

Rare diseases: an historical introduction

Juan Antonio Rodríguez-Sánchez (*) and Raúl Velasco Morgado ()**

(*) orcid.org/0000-0002-9949-9168. Historia de la Ciencia, Universidad de Salamanca. jarshm@usal.es

(**) orcid.org/0000-0002-6958-9090. Historia de la Ciencia, Universidad de Salamanca. rvmorgado@usal.es

Dynamis
[0211-9536] 2022; 42 (2): 351-369
<http://dx.doi.org/10.30827/dynamis.v42i2.27713>

Fecha de recepción: 3 de mayo de 2022
Fecha de aceptación: 3 de septiembre de 2022

1. An emerging health issue (*)

Between slogans that deny, question, or qualify what is “rare”, and others that maintain that “normal” is unreal, the last decades of the 20th century have witnessed the popularisation of “rare diseases”. Despite they did not originally constitute a category in medical taxonomies, their impact on health systems has led to the development of a descriptor in the Medical Subject Headings of the National Library of Medicine of the United States¹, specific atlases and treatises², priority lines of research and a healthcare reorganisation. However, beyond representing another example of how socioeconomic permeates the scientific, this new concept shows new multiple and revealing interactions.

(*) This dossier has been developed within the research projects: “Investigación, redes asistenciales y empoderamiento: respuestas sociales y científicas a las enfermedades raras en la Península Ibérica (1940-2015)” (HAR2017-87318P), funded by the Spanish Ministry of Science, Innovation and Universities, and “Enfermedades raras: cultura visual de la rareza en España y Portugal en la Edad Contemporánea”, funded by the University of Salamanca (PIC2-2020-29)

1. Rare Diseases. MeSH descriptor. Medical Subject Headings. National Library of Medicine. National Center for Biotechnology Information. Accessed May 8, 2021, <https://www.ncbi.nlm.nih.gov/mesh/?term=rare+diseases>
2. Examples can be found in: Manuel Cruz Hernández, and Juan Bosch Hugas, *Manual ilustrado de enfermedades raras* (Madrid: Ergon, 2013); *Orphan Drugs and Rare Diseases*, eds. David C. Pryde, Michael J. Palmer (Cambridge, UK: The Royal Society of Chemistry, 2014); *Rare Diseases*, ed. Zhan He Wu (IntechOpen, 2020), doi: 10.5772/intechopen.83131; and the *Encyclopaedia for professionals* available at Orphanet website, accessed Nov 15, 2022, https://www.orpha.net/consor/cgi-bin/Disease_ProEncyclo.php?lng=EN These few examples shows different perspectives and inclusion criteria in the selection of diseases, revealing the relative instability of the term.

The public perception of “rare diseases” —expressed with the plural that unifies them without erasing their multiplicity—, has been constructed through the media. Patients and family organisations in synergy with the mass media and the support of online social networks have provided their own defining elements: health problems, generally of genetic origin and manifested in the paediatric age group, with difficulties in their diagnosis and treatment and scarce scientific knowledge about them, that represent a challenge for the adequately care of those affected, who also often present a high degree of disability³. This powerful mediatic message also feeds news and advertising with the leading role of popular figures and members of the royal families, who act as ambassadors of solidarity.

The emphasis of the social movement of patients in looking for common characteristics of these more than seven thousand diseases has been an arithmetical strategy. The total number of cases represents between six and eight per cent of the population —about thirty million people affected in the European Union—. This tactic has led them to be considered a public health priority. The application of the Rare2030 study through the European Action Plan for Rare Diseases 2023⁴ is the most recent step in a succession of Community regulations that began in 1997 and that has grounded national plans in the Member States⁵.

However, despite the political and legislative determination, socioeconomic considerations have revived debates on health system models and the sustainability of the welfare state⁶. Although they also have given rise to solidarity demonstrations, the high costs of research, healthcare and drug

-
3. EURORDIS (European Organisation for Rare Diseases), *Rare diseases: understanding this Public Health priority* (Paris: EURORDIS, 2005). Andrew W Knight, Timothy P Senior, “The common problem of rare disease in general practice,” *Medical Journal of Australia* 185, no. 2 (2006): 82-83; Madeleine Akrich, Orla O’Donovan, and Vololona Rabeharisoa, *The entanglement of scientific and political claims: towards a new form of patients activism* (Paris: Papiers de Recherche du CSI, 2013), <https://halmines-paristech.archives-ouvertes.fr/hal-00913925>
 4. Anna Kole, Victoria Hedley, et al., *Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today*. 2021. Accessed Jun 20, 2022, https://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf
 5. Victoria Hedley, Valentina Bottarelli, Ariane Weinman, and Domenica Taruscio, “Shaping national plans and strategies for rare diseases in Europe: past, present, and future,” *Journal of Community Genetics* 12 (2021): 207-216, <https://doi.org/10.1007/s12687-021-00525-4>
 6. See the special number coordinated by Rita María Ferrelli, Bernardino Fantini, and Domenica Taruscio, “Health systems sustainability for rare diseases,” *Annali dell’Istituto Superiore di Sanità* 55, no. 3 (2019): 249-304.

production have been the main reasons for questioning the efficiency of the current health and social care paradigm when it comes to preserving the rights of minorities.

Otherwise, rare diseases have been assumed as an encouraging challenge for reflections and proposals: the promotion of prevention —materialised in neonatal screening and prenatal diagnosis—, the specific training for general practitioners, the development of multidisciplinary teams, and the implementation of comprehensive support services to illness and dependency are some of the critical points detected⁷. Such approaches would hardly have arisen without the transformation of the role of the patient. The right of the lay community to actively participate in public health systems and in defending the importance of knowledge built from the experience has modified the role of the sick person both in her relationship with health professionals and in the individual and collective process of empowerment. New perspectives of citizenship in health, patients, associations and federations of low prevalence diseases have been decisive for the transition to an interdisciplinary approach with complex networks. A system with connections not only between physicians or researchers but also between professionals and society that, from the interpretations of health as a consumer good, has been characterised by a diversity of stakeholders⁸.

Current affairs and multiple approaches will thus be master lines in the historical research on rare diseases. It is precisely these characteristics of temporality and multidisciplinary that will frame it in the history of the present⁹, without omitting its role within the social demand for responses to a problem of unquestionable complexity.

