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Historical account of clinical observations on leprosy and related manifestations in the Comacchio area, Italy, in the XIX century

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SUMMARY

Known before Christ and in ancient Egypt, leprosy was believed to be a mysterious disease of supernatural origin. It covered the body with lumps and sores, dulled the senses, produced altered facial features and mutilation of the limbs. By the 6th century AD, the disease had certainly made its appearance in Western Europe and continued to occur in the following centuries. It was also thought to be attributable to poverty and poor sanitation. Leprosy was not considered an infectious disease until 1873, when physician G. H. A. Hansen first identified *Mycobacterium leprae*, calling it Hansen's bacillus, and the disease was named Hansen's disease.
This paper analyses clinical reports on leprosy observed in Northern Italy, in the Comacchio area near Ferrara (Po Delta), in the 19th century, taking into consideration documents and manuscripts of the time.
The scholars who made the greatest contribution to the description of the disease in and around Comacchio area were Antonio Campana, Andrea Verga, Alessandro Colla, Clodoveo Biagi, Ottone Schrön, Giacomo Sangalli, Raffaele Cavalieri, and local physicians Cristoforo Belloli, and Francesco Ballotta.
Observations on the manifestations of the disease and attempts to cure it, including milk diet, are reported. In particular, this morbid form, which was not found in neighboring territories, was called "Mal di formica" because of its benignity at onset, its slowness and its slow progress. Tubercular Leprosy or Mal di fegato, a form of incurable leprosy was nothing more than the leprosy or elephantiasis described by the Greeks and Hebrews. The people most affected were women, who accounted for two-thirds of the sick. According to some authors, the causes of leprosy could be attributed to overuse of certain rotten or salted fish. Campana was the first to think that a lazaret should be erected for the sick.

Keywords: Leprosy, XIX century, Comacchio, Po delta, Italy.

INTRODUCTION

As early as the second millennium before Christ, traces of leprosy were found in exhumed bodies in China and in mummies from ancient Egypt. A detailed description of the symptoms can be found in the Old Testament Leviticus. Described in the Holy Bible, leprosy occurred with epidemic character in outbreaks in the early Middle Ages. The disease is also reported in imperial Roman times. Leprosy, with its repulsive features, appeared as a disease charged with mystery and supernatural origin. It covered the body with sores, dulled sensitivity and produced alterations in facial features and mutilation of limbs. By the 6th century AD, leprosy had certainly made its appearance in Western Europe. It then continued to

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occur in the following centuries and was always linked to poverty and poor hygienic conditions.
This paper analyzes the clinical aspects of leprosy observed in the Comacchio area (Po Delta), Italy, in the 19th century, taking into consideration documents and manuscripts of the time. First, manuscripts (*Voto*) and a Report (*Relazione*) by Antonio Campana on the establishment of a lazaret at Sant'Agostino in Comacchio were examined [1, 2].
In the 19th century, some authors proposed explanations of the following terms in use, "*mal di fegato*" and "*mal di formica*", also trying to trace the stigmata of the disease in the Comacchio area. In addition, scientists from various states of Italy spoke about leprosy at the Fifth Italian Meeting (Lucca, 1843). The topic aroused great interest and promoted the establishment of a cash prize. Three hundred francs would be awarded to the best *Memoria* that focused on the diagnosis of the disease in relation to similar diseases, comparison with leprosy in the Middle Ages, occasional and predisposing causes along with new proposals for prophylactic and curative means.The greatest contribution in describing the disease in and around Comacchio were from Andrea Verga, Alessandro Colla, Clodoveo Biagi, Ottone Schrön, Giacomo Sangalli, Raffaele Cavalieri and local physicians, Cristoforo Belloli, Leopoldo Pilati, Francesco Ortalli, Francesco Ballotta. Below are their most relevant reports and descriptions of the disease.

