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Editors' view

Rare diseases and orphan drugs

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The word orphan comes from the Greek word orphanos, a child who has lost one parent or both, or an adult who has lost a child. It goes back to the putative Indo-European root ORBH, bereft, as in the Latin word orbus. The obsolete English words orbation and orbity meant orphanhood or childlessness. One who is bereft of freedom is a slave, made to work hard – consider the words for work in some modern European languages, such as the German Arbeit and the Czech robota. In his 1920 play R.U.R. (Rossum's Universal Robots) Karel Čapek introduced the word robot (female robotka) for an imagined race of mechanical men and women. And the etymology reminds us of the link between orphans and the workhouse.

In modern English the word orphan is most commonly used in its original Greek sense, but metaphorical meanings have also emerged. An orphan vehicle, for example, is a discontinued model, and an orphan is a line of type that begins a new paragraph at the bottom of a column or page.

Medical orphans

An orphan virus, such as hepatitis G [1], is not linked to a recognized disease. The term was introduced as long ago as 1954 by Melnick, who described '. . . new viruses, provisionally called "orphan viruses" (as we know so little to what diseases they belong), from patients suspected of having nonparalytic poliomyelitis' [2]. The term is not entirely felicitous – a virus that is initially labelled an orphan may eventually find its missing disease. The same could be said of orphan genes and enzymes. For example, several enzymes have catalytic sites capable of being occupied by millimolar concentrations of ethanol [3]; their physiological roles are not known, at least not yet.

Orphan receptors are receptors that have been identified from gene sequences but have no known endogenous ligand or physiological function. One such, a member of the family of opioid receptors, is called ORL1 or OP4, although it is gradually losing its orphan status. An endogenous ligand, variously called nociceptin [4] and orphanin FQ [5], has been identified, but even non-selective ligands with high affinities for OP1, OP2, and OP3 receptors have very low affinity for ORL1 [6,7] and its physiological role is not known. On the other hand, there are high-affinity ligands that define subtypes of the ORL1 receptor [8].

Rare diseases and orphan drugs

The term orphan disease implies two separate but related concepts. It has been used to describe diseases that are neglected by doctors, and has been applied, for example, to Fabry's disease, alveolar echinococcosis, variant renal cancer, high myopia, and even some common conditions, such as endometrial cancer and tobacco addiction. However, more specifically the term orphan disease is used to designate diseases that affect only small numbers of individuals (so-called health orphans).

There is no satisfactory definition of an orphan disease. In the USA it is defined as one that affects fewer than 200 000 individuals, but in Japan the number is 50 000 and in Australia 2000 [9]. These numbers clearly relate to the population sizes of these countries, but even adjusting for that, the definitions vary from about 1 to 8 in 10 000. The European Community definition is less than 5 in 10 000. The WHO has suggested a frequency of less than 6.5–10

in 10 000, although that seems rather high. There are also lists of diseases, mostly genetic disorders, that are regarded as being rare. As a group they have nothing in common apart from their rarity, but the lists vary strikingly in length; for example, that published by the US National Organization for Rare Disorders contains about 1200 items [10], while NIH's Office of Rare Diseases publishes a list of over 6000, ranging from Aagenaes syndrome (lymphoedema and intrahepatic cholestasis) to Zuska's disease (lactiferous fistulae of the breast) [11].

An orphan drug can be defined as one that is used to treat an orphan disease. For example, haem arginate, used to treat acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria [12], is an orphan drug. However, it comes as a surprise that ibuprofen can also be categorized as an orphan drug, because it has been used to treat an orphan disease, namely patent ductus arteriosus in neonates (whether orphans or not). This observation stresses that barriers to the development of orphan drugs do not occur only at the premarketing stage; in some cases it may not be commercially worth mounting an efficacy trial, even of a drug whose efficacy elsewhere is well established. Indeed, there may be little incentive to mount an efficacy trial of a well established drug in a rare condition, or even in a relatively common condition in a subgroup of individuals – consider the many drugs that are licensed for use in adults but not in children.

In the last 20 years efforts have been made to encourage companies to develop orphan drugs. The Orphan Drug Act in the USA (1983) was succeeded by similar legislation in Japan (1985), Australia (1997), and the European Community (2000) [9]. The encouragement takes three forms: tax credits and research aids, simplification of marketing authorization procedures, and extended market exclusivity [9, 13]. In Europe only the last is available.

In this issue of the *Journal*, Joppi *et al.* show how slow the development of orphan drugs in Europe was during the four years after the introduction of legislation that allowed a drug to be designated an orphan on the basis of rarity of the disease, a plausible mechanism of action, and likelihood of benefit [14]. Of 255 applications to EMEA, only 18 were approved for marketing, and in many cases the supporting studies were poorly designed. This contrasts with reported experience from the USA, where between 1983 and 2002 nearly 1100 drugs and biological products were designated orphan products and 231 were approved. This difference may be due to lack of incentives in Europe compared with the USA, although without directly comparing the two sets of dossiers we cannot know whether there were other reasons; such a comparison would be justified.

Elsewhere, however, it has been suggested, by a pure cost-effective analysis, that the development of orphan drugs is not justified for the majority of rare diseases, since by the main criterion currently used by the National Institute for Health and Clinical Excellence (NICE), such drugs would not be approved for use, at least in the UK, unless their costs were below £30 000 per Quality Adjusted Life Year (QALY) [15]. The tension between equity and affordability is unbearable and pulls in both directions – those with rare diseases deserve to be treated but those with common diseases should not be expected to subsidize them.

All this suggests a new method of defining a rare disease, from the bottom up. If an orphan drug is one that is used to treat a rare disease, a rare disease could be defined as one that is not cost effective to treat, or that costs more than £30 000 per QALY. It also suggests that in Europe we need more incentives to develop orphan drugs and to develop them cost effectively, so as not to compromise our ability to manage other diseases.

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