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Biochemical neonatal screening

Preconceptional and antenatal screening may be preferable in some cases

When neonatal screening was set up for phenylketonuria the arrangements made for collecting blood spots from every newborn on to Guthrie cards and sending them to a laboratory were important steps towards creating an infrastructure for genetic screening. This was soon exploited for the early diagnosis of congenital hypothyroidism. But few biochemical disorders can be detected in the newborn, and it is not necessarily of clinical value to diagnose all those that can be detected. Both phenylketonuria and congenital hypothyroidism fulfil the apparently simple classical requirements for screening: they are important conditions, the diagnosis is obvious, clear information is available, and effective avoiding action is possible.[1] Avoiding action includes genetic counselling to allow the family to avoid the birth of further affected children.

But the limits of those "requirements" are hazy, and scientific progress is constantly moving them. For neonatal screening to be justifiable, how severe should a condition be; how clear the information that may be given; and how effective the avoiding action? To what extent are policy decisions influenced by emotional attitudes—towards prenatal diagnosis or to the ethnic groups concerned—or reluctance to break bad news to parents before it is strictly necessary? How will the possibilities for more precise genetic diagnosis by DNA methods affect its scope?

One example of a condition for which screening is debatable is glucose 6-phosphate dehydrogenase deficiency, which is very common and easy to detect, may have serious consequences, and affects a substantial proportion of the British population. It is not systematically screened for—ostensibly because both infants with jaundice due to glucose 6-phosphate dehydrogenase deficiency and children and adults with haemolytic crises precipitated by broad beans or drugs are said to be readily diagnosed and treated.[2]

Another example is α_1 antitrypsin deficiency, which is common in Europe, may cause juvenile cirrhosis, and enhances the risk of lung disease in later life by increasing vulnerability to environmental pollution. In Sweden a cohort of infants was screened and parents of affected children were advised to refrain from smoking. Follow up suggested, however, that the parent-child relationship had been disturbed in some cases, and on average the parents smoked more than before. Neonatal screening was not recommended.[3] But more recent evidence that breast feeding reduces the incidence of severe liver disease has raised the question again.[4] Should neonatal or some other form of screening be reconsidered?

The rough incidences of the conditions mentioned in this article among newborns in Britain are as follows:

Phenylketonuria	1/10 000
Congenital hypothyroidism	1/4000
Glucose 6-phosphate dehydrogenase deficiency	Up to 20% of boys in some ethnic groups
α_1 antitrypsin deficiency	1/2000
Duchenne muscular dystrophy	1/4000 boys
Sickle cell disease	Up to 2% in some ethnic groups
Cystic fibrosis	1/2000

Duchenne muscular dystrophy can be detected simply and reliably in the newborn.[5] Early diagnosis does not affect outcome, but if all affected infants were identified early some 15-20% of cases might be avoided through family studies and genetic counselling.[6] There has, however, been little enthusiasm for neonatal screening with the primary objective of reproductive counselling, partly because it entails informing the parents of their son's fatal illness long before he has any symptoms. The alternative approach of testing infants who could not walk by 18 months—whose parents would already be worried—proved ineffective.[7] With the increased accuracy of diagnosis of carriers and the increased optimism for future palliation brought about by the identification of the dystrophin gene, might this be the time to reconsider neonatal screening for Duchenne muscular dystrophy?[8]

The high resolving power of DNA technology does not necessarily mean that it will be the best method for mass genetic screening, especially for conditions in which many different mutations may alter the protein product and cause disease. Ultimately its contribution may be that of allowing DNA diagnosis of some conditions and protein based diagnosis of others through identifying the protein concerned, as with Duchenne muscular dystrophy and cystic fibrosis.[8,9] One interesting benefit has already been shown: Guthrie cards constitute a potential DNA store for practically every child born. This has already proved useful for parents of a child who had died without DNA studies who sought prenatal diagnosis for a later pregnancy.[10]

In cystic fibrosis neonatal identification and early treatment may improve the prognosis of affected children and allow parents the option of prenatal diagnosis in subsequent pregnancies. There have been pilot studies of neonatal

screening by assay of immunoreactive trypsin in dried blood spots,[11] but the general tendency seems to have been to await DNA based diagnostic methods, which should give more clear cut results. Now that the cystic fibrosis gene has been identified,[9] the commonest mutation is easy to detect,[12,13] and when the polymerase chain reaction is used dried Guthrie blood spots seem to be an adequate source of DNA for diagnosis.[10] It would be unwise, however, to rush into large scale neonatal screening for cystic fibrosis. Precise genetic diagnosis of a recessively inherited condition raises many new and unsolved problems, as shown by experience with neonatal screening for sickle cell disease.

