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Lorenzo's oil: the sequel

The film *Lorenzo's Oil* dramatically illustrated the predicament of families where there is a child with an untreatable inherited metabolic disease. The oil devised as treatment by the father of a child with X-linked adrenoleukodystrophy (X-ALD) has proved disappointing but new research (Stephen Kemp and colleagues. *Nature Medicine* 1998;4:1261–8. See also News and Views, pages 1245–6) brings hope of effective treatment and illustrates a new direction in gene therapy.

There are probably many redundant genes in animal and human cells, which have the capacity to bring into play alternative metabolic pathways. Chemical agents are capable of stimulating the expression of such genes and investigators at Johns Hopkins University have shown that 4-phenylbutyrate (4PBA) may be such an agent for X-ALD cells.

The defect in X-ALD is in the gene encoding the peroxisomal membrane protein, ALDP (adrenoleukodystrophy protein). What the Baltimore researchers have shown is that 4PBA treatment of X-ALD fibroblasts induces the expression of the ALD related protein (ALDRP) gene, causes peroxisomal proliferation, and results in increased β oxidation of very long chain fatty acids (VLCFA). When they gave 4PBA to X-ALD mice there was a substantial fall in VLCFA (almost to normal) in brain and adrenal glands. Trials in patients with X-ALD seem called for.

The effects of 4PBA may not be restricted to X-ALD. It has been used to promote fetal haemoglobin production in haemoglobinopathies and to stimulate the aberrant CFTR gene in cystic fibrosis. The awakening of dormant genes seems an exciting possibility but clearly excitement must not be allowed to run ahead of the facts.

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