Andrea Verga, at the fifth meeting of Italian scientists (1843), focused on the environment and the development of disease

Andrea Verga lived there long enough to investigate, with the intent of presenting a *Memoria Commentario del dottor Andrea Verga*, which he will then publish in 1846, the health situation in the Comacchio ares that he knew very well [3].
The inhabitants of Comacchio (*Comacchiesi*) were 7.000 in the mid-nineteenth century. 2.000 cultivated the *Bosco eliceo* and lived along the beach. Others led a semi-aquatic life (*vita semiacquatica*), some others were taking care of salt pans, some were hunters, some fishermen. The main source of wealth of the *Comacchiesi* always came from eels. Comacchio, light look like Venice, but it is connected to the mainland.
Among the *Comacchiesi* there was a terrible disease that was not found in the neighbouring territories. It was the so-called *Mal di formica* due to its benignity when it begins and its slowness when it proceeds. It has also been generally referred to as *Mal di fegato*. It is similar to some extent to turkey disease, covering the wattles and the entire head with tubercles and scabs (*vuolsi analogo ad una certa malattia dei tacchini, che copre di tubercoli e di croste I bargiglioni e tutta la testa di quei gallinacei, guastandone contemporaneamente il fegato* [3]. The ailment usually indicated its origin in some mental illness (*patema d'animo*, emotional distress), according to humoral theories.
No one would have dared uttering the word leprosy at that time. Neither Bonaveri nor Proli, who wrote the history of the city, would mention it.
Verga says that, during the Cisalpine Republic, a Committee chaired by illustrious scientist from Ferrara Antonio Campana was founded in June 1806. It was established that the *Mal di fegato* and the *Mal di formica dei Comacchiesi* were nothing other than the leprosy or elephantiasis of the Greeks and Jews. The wisest measures were dictated in order to eradicate it and the segregation of lepers was ordered in the former convent of Sant'Agostino.
According to Andrea Verga, Cristoforo Belloli, *medico condotto* (local physician) in Comacchio, had repeated the judgment of the commission in a *Memoria (Effemeridi chimico-mediche, Milano, semestre I, tom I, (pag. 123).* Following the political changes, these premises were assigned to the Austrian garrison instead[1].

Mal di fegato, health situation in Comacchio - Report by Antonio Campana (1806)

In the Ariostea (Municipal Library of Ferrara) we found the manuscript *Voto sulla malattia regnante in Comacchio chiamata Male di fegato* dated June 29, 1806, in which Campana focuses on the health situation in Comacchio at that timeand quotes the report by L. Pilati, by affirming that *Comacchio*'s *Mal di fegato* is nothing but leprosy or elephantiasis [1]. According to Campana, this is a very important report, which must draw the attention of the government to end a very serious health situation[2]. Campana also examined previous reports he had received from the *Delegazione Medica*. After reading them he became even more convinced

1 *Although the lazaret was activated, it would, however, be permanently abandoned in the aftermath of the Congress of Vienna (1815) when it was turned into an Austrian fortress.*
2 *La malattia di Comacchio impropriamente chiamata mal di fegato […] La relazione del Sig. L. Pilati […] è un oggetto importantissimo.*