Abnormal haemoglobins can be detected cheaply and reliably by electrophoresis, and neonatal screening with follow up both reduces early mortality in sickle cell disease and also allows parents to be counselled about later pregnancies.[14] Neonatal screening identifies about 40 heterozygotes for every homozygote detected (with cystic fibrosis the ratio would be closer to 100:1). What should be done for these babies? Clearly they should also be followed up because their parents will include numerous couples at risk who could be counselled before they have affected children. But there are no special counselling resources for families of carriers; the neonatal period is a sensitive time; most people are unfamiliar with recessive inheritance; there are pitfalls such as accidental revelation of non-paternity; and there is no mechanism to ensure that a genetic diagnosis remains attached to a person's medical records for life. Current thinking holds that it is better to leave families in ignorance than to inform them without counselling, so unless a trained haemoglobinopathy counsellor is available many families with asymptomatic (heterozygous) infants are not informed at all. Adequate resources for counselling for common genetic traits will be available only when it is perceived as a task for primary care workers and they have been given training, and that will take time.

Furthermore, neonatal screening is an inefficient method for detecting couples at risk of having children with recessively inherited disorders. Only half of the couples at risk can be found by following up the parents of heterozygous infants as one quarter will already have had an affected child and the quarter who have had a normal child will escape detection. This leads to the consideration that most really precise genetic methods could be used just as well antenatally—to detect adult carriers of a disorder—as postnatally, when the result tells them that their child is already affected. Antenatal screening or screening before pregnancy allows the choice of prenatal diagnosis, and genetic counselling—however imperfect—is now becoming a familiar concept in antenatal clinics.[15]

As diagnostic methods become more precise the possibilities for neonatal diagnosis will certainly increase; but when the prime objective is reproductive counselling screening is likely to be pushed back to the antenatal period and earlier. Ultimately, this could actually reduce some indications for neonatal screening.

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Thiazides in the 1990s

The risk:benefit ratio still favours the drug

Though thiazide diuretics have been in regular use for over 30 years, debate about their role in therapeutics seems to increase as the years go by. Thiazides have been a mainstay in treating hypertension, in which (together with β adrenoceptor antagonists) they have been the drugs of first choice. They also have useful diuretic actions, particularly in conditions such as congestive heart failure. Thiazides work in hypertension in the long term by lowering peripheral resistance rather than by their diuretic effect,[1] and they are usually regarded as superior to loop diuretics in this condition.[2] The dose commonly used in hypertension, however, has probably been unnecessarily high; studies with cyclopenthiazide have shown that the fall in blood pressure is as good with 125 μg (a dose lower than currently marketed) as it is with 500 μg.[3,4]

Thiazide diuretics have always been known to be able to produce adverse effects, though when set against their volume of use their safety record is good.[5,6] Some controversy has arisen in the context of long term treatment of hypertension when thiazide diuretics have been alleged to have long term harmful effects. In the multiple risk factor intervention trial thiazide diuretics were suggested as the cause of an increase in the number of cardiac deaths in a subgroup of patients with minor electrocardiographic abnormalities.[7] This was, however, a retrospective conclusion, and data from similar studies such as the hypertension detection and follow up program and the Medical Research Council hypertension trial failed to confirm the observation.[8,9] Thiazide diuretics are well known to cause hypokalaemia; in Britain some 76 000 patients having long term treatment with these drugs may have a serum potassium concentration below 3·0 mmol/l.[10] Hypokalaemia (by causing cardiac arrhythmias) has been suggested as the cause of the postulated increase in the number of deaths. Nevertheless, the serum potassium concentrations do not correlate well with intracellular concentrations of potassium, and while the issue remains controversial,[10,11] the evidence does not suggest that hypokalaemia induced by thiazides is an important cause of cardiac arrhythmias.[12-14] Thiazides have also been alleged to be harmful to patients in the long term