Rembert Dodoens (1517-1585) Pioneer in Rare Diseases and Orphan Drugs

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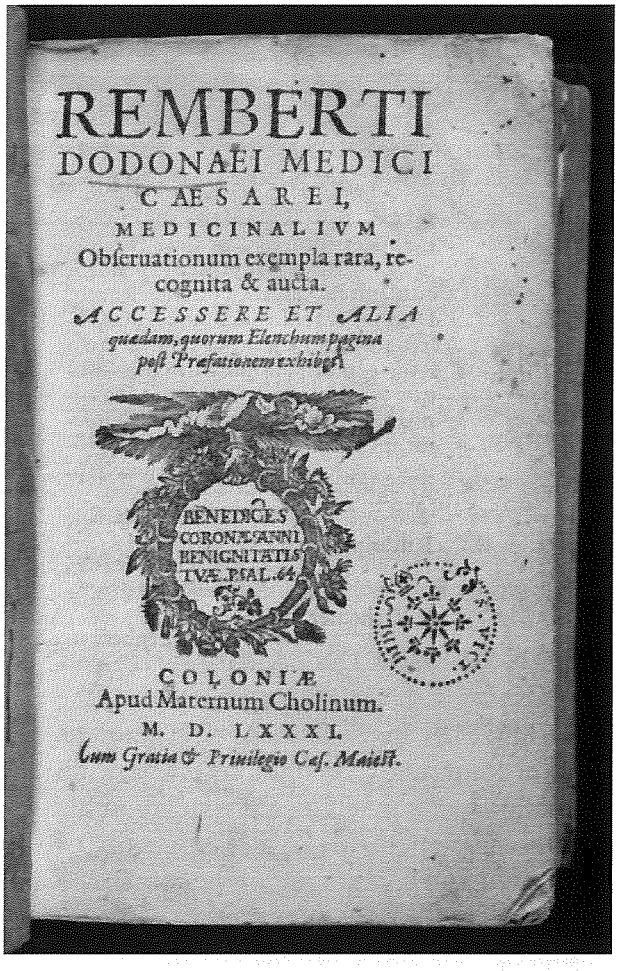
A rare disease is a life-threatening or chronically debilitating condition with a very low prevalence. Several institutions such as Food and Drug Administration (FDA), European Medical Agency (EMA) and Therapeutic Goods Administration (TGA) have put in place recently a regulatory framework to facilitate 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?

Rembert Dodoens was a Flemish physician also known as Rembertus Dodonaeus [1]. He was born in Mechelen (actually Belgium) on 29th of June 1517. He did his studies at the Collegium Trilingue (founded by Desiderius Erasmus in 1518) in Leuven as did Andreas Vesalius and at the University of Leuven (medicine, cosmography, geography) where he graduated as a physician in 1535. After his studies he established himself as a physician in his hometown Mechelen and turned down a position of professor in medicine at the University of Leuven and court physician of king Philip II of Spain. After extensive travelling he joined the Faculty of Medicine at Leiden University as a professor in 1582 where he died on 10th of March 1585. He was married twice and had five children. His most famous writing is his "Cruydenboeck" that can be considered as the first Pharmacopoeia of medicinal herbs [2]. In 1581 he wrote "Medicinalium observationum exempla rara" [3]. Two copies of this book written in Latin are kept at the tabularium of the central library in the University in Leuven: the first edition (1581, 397 pages, printed by Maternus Cholinus in Köln) is catalogued as DPA510 and the second (1585, printed by Christopher Plantijn in Antwerp) is catalogued as 7A875. In 1543 Andreas Vesalius, his schoolmate in Leuven, had published the seven volume revolutionary work on human anatomy, "De Humani Corporis Fabrica", based on dissections of human bodies. In 1546 Hieronymus Fracastorius, a colleague of Vesalius in Padua, suggested that epidemic diseases could be caused by transferable tiny particles in his "De Contagione et contagiosis Morbis" [4].

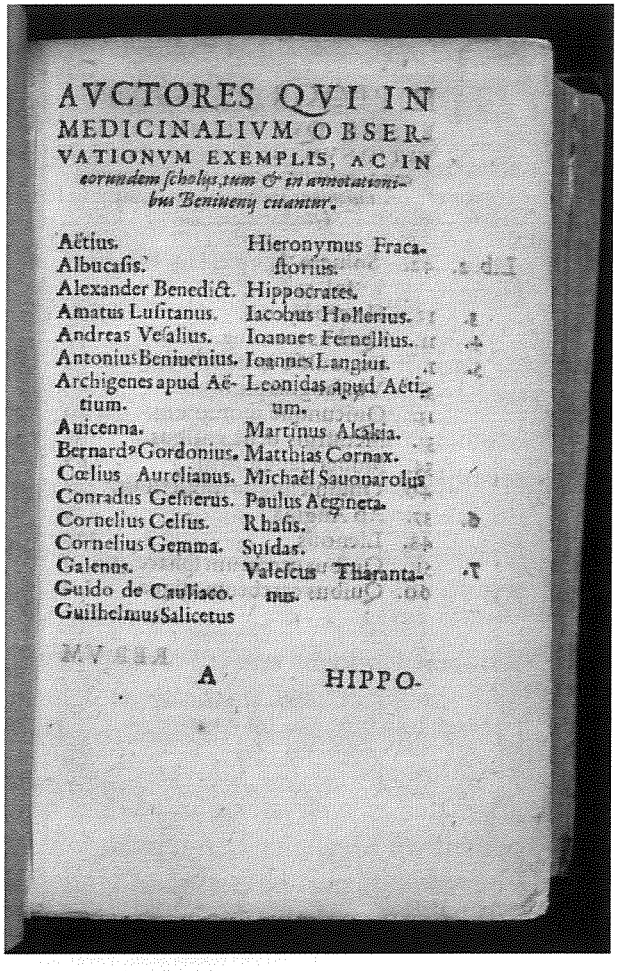
"Medicinalium observationum exempla rara, recognita et aucta. Accessere et alia quaedam, quorum elenchum pagina post praefationem exhibit" is the last book written by Rembert Dodoens medici Caesarei and co-authored by Valesco de Tarenta, Alexander Benedictus, Antonio Benivieni, Maternus Cholinus, Mathias 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 [5].