-
7. Maravillas Izquierdo, Alfredo Avellaneda, "Enfoque interdisciplinario de las enfermedades raras: un nuevo reto para un nuevo siglo," *Medicina Clínica (Barcelona)* 121, no. 8 (2003): 299-303; Manuel Ortega, "Las enfermedades raras como paradigma científico en atención primaria," *Cuadernos de Gestión* 10, no. 2 (2004): 41-44; Francesc Palau, "Enfermedades raras, un paradigma emergente en la medicina del siglo XXI," *Medicina Clínica (Barcelona)* 134, no. 4 (2010): 161-168; Georgi Iskrov, Rumen Stefanov, and Rita María Ferrelli, "Health systems for rare diseases: financial sustainability," *Annali dell'Istituto Superiore di Sanità* 55, no. 3 (2019): 270-275.
 8. *The dynamics of patient organizations in Europe*, eds. Madeleine Akrich, João Nunes, Florence Paterson, and Vololona Rabeharisoa (Paris: Presses de l'École des Mines, 2008).
 9. About this historiographical approach, see, between others: Eugenia Allier Montaño, "Balance de la historia del tiempo presente. Creación y consolidación de un campo historiográfico," *Revista de Estudios Sociales* 65 (2018): 100-112.

2. Disease and rarity

From a diachronic point of view, the relationship between disease and “rarity” —understood as something extraordinary or infrequent— has taken many different forms throughout history. Furthermore, over the same time period, very different concepts have coexisted due to the forging of new meanings, the survival of previous notions and the different uses of the concept by the different agents involved. That is why, when we propose to present a dossier on rare diseases, we must first delimit certain concepts and do so from a *longue durée* perspective.

The classical and iatrogenic concept of “rare disease” has its origin in the 17th century medicine. In the context of the science of this period, the interest in the extraordinary in the natural world was a constant in the cabinets of curiosities (*Wunderkammern*) of scholars and collectors, where rare items were among the most prized components¹⁰. Medical culture, of course, was no stranger to those practices of knowledge production and to this new approach to Nature, with curiosity and wonder. By assuming the Sydenhamian concept of morbid species, medicine as a science generated rarities in the same style that natural history did. In this framework, these can be understood, either as anomalous manifestations of Nature or as rare expressions of it. Thomas Sydenham himself supported the first of these theses, rejecting them when constructing new species, but the highly influential Hermann Boerhaave chose to accept them as infrequent forms and, therefore, collectable, awaiting the appearance of new ones that would define a different species¹¹. As a consequence of this position, the diagnosis of singular cases began to gain value in epistemological terms, but also in terms of scientific authority. The publication of rare case collections became a genre itself and a good example of its success is the *Observationum rariorum* of the Dutchman Stalpartii van der Wiel (1620-1702), which was translated

10. See: Lorraine Daston, and Katharine Park, *Wonders and the order of nature, 1150-1750* (New York: Zone Books, 1998) and José Ramón Marcaida López, *Arte y ciencia en el Barroco español: Historia natural, coleccionismo y cultura visual* (Madrid: Fundación Focus-Abengoa; Marcial Pons Historia, 2014).

11. Pedro Lain Entralgo, *La historia clínica: historia y teoría del relato patográfico* (Madrid: CSIC, 1950), 224.

from his mother tongue into Latin and French and reedited several times until the 18th century¹².

During the *Ottocento*, anatomoclinical and laboratory medicine created hundreds of new diseases some of them of low prevalence. Due to its specific characteristics, anatomical singularity became the medical rarity par excellence during this period. The development of teratology as a discipline and of paediatrics as a speciality encouraged a special interest in dysmorphogenetic syndromes. Rare cases were “collected” through diagnosis and exhibited in meetings, scientific journals, and anatomical and anthropological museums. We cannot forget that these practices were generated in a social context in which there was a public interest in anatomical rarities and freak shows frequently circulated in the streets of towns and cities¹³.

Several social changes determined the construction of a new concept of rare diseases during the second half of the 20th century. The molecularisation and geneticisation of the pathology defined thousands of new nosological entities that, due to the idiosyncrasies of the biomolecular model, usually have a low or very low prevalence¹⁴. As anticipated above, in a capitalist context, one of the most important consequences of this phenomenon was the emergence of a financing problem. In 1962, the Kefauver Harris Amendment to the United States Federal Food, Drug, and Cosmetic Act forced pharmaceutical companies to demonstrate the efficacy of drugs, a requirement that substantially increased the research and development processes. Given this new legal framework, diseases with a low prevalence were clearly unattractive to the pharmaceutical industry due to their limited target customers¹⁵. In response, a significant social movement emerged led by the patients’ associations themselves.

However, in the absence of a sufficiently strong associative fabric, the response of society was really slow, even though the parents of affected children of some low-prevalence entities were the first to join the associative

-
12. Stalpartii Van der Wiel, *Observationum rariorum medic. Anatomic. Chirurgicarum centuria prior. Accedit de unicornu dissertatio* (Leiden: 1687).
 13. On freak shows, see: Robert Bogdan, *Freak Show: Presenting Human Oddities for Amusement and Profit* (Chicago, Londres: The University of Chicago Press, 1988).
 14. Regarding molecularisation and geneticisation and its relationship with rarity, see Raúl Velasco Morgado’s paper in this dossier.
 15. Koichi Mikami, “Orphans in the market: The history of orphan drug policy,” *Social History of Medicine* 32, no. 3 (2019): 609-630.

movement¹⁶. In fact, one of the earliest patient organisations was the NTSAD (National Tay-Sachs & Allied Diseases Association), founded in 1957 by five couples from the New York area with affected children¹⁷.

It was not until 1983 that several associative leaders created a National Organization for Rare Disorders (NORD) to demand from Congress a specific regulation for this type of diseases. In the same year, the Reagan administration passed an Orphan Drug Act that provided huge profits to pharmaceutical companies investing in drugs for low-prevalence diseases. Consequently, the concept of “orphan drug” was built, bringing a new meaning to rare diseases. From that legislative text, the term was defined statistically and linked to an economic and political problem. The relationship with these axes is such that the threshold for legally affirming that a disease is rare is different in each country or region: while in the United States, it is established below 200,000 people affected (approximately 1 in 1700), in the European Union this limit is 5 in 10,000 (approximately 1 in 2000), while in North Korea, for example, the threshold is in 20,000 patients in the country (approximately 1 in 2500).

