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EDITORIAL

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The Paleoepidemiology of Leprosy: an Overview*

Introduction: paleoepidemiology and the ecology of diseases

The paleoepidemiology of an infectious disease should ideally start by tracing its origin, that is, the prime encounter of man with the germ, its reservoirs and its vectors, in a long-vanished ecology. Next, the subsequent interplay of the host and the parasite should be followed as they travel together through ages and places, overtaking fresh populations.

For diseases of recent emergence, the matter is often hard enough. But at least, through observation and experimentation, some hypotheses on their origins and mechanisms of transmission can be tested. For ancient diseases, however, the approach is purely speculative. Let us take cutaneous leishmaniasis as an example. In a recent book on the history of tropical diseases,[1] the following account is given of its origin: "Sandflies have been in existence for 30 million years and, feeding on the juice of plants in which flagellate protozoa live, they presumably became infected with the ancestors of Leishmania parasites, . . . lizards, and later, small rodents became the sandflies' chosen prey . . . (then) man as a hunter-gatherer, became infected when he came into contact with these rodents. . . ."

The more complex the natural history of a disease, the easier it becomes to propose some sort of sensible scenario for its origin. This may seem a paradox, but the reason, however, is simple. The epidemiological factors to be taken into account, such as the biology of an obligatory vector, the dispersion of an intermediate host, or the biotope of an animal reservoir, raise many constraints which curtail our freedom to make hypotheses. Concerning leprosy, this ill-famed, centuries-old, epitome of all scourges, there is no hint to lead us to reasonable guesswork, no mosquito and no extra-human reservoir, but for an occasional monkey or an exotic mammal such as the armadillo. Unless further evidence proves otherwise, man is the only host as well as the only reservoir for the etiological agent,

* Presented at the OCEPID: Past and Present of Leprosy, Bradford, U.K., July 1999.

[1] Miles, M. A. (1996): New World leishmaniasis. In Cox, F. E. G.: *The Wellcome Trust Illustrated History of Tropical Diseases.* The Wellcome Trust Publ., London; 206–229.

Mycobacterium leprae. Since the bacillus has never been cultivated *in vitro*, it looks as though it has lost the genetic machinery required to grow outside the human body. It may thus be safely assumed that it is an old mycobacterium that has diverged and became an obligatory parasite of man early in the course of evolution. The nearly completed deciphering of its genome and the comparison of it with that of *M. tuberculosis* and possibly of other mycobacteria should help to elucidate its origin.

The transmission is rather unimaginative: people to people, from an infected individual to a susceptible person. Leprosy is a cosmopolitan disease. Notwithstanding differences in climates and environments, at one moment or another it has been occurring in all types of habitats occupied by man. While there is no suggestive paleontological evidence regarding its transmission in protohistoric populations, its spread and geographic distribution over the centuries show a number of singularities. Yet, historical observations may possibly provide some clues to broaden the debate.

Early records of leprosy at the dawn of history

Written records of diseases with symptoms resembling those of leprosy suggest that it could have existed in ancient times in Egypt, India, and China.

In Egypt, Huspati (Horus-Dên), a quasi-mythical Thinite king of the First Dynasty (~3500 BC), is reported in papyrus dating from ±1500–1200 BC as having suffered from a disease whose signs are evocative of leprosy.[2] In India, a precise clinical description was given in a compilation of writings dating from about 600 BC (Sushraka Samhita).[3] In China, the Nei Ching, a collection of medical texts assembled between the 8th and the 3rd centuries BC, but attributed to Huang-Ti, a legendary emperor who lived around 2600 BC,[4] lists among the symptoms the loss of eyebrows together with nodules and ulcerations of the skin.

That the records attesting to the existence of leprosy in earlier times were actually compiled much later does not necessarily preclude their veracity, for they were generally meant to be a recollection of traditional knowledge.

The congruence of the given description with the clinical signs of the disease is a much more delicate issue. For example, according to Biblical experts, the condition described in Leviticus under the term of 'Za'raath does not refer specifically to leprosy but is said to encompass a large variety of skin diseases or blemishes of all kinds.[5] It is, therefore, very doubtful whether leprosy was brought to Canaan by the Jews returning from Egypt, despite an anthropomorphic jar reminiscent of a leonine (lepromatous) facies excavated in Palestine and contemporaneous with the Exodus (1400–1300 BC).[6, 7]

Anecdotal evidence is perhaps at times more convincing than official chronicles. That leprosy was common around the 4th century BC in China is suggested by a narrative of the time vividly relating how, in order to elude arrest, a bandit cleverly disguised himself as a patient by varnishing his skin and shaving his eyebrows![4]

Artifacts suggestive of leprosy dating from these early periods are few. Apart from the clay ware found in Palestine, statues conceivably exhibiting mutilations were discovered in the Indus Valley. In Egypt, indisputable evidence of the existence of leprosy is relatively recent. Four skulls from the 2nd century BC present lesions of the nasal bones specific to leprosy.[8] Evidence in two Coptic mummies with bone lesions of the extremities comes from a much later period, well into the Christian era.[9]

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[2] Brugsch. Quoted in Scott, H. H. (ref. 10).