that the endemic *Mal di fegato* in Comacchio was a form of incurable leprosy or elephantiasis.
It was also noticed, that in most cases, the incurable disease attacked the poor class, deforming their body, making them stupid, threatening their morality. It would have killed the most unhappy, full of stinking ulcers, and often blind. This would happen after leading a miserable and desperate life for twelve to fifteen years.
Campana wrote that it was not possible to know when the disease could have appeared in the city. The physicians Bonaveri and Prioli did not mention it.
Campana says: the disease wasn't mentioned at all, although it certainly afflicted more people even with greater vigour and intensity. In the previous fifty years the number of sick people was no less than forty. In 1804 there were seven infected individuals, while then, there were twelve or perhaps even more because not everyone declared it sometimes out of shame. Comacchio leprosy would be found in many maritime countries of Europe, such as in eastern Bosnia, Finland, *Gotlandia* (Swedish island), and Norway in particular. Prospero Alpino's descriptions of the leprosy of Egypt, as well as the other leprosariums of India and America do not appear to be any different from those of Europe. The philosopher Peysonnel described the leprosy in Guadalupe by order of his government. The symptoms matched perfectly with those in Europe. The leprosy mentioned in the Old Testament is surely different and much more contagious without a doubt. In Norway it was a common opinion (*Linneo Amoenitates accademicae, vol. 7 p. 104)* that leprosy was the effect of a very small worm called *Gordio marino* (Marine Gordium), which produces pustules similar to that of leprosy, by penetrating into the flesh of many fishes. The worms could have spread through food to predisposed individuals by producing leprosy. The disease would not have been endemic in Comacchio, but it may have been carried there by trade routes across the sea.
According to Campana, people had to be isolated, it was desirable to set up a lazaret, entrusted to a skilled and learned doctor[3]. The doctor also had the task of observing the disease of which very little was known: the affected parts, the hardened fleshy parts, the bones of the phalanges, the presence of particular substances or worms[4] were diligently analysed. A well-designed lazaret would certainly have been helpful to the population.

Report made by Antonio Campana in Comacchio to determine where the lazaret for leprosy would be built and its characteristics in accordance with the Health Regulations, October 17, 1806
Campana makes an inspection in Comacchio to assess the health situation in order to identify the location of the lazaret [2].
The most affected people were women who accounted for two-thirds of the sufferers. Men were mainly fishermen, therefore often outside their homes, so they were less exposed to the infection.
The Doctor in Comacchio at that time was Pilati.
In the history of Comacchio (Bonaveri and Proli) neither leprosy nor *mal di fegato* were ever mentioned.
The disease would have occurred 60 years earlier. One family would have been infected by using wool coats previously used that were supplied from distant countries. Care would have been needed, sanitizing all the goods and proving their origin, making sure they did not come from infect-

Figure 1 - Former Monastery of St. Augustine, in Comacchio.

3 *Che tutti quegl'infelici che vi saranno trasportati […] secondo il proprio stato trovare adattato sollievo. Il medico al quale sarà confidata la gelosa incombenza di assistere quei sventurati dev'essere un uomo abile e dotto. Egli deve fare tutti i possibili tentativi per soccorrere la languente umanità.*

4 […] *una diligente analisi fatta sulle parti affette, cioè le parti carnose indurite, e sulle stesse ossa delle falangi […] ed indicare l'esistenza, e l'abbondanza di qualche particolare sostanza, così pure indagare se esiste o no qualche verme.*

ed countries[5].
The place is identified with the Convent of St. Augustine (Figure 1). It is located on a peninsula connected to the mainland by a small drawbridge (*piccolo ponte levatoio*) ensuring its isolation.
Baths were one of the most beneficial treatments that would provide relief to the unhappy. Two marble baths were prepared, divided in two by a wall (the women's and men's) so that only one boiler could be used.
The Physician, the Surgeon (*Chirurgo*), the Confessor could enter, but only if covered by a shiny cloth (*sopravesti di tela lucida*). When coming out, they would put it in a room for disinfection (*camera di espurgo*) and they would wash their hands with water and vinegar.
The dirty clothes were placed through a small opening made on the floor leading to a washhouse (*trogolo*), where some common lye (*ranno* or *liscivo*) was put every week. The washerwoman would not have washed them until they had completely soaked inside for at least an hour.
Fish was not included on the menu for the infected, as well as for the attendants and the caretakers.

