

A double-edged sword

The technical fix for one genetic disorder had unforeseen repercussions.

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In 1960, Robert Guthrie, a microbiologist and physician working in Buffalo, New York, devised a simple way to measure the level of phenylalanine in the blood of children with the genetic disorder phenylketonuria (PKU). Guthrie's interest in the problem was intensely personal — he had a son and a niece who were mentally retarded. The niece's condition was due to PKU, in which a defective liver enzyme results in an inability to metabolize phenylalanine, an essential amino acid found in all dietary proteins.

In such patients, phenylalanine accumulates to toxic levels, often causing severe mental retardation and physical and behavioural abnormalities. Physicians reasoned that at least some children could be helped by a diet from which most of the offending amino acid had been removed. But before Guthrie, there was no practical way to monitor blood phenylalanine levels.

Building on his work on measuring drug levels in cancer patients, Guthrie developed such a test. It involved adding a blood specimen, on a disk of filter paper, to a culture of bacteria unable to metabolize their own phenylalanine. If the blood came from an individual with PKU, the bacteria sprang into life.

Although this was an important achievement, the key to controlling PKU seemed to lie in diagnosing the condition as soon after birth as possible, before the infants' developing brains were damaged. The existing 'wet diaper' test, in which a drop of ferric chloride added to a urine-soaked diaper turned green if the infant had PKU, was unreliable until the age of eight weeks, by which time the infant might have suffered irreversible brain damage. Guthrie's method was much more sensitive, detecting abnormal blood phenylalanine levels by the third day of life. It was also convenient and — partly due to Guthrie's refusal of royalties — inexpensive.

Guthrie's test converged with the commercial release of a PKU formula in 1958. At this time, general frustration over the inability to treat mental retardation was shifting the emphasis from providing the retarded with social and rehabilitative services towards scientific treatment. In 1961, President John F. Kennedy, whose sister had long been institutionalized for mental retardation, announced a major national campaign. In this context, the Guthrie test received enormous publicity and government support. Even before a government-sponsored trial of the test had ended, the state of Massachusetts made it mandatory, and by



Screen test: a simple procedure can identify infants with the genetic disorder phenylketonuria.

the mid-1970s, PKU testing was routine.

The control of PKU generated such excitement because it seemed to offer a template for future successes. PKU is rare, occurring only once in every 11,000–15,000 births in the United States and most of Western Europe. But it was hoped, and often assumed, that dietary therapy would cure many other forms of mental retardation and illness. Alas, this was not to be.

Even in PKU, treatment turned out to be prolonged and arduous. When mass screening began, it was expected that children could resume a normal diet at about age five, when gross brain development was complete. But as evidence grew that ending the diet could result in significant deterioration, scientists became more cautious. It is not easy, however, to follow a 'diet for life'. And even individuals who are treated early and well often have subtle cognitive and behavioural impairment.

Both preparing and eating the PKU diet is burdensome: it requires substitutes for most protein foods, such as bread, rice, pasta, meat, fish, eggs and dairy products. These are supplemented with a special formula containing the other amino acids. Both the low-protein foods and the formula are

expensive. And, of course, many of the social pleasures of eating are lost.

Individuals with PKU do not usually feel sick, so they lack an important incentive to comply with the diet. Compliance is particularly hard for pregnant women, who must drink more of the formula at a time when many are nauseated by it. If they fail to maintain metabolic control, the effects on their offspring can be catastrophic. At high levels, phenylalanine is a teratogen — over 90% of the infants of untreated PKU mothers will be irreversibly retarded. This problem of 'maternal PKU' is an unintended consequence of screening. Before the Guthrie test, few women with PKU bore children. Now, fortunately, many marry and have families. But unless maternal PKU can be controlled, much of the benefit of screening might be erased by the birth of children to untreated women.

PKU has become an exemplar for the promise of genetic medicine. It is true that screening and treatment have allowed many individuals who would have been severely damaged to attend school, hold jobs, and live otherwise normal lives. But the history of PKU also provokes scepticism about simple scientific fixes. 'Solving' the initial problem created the new one of maternal PKU. Moreover, for men and women, coping with PKU has turned out to be a lifelong effort, requiring substantial psychological, financial and social support. The path of scientific prevention did not, after all, obviate the need for social services; if anything, it has increased their importance. ■

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