[3] Dharmendra (1978): *History of Spread and Decline of Leprosy*. Dharmendra, ed. Kothari Med. Publish. House, Bombay; 7–21.

[4] Skinsnes, O. (1985): Understanding of leprosy in ancient China. Int. J. Lepr. 53; 289–307.

[5] Jeanselme, E. (1934): *La Lepre*. G. Doin Ed., Paris.

[6] Cochrane, R. G. (1964): The history of leprosy and its spread throughout the world. In: Cochrane, R. G. *Leprosy in Theory and Practice*. John Wright & Sons, Bristol; 1–12.

[7] Yeoli, M. (1955): A facies leontina of leprosy on an ancient Canaanite jar. J. Hist. Med. 10; 331.

[8] Dzierzykray-Rogalski (1980): Palaeopathology of the Ptolemaic inhabitants of Dakhleh Oasis (Egypt). J. Hum. Evol. 9; 71–74. Quoted in Sansarricq, H. (ref. 42).

[9] Anderson, J. G. (1969): Studies in the medieval diagnosis of leprosy. (Thesis for Doctor of Medicine) Dan. Med. Bull. 16 (Suppl. 16).

In which of those areas did leprosy first make its appearance? There is no straight answer. If we trust the legacy of traditions as embodied in later records, leprosy could well have been prevalent in all three regions at the dawn of their respective histories. That the possible presence of the disease was attested to earlier in Egypt is no argument. The chronology of historical events has often more to do with the presence of historians than with the occurrence of the events themselves, as is the case for so many phenomena.

There is therefore no conclusive argument to settle the issue of leprosy's first appearance. Egypt comes to mind, however, as a good candidate, although it has been claimed that studies conducted on mummified remains run contrary to this statement. Indeed, among 1844 mummies from 600 BC to 600 AD examined by Moller-Christensen for pathognomonic signs, only two presented bone lesions indicative of the disease.[9] This argument is not convincing. For osteological evidence of leprosy to show up in a significant number of remains, several conditions must be filled: a high prevalence of the disease, a large proportion of patients with bone lesions, the fact that leprosy was not less frequent in the social classes where embalming was more likely to take place, and that there was no negative selection regarding these funeral practices because of disease.

If leprosy was present in Egypt's protohistory, possibly serving as a relay to its spread eastward to India and China, where then did it come from? It is known that very early in history, commercial exchanges were already most active with Nubia and Darfur (now the Sudan), countries that were situated at the gates of the huge African hinterland. Negro slaves were imported into Egypt at the time of Ramses II (circa 1300 BC).[10] Could leprosy have then been introduced into Egypt from deeper regions in the belt of land extending from Abyssinia to Nigeria?

At this stage, it is tempting to make a link with what occurred some six or seven thousand years later. Between 1500 to the mid-18th century, leprosy was prevalent among those unfortunate enough to be captured in the interior of the African continent, taken to the coast and exported to America as slaves. It is difficult to accept that "Black Africa" was free of leprosy until Arab traders and Portuguese navigators imported it between the 10th and 15th centuries AD.[11] The disease had probably been present in the heart of the continent for many centuries.

Could it be thus that the cradle of leprosy could be found where the first modern humans made their appearance eons ago?

As in so many instances, Lucretius[12] (99–44 BC) was perhaps correct in his intuition when he wrote ". . . *elephas morbus qui propter flumina Nili gignitur Aegypto in media, neque praeterea usquam* . . ."— from Egypt, along the Nile, and nowhere else . . .

Expansion of leprosy in historical times and invasion of Europe

While leprosy presumably already existed in Egypt and further east in early history, it made a belated entry into Greece and Rome.

Literary sources of Greek and Latin origins raise peculiar problems of semantics. The group of skin conditions referred to as lepra in the Hippocratic texts does not apparently include the disease we came to know in modern parlance as leprosy. Conversely, the disease entity most precisely and accurately described by the Latin authors Celsus (25 BC–37 AD) and especially Areteius of Cappadocia (circa 200 AD) that we may recognize as leprosy is designated by the term "elephantiasis."[9]

According to Pliny the Elder (23–79 AD), elephantiasis, by now designating leprosy, was introduced in Rome around 62 BC by the armies of Pompey returning from the campaign against Mithridates, King of Pont.[9]

That the ailment was not common in Rome may be surmised from the fact that it was not included in those defects rescinding the sale of slaves, as was the case for phthi-

[10] Scott, H. H. (1943): The influence of the slave trade in the spread of tropical disease. Trans. R. Soc. Med. Hyg. 37; 169–188.

[11] Trautman, J. R.: The history of leprosy. In Hastings, R. C. (ref. 54).