During the following decade, patient associations themselves proceeded to give a new meaning to the term “rare”. In this way, they tried to make visible the medical and social effects linked to the ignorance of the minority. Despite opinions contrary to its use and slogans that seemed to

-
16. Regarding the associative movement phenomenon in rare diseases see: Volona Rabeharisoa, “The struggle against neuromuscular diseases in France and the emergence of the ‘partnership model’ of patient organization,” *Social Science & Medicine* 57, no. 11 (2003): 2127-2136, doi: [https://doi.org/10.1016/S0277-9536\(03\)00084-4](https://doi.org/10.1016/S0277-9536(03)00084-4); Volona Rabeharisoa, “From representation to mediation: the shaping of collective mobilization on muscular dystrophy in France,” *Social Science & Medicine* 62, no. 3 (2006): 564-576, doi: <https://doi.org/10.1016/j.socscimed.2005.06.036>; Michel Callon, and Vololona Rabeharisoa, “The growing engagement concerned groups in political and economic life: lessons from the French Association of Neuromuscular Disease Patients,” *Science, Technology & Human Values* 33, no. 2 (2008): 230-261, doi: <https://doi.org/10.1177/0162243907311264> and, in the general framework of European associationism: Akrich, Nunes, Paterson, Rabeharisoa, *Dynamics of patients organizations*; Vololona Rabeharisoa, Michel Callon, Angela Marques Filipe, João Arriscado Nunes, Florence Paterson, and Frédéric Vergnaud, *The dynamics of causes and conditions: the rareness of diseases in French and Portuguese patients’ organizations’ engagement in research* (Paris: Centre de Sociologie de l’Innovation, 2012. CSI Working Papers Series, 26).
 17. Emily Kennedy Anthes, “The Chosen Genes: Jews, Genetics, and the Future of Ethnic Medicine,” (Master diss., Massachusetts Institute of Technology, 2006), 16, <https://dspace.mit.edu/handle/1721.1/39446>

contradict its adoption, the term “rare diseases” became part of the name of most organizations, institutions and legal regulations¹⁸.

The emergence of this new socioeconomic concept did not mean the disappearance of the classical iatrocetric one. Quite the contrary, both were forced to coexist —and to mutually adapt to each other—, as were the actors involved themselves: clinicians, researchers, pharmaceutical companies, states and, of course, patients, their families and their associations. Each of these actors uses the term “rare disease” in different ways and with different objectives. This led Caroline Huyard to define rare diseases as a boundary object using the term coined by Joan Fujimura for this type of phenomenon¹⁹.

3. From the social sciences to the history of science

The history of rare diseases has encountered some obstacles to its development. The social history of public health has been aimed at research problems with a measurable economic or epidemiological impact. From this perspective, a minority disease did not have the appropriate characteristics to be chosen as a historiographical topic. The appearance of the new socioeconomic concept of rare diseases—plural and unifying— was the key to the emergence of academic works in this line.

Since the late 2000s, the social sciences began to dissect the term. The aforementioned Caroline Huyard’s works on the problem are fundamental, especially her article “How did rare disorders become ‘rare diseases?’” (2009) and her monograph *Rare. Sur la cause politique des maladies peu fréquentes*, published in 2012²⁰. At the same time, and also from sociology, several

-
18. The most used term internationally is “rare diseases”, followed very far by “orphan diseases”. The use of other terms as “rare disorders”, “rare conditions”, “neglected diseases” or “low-frequency diseases” is very scarce. Trevor Richter *et al.*, “Rare disease Terminology and Definitions – A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group,” *Value in Health* 18 (2015): 906-914, <http://dx.doi.org/10.1016/j.jval.2015.05.008>
 19. Caroline Huyard, “How did uncommon disorders become ‘rare diseases?’ History of a boundary object,” *Sociology of Health & Illness* 31, no. 4 (2009): 463-477, doi: <https://doi.org/10.1111/j.1467-9566.2008.01143.x>; Joan H. Fujimura, “Crafting science: standardized packages, boundary objects and ‘translation’,” in *Science as Practice and Culture*, ed. Andrew Pickering (Chicago: University of Chicago Press, 1992), 168-211.
 20. Huyard, “How did uncommon disorders become ‘rare diseases?’”; Caroline Huyard, *Rare. Sur la cause politique des maladies peu fréquentes* (Paris: EHESS, 2012).

authors, such as Volona Rabeharisoa, Madeleine Akrich, Michel Callon and João Nunes, have dedicated works to outlining the phenomenon from the study of patient associationism, with neuromuscular diseases being the most studied case in the European geographical context. Their research is part of the MEDUSE project (Governance Health and Medicine: Opening Dialogue between Social Scientists and Users) involving four countries (France, Belgium, Portugal and the United Kingdom)²¹.

Recourse to the social sciences is usually referred to as one of the characteristics of the history of the present. The reinterpretation of *évènementielle* history, the questioning of the supposed objectivity/subjectivity binomial, the place of memory and, consequently, the use of methodologies with oral sources, are also often cited as typical of this historiographical trend²². This approach makes it possible to address a current issue, both in terms of its conceptualisation and the debate generated, and stimulates historical analyses of the unconnected origins of the problem. For this reason, the incorporation of the history of medicine and science into the debate has been very recent. In a 2019 article, Koichi Mikami explored the initial problems of the US Orphan Drug Act, describing it as market-based, and began to explore the first legislative initiatives in the Old Continent, focusing on the case of the United Kingdom²³. Along the same lines, Luiz Alves Araújo Neto and Luiz Antonio Teixeira have studied the creation of public policies for these diseases in Brazil since the 1990s and have tried to describe how health systems have been modified by the new agendas imposed by this new nosotaxic group²⁴.

From the point of view of the history of diseases, some low-prevalence morbid entities have attracted the attention of medical historiography for different reasons. Genetic diseases are a particular case due to their high impact on the public sphere. Recent monographs, such as those by Andrew Hogan²⁵ and Soraya de Chadarevian²⁶, have revealed multiple aspects of

21. See n. 16.

22. Israel Sanmartín, "Las historias inmediatas y del presente en la historiografía actual," *Historiografías* 15 (2018): 36-51.

