about 50% of those with high total cholesterol levels at baseline had levels above the 75th centile 12 years later, and over 50% of those with LDL-cholesterol above the 75th centile persisted in this centile. In the Muscatine study⁵⁹ 2,367 children aged 8–18 years were examined on several occasions and followed-up to age 20–30 years. Of children with cholesterol concentrations exceeding the 75th centile on two occasions, 75% of the girls and 56% of the boys would not qualify for intervention as adults by the National Cholesterol Education Program criteria, and even when the 90th centile was taken as cut off, 57% of girls and 30% of boys would still not have qualified for intervention.

Whilst dietary advice may be effective and safe, drug therapy for hypercholesterolaemia in the paediatric age group should not be undertaken lightly.⁵⁸ The long-term effects of these drugs may

increase mortality and morbidity from other causes. A number of intervention programs have reported their findings. The Pawtucket Heart 'healthy eating program', a school curriculum teaching healthy choices at mealtimes and in the selection and preparation of food, designed to reduce total fat and in particular saturated fat consumption, achieved a 10% reduction in serum cholesterol levels in those who had been above 170 mg/dl at baseline.⁵⁴

The Heart Smart cardiovascular programme developed a cardiovascular health-conscious curriculum in school over one year as part of the general science course. There was an additional cardiovascular fitness programme. A separate family health promotion programme was developed for children found to be in a high-risk group based on the outcome of screening for cardiovascular risk factors and LDL-cholesterol levels. Reduction in cholesterol levels and improvement in fitness levels were reported.⁵³ In Finland, two family-based studies achieved reductions in cholesterol levels of 15%, whilst two community and school-based studies reduced smoking by 30% at 2 years, compared with controls.⁵² The cost benefit of these programs and their long-term effectiveness need to be evaluated before recommendations can be made for their widespread adoption.

Vitamins and IQ

Although it is well recognized that deficiencies of specific vitamins will, if major or prolonged, lead to specific deficiency syndromes, there is less known about the possibility that subclinical inadequacies in diet may adversely affect cognition and psychological functioning. A number of studies have shown improvement in functioning of anaemic school children when treated with iron.⁶⁰⁻⁶² Similarly improved development has been shown in iron-deficient preschool children following supplementation.⁶³

Inadequacy of vitamins and minerals is less easy to quantify. Dietary assessments will give some indication but the recommended daily allowances (RDA) are only a broad guide on a population basis, that is, at least 50% of the normal population will consume less than the RDA. Also individual requirements may vary substantially so that a dietary intake which is sufficient for one individual may be inadequate for another.

In order to test the hypothesis that a low intake of vitamins or minerals may prevent optimal psychological performance, Benton and Roberts⁶⁴ carried out a study on 90 Welsh school children, aged 12-13 years. Dietary adequacy or otherwise was assessed—somewhat shakily—by 3 day dietary

diaries filled in by the children who were divided into three groups of 30, matched for sex, school performance and social factors. One group received no treatment whilst the other two received multivitamin/mineral supplementation or placebo on a double-blind basis for 8 months. The supplemented group but not the placebo or the untreated group was reported to show a significant increase in non-verbal intelligence. The significance of this increase has been the subject of much controversy.⁶⁵⁻⁷¹ A further study⁷² of 167 children aged 13 years gave conflicting results with only boys on a poor diet showing a small effect of supplementation. The implication that dietary deficiencies may be hampering development in affected children is clearly an important one and several similar studies followed. Crombie *et al.*⁷³ tested 86 Scottish children aged 11-13 years before and after a 7 month period of supplementation with vitamins and minerals on a double-blind basis. The dietary supplementation failed to improve the performance of the school children in tests of reasoning. Similar negative findings were reported in a group of 154 London school children aged 11-12 years after a 4 week period of supplementation⁷⁴ and also in another group of 227 children aged 7-12 years.⁷⁵ The authors concluded that learning ability in a cross-section of British school children was not limited by the quality of their diets.

A rather different conclusion was drawn by workers who conducted a large study on 615 Californian school children aged 12-16 years.⁷⁶ The children were divided into four subgroups who received supplementation at 0%, 50%, 100% and 200% of the US RDA. Only the group supplemented at 100% showed any improvement in non-verbal intelligence. It is difficult to suggest a convincing physiological explanation for the lack of any improvement in the 200% treatment group, leading to one view that the positive result occurred by chance. Doubt also arose because the improvement was said to occur in children from all four schools involved in the study, yet one was in an area of socio-economic deprivation whilst another was in a very privileged area with nearly half the children having IQs above 120. As pointed out by one author⁷⁷ a nutritional explanation seems unlikely.