[12] Lucretius: *De Rerum Natura VI.* Les Belles Lettres Ed., 1948, Paris, 1114–1115.

sis (tuberculosis), fevers, eyesores and mental disorders.[5]

Following the Roman conquests, leprosy spread to Gaul as well as to Germany, where Galen (±150 AD) signals its presence, and thereafter to the whole of Europe during the Middle Ages,[13] although the possibility of a prior contamination of Spain by the Phoenicians as early as the 10th century BC has been theorized by some authors.[14] The Vikings brought it to Scandinavia. In Iceland, a bishop was to be deposed in 1413 because his deformities prevented him from celebrating mass.[5] At the time of the Crusades, the bacillus shuttled back and forth between Europe and the Near East.

The fear of contagion was great. Gloomy rituals were set up to exclude the patients from social life. Lazarets were built from Spain to Scotland, which at least attest to a wide dissemination of the disease.[6] At one time or another, Belgium would have counted 42 lazarets, England 99, Normandy 318, and the whole of France over 2000. Figures of that sort can be misleading. In all likelihood, judging from their ruins, most of these institutions housed a small number of patients at a time, and most probably not all suffered from leprosy. That at least some of the people consigned to these lazarets were actually affected with leprosy is confirmed by the excavations conducted in Denmark by Moller-Christensen in the 1950s, which demonstrated characteristic bone changes in a number of skulls.[15] In addition, this author identified specific alterations in the maxillary bones which, after having been validated radiologically in living patients,[16, 17] can now be used as a standard to verify the diagnosis of leprosy in osteo-archaeological material.

While it cannot be doubted that leprosy was widely disseminated in Europe during the Middle Ages, it is impossible to even hazard a guess about its actual prevalence, its distribution or its relative frequency in towns as compared to the countryside. It is possible that, because of the fear it inspired and the morbid stigma attached to its name, the prevalence of leprosy has been grossly exaggerated. It has been suggested that in the 13th century the number of patients in England did not exceed a few thousand.[18] Indeed, more is known about the epidemiology of the lazarets than about the epidemiology of the disease itself!

In contemporary Europe, two localized outbreaks are worth mentioning. One started in Memel (now Klaipeda, Lithuania) in 1840, the other occurred in the island of Oesel (now Saaremaa, Estonia) at the turn of the century.[5, 14] In Oesel, the spread followed a pattern of slow diffusion, propagating from village to village, farm to farm.

There are two main conclusions to this story. Firstly, it is most likely that leprosy was not introduced into Europe by the Indo-Europeans during successive waves of migrations, be it the Celts, the Germans, the Greeks or the Italians. Either the disease did not, or did not yet, exist at the site where these migrations originated, somewhere in the steppes or the plateaus of Central Asia, 7000 or 8000 years ago, or the conditions for its transmission were not met during the long westward trek, meaning that *M. leprae* got lost "en route."

Second, there is no climatic or other geographic factor determining the distribution of leprosy. From the sun-scorched banks of the Nile to the frost of Iceland, the determining factor responsible for the traveling of the bacillus is man.

Leprosy in the New World

After having reached its peak in Europe, leprosy worked its way to fresh ground on the American continent. There is no record of the disease being prevalent among the First Nations people before the arrival of the Europeans. Since the Conquistadors and the first colonizers came from regions of

[13] Chaussinand, R. (1955): *La Lepre.* Expansion Scientique Francaise, Paris.

[14] Contreras, F. and Miquel, R. (1973): *Historia de la lepra en Espana.* Grafica Hergon, Madrid.

[15] Moller-Christensen, V., *et al.* (1952): Changes in the anterior nasal spine and the alveolar process of the maxillary bone in leprosy. Int. J. Lepr. 20; 335–340.

[16] Melsom, R. S. (1953): Changes in the maxillary bone in leprosy; a clinical and roentgenological examination. VI Congress Internacional de Leprologia, Madrid; 747–750.

[17] Lechat, M. F. and Chardome, J. (1955): Alterations radiologiques des os de la face chez les lepreux Congolais. Ann. Soc. Belg. Med. Trop. 35; 603–611.

[18] Richards, P. (1977): The medieval leper and its northern heirs. Quoted in Ell, S. R. (ref. 55).

Europe, mainly Spain and Portugal, where leprosy was not uncommon, and were in addition accompanied by physicians and priests supposedly well acquainted with its symptoms, it is unlikely that cases of the disease among the natives would have escaped attention. Even at present, leprosy is only exceptionally, if at all, observed in indigenous people. To the best of our knowledge, it has never been reported in tribes with no previous contact with strangers.

Anthropomorphic earthenware from the pre-Colombian era once believed to represent leprosy lesions are now said to suggest, rather, leishmaniasis ("*espundia*") or blastomycosis.[19]

In conclusion, it can be accepted that the Mongoloid people who migrated across the Bering Strait land bridge some 14,000 years ago did not carry the leprosy bacillus with them. It first came to the Americas with the European invaders, then with the slaves from Africa and, finally, with laborers imported from China.