Report by Alessandro Colla - Ferrara Academy's Proceedings (1827-29)
In the Proceeding of the Ferrara Academy (1827-29) an important report by Alessandro Colla was found. According to Verga, it is also cited by Alibert in his comprehensive treatise on skin diseases [4].
Colla claims to have repeatedly witnessed this disease's most terrible features. The cutaneous eruption used to form its pathognomonic character the same way as it was described by some ancient writers in the Indies, in the *Magnagrecia*, in *Arabia* and above all of Judea.
It could have arrived at the time of the Crusades through these imports, when Italy maintained a very active trade with the Levant coast. In regards the reasons explaining the persistence of the disease in Comacchio, Colla identifies them in the continuous consumption of fish and salted meats, also associated with living in dirty environments.
The extraordinary protrusion of the eye sockets, the sunken eyeballs, the low forehead and the presence of zygomatic prominences were signs from which it was easy to predict a possible development of the disease. The age at which it usually manifests is after puberty.
The remedies were normally those recommended for skin diseases. The method of Pilati, a doctor already mentioned in the documents of Campana, was considered very advantageous. Frequent bloodletting, decoctions of diaphoretic substances, bath of lukewarm and sulphurous water were both the cure to delay the development and a way to slow down the stages of this disease. Though, according to the doctor himself, even such a method was useless.

Andrea Verga - a commentary on the leprosy
During his stay in Comacchio, Verga had the opportunity to study a dozen patients [3].
The *Mal di formica* occurs preferably in female patients after puberty. It starts with fixed pains in one or more toes on the foot. After a feeling of tingling, a blister would appear. Only after applying a poultice (*cerotto o cataplasma*) this would burst by getting some relief for the patient.
As the disease progresses and fresh water baths and general bloodletting are no longer enough, the detachment of some phalanx and limbs begins until it would lead to blindness.
In males, on the other hand, *mal di fegato* was observed. Long before the disease developed, the terrible fate awaiting them could be read on the faces of the poor wretches: the face lost its softness, even taking on a shiny hue that gradually changed from dark red to purplish red; the eyebrows became prominent, hard, uneven and increasingly hairless, especially at the extremities; the cheekbones rose due to the clogging of the cellular tissue and skin covering them; the lips became dry and thick and the ear pinnae became large and irregular with absolute or relative narrowing of the lobule. The man who felt his face swelling in places, hardening and aching here and there, cracking and becoming covered with scabs, would surely become apprehensive and tremble at the thought of his unfortunate fate.
The therapies of the time were the *dieta lattea* (milk diet), the mercurial treatment, simple and steam baths, blood emission, mild purgatives, sweat decoctions, lukewarm sulphurous baths. Ortalli, a doctor of Comacchio, attempted the inoculation of

5 *Avvi chi crede che solo da sessant'anni a questa parte si sia manifestata questa malattia ed incolpasi una famiglia, che restò infetta adoperando capotti di lana usati, provveduti da lontani Paesi. Converrà perciò usare particolari riguardi pe' tali cose, sottoponendole nel caso a regolari espurghi, e provando la provenienza da Paese puro.*

Vajuolo arabo Arab smallpox, cow pus, venereal scabies, although without success.
Il volto del lebbroso che fin dal principio ha un non so che di mostruoso e di leonino … abbia a sparire alla fine ogni vestigio di umana fisionimia, the face of the leper that from the beginning has something monstrous and lion-like … in the end every resemblance of human physiognomy disappears.