Unfortunately, the results of the Californian study were widely publicised by the media, with the results that many British parents rushed to buy vitamin supplements for their children. There was a surprising lack of interest amongst Californian parents. One observer⁷⁸ commented: 'perhaps Californians consume so many vitamins that they are too intelligent to believe it.' Further carefully designed trials are required but there is as yet no scientific basis for vitamin and mineral supplementation in normal school children unless they

clearly have deficient dietary intake for whatever cause.

Vitamins, minerals and mental retardation

Similar studies though with much smaller numbers have been carried out on retarded children in the hope of improving their development. A total of 15 children with Down's syndrome aged 7 months to 5 years were studied in a placebo-controlled cross-over trial.⁷⁹ High dosage multivitamin and mineral supplements resulted in decreased developmental progress. The only beneficial effects reported by the parents were improved general appearance and skin freshness. Another study⁸⁰ involving vitamin supplementation in 18 severely subnormal children also failed to show any significant therapeutic effect.

Vitamins and neural tube defects (NTD)

The possible relationship of diet with neural tube defects has been debated for over 30 years. During the second world war, severe food deprivation occurred in a number of European countries and in the immediate post-war period an increase in babies born with neural tube defect was noted.⁸¹

Epidemiological studies showed a strong correlation between neural tube defects and social class,⁸² and folate status at the end of pregnancy showed a marked difference between mothers of NTD infants and controls.⁸³ Smithells⁸⁴ recorded lower dietary intakes in early pregnancy in mothers of lower social class and a second study⁸⁵ confirmed this finding and demonstrated an association between NTD recurrence and poor diet in the first trimester.

Smithells *et al.*⁸⁶ reported their findings in 1980 of a trial of periconceptional vitamin supplementation in women who already had at least one affected infant. The supplement (Pregnavite Forte F) was given for at least 28 days before conception and for the first 2 months post-conception. Only one of 178 infants born to supplemented mothers was affected whilst 13 of 260 infants of unsupplemented mothers had neural tube defects. The same group has reported further data⁸⁷ on larger numbers confirming a recurrence risk of less than 1% for the supplemented mothers and around 5% for unsupplemented mothers.

Various criticisms were made of the mode of selection to receive intervention. Other questions still unanswered at this time include which vitamin or micronutrient or other factor is responsible for the protective effect, what is the critical period for intervention, is the treatment as effective in preventing occurrences of NTD as it appears to be for recurrences, what is the most effective way of protecting the whole population, and is the inter-

vention wholly without risk of teratogenesis?

The recently published results of the Medical Research Council multi-centre recurrence trial⁸⁸ provide clear evidence of the role of folic acid in prevention of neural tube defects. This randomized trial involved 33 centres in seven countries over an 8 year period. A total of 1,817 women who had had a previous NTD baby participated. The women received either folate (4 mg per day) or a mixture of other vitamins or both or neither. Of 1,195 pregnancies, 27 produced infants with NTD. Only seven such infants were born to mothers who had received folate whilst the remaining 20 were born to mothers who had not. In the two folate groups the recurrence rate was 1% compared with 3.5% in the other two groups. The results were so conclusive that the trial was discontinued before the full planned number of mothers had been recruited.

It is widely recommended, and endorsed by the former Chief Medical Officer, Sir Donald Acheson, that periconception folate supplementation should be given to all women who have had an affected pregnancy. A further consideration is whether some basic foods should be fortified with folate in order to increase the intake in all women likely to become pregnant. This inevitably implies supplementation for the rest of the population too. Foods rich in folate should be eaten, that is spinach, cabbage, sprouts and broccoli (lightly cooked only) whilst lettuce, rice, bread, fruit and nuts are also good sources. It is, however, somewhat disheartening to note that a kilogram of raw cabbage contains only 0.9 mg of folic acid.⁸⁹ Uncertainty remains as to whether dietary strategy alone will suffice to protect against the birth of babies with neural tube defect.

Growth hormone

Information regarding the benefits and more recently the safety of human growth hormone (hGH) administration in childhood is rapidly expanding. The widespread availability of recombinant growth hormone (rhGH), free from the risk of Creutzfeld-Jacob disease, has enabled the optimal dosage frequency for maximal growth in classical hGH deficiency to be better established, and has also markedly expanded the field of therapy. This raises ethical issues over who should receive growth hormone, apart from the medical issues of delineating those who will most benefit from it.