23. Mikami, "Orphans in the market".

24. Luiz Alves Araujo Neto, and Luiz Antonio Teixeira, "New problems of a new health system: the creation of a national public policy of rare diseases care in Brazil (1990s-2010s)," *Salud Colectiva* 16 (2020): e2210, <https://doi.org/10.18294/sc.2020.2210>

25. Andrew J. Hogan, *Life histories of genetic disease: patterns and prevention in postwar medical genetics*, (Baltimore: Johns Hopkins University Press, 2016).

26. Soraya de Chadarevian, *Heredity under the Microscope: Chromosomes and the Study of the Human Genome*, (Chicago, Londres: The University of Chicago Press, 2020).

the constitution of clinical genetics and the construction of genetic diseases. Among these, gonadal dysgenesis has received special attention because of its relationship to the debates around gender and genetic sex.²⁷ Metabolic diseases have also received some attention but among more than a thousand disorders classified as inborn errors of metabolism, only a tiny group has been historically analysed. Given its interest in the origins of molecular practices of secondary prevention through newborn screening, the most studied has been phenylketonuria²⁸. In addition, due to its interesting association with minority ethnic groups in its clinical construction, Tay-Sachs disease has been also the subject of monographic studies²⁹. Finally, rare diseases related to communicable diseases have been a particularly neglected group, although post-polio syndrome has been an exception, due to its connection with a previous epidemic phenomenon³⁰. However, the linking of all these diseases

-
27. See: Monica de Paula Jung, Maria Helena Cabral de Almeida Cardoso, Maria Auxiliadora Monteiro Villar, and Juan Clinton Llerena Jr., "Revisitando o desvendamento da etiología da síndrome de Turner," *História, ciências, saúde - Manguinhos* 16, no. 2 (2009): 361-376, <https://doi.org/10.1590/S0104-59702009000200005>; David Andrew Griffiths, "Shifting syndromes: sex chromosome variations and intersex classifications," *Social Studies of Science*, 48, no. 1 (2018): 125-148, doi: 10.1177/0306312718757081.
 28. Diane B. Paul, "How PKU became a genetic disease," in *Human heredity in the Twentieth Century*, eds. Bernd Gausemeier, Staffan Müller-Wille, Edmund Ramsden (London – New York: Routledge, 2013), 179-192; Diane B. Paul, Jeffrey P. Brosco, *The PKU Paradox: A Short History of a Genetic Disease*, (Baltimore: Johns Hopkins University Press, 2013) and Diane B. Paul, Paul J. Edelson, "The struggle over metabolic screening," in *Molecularizing biology and medicine. New practices and alliances, 1910s-1970s*, eds. Soraya de Chadarevian, Harmke Kammaing (Amsterdam: Harwood Academic Publishers, 1998), 203-220.
 29. Shelley Z. Reuter, *Testing fate: Tay-Sachs disease and the right to be responsible* (Minneapolis: University of Minnesota Press, 2016).
 30. The necessary location of post-polio syndrome as history of the present and the use of oral sources impregnates its historical research with reinterpretations motivated by its current health impact. For this reason, its presence has appeared explicit or implicit in many publications, especially in the collective ones and in those that have evaluated the impact of polio at a national level. An example of this is the special issue that appeared in this same journal and coordinated by Rosa Ballester and María Isabel Porras, eds. "Políticas, respuestas sociales y movimientos asociativos frente a la poliomielitis: la experiencia europea (1940-1975)," *Dynamis* 32, no. 2 (2012): 273-414. Danielle Fialho da Silva has worked on the problem in recent years: "Redes de solidariedade do sentir e do resistir: associativismo dos pacientes com fibromialgia e síndrome pós-pólio nos meios digitais (2004-2021)" (PhD diss., Casa de Oswaldo Cruz/Fiocruz, 2021); Juan Antonio Rodríguez-Sánchez, and Inês Guerra, "La 'rara' secuela de una epidemia: el caso del síndrome postpolio," in *Enfermedades raras. Contribuciones a la investigación social y biomédica*, ed. Juan Coca (CEASGA, 2019); Daniela Testa, *Del alcanfor a la vacuna Sabin: la polio en la Argentina* (Buenos Aires: Biblos, 2018); Dora Vargha, *Polio across the Iron Curtain: Hungary's Cold War with an epidemic* (Cambridge: CUP, 2018). A review of the subject can be found in

to rarity has been only tangentially addressed and, with a few exceptions, they have been studied without assuming their inclusion within rare diseases, with their common and differentiating elements as a group.

It is necessary to understand that not all people affected by rare diseases have felt comfortable under the umbrella of the new category, as exemplified by post-polio syndrome itself, whose patients have had to cope with the difficult combination of its epidemic causes and its minoritarian consequences³¹. Amyotrophic lateral sclerosis, with a long history, has also tried to free itself from the limitations of the label; and even haemophilia, with a past that gives it an identity with a well-differentiated profile³². In these cases, history has transitioned between testimonial forms, both from patients and doctors, narrative histories, and investigations in which the minority nature has not been emphasised.

Within the historiographical line of visual studies of medicine and science, rare diseases have only timidly begun to be addressed, although the study carried out by Liliana Costa and Ana Isabel Veloso on the image in cinema for the period of the last two decades of the 20th century and the first two decades of the 21st century using content analysis as a method can be highlighted³³.

Our research group has worked on the problem in recent years and, in addition to this dossier, two collective monographs have been prepared and will be published soon: one edited by ourselves and another in collaboration with Inês Guerra (Universidade da Maia, Portugal) and Dilene Raimundo (Casa de Oswaldo Cruz, Brazil). Both volumes contain works that, among others, use quantitative and qualitative methods from the social sciences to

Juan Antonio Rodríguez-Sánchez, "Un presente lleno de historia(s): la poliomielitis, entre las secuelas y el legado", *Dynamis* 40, no. 2 (2020): 505-516.