Lebbra tubercolare o Mal di fegato di Comacchio - Report by Clodoveo Biagi at the Società Medico Chirurgica di Bologna (1844)
The report *Di una lebbra tubercolare o Mal di fegato di Comacchio* by physician Clodoveo Biagi, read on May 28, 1844 at the *Società Medico Chirurgica di Bologna* is accompanied by two *Tavole illustrate* [5].
These were present in a report read in 1835 by physician Raffaele Cavalieri, never published and forgotten.
The *Tavole* (Figure 2) show two lepers (*sono ritratte le facce di due lebbrosi*): one represents Giuseppe Cinti from Comacchio cured in Bologna in 1834, the other image of the tubercular leprosy (*Lebbra tubercolare*) reported by Alibert in his treatise (Figures 2 and 3). The images are defined very similar. Cinti represents the case study, showing the signs of an acute disease. Everything corresponds to what was reported by prof. Medici in Physiological, Pathological and Therapeutic Notes (*Cenni fisiologici, patologici e terapeutici*).
Among the causes we have heredity (an aunt, a leap of generation), the quality of food (fish), working in the saltworks.
First, hospitalization in Bologna results in a change of climate. Treatments such as administering tartar emetic, milk diet, and iodine (*iodio, Idriodato di Potassa*) proved ineffective. Vipers were then administered raw with sugar, decapitated and skinned. A decoction of *Calamita montana*, wine, sufficient food and steam baths were also needed. Only afterwards was a viperine broth administered. Forty-six vipers were consumed. No improvement in health was observed.
Cavalieri says the ineffectiveness of the treatments showed that this has nothing to do with skin inflammation or other types of inflammation[6].
Iodine combined with extract of *Aconito napello* and then mercurial was used again (as already used by Antonio Asdrubali). Asdrubali thought it was a degeneration of syphilis (*Perché è opinione ancora di alcuni esser la Lebbra una degenerazione della sifilide*).
Then the creosate washes were experimented for external use, then moved to internal use: frictions of mercurial ointment, hot baths and clutches of Clarche's calomel. Other remedies were: barite solution, arsenicals, Asian ointment and pills, Flowler's solution. After three years of treatment and four years of illnesws, the young Giuseppe Conti from Comacchio, portrayed in the *Tavola* (Figure 2), died.

Figure 2 - From Cavalieri Raffaele. The Tavole show two lepers: the first one (left side) represents Giuseppe Cinti from Comacchio cured in Bologna in 1834, the second (right side) is an image of the tubercular leprosy (*Lebbra tubercolare*) reported by Alibert in his treatise. The images are defined very similar [5].

Franceso Ballotta, Report on leprosy in the Scientific Session of Società medico-chirurgica di Bologna (1852)
Ballotta, *Medico primario* (Chief Physician) of Comacchio, report on leprosy in the Scientific Session of Società medico-chirurgica di Bologna on October 30, 1852 [7].
He advanced that there is no cure in his opinion. He cites remedies suggested by Galen and Avicenna: the meat of snakes, crocodiles, turtles, lizards, snails, frogs, salamanders almost as if in these amphibians the specific antileper could be found (*quasi stesse riposto in questi anfibi l'antilebbroso specifico*).
As for attempted remedies, he lists sulfur, antimony, arsenic, mercury, iodine, ammonia, many ac-

6 *Una cura sì decisamente stimolante, sostenutasi a lungo senza aversi alcun indizio di eccitamento aumentato, pone l'ultimo suggello di verità agli argomenti che provano la lebbra di Comacchio non essere una cutite, né altra infiammazione qualunque.*

ids, hemlock, dulcamara, holy wood, cinchona, potash, cantharides, all sort of bitter grass, all antiscorbutic plants, diaphoretic, diuretic, and bloodletting, leeches, suckers, and baths, liniments, washes, and thousand other external remedies (emollient, refrigerant, dessicants, corrosives).
As for the arsenic deutoxide proposed by Della Porta, tested at the Maggiore Hospital in Bologna, it did not lead to any results on the hospitalized in Comacchio.

Ottone Schrön - Lessons (1878)
Ottone Schrön (the lessons are reported by Agostino Casini in 1878), professor of Pathological Anatomy at the Royal University of Naples, says that the Elephantiasis of Arabs is the true (endemic) elephantiasis, in which ulceration is an exceptiion [8].
The elephantiasis of the Greeks, on the other hand, is *lepra* (leprosy); *si formano bottoni i quali ulcerano* (with ulceration).
In sporadic elephantiasis, they are deep abscesses which, by opening outwards, cause tissue ulceration. Ulcerations of sporadic elephantiasis and those of the leprosy should not be confused.
Leprosy – it is still said – was imported in Europe, even before the Middle Ages. It lost many of its characteristics; it also certainly lost in terms of geographic extension and intensity.
At the end of the 19th century it was limited to the countries of Northern Europe, Norway (1:100 in the population) and the northern coast of Russia; in the South we had only few cases like in Spain, Portugal and Italy.
At that time a certain contagion of ulcerative leprosy was not denied, but also the hereditary influence was considered.
We still have the formation of nodes that repeat the structure of granulomas [...] once the node is formed, there is a softening [...] in *lepra mutilans* whole limbs can fall off in a very short time (*Si ha formazione di nodi che ripetono la struttura dei granulomi* [...] *formatosi il nodo, vi è il rammollimento* […] *nella lepra mutilans interi arti possono cadere in un momento* […]).

