

Rare disease day; 500 years ago

A rare disease is a life-threatening or chronically debilitating condition with a very low prevalence. Several institutions such as Food and Drug Administration (FDA), European Medical Agency (EMA) and Therapeutic Goods Administration (TGA) have put in place recently a regulatory framework to facilitate the development of so called “orphan drugs” for the in-vivo prevention, diagnosis and treatment of these rare disorders. But were there any pharmaceutical interventions to save the lives of these patients before the “orphan drug”-regulation in 1983?

On February 29th (rare date) we organize worldwide the Rare Disease Day.

Rembert Dodoens was a Flemish physician also known as Rembertus Dodonaeus. He was born in Mechelen (actually Belgium) on 29th of June 1517. His most famous writing is his “Cruydenboeck” that can be considered as the first Pharmacopoeia of medicinal herbs. In 1581 he wrote “Medicinalium observationum exempla rara, recognita et aucta. Accessere et alia quaedam, quorum elenchum pagina post praefationem exhibit” is the last book written by Rembert Dodoens medici Caesarei and co-authored by Valesco de Tarenta, Alexander Benedictus, Antonio Benivieni, Maternus Cholinus, Mathias Cornax, Achilles Pirmin Gasser and Gilles de Hertoghe. After a general introduction and a list of cited authors (incl A Vesalius and H Fracastorius), Rembert Dodoens gives us in this multicentric study an extensive list of 189 (54 by Dodoens, 111 cases by Benivenius, 6 by Tarenta, 16 by Benedictus, and 1 patient by Cornax and Gasser) rare diseases in the 16th century such as Aneurisma, Calculus in vesica (stone in the bladder), Catalepsis (seizure), Diabetes, Dysenteria, Gemini pueri (twins), Lapides in vessica fellis (gall stones), Mania cum Melancholia affinitatem habet (M associated with M), Scorbutus, Tetanos, Vermis in vesica (worm in the bladder) and Vomitus sanguinis (vomiting blood). Every casus is followed by a scholion and an annotatio by Dodoens. These are all macroscopic (“de visu et de manu”) or organoleptic observations (“a capite ad calcem”) as Antoni Van Leeuwenhoek (1632-1723) started to use a microscope in cel- and microbiology only in 1674.

For surgical procedures dr Dodoens called upon his local barber-surgeons (amputatio) or stone-cutters (lithotomia). For pharmacological treatment dr Dodoens referred to his own “Cruydenboeck” (Book of Herbs, Mechelen, 1554) with “Plaetse, Tijt, Naem, Natuere, Kracht ende Werckinghe” (flowering place and time, name, identification, pharmacological activity) of 942 plants in 715 wood-block images. Only at the end of the nineteenth century the pharmaceutical industry will take over the manufacturing of medications. Today the European Medicines Agency authorized 118 orphan drugs for oral, parenteral, topical and buccal use. Most of these medications are intended for the treatment of rare cancers (also in children).

Throughout the Middle Ages, to be diagnosed with a (rare) disease had major social (“stigmatization”) and medicinal implications for the individual. Some communities, knowing the importance of an accurate diagnosis, established multidisciplinary groups (“expert centers”) to review suspected cases. Representatives from the church, physicians and people with the disease

("patient representatives") were typically members of these groups. Cousin marriage was common six centuries ago in Europe what most probably resulted in multiple genetic diseases. These disorders could not yet be diagnosed on DNA as James Watson and Francis Crick discovered the double helix only in 1953. The first description of a rare disease attributed to inheritance (alkaptonuria) was by Archibald Garrod in 1902 on the basis on the black color of the urine of his patients. Children were born at home from teenage house-mothers sometimes with the help of a midwife following the guidelines of Eucharius Rhodion's "Der Rosengarten" (1513). Long-time breastfeeding by the mother or eventually by a wet nurse was general practice. Infanticide became exceptional in the sixteenth century and unwanted children were left at the door of church or abbey and the clergy was assumed to take care of their upbringing.

For the last 500 years at least, there has always been interest of the medical and pharmaceutical profession for the diagnosis and treatment of disorders with a low prevalence. Since the end of the last century national agencies (EMA, FDA, TGA) accorded incentives to the pharmaceutical industry to stimulate the marketing of better treatments for patients with rare disorders.

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