Among the Conquistadors and the first colonizers, Jimenez de Quesada, the founder of Bogota, was affected and contaminated some persons of his entourage.[14]

It is the slave trade which apparently played the major role in the introduction of leprosy into the New World. The number of slaves deported from trading stations in Africa between 1511 and 1787 oscillates between 10 million and 50 million, the latter figure[20] according to the British Admiralty. Most of the slaves were imported from the western coasts of Africa, extending from Senegambia (Senegal) to Benguella (Angola), and from as far away as Mozambique on the Indian Ocean. It is not known how common leprosy was at that time in that part of the world. Judging from the high prevalence recorded a few centuries later during the Colonial period, it can be presumed that the disease had been widely disseminated in Africa for a long time, as already mentioned.

The number of these so-called involuntary migrants who ultimately reached the American shores was, however, much less than those captured in the African hinterland. "Sanitary control" was carried out before shipment to exclude people in poor health or with visible defects, although it is reported that in later years, as the contraband trade developed, the prevalence of diseases among smuggled slaves increased sharply.[10] Of those embarked, it is said that a large proportion, at times up to more than one half of the ship load, died or were otherwise disposed of during the ocean crossing, or the "Middle Passage" as it came to be called, insurance policies being an additional incentive not to keep sick patients on board until termination of the journey.[10] Despite the above checks, the number of leprosy patients among the slaves delivered to their destination would not have been insignificant. In addition, some of them still in the latent stage, having been infected in their homeland, were bound to develop the clinical disease after arrival.

That the disease was present among the African slaves is attested by the fact that in Cuba the bills of sale stipulated that for leprosy, and likewise for mental disorders, contrary to other ailments, the buyer had the license to return the object of the transaction within 2 months if found to be affected by these conditions[20]

The immigration of Chinese laborers to Cuba, at the time a colony of the Spanish Crown, began in 1847, the very same year the slave trade was officially abolished. In the 27 years that followed, an estimated 132,000 Chinese entered the island, many of them originating from Guang-Dong and Yunnan, provinces where leprosy was prevalent. From 1800 to 1899, out of 1393 patients hospitalized in the San Lazaro Hospital in Havana, 202 (14.5%) were natives of China (the first Chinese national having been admitted not earlier than 1850).[20]

Migrations and secluded, remote or otherwise singular areas

Slow diffusion in contiguous areas and mosaic patterns. The spread of leprosy in areas adjacent to each other was observed as recently as the present century among

[19] Krumbach, H. (1986): Zur Frage der Lepra im pra.-und post-kolumbischen Amerika. In *Aussatz; Lepra; Hansen-Krankheit. Ein mensheitsproblem in Wandel.* Vol. 2. Wolf, J. H. ed. DAHW, Wurzburg; 201–209.

[20] Gonzalez Prendes, M. A. (1963): *Historia de la Lepra en Cuba.* Academia de Ciencias de la Republica de Cuba, La Habana.

the Aborigines of Wandammen Bay, Irian Jaya and in the Northern Territory of Australia.[21, 22] In Western Australia, the disease was reportedly imported by crews of pearl-fishing boats and was propagated inland from the coast with successive intervals setting up small foci along the rivers.[23]

This pattern of diffusion may explain the slow dispersion of leprosy in prehistoric time, the disease remaining sequestered in secluded populations for untold centuries until some social break up set it free to flare elsewhere. The more compartmentalized the group, the slower will be the diffusion.

Different opportunities for contact could also explain the fragmented distribution of the disease observed in some parts of Africa, where strongly contrasted prevalences ranging from high to low may coexist in adjacent areas. The same differences are mentioned for tribes of Papua New Guinea living in adjacent valleys. Although the suggestion is admittedly quite speculative, this pattern of mosaic or patchwork could reflect, up to the present, some vestige of the respective isolation of tribes until the recent past. The more exchanges between contiguous areas, through trade or otherwise, the faster will be the spread of leprosy and the more homogeneous will become the distribution of prevalence.

Transmigration. There are historical records of the transmigration of populations with a high prevalence of leprosy into an environment already occupied by other groups with low or no prevalence. Such transplantations may be regarded as experiments where the spread of the disease can be observed as the two populations come into contact.

The transmigration of leprosy patients does not necessarily result in the dissemination of the disease in the new location. Transmission may remain largely limited to, and persist for generations within, the immigrant groups if these do not mingle with the host population. It is then cultural isolation, reducing the opportunities for infective social contacts, rather than geographic confinement, which will restrain transmission to the outside.

An example of such migration is given by the French colonists who settled in Tracadie, New Brunswick, Canada, and Louisiana, U.S.A., following their expulsion from Nova Scotia at the time of the "Grand Dérangement" in 1755. The Acadian focus, which is scattered among the parishes of Louisiana, has been active up to this day, with many cases still occurring in the Cajun population.[24] (This direct importation of the disease from Canada to Louisiana has however been contested. It is now claimed that the Acadians picked up the disease in the Caribbean during the 18th century.[11])

An outbreak of high prevalence was also observed in the penal institutions of French Guiana.[25] From 1852 until 1939, 71,667 male convicts were transported to this French territory. The two first cases of leprosy were diagnosed in 1883. The number of cases which have occurred since then has not been recorded. It has however been reported that for the period 1939–1948, the prevalence averaged 4.6%. A recalculation of the incidence for the decennium 1939–1948 yields a figure of 4.15 cases per 1000 person-years. That all ethnic groups, European, Arab, Asian and African, were indiscriminately affected militates in favor of social factors, such as living in overcrowded and unhygienic conditions, as a significant determinant in the transmission of the disease.