31. Juan Antonio Rodríguez-Sánchez, and Inês Guerra Santos, "Cuerpos deslegitimados, síndromes ignorados: de la poliomielitis al síndrome post-polio en España," *Clio & Crimen* 16 (2019): 393-412.
32. We must mention here the framework provided in the work by Charles A. Owen, *A History of Blood Coagulation* (Rochester: Mayo Foundation, 2001). The links with the European Royal Houses attracted attention to this coagulopathy as demonstrated by the classic works of George I.C. Ingram, *The history of haemophilia* (Margate: Eyre&Spottiswoode, Thanet Press, 1976). From the 1980s the history of hemophilia was linked to that of the HIV pandemics, much richer in historiographic production. See, as example: Susan Resnik, *Blood saga: hemophilia, AIDS, and the survival of a community* (Berkeley: University of California Press, 1999). The most recent contribution is: Stephen Gregory Pemberton, *The bleeding disease: hemophilia and the unintended consequences of medical progress* (Baltimore: Johns Hopkins University Press, 2011).
33. Liliana Vale Costa, and Ana Isabel Veloso, "Portraying rare and misdiagnosed diseases in movies: a Content Analysis, 1980-2018," in *Communicating Rare Diseases and Disorders in the Digital Age* (IGI global, 2020).

address the phenomenon of associationism, the construction of experts in low-prevalence diseases and scientific collecting practices related to rarity or the image of this group of diseases projected by the press since the beginning of the 21st century³⁴.

4. A history of rare diseases: transnational perspectives, multidisciplinary approaches

The historical approach to rare diseases must start from an integrative perspective of multidisciplinary, both in approaches and methodologies. This dossier has been designed on this premise and the most consolidated and suggestive lines of historical research have been selected for an understanding of the problem in its complexity. The various geopolitical spheres —Japan, Brazil and the Iberian Peninsula— provide a rich transnational comparative historical study. The discussed topics address the defining characteristics of rare diseases, from the perspective of a history of the present ranging from political history to visual studies, with attention to healthcare spaces, professional expertise and, especially, patients, their associative movements, and their impact on legislation.

The medical and scientific aspects of minority diseases have been studied for different periods and historical contexts. The iatrogenic and individualising conception of some anatomoclinical syndromes dates back to the 19th century, but its peak is linked to the development of genetic pathology. Medical treatises constitute an exceptional catalogue, due to their descriptive and pedagogical function and their role in the construction of these entities, supported by images showing distinctive and, if possible, pathognomonic signs. In their paper, Juan Antonio Rodríguez-Sánchez and María José Ruiz Somavilla explore the visualities generated on Turner syndrome in the second half of the 20th century and show how the portrayed patients disappeared as people to become stereotypes that would end up making diagnosis difficult due to their infrequent coincidence with the real manifestations.

34. *Conocimiento y empoderamiento: las enfermedades raras y el síndrome postpolio (1950-2018)*, edited by Juan Antonio Rodríguez-Sánchez, Raúl Velasco Morgado, Inês Guerra Santos, and Dilene Raimundo (Salamanca: Ediciones Universidad de Salamanca, in press) and *Las enfermedades raras: una historia del presente*, eds. Juan Antonio Rodríguez-Sánchez, and Raúl Velasco Morgado (Madrid: La Catarata, in press).

The beginnings of specialised clinical care for low-prevalence diseases are studied by Raúl Velasco Morgado. Based on the case of the Institute of Clinical Biochemistry “Fundación Juan March” in Barcelona, his article studies the birth of “reference centres” in Spain as a direct consequence of the process of molecularisation of biomedicine. These new laboratory-centered spaces were the result of the need to centralise care and research for a single low-prevalence condition for an large geographical area in terms of efficiency, but not only. It is a story in which the actors multiply: doctors, researchers, politicians, health managers and parents of affected children; and all have with their own interests in the process of setting up such type of centres. In addition, the Spanish context of late Francoism and the democratic transition with its idiosyncrasy in terms of the social perception of intellectual disability, and the North American influence in transit through the trips of Spanish researchers will appear in this work as very relevant agents in the entire process.

These diagnostic and healthcare needs are also present in the remaining papers, with approaches to the problem in Japan, Brazil and the Iberian Peninsula. However, it is the focus in the search for therapeutic responses —as the core of the interactions between the agents mentioned— that shows a common link in these works and provides a transnational perspective. Scientific advances and the development of the pharmaceutical industry, especially biotechnology, have raised expectations not only among health professionals but mainly among affected people and their families. It is they who, exemplifying the transformation of the patient’s role, will be a key element in the development of regulations on rare diseases in the analysed countries.

Both Velasco-Morgado and Mikami have identified a history of social movements since the late 1960s. The first one shows, in the dictatorial Francoist context of restricted associationism, the particular role of a leader of ASPANIAS (Association of Parents of Subnormal Children and Adolescents) and FEAPS (Spanish Federation of Associations for the Protection of Subnormal People) in the financing of the aforementioned reference centre in Barcelona. For his part, Mikami analyses the role that, with its founding in 1969, the SMON (Subacute Myelo-Optic Neuropathy) National Support Group played in the initiation of Japanese policies on “intractable diseases”, a concept that would be adopted for other health problems including various rare diseases.

Mikami’s work encourages reflection on the health problems that have acted as triggers, sometimes for social movements, and sometimes for institu-

tional responses. Myopathies in France³⁵, familial amyloidotic polyneuropathy (paramyloidosis or *doença dos pezinhos*) in Portugal or the particular case of toxic oil syndrome (TOS) in Spain³⁶ serve as examples to promote the creation of research centres. It is necessary to highlight the parallelism between TOS and SMON, due to their toxic cause and legal consequences, which precisely separated them from the institutional responses they motivated. With the impact of these problems and their immediate consequences (in research, healthcare and regulatory legislative support), other minority diseases became part of the political agendas thanks to the actions of the affected people.

However, this coexisting duality stems from the successive changes in associationism and in the roles of patients (by valuing their experience and knowledge and the various interests for their empowerment), and in the models of citizenship in health fostered by the promotion of neoliberal policies. As a result, the right to health, citizen responsibility and the transformation of health systems have placed patients in the sphere of the health consumer in which the drug is the most precious asset³⁷. In their article, João Rui Pita and Ana Leonor Pereira, reveal how there were movements in Portugal that involved various actors, in an alliance between the *Associação Portuguesa da Indústria Farmacêutica* (APIFARMA) [Portuguese Association of Pharmaceutical Industry] and several patient associations, prior to the implementation of European legislation on orphan drugs.