In addition to children shown on provocative testing to have unequivocal hGH deficiency, hGH has now been used in many short stature syndromes including Turner's, Noonan's, Down's, skeletal dysplasias, intrauterine growth retardation (IUGR) and growth failure induced by chronic

disease such as renal failure, asthma, arthritis and thalassaemia. It has been used to treat slowly growing and normally growing short children. Interest has spread to its use to correct catabolic states after extensive burns and surgery, and to replacement therapy in hGH-deficient adults.^{90,91}

It has emerged that the response of a child to hGH is related to the pre-treatment growth velocity, the dose of hGH used and the frequency of administration, and the condition being treated.^{90,92,93} Giving hGH to children other than those with hGH insufficiency rarely seems to achieve a consistent and sustained increase in growth rate and for some may shorten the growing period, most notably at puberty.⁹¹ Although short-term increments in growth velocity have been demonstrated for a number of conditions other than hGH deficiency, there is insufficient data on whether increments in final adult height are achieved to allow any firm recommendations to be made. Furthermore, growth hormone has effects on fatty acid metabolism which may theoretically hasten the development of atherosclerosis, impair glucose metabolism, and through its effects on cell division stimulate neoplastic change. Estimates from hGH-deficient children suggest that the latter risk is small and any increment is of the order of 1–2 fold.^{94,95} It remains important that such therapy continues to be administered in settings that allow delineation of those children who will most benefit, both to optimize therapeutic regimes and to ensure long-term follow-up to document whether the short-term gains in height velocity are converted into a significant increment in final adult height.

There is increasingly firm evidence to support the use of rhGH in Turner's syndrome. Used alone or in combination with sex steroids, rhGH can stimulate significant growth, and higher than standard doses (up to 1.35 IU/kg/week, on a daily dosage) may achieve better results.⁹⁶ The addition of low-dose oestrogen does not significantly enhance the clinical response to hGH but the combination with oxandrolone appears to be synergistic. Whilst it will be several years before final height data emerge, preliminary results over periods of 3–5 years have shown that of the girls receiving rhGH alone, 82% are above the 50th centile on a Turner's height chart, with 18% above the 10th centile on a normal female growth curve.⁹⁷ Of those receiving combination therapy, 98% are above the 50th centile on the Turner's height chart, with 33% above the 10th centile for normal female growth. Low dose oxandrolone (0.0625 mg/kg/day) is recommended to avoid virilization. Use of rhGH may allow many of these girls to reach adult heights over 150 cm. Furthermore rhGH therapy allows the introduction of feminizing doses of oestrogens at a more physiological age than has

been advocated previously, to greater psychological advantage.^{90,97–100}

The position for Noonan's syndrome is far less clear. A significant increment in height velocity from 4.8 to 7.6 cm/year over 12 months has been demonstrated, but any long-term benefits remain unproven.¹⁰¹ The demonstration of abnormalities in growth hormone secretion in a group of children with Down's syndrome led to a trial of rhGH therapy, again with excellent increments in height velocity over one year, but unproven long-term benefits and unknown long-term effects particularly with regard to risks for neoplasia.¹⁰² Preliminary studies suggest that rhGH, as well as increasing height in a group of children with Prader Willi syndrome, may have a beneficial effect on hyperphagia and obesity.¹⁰³ Little attention has been paid to the role of rhGH in the management of skeletal dysplasia. A total of 21 children with hypochondroplasia have received 3 years of rhGH therapy. The initial rapid acceleration of growth was not maintained, although the growth rate remained above the pretreatment level over the whole period of observation.^{90, 104}

A proportion of children who are growing slowly, with growth patterns similar to classic GH deficiency, pass provocative tests of pituitary function. Some have evidence of neurosecretory dysfunction, and it may be that there is no clear boundary between GH deficiency and sufficiency.^{92,94,95,105} Both those who secrete subnormal levels of GH and grow slowly and those who are short but with a normal growth velocity respond to exogenous GH with growth acceleration, but the response of the latter group is smaller.^{93,106} Dosage needs regular adjustment on the basis of surface area for a sustained growth response.¹⁰⁷ There are no data regarding final height, optimal dosing nor duration of treatment, particularly with regard to growth in puberty, when under- or overtreatment may result in shortening of the duration of puberty and a negative effect on final height.⁹⁰ Administration of high dosage hGH (0.3 U/kg/day) for 2 years prior to the expected pubertal growth spurt allowed near normalization of adolescent height for 10 children with short stature who were less than the first percentile. However, this dosage was associated with a moderate reversible hyperinsulinaemia with alteration in glucose metabolism, although in other studies glucose tolerance and glycosylated haemoglobin have remained normal.¹⁰⁸ Several arguments prevail against the use of growth hormone in those without a true growth hormone deficiency, in whom we do not yet know the final benefits or otherwise of therapy. For the patient and family there is a cost in terms of discomfort and stress of daily injections and the risks of side effects of long-term high-dose treatment, without an

absolute guarantee of successful outcome. There is the additional monetary cost of the treatment to the health service or individual. Constitutional growth delay at puberty may be better, more cheaply and as effectively treated with oxandrolone as with growth hormone, if treatment is deemed to be indicated for a self-resolving condition.^{107,109}