According to a different pattern, the arrival of patients in a previously unaffected area does not result in the production of new foci. It could be that the newcomers will adopt the mode of life of the host population—as ill-defined as the term might be—which in some way will curb the trans-

[21] Leiker, D. L. and Sloan, N. R. (1954): Leprosy in Netherlands New Guinea. Int. J. Lepr. 22; 431–439.

[22] Hargrave, J. C. (1980): *Leprosy in the Northern Territory of Australia with Particular Reference to the Aborigenes of Arnhem Land and the Regions of the Northern Territory.* Government Printer of the Northern Territory.

[23] Lechat, M. F. (1986): Prospect for eradication of leprosy. Conference for the closing of the last leprosy hospital in Australia, Perth, WA, 1986.

[24] Feldman, R. A. and Sturdivant, M. (1973): 100 years of leprosy in Louisiana: an epidemiological analysis. 10th International Leprosy Congress, Bergen, 1973, Abstracts; 116–117.

[25] Floch, H. (1951): La lepre au bagne Guyanais: son evolution durant un siecle (1852–1950); ses particularites. Int. J. Lepr. 19; 283–295.

mission of the bacillus. Illustrative of this is the story of the Scandinavian immigrants who settled in the Upper Mississippi Valley in the 19th century.[26, 27] The disease died out after the second generation. Social and economic factors have been invoked to explain this observation.

Although not sufficiently documented, these observations seem to confirm that social contact is a determining factor in governing the transmission of the disease. Both of these patterns would be difficult to reconcile with a supposed intervention of an extra-human reservoir.

Virgin communities; the Pacific islands. The Pacific islands constitute a sort of laboratory in which one can watch the introduction of leprosy in hitherto virgin populations. The diffusion of leprosy in a number of those islands reveals two principal epidemiological patterns, i.e., outbreaks of leprosy, and transmission limited to a few families.

Outbreaks are characterized by a rapidly increasing incidence following the occurrence of the first cases. After a few years, a large part of the population may be affected—one-third of the natives in Nauru Island in 1929,[28] one-fifth in Reao and Pukarua Island, Tuamotus, French Polynesia[29] in 1936. Other sites of epidemics are the Northern group of the Cook Islands and Aitutaki, in the Southern group,[30] and New Caledonia.[31] These outbreaks are often subsequent to the arrival of a particular individual said or known to have had leprosy. If the legend of introduction of leprosy into previously unaffected communities by Chinese laborers and crews of whaling ships (Hawaii,[32] Western Samoa[33]) must be accepted with caution, more interesting examples are those in which the first case is clearly defined, sometimes with the name and the medical history clearly recorded.

The unparalleled story of the Nauru epidemics is truly remarkable.[28] The introduction of leprosy to this island, at that time a German colony, is ascribed to a woman native of the Gilbert archipelago (now the Republic of Kiribati), who arrived in Nauru in 1911 or 1912. Recognized on arrival as having leprosy and barred from entry for that reason by the medical officer in charge, she was however allowed to stay by the Governor. She took a 13-year-old girl as a servant, and died 2 years later. In 1920, the girl, by then 22, in turn developed leprosy. Soon thereafter three additional cases were detected. All were isolated. A few months later, the pandemic of Spanish influenza reached Nauru, killing 30% of the population as well as all the leprosy patients but one. The next year, 1922, 25 new cases appeared. By the end of that year, after a survey had been conducted among the entire Nauruan population of 1113 persons, the number of cases diagnosed had increased to 139, yielding a prevalence of 125 per 1000. Soon, almost every family had at least one member affected. By the end of 1929, no fewer than 438 cases had occurred among the autochthonous population, which corresponds to a 7.5-year period—a prevalence (1922–mid-1929) of 36.5%. The epidemic thereafter subsided, partly due to the forced emigration of the population to the island of Truk (now Chuuk, Micronesia) and partly to the elimination of the patients during the Second World War occupation by the Japanese military. It is, however, not yet completely extinct. The latest information reports an average of two cases detected per year between 1982 and 1994 (1994 population 9900), in spite of early detection and effective multiple chemotherapy.[34]

[26] Washburn, W. L. (1950): Leprosy among Scandinavian settlers in the Upper Mississippi Valley, 1864–1932. Bull. Hist. Med. 24; 123–148.

[27] Doull, J. A. (1962): The epidemiology of leprosy; present status and problems. Int. J. Lepr. 30; 48–66.

[28] Wade, H. W. and Ledowsky, Y. (1952): The leprosy epidemic at Nauru: a review with data on the status since 1937. Int. J. Lepr. 20; 1–29.