On the other hand, the work of Luiz Alves Araújo Neto and Luiz Antonio Teixeira addresses the problem in Brazil, where they look for the links between the discourses on the right to health and the legislation on rare

35. Vololona Rabeharisoa, and Michel Callon, *Le pouvoir des malades: l'association française contre les myopathies et la recherche* (Paris: Les Presses de l'École des Mines, 1999).

36. Gregoria Hernández Martín, and José Martínez-Pérez, "Cambio político, enfermedad y reforma sanitaria: la respuesta asistencial al Síndrome del Aceite Tóxico (España, 1981-1998)," *Asclepio* 63, no. 2 (2011): 521-544, <https://doi.org/10.3989/asclepio.2011.v63.i2.504>. The syndrome gave rise in 1996 to the creation of the CISAT [Centro de Investigación del Síndrome del Aceite Tóxico (Research Center on Toxic Oil Syndrome)] within the Carlos III Health Institute, and it would also be the one to host research on rare diseases five years later, changing its name to CISATER. See: Esther Vicente *et al.*, "Vigilancia de las enfermedades raras en España: el Registro Estatal de Enfermedades Raras (ReeR)," *Revista Española de Salud Pública* 95 (2021): e202111186, https://www.sanidad.gob.es/biblioPublic/publicaciones/recursos_propios/resp/revista_cdrom/VOL95/C_ESPECIALES/RS95C_202111186.pdf

37. *Health and Citizenship: Political cultures of health in Modern Europe*, eds. Frank Huisman, and Harry Oosterhuis (London – New York: Routledge; 2016); Alex Mold, *Making the Patient-Consumer: Patient organisations and health consumerism in Britain* (Manchester: Manchester University Press, 2015).

diseases. Their argument attempts to take the phenomenon back to the mobilizations for the “redemocratisation” of Brazil of the 1970s and 1980s and the social construction of a relationship between democracy and the health conditions of the population.

The tensions between an activism demanding those rights and a pragmatic one that invokes solidarity to raise funds for the development and commercialisation of new drugs are also present in the article by Rodríguez-Sánchez and Ruiz Somavilla when analysing the role of the media in the creation of a visuality for the socioeconomic concept of rare diseases. In their case study, the photographs of mothers, families, and children affected by lysosomal storage diseases provided a humanising perspective on the issue and helped raise social awareness

The political problem of rare diseases and orphan drugs is therefore the backbone of the studies in this dossier. In all cases, the United States Orphan Drug Act of 1983 is the Rubicon for establishing antecedents, consequences, and disparities. Legislation on rare diseases in Japan, Brazil and the European Union has had different chronologies, roots and developments. In Japan, the starting point was the SMON crisis, the public debates and the relations between associations and patients that led in 1972 to the first policies for a set of health problems that were described as “intractable diseases”. According to Mikami, in the 1990s, following the international movement originating in the US, rarity was included as a requirement for the introduction of a new disease into the group, being defined as those affecting fewer than 50,000 individuals. The Japanese case would therefore be a late appropriation of the North American movement, but on a previously well-fertilised substrate, forged in the public and political arena.

Portugal and Spain implemented the European regulations in their respective countries’ legislation: since 1997, EURORDIS (European Organization for Rare Diseases) promoted associative development in member countries to generate greater pressure on the European Commission to establish a legal framework for rare diseases. The Orphan Drug Regulation of 2000 was the first result, accompanied by the creation of a Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). Nine years later, the Council Recommendation on the Action in the Field of Rare Diseases³⁸

38. Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). *Official Journal of the European Union*, 3 Jul 2009, C 151, 7-9.

would give rise in Spain to the first *Estrategia en Enfermedades Raras del Sistema Nacional de Salud* [Strategy on Rare Diseases of the National Health System] (2009)³⁹. However, according to Pita and Pereira, due to the direct action of EURORDIS, Portugal made public its *Programa Nacional para as Doenças Raras* [National Programme for Rare Diseases] a year earlier⁴⁰.

The United States and European legislation were benchmarks in the debates that arose in Brazil, analysed by Neto and Teixeira in their article. The right to health adopts different interpretations and one of them, the right to a specific medication, would represent the greatest budgetary pressure on the Brazilian Unified Health System and a test of its possibilities and limitations. Scientific evidence, legal principles and moral values came into play before the promulgation of a National Policy for the Integral Care of People with Rare Diseases in January 2014.

Political agents, pharmaceutical companies, health and science professionals, and patients and their relatives thus constitute a set of relationships that combine national idiosyncrasies with the need for international networks in which the minority is no longer a minority. The transnational approach presented in this dossier can contribute to an enriching reflection on the multiple variables that act in the changes of an unfinished process. ■

Bibliography

- Akrich, Madeleine, João Nunes, Florence Paterson and Vololona Rabeharisoa, eds. *The dynamics of patient organizations in Europe*. Paris: Presses de l'École des Mines, 2008.
- Akrich, Madeleine, Orla O'Donovan and Vololona Rabeharisoa. *The entanglement of scientific and political claims: towards a new form of patients' activism*. Paris: Papiers de Recherche du CSI, 2013.
- Allier Montaño, Eugenia. "Balance de la historia del tiempo presente. Creación y consolidación de un campo historiográfico," *Revista de Estudios Sociales* 65 (2018):100-112.

39. *Estrategia en Enfermedades Raras del Sistema Nacional de Salud aprobada por el Consejo Interterritorial del Sistema Nacional de Salud el 3 de junio de 2009* (Madrid: Ministerio de Sanidad y Política Social, 2009).

40. Grupo de Trabalho sobre Doenças Raras. *Programa Nacional para Doenças Raras (PNDR)* (Direcção Geral de Saúde, 2008), [http://www.europlanproject.eu/DocumentationAttachment/National%20Programme%20for%20Rare%20Diseases%202008-2015%20-%20portuguese%20\(p\).pdf](http://www.europlanproject.eu/DocumentationAttachment/National%20Programme%20for%20Rare%20Diseases%202008-2015%20-%20portuguese%20(p).pdf) See also: Rabeharisoa et al., *The dynamics of causes and conditions*.