Growth failure arising from other medical conditions may be amenable to rhGH therapy. Cranial and cranio-spinal irradiation for malignancy is associated with growth failure, but not always with clear evidence of GH deficiency. When cumulative height losses from radiotherapy were compared, spinal irradiation resulted in a mean height loss of 1.4 s.d. Additionally growth hormone deficiency contributed to a mean height loss of 1 s.d. after cranial irradiation and 1.6 s.d. after cranio-spinal irradiation.¹¹⁰ Although rhGH increased the height velocity to the normal rate for age, catch up growth was not seen, even when the dosage was increased in the second and third year of one study from 13 U/m²/week to 18 U/m²/week.¹¹¹ This is still well below dosages recommended for other short stature syndromes. However, attempts to increase the adolescent growth spurt to improve final height in 32 children with isolated growth hormone deficiency after cranial irradiation (1,800–2,400 cGy) by using 30 U/m²/week compared to 15 U/m²/week, did not show any significant increment in growth velocity. They did show a trend to advanced pubertal maturation on the higher dose.¹¹¹ The limiting factor to success of growth hormone therapy may be the small degree of bone age retardation, and the demonstrably younger age, especially for females, at entering puberty. Earlier treatment or the use of lateinizing hormone releasing hormone (LHRH) analogues to delay puberty may be beneficial.^{110,112}

In renal failure haemodialysis does not restore normal growth rates and the catch-up growth after transplantation does not always normalize height. Although the levels of GH may be high in uraemia, there is also an excess of insulin-like growth factor binding proteins (IGF-BP), leading to a relative deficiency of IGF-1 and a rise in IGF-BP3 as creatinine clearance falls. Exogenous growth hormone improves the ratio of IGF-1:IGF-BP3, and gives impressive results in incremental growth velocity in the short term.^{113,114} Growth hormone therapy should not be the first means of augmenting growth, and should only be implemented after scrupulous attention to nutrition, acid base status, and electrolyte and calcium balance, which may also improve growth.¹¹⁵ Growth velocity in 29 prepubertal children with chronic renal failure and 39 pre- and post-pubertal children with renal transplants from the European joint collaborative study was significantly increased by doses of rhGH

of 30 IU/m²/week, daily (approximately 1.0 IU/kg/week) over a one year period. This effect was greater in the group with chronic renal failure than in the transplanted group, possibly as compliance in the latter group was harder to achieve and these patients also had the effects of immunosuppressive therapy on growth. Despite theoretical risks of hypercalciuria, hyperfiltration, hypertension, increased immunoreactivity, and additive effects of rhGH on carbohydrate metabolism to the diabetogenic effect of steroids, only slight increments in creatinine and falls in glomerular filtration rate were seen. Rejection was seen in two patients.^{90,116} Increase in height s.d. score was not seen.¹¹⁷ A positive correlation between pretreatment height velocity and the observed rhGH effect suggest that it may be best to start treatment early.¹¹⁴ Results of up to 3 years treatment in chronic renal failure have shown significant increases in height velocity for each 12 month interval, without acceleration of bone age greater than the increment in chronological age.¹¹⁸

The next few years should see the role of growth hormone more clearly delineated. One body of opinion favours the use of growth hormone responsiveness and not growth hormone deficiency as the criterion for treatment, reserving treatment for those children who are handicapped by short stature (height less than the first centile). Children above that centile may permissibly be treated but there should be no obligation to do so, thus eliminating the burden of severe short stature without aggravating heightism in society.⁹⁴

Meanwhile, for those who received pituitary-derived human growth hormone (hGH), more precise information on the risks of Creutzfeld–Jacob disease is emerging. Epidemiological follow-up of 6,284 recipients of hGH, had by 1991 detected seven cases, six presenting with ataxia and imbalance, rather than altered mentation, and one patient died in the preclinical incubation period. All seven cases occurred in the 700 hGH recipients who started therapy before 1970, and had received hGH for longer than the average in that cohort. Since only 10% of the cohort has been followed-up for the 15 year average incubation interval from midpoint of hGH therapy to onset of symptoms, the majority of patients have still to attain the full incubation period to express Creutzfeld–Jacob disease. By 1992 over 37 cases had been reported worldwide of whom eight are UK residents. Although the duration of pituitary hGH therapy was thought to be the major risk factor,¹¹⁹ treatment as short as 2 weeks in duration has now resulted in Creutzfeld–Jacob disease.¹²⁰ All efforts are being made to provide informed counselling for those at risk from this treatment.

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