[29] Lonie, D. A. (1959): Trends in leprosy in the Pacific. Technical Info. Circular No. 32 (mimeograph), South Pacific Commission, Noumea.

[30] Numa, J. (1953): The prevalence of leprosy in the Cook Islands. Int. J. Lepr. 21: 151–160.

[31] Ragusin, R. (1951): Le lepre en Nouvelle-Caledonie et dependances. Int. J. Lepr. 19; 413–421.

[32] Wayson, N. E. and Rhea, T. K. (1934): Leprosy, observations on its epidemiology in Hawaii. Publ. Health Bull. 212; 1–32.

[33] Sloan, N. R. (1954): Leprosy in Western Samoa and the Cook Islands. Technical Paper No. 69 (mimeograph), South Pacific Commission, Noumea.

[34] WHO Regional Office for the Western Pacific (1995): Epidemiological review of leprosy in the Western Pacific Region 1982–1994. WHO-WPRO, Manila.

In other islands the spread of leprosy is reported to have been limited to a few families, as in Niue Island and Eastern (American) Samoa.

In Niue, where the disease was reportedly introduced by a resident returning from Hawaii, 30 cases only have been registered in 70 years (up to 1949) among a population of approximately 5000, leprosy being almost wholly confined to two family groups.[35] No new cases have been reported in recent years. In American Samoa, 41 out of 45 known cases in 1953 were from only three family groups.[36]

These island outbreaks raise interesting points. To what extent may genetic or environmental factors explain these different patterns? This remains an unanswered question. As bewildering is the fact that in Nauru the large majority of patients were affected by the tuberculoid (now called paucibacillary) type of the disease, a clinical form that is reputedly not or only very slightly contagious.

That leprosy continued being transmitted in Nauru until the beginning of the war in the Pacific remains also without a satisfactory explanation, especially in view of the fact that all of the patients except one (the girl who was contaminated by the index case) had succumbed to the influenza pandemics, and notwithstanding the early enforcement of isolation.

Colonia Tovar, a genetic isolate. Colonia Tovar, a small and until recently isolated community in Venezuela, presents a strange illustration of high prevalence coupled with high inbreeding.

Between 1843 and 1856, 146 immigrants from Germany settled in this isolated valley in the state of Aragua.[37, 38] In 1950, about a century later, a survey of 1126 inhabitants, almost the entire resident population, disclosed a prevalence of 100 per 1000 (113 cases) in sharp contrast with the rest of the state of Aragua, where the prevalence did not exceed 1.35 per 1000.

The original site of contamination remains unknown. Did the disease stem from a contact with an occasional case in the Creole population upon arrival in America, or was it present in the immigrant population at their place of origin in the Black Forest? Did the high prevalence result from the existence of some environmental peculiarity specific to the valley, which incidentally seems to benefit from a microclimate and is rumored to have an unusual ecology?[39] Could inbreeding have played a role, which would suggest the intervention of genetic factors in the susceptibility to leprosy?[37] Was the containment of the disease in the population due to geographic as well as cultural isolation, verging on spontaneous segregation? These questions remain unanswered.

Leprosy on the decline

In Western Europe, after having reached a peak in the 12th and 13th centuries, leprosy then started to decline until it had all but disappeared by the turn of the 20th century. Residual foci persisted in the Baltic states, in Greece, in the Iberian Peninsula and in the Balkans.

The very term "decline" is however misleading, since it may apply to two quite distinct epidemiological indicators: prevalence, depending on the number of patients affected with the disease at a given moment, or incidence, corresponding to the number of new cases occurring during an interval of time.

Taking as an example two of the Baltic countries, the number of patients (prevalence) in Latvia dropped from 977 cases in 1900 to 207 in 1933, a more than 75% decrease, and in Estonia from 316 in 1920 to 113 in 1940.[40] No conclusion, however, can be drawn as to the pace at which leprosy "declined," or when this "decline" started. Only incidence, reflecting transmission, will tell.

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[35] Dempster, G. O. L. (1949): Leprosy in Niue Island; a note on the history of the disease. Int. J. Lepr. 17; 411–414.

[36] Sloan, N. R. (1954): Leprosy in American Samoa. Technical Paper No. 62 (mimeograph), South Pacific Commission, Noumea.

[37] Convit, J., *et al.* (1952): Estudios sobre la lepra en el grupo etnico aleman de la Colonia Tovar. Int. J. Lepr. 20; 185–193.

[38] Lechat, M. F., *et al.* (1967): A study of blood groups and leprosy in the population of Colonia Tovar, Venezuela. Int. J. Lepr. 35; 488–493.

[39] Lechat, M. F. Personal observation.

[40] Leprosy Briefs (1957): 8; 37–38, Leonard Wood Memorial, Washington, D.C.

An exhaustive study of the annual incidence rates (and cohort-based incidence rates recording the year of birth) for the period 1855–1920 has been carried out in Norway by Irgens.[41] In the coastal part of the country where 97.8% of the 6652 patients with year of onset within the observation period were living, the prevalence fell from 35.2 per 10,000 in 1855 to 1.2 in 1920. During the same period, the incidence declined 100 times from 33.4 to 0.3 per 100,000.