- Anthes, Emily K. "The Chosen Genes: Jews, Genetics, and the Future of Ethnic Medicine." Master diss., Massachusetts Institute of Technology, 2006.
- Araújo Neto, Luiz Alves, and Luiz Antonio Teixeira. "New problems of a new health system: the creation of a national public policy of rare diseases care in Brazil (1990s-2010s)." *Salud Colectiva* 16 (2020):e2210. <https://doi.org/10.18294/sc.2020.2210>
- Ballester, Rosa, and María Isabel Porras, eds. "Políticas, respuestas sociales y movimientos asociativos frente a la poliomielitis: la experiencia europea (1940-1975)". *Dynamis* 32, no. 2 (2012):273-414.
- Bogdan, Robert. *Freak Show: Presenting Human Oddities for Amusement and Profit*. Chicago y Londres: The University of Chicago Press, 1988.
- Callon, Michel, and Vololona Rabeharisoa. "The Growing Engagement Concerned Groups in Political and Economic Life: Lessons from the French Association of Neuromuscular Disease Patients", *Science, Technology & Human Values* 33, no. 2 (2008): 230-261. <https://doi.org/10.1177/0162243907311264>
- Cruz Hernández, Manuel, and Juan Bosch Hugas. *Manual ilustrado de enfermedades raras*. Madrid: Ergon, 2013.
- Daston, Lorraine and Katharine Park. *Wonders and the order of nature, 1150-1750*. Nueva York: Zone Books, 1998.
- EURORDIS (European Organisation for Rare Diseases). *Enfermedades Raras: el conocimiento de esta prioridad de la Salud Pública*. París: EURORDIS, 2005.
- Ferrelli, Rita María, Bernardino Fantini and Domenica taruscio. "Health systems sustainability for rare diseases." *Annali dell'Istituto Superiore di Sanità* 55, n.º 3 (2019):249-304.
- Fujimura, Joan H. "Crafting science: standardized packages, boundary objects and 'translation'". In *Science as Practice and Culture*, edited by Andrew Pickering, 168-211. Chicago: University of Chicago Press, 1992.
- Griffiths, David Andrew. "Shifting syndromes: sex chromosome variations and intersex classifications." *Social Studies of Science*, 48, no. 1 (2018): 125-148. doi: 10.1177/0306312718757081.
- Hedley, Victoria, Valentina Bottarelli, Ariane Weinman and Domenica Taruscio. "Shaping national plans and strategies for rare diseases in Europe: past, present, and future." *Journal of Community Genetics* 12 (2021): 207-216. <https://doi.org/10.1007/s12687-021-00525-4>.
- Hernández Martín, Gregoria, and José Martínez-Pérez. "Cambio político, enfermedad y reforma sanitaria: la respuesta asistencial al Síndrome del Aceite Tóxico (España, 1981-1998)." *Asclepio* 63, n.º 2 (2011):521-543. <https://doi.org/10.3989/asclepio.2011.v63.i2.504>.
- Huisman, Frank, and Harry Oosterhuis, eds. *Health and Citizenship: Political cultures of health in Modern Europe*. London – New York: Routledge, 2016.
- Huyard, Caroline. How did uncommon disorders become 'rare diseases'? History of a boundary object. *Sociology of Health & Illness*. 2009; 31(4): 463-77. doi: <https://doi.org/10.1111/j.1467-9566.2008.01143.x>.
- Huyard, Caroline. *Rare. Sur la cause politique des maladies peu fréquentes*. Paris: EHESS, 2012.

- Ingram, George I.C. *The history of haemophilia*. Margate: Eyre&Spottiswoode, Thanet Press, 1976.
- Iskrov, Georgi, Rumen Stefanov and Rita Maria Ferreli. "Health systems for rare diseases: financial sustainability." *Annali dell'Istituto Superiore di Sanità* 55, n.º 3 (2019): 270-275.
- Izquierdo Martínez, Maravillas, and AlfredoAvellaneda Fernández. "Enfoque interdisciplinario de las enfermedades raras: un nuevo reto para un nuevo siglo." *Medicina Clínica (Barcelona)* 121, no. 8 (2003): 299-303.
- Jung, Monica de Paula, Maria Helena Cabral de Almeida Cardoso, Maria Auxiliadora Monteiro Villar, and Juan Clinton Llerena Jr. "Revisitando o desvendamento da etiologia da síndrome de Turner." *História, ciências, saúde - Manguinhos*, 16, no. 2 (2009): 361-376. <https://doi.org/10.1590/S0104-59702009000200005>
- Knight, Andrew W., and Timothy P. Senior. "The common problem of rare disease in general practice." *Medical Journal of Australia* 185, no. 2 (2006): 82-83.
- Kole, Anna, Hedley, Victoria, et al. *Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today*. 2021. https://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf
- Lain Entralgo, Pedro. *La historia clínica: historia y teoría del relato patográfico*, Madrid: CSIC, 1950.
- Marcaida López, José Ramón. *Arte y ciencia en el Barroco español: Historia natural, coleccionismo y cultura visual*, Madrid: Fundación Focus-Abengoa; Marcial Pons Historia, 2014.
- Mikami, Koichi. Orphans in the market: The history of orphan drug policy. *Social History of Medicine*. 2019; 32(3): 609-30.
- Mold, Alex. *Making the Patient-Consumer: Patient organisations and health consumerism in Britain*. Manchester: Manchester University Press, 2015.
- Orphanet. *Encyclopaedia for professionals*. https://www.orpha.net/consor/cgi-bin/Disease_ProEncyclo.php?lng=EN
- Ortega Calvo, Manuel. "Las enfermedades raras como paradigma científico en atención primaria." *Cuad Gestión* 10, no. 2 (2004):41-44.
- Owen, Charles A. *A History of Blood Coagulation*, Rochester: Mayo Foundation, 2001.
- Palau, Francesc. "Enfermedades raras, un paradigma emergente en la medicina del siglo XXI." *Medicina Clínica (Barcelona)* 134, no. 4 (2010): 161-168.
- Paul, Diane B. "How PKU became a genetic disease." In *Human heredity in the Twentieth Century*, edited by Bernd Gausemeier, Staffan Müller-Wille, Edmund Ramsden, 179-192. London – New York: Routledge, 2013.
- Paul, Diane B., and Jeffrey P. Brosco. *The PKU Paradox: A Short History of a Genetic Disease*. Baltimore: Johns Hopkins University Press, 2013.
- Paul DB, and PJ Edelson. The struggle over metabolic screening. In: Chadarevian S, Kamminga, H, editoras. *Molecularizing biology and medicine. New practices and alliances, 1910s-1970s*. Amsterdam: Harwood Academic Publishers; 1998, p. 203-20. Paul, Diane B., and Edelson, Paul J. "The struggle over metabolic screening." In *Molecularizing biology and medicine. New practices and alliances, 1910s-1970s*,