Giacomo Sangalli – Treatise on pathological anatomy (1878)
In 1878 Giacomo Sangalli, in *La scienza e la pratica della Anatomia Patologica* [9] - *Delle infiammazioni semplici e specifiche in specie*, talks about leprosy.
Sangalli tries to justify the terminologies with which the Comacchio leprosy was called.
As for liver *Mal di fegato*, it could find justification from the humoral theory of the four elements and four temperaments. According to the ancient, leprosy originates from the liver (*ex cholera*)[7].
Belloli, a doctor from Comacchio, thought that the disease was due to obstructions of the liver.
As for the denomination *mal di formica*, when Sangalli wrote about it was no longer in use and it was simply called *mal del paese*[8].
In regards to *mal di formica*, Sangalli cites ancient authors who report tingling and itching of the skin as the first symptoms on the first development of the disease (*il formicolio e il prurito alla pelle sul primo sviluppo della malattia*).
He says: this explanation seems more plausible to me than the one expressed by Ballotta, who deduced it from the slowness of the disease: isn't the *mal di fegato* of that country equally slow [10]?
Sangalli says that leprosy is a rare disease in Italy, limited to Sicily, in some towns of Upper Piedmont, in Comacchio, in Lombardy.

Leprosy, state of art of a multifaceted disease
Leprosy, also known as Hansen's Disease, is a chronic infectious disease caused by *Mycobacterium leprae* that primarily affects the skin, mucous membranes, and peripheral nerves with formation of granulomatous lesions, the consequences of which can be very disabling. *M. leprae* is an acid alcohol-resistant obligate intracellular bacterium similar to *Mycobacterium tuberculosis*, which was first identified in 1873 by Norwegian physician Gerhard Henrik Armauer Hansen, from which both the pathogen and the disease are named (Hansen's bacillus or BH and Hansen's Disease).
M. leprae has always been considered the sole pathogen responsible for leprosy, until *Mycobacterium lepromatosis*, a species distinguished from the former by several sequences subjected to analysis of the gene encoding for the 16S subunit of ribosomal RNA (16S rRNA), was discovered as an additional cause of Hansen's Disease in Mexico in 2008.
Most cases of leprosy, according to data granted

7 *Non farebbe mai meraviglia se qualche antico medico di Comacchio, accettando codeste idee sulla causa della lebbra, avesse denominato il male di quel paese dall'organo produttore?*
8 […] *io non l'ho udita né dall'esimio dott. Piancastelli, che da dodici anni ivi tiene il primato nell'esercizio della medicina, né dagli abitanti di quella misera città: ora si chiama semplicemente il "male" del paese.*

by different countries and surveyed by the World Health Organization, were found as of 2020 mainly in Africa (*e.g.*, Ethiopia, Democratic Republic of Congo, Nigeria) and Southeast Asia. In addition, an important share of cases has been reported in Brazil, India, and Indonesia. It is worth mentioning how, as a result of the tremendous efforts of the World Health Organization, the number of cases since the 1980s has drastically decreased. In fact, WHO, under the enhanced global strategy for further reducing the disease burden due to leprosy, has charted the way to eliminate leprosy as a public health problem by supporting countries where it is still endemic to follow these protocols. However, due to the increasing rate of the migration flows, in Italy and in Europe, leprosy should be considered among the differential diagnosis in patients with cutaneous and neurological signs, especially when originating from endemic countries [11]. The cornerstones of the actual strategy to reduce disease burden, are early detection of cases, timely access and completion of treatment (polychemotherapy), seeking to ensure, with integrated health services, a high standard of care.