What was the cause of the decline? Several reasons have been put forward to explain the downturn in Europe in the late Middle Ages, such as higher fatality rates in leprosy patients during plague epidemics (the Black Death) in the 14th century, the modification of eating patterns, or the development of immunity associated with the spread of tuberculosis.[42] This last hypothesis deserves more than a cursory mention. Numerous studies have demonstrated some degree of association in the cell-mediated immunity against *M. leprae* (Mitsuda test) and *M. tuberculosis* (PPD). After much debate, there is mounting evidence that vaccination by a combination of BCG with killed *M. leprae* confers a significant degree of protection against leprosy.[43, 44] Competition between the two bacilli could therefore account, at least in part, not only for the recession of leprosy, but also for the variations observed in its spread and its distribution.

One may further indulge in some speculation. A number of observations in animals have led to the general acceptance that exposure to given mycobacteria influences subsequent responses to other mycobacterial species.[45] For example, the observed protection against tuberculosis imparted by BCG is influenced by previous exposure to environmental mycobacteria. Such exposure could either enhance or reduce the susceptibility to *M. leprae.* In this respect, it should be noted that vaccination by a preparation of *M. avium-intracellulare* (ICRC vaccine) has been found to confer a degree of protection against leprosy similar to that produced by the combination of BCG with killed *M. leprae.*[44] Mycobacteria are ubiquitous in the environment. They could possibly modulate transmission not only by increasing or lowering the resistance to infection by *M. leprae,* but also by acting on the poorly elucidated immunological mechanisms which govern the transformation of the subclinical infection into an overt disease, either by shortening or lengthening the duration of the latent stage and/or by altering the relative proportion of individuals who respectively develop the multibacillary (with high infectivity) or the paucibacillary (with low infectivity) clinical types.

The distribution of a large range of mycobacteria could, therefore, have played a determinant role in the susceptibility of individuals and populations to infection by *M. leprae* and, as a consequence, could have exerted an effect on the dissemination of the disease and its time trends. The paleoepidemiology of leprosy could thus be reduced to a chapter in the immunogenicity of mycobacteria, past and present.

In recent centuries, the improvement of socioeconomic standards might to some extent explain the decline of leprosy (as exemplified by the Scandinavian settlers in Minnesota, U.S.A.), although, to quote Fine, "Whether the responsible factor is soap or nutrition or living conditions or crowding or clothing no one knows."[46]

Due to the large-scale implementation of highly effective drugs for the treatment and cure of leprosy, it is becoming impossible to study the decline of incidence under natural conditions. Even the Norwegian study, the best of its kind, is not devoid of such a bias, for segregation could also have played a role.

[41] Irgens, L. M. (1981): Leprosy in Norway: an epidemiological study based on a national patient registry. Lepr. Rev. 51 (Suppl. 1); 1–130.

[42] Sansarricq, H. (1995): Histoire de la lepre. In Sansarricq, H. (ref. 57).

[43] Karonga Prevention Trial Group (1996): Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet 348; 17–21.

[44] Gupte, M. D., *et al.* (1998): Comparative leprosy vaccine trial in South India. Indian J. Lepr. 70; 369–388.

[45] Stanford, J. L. (1978): The importance of environmental mycobacteria. In Chatterjee (ref. 56).

[46] Fine, P. (1992): Reflections on the elimination of leprosy. Int. J. Lepr. 60; 71–80.

Conclusions: from the past to the future

A worldwide program of treatment with a combination of highly effective drugs (multiple drug therapy, MDT) has been launched in the context of the 1991 World Health Assembly (WHA) Resolution on the "Elimination of Leprosy as a Public Health Problem."[47] The target of this program is to detect and cure such a large number of patients that the prevalence will be brought down to rates below 1 case per 10,000 population. At such a low level of prevalence, it is assumed that the proportion of infective patients in the population will become insufficient to sustain transmission. The incidence will then tend to zero, and the disease will ultimately die out.

Over the last 15 years or so, some 10.7 million patients have indeed been discharged.[48] The number of registered patients has fallen from 5.4 million worldwide in 1985 to about 800,000 at the start of 1998.[49]

Nevertheless, in a number of countries, and in spite of a considerable decline in prevalence, the number of cases detected in recent years remains quite high.[49] Several excellent reasons of an operational nature are at hand to explain this observation. The situation, however, continues to give cause for concern and is by no means elucidated.

Several questions may be raised. Is the natural decline of leprosy as observed in the past a warrant for a similar decline under today's conditions of MDT? Is the general assumption underlying the present strategy that man is the only reservoir and source of infection a valid one? Should alternative strategies be envisaged in special situations in order to accelerate elimination or ultimately ensure eradication?

