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Lorenzo goes to Hollywood

How's this for an idea for a movie storyline? A wealthy couple discover that their young son has a fatal hereditary disease for which there is no known cure. But despite having no prior medical or scientific knowledge, they embark on extensive research, organize symposia and against incalculable odds devise and market a simple mixture that becomes a vital tool to help treat their affected son and many others like him. Sound a little far-fetched? Indeed, but truth, they say, is stranger than fiction, and based on the above true story, Universal Pictures has just released the film *Lorenzo's Oil*, which opened across the United States last month and will shortly be released elsewhere.

"★ ★ ★ ★ This is probably the first — and last — Hollywood picture to grapple with the complexities of fatty acid metabolism."

The disease that struck 5-year-old Lorenzo Odone in 1983 was adrenoleukodystrophy (ALD), a disorder of peroxisomes (small cellular organelles) characterized by deficiencies in the β-oxidation of very long chain fatty acids (VLCFAs), causing them to accumulate in the brain white matter and destroy the myelin sheath that surrounds the neurons. Apart from being genetically heterogeneous — most cases are X-linked but there is a rare autosomal neonatal form of ALD, which closely resembles the archetypal peroxisomal disorder, Zellweger syndrome (including neurologic defects and death in early childhood) — ALD exhibits many different phenotypes. The most severe cases affect young boys such as Lorenzo, who suffer seizures and disturbances of speech and movement, leading to paralysis, deafness and sometimes blindness. However, members of the same family can be either mildly affected with just adrenal insufficiency (Addison's disease), or severely ill, compounded by neurological deterioration. About a quarter of cases have adrenomyeloneuropathy (AMN), a slowly progressive variant that affects adults with little or no cerebral impairment or effect on lifespan. The cause of these curious differences is unknown — it may be due to immunological factors, for example, or possibly a modifying autosomal locus.

As the central defect involves fatty acid metabolism, the likely candidate gene was long suspected to be the enzyme lignoceroyl-CoA ligase, especially as its activity is deficient in ALD fibroblasts. The enzyme has yet to be purified, but there is evidence that its gene is not X-linked, suggesting that a defect in this gene is not the primary genetic lesion.

More concerned with the immediate fate of their son after his diagnosis than the long-term quest to identify the mystery ALD gene, Lorenzo's parents, Augusto and Michaela, decided to take on the rather cautious medical establishment. In October 1984 they funded a meeting of 38 experts at the first ALD conference in Baltimore, that had been organized by Hugo Moser, director of the Kennedy Krieger Institute in Baltimore and a leading authority on ALD. The highlight of the gathering was the suggestion from William Rizzo that oleic acid ($C_{18:1}$) might have a beneficial effect in lowering VLCFA levels in ALD tissues (Rizzo, W.B. *et al. Neurology* **36**, 357–361; 1986). After a long search, the Odones finally located a supplier of an edible form of oleic acid and tested it, first on Michaela's sister, Deirdre, and then Lorenzo. Although his fat levels were soon reduced by half,

they were still twice the normal amount (Michelmore, P. *Reader's Digest*, 109–114; June 1992). The next step, devised by Mr Odone, was to supplement the oleic acid with erucic acid ($C_{22:1}$), another monounsaturated acid and a component of rapeseed oil. With the indefatigable help of Don Suddaby, a British biochemist who plays himself in the film, 'Lorenzo's oil' was synthesized in pure form and has helped to return fatty acid levels to normal in Lorenzo and many other ALD victims.

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Two thumbs up. These enthralling events are portrayed with admirable intensity and conviction in *Lorenzo's Oil*. Directed and co-written by Australian George Miller (a former doctor who is best known for directing the *Mad Max* trilogy) and boasting the star power of Nick Nolte and Susan Sarandon as Lorenzo's parents and Sir Peter Ustinov as a medical expert, *Lorenzo's Oil* is a compelling medical thriller, avoiding the mawkish trappings that might easily have enveloped it. More than any motion picture in recent memory (with the possible exception of *Awakenings*), it will heighten public awareness of the burdens imposed upon patients and their families by errors in metabolism, and should be welcomed by those working in the fields of medicine and genetics. After all, this is probably the first—and last—Hollywood picture to grapple with the complexities of fatty acid metabolism.

But in emphasizing the courage and tenacity of the Odones in their overwhelming desire to find a treatment for ALD, *Lorenzo's Oil* tends to downplay the efforts and cooperation of the researchers working on the disease. In particular, Moser has some reason to be unhappy with his portrayal (under a different name) by Mr Ustinov, although Moser says the film is touching and powerful and will have immeasurable benefits for ALD and genetic disease in general.

The 4:1 mixture of glyceryl trioleate and trierucate that constitutes 'Lorenzo's oil' has proved so successful, albeit in a limited capacity, that despite still waiting for Food and Drug Administration approval in the United States, it is already being widely distributed to ALD patients. Moser and others have performed thorough studies of the dietary effects of 'Lorenzo's oil' on more than 200 ALD patients (Moser, H.W. *et al. J. Inher. metab. Dis.* **15**, 645–664; 1992), and there is no doubt that it can effectively reduce plasma levels of saturated fatty acids to the normal range within a matter of weeks. For patients with AMN or Addison's disease only, the diet seems to prevent any serious decline in neurological function (the oil is supplemented with additional sources of vitamins and essential fatty acids). Sadly, however, for patients such as Lorenzo with the childhood cerebral form of ALD, the oil may delay but does not seem able to halt the irrevocable course of the disease. Lorenzo himself, now 14 years old, is in a vegetative state, for he cannot speak and has only partial contact with the outside world.

With an even more aggressive research programme clearly warranted to combat this devastating disease, the Odones have founded an organization known as the 'Myelin Project' to support research on remyelination therapies, not only for ALD but also for numerous other disorders including multiple sclerosis. Most of the money so far has been raised in Italy, but the project will receive invaluable publicity through Universal Pictures at theatres showing *Lorenzo's Oil*.

While *Lorenzo's Oil* concludes with a sombre reminder of the unremitting course of ALD, there is cause for renewed hope. Writing in *Nature*, Patrick Auborg and Jean-Louis Mandel from INSERM in Paris and their colleagues (including Moser) now describe the positional cloning of the putative ALD gene from the long arm of the X chromosome (Xq28) (Moser, J. *et al. Nature*, in the press). The gene, which sits very close to the cluster of genes controlling colour vision, contains partial and in some cases non-overlapping deletions in six out of 85 ALD patients studied. The predicted gene product is a member of the 'ATP binding cassette' family of membrane transport proteins that includes the cystic fibrosis and multidrug-resistance proteins. Most interestingly, the ALD protein shows significant homology to the 70 kD peroxisomal membrane protein (PMP70) which is mutated in some forms of Zellweger syndrome (Gartner, J. *et al. Nature Genet.* 1, 16–23; 1992). Auborg and colleagues suggest that the normal function of the ALD protein may be to transport the crucial lignoceroyl-CoA ligase into the peroxisomal membrane.

In time, their discovery may yield effective treatments for ALD and myelin disorders in general.

Wouldn't it be something if Hollywood made a film about that?! □