M. leprae, like all mycobacteria, possesses peculiar characteristics: it does not grow in common culture media, growth times are relatively slow, and common staining (*e.g.*, Gram stain) is not used to observe them, due to the complex structure of waxes and lipids that give it the special dyeing properties. The bacterium, an obligate aerobe, prefers temperatures below 37° C; in fact, it is located in the "coldest" parts of the body such as the skin, peripheral nerves, testicles, and ears; it also has a tropism for phagolysosomes of macrophages and infects Schwann cells of peripheral nerves the most.

The mode of contagion, although leprosy has been present since ancestral times, to date is still not entirely clear. It is assumed that transmission occurs through nasal secretions from person to person, by respiratory route with close and long-term contact with an infected person; the bacterium has a very slow growth and the incubation period can vary from 6 months to 10 years. Hansen's bacilli, once infection has occurred, multiply within the monocyte-macrophage system; if macrophages, even in a patient's immunosuppressed status, fail to stem the infection, the disease evolves with interest of histiocytes in the dermis and peripheral nerves.

Depending on the efficiency of the cell-mediated immune response, the clinical picture may converge into two different paths: the first, with development of a tuberculoid form, less severe but also less widespread and contagious, localized to skin lesions (paucibacillary <5), and the second, with a lepromatous form, more severe and contagious consequent to a poor cell-mediated response; the latter is a systemic form with widespread bacterial infiltration at the skin, kidneys, testes, and nerves, with a much higher number of skin lesions and mutilations (multibacillary >6).

The development of symptomatology, depending on the case more or less severe, depends essentially on the patient's immune response. The characteristic clinical signs of the disease, by which the infected person comes to observation, concern the appearance of skin lesions of different types, whether tuberculoid or lepromatous leprosy. In the tuberculoid form, the lesions are generally asymmetrical, like true erythematous plaques, nonpruritic whose affected areas are at times in-

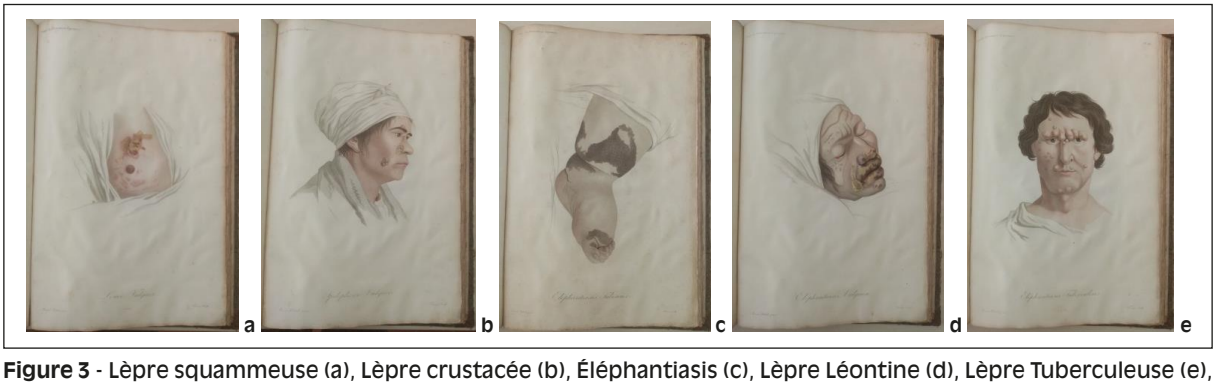

Figure 3 - Lèpre squammeuse (a), Lèpre crustacée (b), Éléphantiasis (c), Lèpre Léontine (d), Lèpre Tuberculeuse (e), Jean Louis Alibert, Clinique de l'Hopital Saint-Louis, 1833. Planches 38-42 [6].

sensitive to pain due to involvement of the underlying peripheral nerves. In the lepromatous form, in which other anatomical districts such as the testes, kidneys or nose are involved, the lesions present with nodular appearance of symmetrical shape. In the latter, the involvement of the nervous system with interest of peripheral nerves is much more severe than in tubercular, with large areas characterized by greater and complete insensitivity. The skin tends to become thickened and wrinkled with changes also affecting the ears, nose, and eyebrows.

