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Rare diseases, orphan drugs, and orphan diseases

Rare comes from the Latin *rarus* (loosely spaced or sparse) and eventually from the putative Indo-European root *ERE*, denoting separation, as in hermits and eremites and the net-like structures *rete*, *retinaculum*, and *retina*.

Orphan comes from the Greek *orphanos* (a child deprived of one parent or both, or an adult deprived of a child). Metaphorically it denoted poverty and unsupplied food. Its Indo-European root was *ORBH* (bereft) giving the Latin *orbus* and the obsolete English words *orbat* and *orbity* (orphanhood or childlessness). One bereft of freedom is a slave, forced into hard work, as in the German *Arbeit* and the Czech *robot*. Karel Čapek coined the word *robot* (female *robotka*) in his play *R.U.R. (Rossum's Universal Robots, 1920)* to denote an imagined race of mechanical people. And the etymology reflects the link between orphans and the workhouse.

Modern metaphorical meanings of orphan include a discontinued model of a motor vehicle and a line of type beginning a new paragraph at the bottom of a column or page. An orphan virus, such as hepatitis G, is one without a recognised associated disease. Orphan enzymes have catalytic sites that can be occupied by millimolar concentrations of ethanol but have no known physiological roles. Orphan receptors, such as the opioid *OP4* receptor identified from gene sequences, have no known endogenous ligands or physiological functions.

Rare diseases—The National Institutes of Health Office of Rare Diseases lists more than 6000, from Aagenaes syndrome to Zuska's disease. The US definition of a rare disease is one that affects less than 200 000 individuals; the corresponding number in Japan is 50 000 and in Australia 2000. These numbers translate to prevalences of 1-8 in 10 000. The European Community definition is less than 5 in 10 000, and the World Health Organization has suggested less than 6.5-10 in 10 000. Below I suggest an alternative.

Orphan drugs—The US Orphan Drug Act (1984) defines an orphan drug as one with "efficacy against a disease affecting fewer than 200 000 people ... or one that ... will not be profitable for seven years." So,

orphan drugs are either drugs that are used to treat rare diseases (such as haem arginate for porphyrias) or drugs that are too costly to develop. Of course, they are often both, but one does not necessarily imply the other. For example, ibuprofen is an orphan drug when used to treat the rare disease patent ductus arteriosus in neonates (orphans or not). Conversely, drug companies have not thought it profitable to seek authorisation for amitriptyline in post-herpetic neuralgia, making it an orphan drug.

Orphan diseases—This term has been used to denote neglected diseases—for example, Fabry's disease, alveolar echinococcosis, and even some common conditions such as endometrial cancer and diabetes in preschool children. However, it is more often used as a synonym for rare diseases, although some rare diseases respond to drugs that are not orphans.

Now the main criterion currently used by the National Institute for Health and Clinical Excellence (NICE) for approving drugs for use in the United Kingdom is that cost should be below about £30 000 per quality adjusted life year (QALY). This suggests a different method of defining a rare disease. If an orphan drug is one that costs over (say) £30 000 per QALY, and if a disease is a rare disease if an orphan drug is used to treat it, then a rare disease could be defined as one whose treatment costs more than £30 000 per QALY. Or perhaps we should distinguish rare diseases (defined by prevalence) from orphan diseases (defined by cost). And while we're at it, we might call orphan drugs, unQALYfied drugs.

Jeff Aronson *clinical pharmacologist, Oxford*
(jeffrey.aronson@clinpharm.ox.ac.uk)

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