Regarding the first question, the ongoing elimination program postulates that, when it reaches very low levels of prevalence, the disease should gradually fade away, replicating the pattern of natural recession allegedly observed in some countries.[50] It should be stressed, however, that low prevalence may refer to two contrasting situations, that is, "natural low prevalence" as observed in the past before the advent of effective treatment on the one hand, and "induced low prevalence" as engineered by the successful implementation of effective treatment on the other.[51] The two dynamics are fundamentally different. Untreated leprosy "au naturel" is a life-long ailment. It is only after some delay, reflecting the expectancy of life and death rates of the patients, that a decline in prevalence will follow a decline in incidence. On the other hand, leprosy treated with MDT is a relatively short disease whose duration does not exceed by definition the maximum of 2 years required by the standard treatment. The decline in prevalence, resulting from discharging cured patients, will therefore precede the decline in incidence. In simple terms, in the first scenario, prevalence is the effect and incidence is the cause. In the second one, prevalence is the cause and incidence is the effect. It is therefore deceptive to expect that a decline in prevalence engineered by MDT will, at low levels, necessarily "plug in" to the dynamics of the natural recession referred to above.

As case-detection rates tend to approximate to incidence rates, with the progressive clearing of the backlog of long-standing undetected cases, the number of new cases should gradually start to decrease. If not, the situation would then become one of real worry. It would perhaps call for a reassessment of many of the central assumptions of the current strategy, including those of man being the exclusive reservoir of *M. leprae* and the clinical patient being the sole source of infection.

Is the vexing possibility of an extra-human reservoir of *M. leprae* in animals, in the vegetation, or in the soil to be rejected

[47] World Health Assembly (1993): Handbook of Resolutions of the WHA and the Executive Board, Vol. III, 1985–1992. 3rd edn. WHO, Geneva; 117–118.

[48] World Health Organization (1998): Action Programme for the Elimination of Leprosy; Status Report. Geneva, WHO/LEP/98.2, 1998.

[49] World Health Organization (1998): Progress towards leprosy elimination. Wkly. Epidemiol. Rec. 73; 188–190.

[50] Noordeen, S. K. (1995): Eliminating leprosy as a public health problem: why the optimism is justified. Int. J. Lepr. 63; 559–566.

[51] Lechat, M. F. (1999): Taking home lessons. Proceeding of the 15th International Congress of Leprosy, Beijing, 1998. Int. J. Lepr. 66; 562–566.

off hand? For a while, sphagnum moss bogs were incriminated as a potential microhabitat for *M. leprae*.[52] However, the spread of leprosy at all latitudes throughout history, its distribution in clusters, and its dissemination closely following human movements, make it unlikely that a universal extra-human reservoir is involved.

Could it be then that individuals with subclinical infection act as a source of contamination and, therefore, transmit the disease? If so, it could explain why leprosy may continue to be rampant in a population. The outbreak in Nauru provides a sort of natural experiment, suggesting that infected individuals could indeed serve as a source of infection before the onset of clinical manifestations.

Advances in the knowledge of the molecular biology of *M. leprae* and the development of adequate tools for identifying subclinical infection or a carrier state could help to answer those questions.

Conditions which in the past were shown to be associated with the spread of leprosy, such as geographical or social isolation, migration, overcrowding, inbreeding or prime exposure, could call for the development of methods of primary prevention, such as chemoprophylaxis or immunoprophylactic vaccination.[53]

Finally, in spite of the large-scale implementation of MDT, there are still perhaps some enclaves, "fossils" of primeval leprosy so-to-speak, where the natural epidemiology of the disease may be observed. In the context of the WHO program, a most innovative initiative was launched under the title of SAPEL (Special Action Projects). It consists in the identification of populations for which imaginative and unusual approaches should be designed in order to reach and treat the patients. SAPEL projects include, among others, pygmies in equatorial forests, nomads in subsahelian deserts, settlers in virgin territories, riverine populations of the Amazon basin, and tribes in the hills of South-East Asia. Bridging the present with the past, epidemiological information collected during these projects could improve our understanding of the dynamics of leprosy in remote and little-known human groups. These communities live under conditions which at times still bear some resemblance to the ecology of the past. Their study could contribute both a better knowledge of the paleoepidemiology of leprosy and to an improved management of the control of the disease in the years to come.

The study of the epidemiology of the past should not only bring with it an intellectual gratification, but also stimulate us to be better prepared for new developments in the future.

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[52] Kazda, R., *et al.* (1981): Occurrence of non-cultivable sphagnum bogs acid-fast bacilli in the environment and their relationship with *Mycobacterium leprae*. Lepr. Rev. 52, (Suppl. 1); 85–91.

[53] Fine, P. (1996): Primary prevention of leprosy. Int. J. Lepr. 64 (Suppl.); S44-S49.

[54] Hastings, R. C., ed. (1994): *Leprosy.* 2nd edn. Churchill Livingstone, Edinburgh.

[55] Ell, S. R. (1994): Leprosy in history. In Hastings, R.C. (ref. 54).

[56] Chatterjee, B. R. (1978): *Leprosy; Etiobiology of Manifestations, Treatment and Control.* Statesman Commercial Press, Calcutta.

[57] Sansarricq, H. (1965): *La Lepre.* Ellipses, Paris.