- edited by Soraya de Chadarevian, Harmke Kamminga, 203-220. Amsterdam: Harwood Academic Publishers, 1998.
- Pemberton, Stephen Gregory. *The bleeding disease: hemophilia and the unintended consequences of medical progress*. Baltimore: Johns Hopkins University Press, 2011.
- Pryde, David C., and Michael J. Palmer, eds. *Orphan Drugs and Rare Diseases*. Cambridge, UK: The Royal Society of Chemistry, 2014.
- Rabeharisoa, Vololona. "The struggle against neuromuscular diseases in France and the emergence of the 'partnership model' of patient organization." *Social Science & Medicine* 257, no. 11 (2003): 2127-2136. Doi: [https://doi.org/10.1016/S0277-9536\(03\)00084-4](https://doi.org/10.1016/S0277-9536(03)00084-4)
- Rabeharisoa, Vololona. "From representation to mediation: the shaping of collective mobilization on muscular dystrophy in France." *Social Science & Medicine* 62, no. 3 (2006): 564-576. Doi: <https://doi.org/10.1016/j.socscimed.2005.06.036>
- Rabeharisoa, Vololona, and Callon, Michel. *Le pouvoir des malades: l'association française contre les myopathies et la recherche*. Paris: Les Presses de l'École des Mines, 1999.
- Rabeharisoa, Vololona, Michel Callon, Angela Filipe Marques, João Arriscado Nunes, Florence Paterson and Frédéric Vergnaud. *The dynamics of causes and conditions: the rareness of diseases in French and Portuguese patients' organizations' engagement in research*. CSI Working Papers Series, 26. Paris: Centre de Sociologie de l'Innovation, 2012.
- Reuter, Shelley Z. "Testing fate: Tay-Sachs disease and the right to be responsible." Master diss, University of Minnesota Press, 2016.
- Resnik, Susan. *Blood saga: hemophilia, AIDS, and the survival of a community*. Berkeley: University of California Press, 1999.
- Richter, Trevor, Sandra Nestler-Parr, Robert Babela, Zeba Khan, Theresa Tesoro, Elizabeth Molsen and Dyfrig Huges. "Rare disease Terminology and Definitions – A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group." *Value in Health* 18 (2015): 906-914. <http://dx.doi.org/10.1016/j.jval.2015.05.008>
- Rodríguez-Sánchez, Juan Antonio. "Un presente lleno de historia(s): la poliomielitis, entre las secuelas y el legado". *Dynamis* 40, no. 2 (2020): 505-516.
- Rodríguez-Sánchez, Juan Antonio, and Inés Guerra Santos. "La 'rara' secuela de una epidemia: el caso del síndrome postpolio." In *Enfermedades raras. Contribuciones a la investigación social y biomédica*, edited by Juan Coca, 129-175. CEASGA, 2019.
- Rodríguez-Sánchez, Juan Antonio, and Inés Guerra Santos. "Cuerpos deslegitimados, síndromes ignorados: de la poliomielitis al síndrome post-polio en España." *Clío & Crimen* 16 (2019): 393-412.
- Rodríguez-Sánchez, Juan Antonio, and Raúl Velasco Morgado, eds. *Las enfermedades raras: una historia del presente*. Madrid: La Catarata, en prensa.
- Rodríguez-Sánchez, Juan Antonio, Raúl Velasco Morgado, Inés Guerra Santos and Dilene Raimundo, eds. *Conocimiento y empoderamiento: las enfermedades raras y el síndrome postpolio (1950-2018)*. Salamanca: Ediciones Universidad de Salamanca, en prensa.

- Sanmartín, Israel. “Las historias inmediatas y del presente en la historiografía actual,” *Historiografías* 15 (2018):36-51.
- Silva, Danielle Fialho da. “Redes de solidariedade do sentir e do resistir: associativismo dos pacientes com fibromialgia e síndrome pós-pólio nos meios digitais (2004 – 2021).” PhD diss. Casa de Oswaldo Cruz/Fiocruz, 2021.
- Testa, Daniela. *Del alcanfor a la vacuna Sabin: la polio en la Argentina*. Buenos Aires: Biblos, 2018.
- Vale Costa, Liliana and Ana Isabel Veloso. Portraying Rare and Misdiagnosed Diseases in Movies: A Content Analysis, 1980-2018. In *Communicating Rare Diseases and Disorders in the Digital Age*. IGI global, 2020.
- Vargha, Dóra. *Polio across the Iron Curtain: Hungary's Cold War with an epidemic*. Cambridge: CUP, 2018.
- Vicente, Esther, Eva Ardanaz, Enrique Ramalle-Gómara, Luis J. Echevarría, M. Pilar Mira, Juan Pablo Chalco-Orrego, Consuelo Benito, Sandra Guardiola-Villarroig, *et al.* “Vigilancia de las enfermedades raras en España: el Registro Estatal de Enfermedades Raras (ReeR).” *Revista Española de Salud Pública* 95 (2021): e202111186. https://www.sanidad.gob.es/biblioPublic/publicaciones/recursos_propios/resp/revista_cdrom/VOL95/C_ESPECIALES/RS95C_202111186.pdf
- Wiel, Stalparti Van der. *Observationum rariorum medic. Anatomic. Chirurgicarum centuria prior. Accedit de unicornu dissertatio*. P. Vander au: Leiden, 1687.
- Wu, Zhan He, ed. *Rare Diseases*. IntechOpen, 2020. doi: 10.5772/intechopen.83131. ■