REMBERTI
DODONAEI MEDICI
CAESAREI,
MEDICINALIVM
Obseruationum exempla rara, recognita & aucta.
ACCESSERE ET ALIA quædam, quorum Elenchum pagina post Præfationem exhibet.

BENEDICES CORONÆ ANNI BENIGNITATIS TVÆ. PSAL. 64.

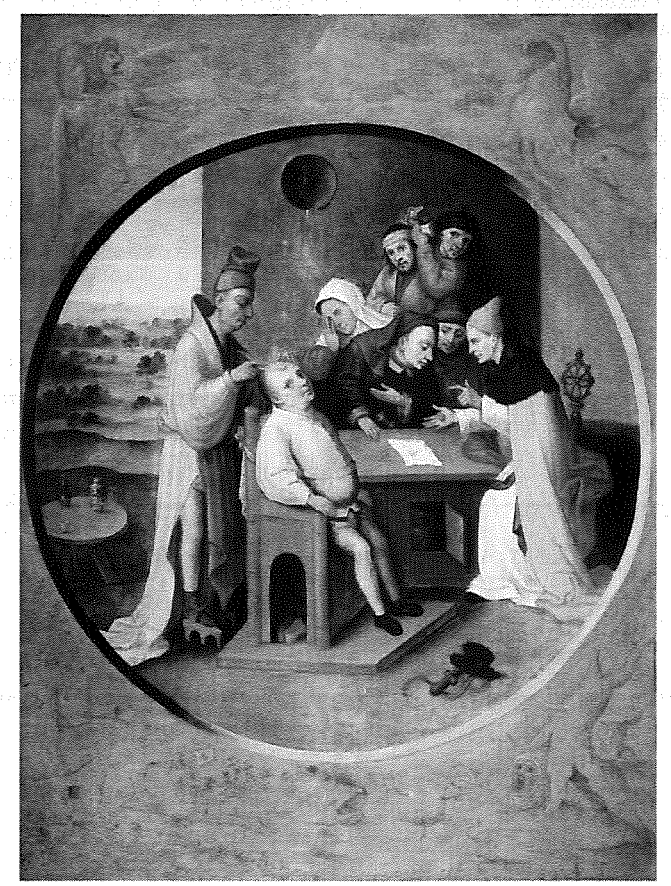
COLONIÆ
Apud Maternum Cholinum.
M. D. LXXXI.
Cum Gratia & Priuilegio Cæs. Maiest.



AVCTORES QVI IN MEDICINALIVM OBSERVATIONVM EXEMPLIS, AC IN *eorundem scholijs tum & in annotationibus Beninenij citantur.*

Aëtius.
Albucasis.
Alexander Benedict.
Amatus Lusitanus.
Andreas Vesalius.
Antonius Beniuenius.
Archigenes apud Aëtium.
Auicenna.
Bernard⁹ Gordonius.
Cœlius Aurelianus.
Conradus Gesnerus.
Cornelius Celsus.
Cornelius Gemma.
Galenus.
Guido de Cauliaco.
Guilhelmus Salicetus
Hieronymus Fracastorius.
Hippocrates.
Iacobus Hollerius.
Ioannes Fernellius.
Ioannes Langius.
Leonidas apud Aëtium.
Martinus Alcàkia.
Matthias Cornax.
Michaël Sauonarolus
Paulus Aegineta.
Rhasis.
Suidas.
Valescus Tharantanus.

A HIPPO-



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. Operating procedures for the production of his "orphan drugs" from plant material (bolus, confectio, decoctum, electuarium, hostia, pilula, potio, pulvis, syrupus, trochiscus for internal use and balneum, cauterium, clysterium, collyrium, emplastrum, gargarisma, lotio, unguentum for external use) are mentioned at the end of some monographs. Standardization of these compounding procedures by local pharmacists continued further with the publication of several city and (supra)national pharmacopoeias. 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 [6]. 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 [7,8]. 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. Diagnostic (uroscopy) and surgical procedures have changed tremendously over time. As most of these diseases have a genetic background the contribution of genetic laboratories has been tremendous. Life-style changes (scorbutus/vitamin C) and vaccinations (tetanos/Clostridium) have almost eliminated some and a better understanding of the diseases has led to prevention and better (intravenous) therapy. Compounding medications following Standard Operating Procedures and Good Manufacturing Practice is still practiced today but most of the medicinal products for the prevention, diagnosis and treatment of a limited number of rare diseases are now commercially available. More basic research and randomized clinical trials are needed for the cure of patients with other (ultra-)rare diseases.

No competing interests

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