There is also another form of the disease known as borderline, in which the clinical manifestations of both tubercular and lepromatous manifestations are present.

Complications of Hansen's Disease arise mainly from involvement of the nervous system, with worsening of peripheral neuropathy (sensory polyneuropathy) resulting in total loss of sensation, with inability on the part of the patient to perceive any kind of pain: thus, subjects may cut themselves, burn themselves, quite unconsciously with even very serious results, such as loss of fingers.

In the lepromatous form, as mentioned earlier, it is possible to have a disseminated manifestation of the symptomatology, affecting, for example, the eyes with corneal insensitivity and glaucoma, the kidneys with amyloidosis and renal failure, and in men with involvement of the testes and reduction of testosterone with infertility problems.

Finally, whatever the type of Hansen's Disease, the patient's immune system can produce two inflammatory reactions, known as leprosy reactions: type 1 reactions, caused by an increased cell-mediated response, which if not treated in a timely manner can cause major nerve damage whose lesions, like those on the skin, undergo further inflammation. In these reactions, the peripheral nerves may also undergo massive edema and aggravation of nerve function; type 2 reactions, known as systemic reactions resulting in vasculitis and generalized phenomena such as lymphadenitis, orchitis, arthritis, and glomerulonephritis, probably due to deposition of immune complexes or due to excessive T-helper lymphocyte response, although the mechanism is not yet fully understood.

Definitive diagnosis of Hansen's disease involves the search for acid alcohol-resistant mycobacteria on skin biopsies of infected tissues, through microscopic examination - after Ziehl - Neelsen staining) of the skin scrapings of the same lesions, once they have arrived at the laboratory according to the correct sampling and transport methods. Biopsies should be taken from nodules, macules or papules generally employing the slit smear technique, taking tissue from six sites (*e.g.*, earlobes, elbows, lower limbs) and quantifying the number of bacilli according to a bacteriological index of 1 to 6, after examining 100 fields under an immersion microscope. The gold standard laboratory test for the diagnosis of leprosy is undoubtedly skin biopsy followed by microscopic examination for bacilli. Biohumoral examinations (CBC, clinical chemistry) can be supportive but are not helpful in the etiologic diagnosis; a picture of altered inflammatory indices-aspecifically, such as ESR (erythrocyte sedimentation rate) and C-reactive protein-is possible, and in the lepromatous form, the finding of hypergammaglobulinemia is not uncommon. IgM antibodies to *M. leprae* are specific but do not have a high sensitivity and may be present even in completely asymptomatic infections.

Additional supportive instrumental tests include the histamine test, pilocarpine test, and Mitsuda-Hayashi intradermal testing, similar to the Mantoux test for tuberculosis bacillus.

The development of early therapy is essential to reduce nerve impairment. Drug therapy is often a combination of multiple drugs such as dapsone , rifampin, and clofazimine. Lifelong maintenance antibiotic therapy is also used in certain cases. The use of antibiotic therapies that may be subject to minor changes during the course of life are helpful in halting the progression of the disease, but if nerve damage is already present, it may not go to cure. In this regard, both diagnosis and timely drug treatment are essential, while the best prevention relies on avoiding contact with the secretions and lesions of infected persons.

CONCLUSIONS

Giacomo Sangalli stated that leprosy in the nineteenth century was a rare disease in Italy, limited to Sicily, some towns in Upper Piedmont, Lombardy, and Comacchio.

Scholars from Ferrara who made important and original contributions in describing the disease and possible cure in and around Comacchio were Antonio Campana, Alessandro Colla, and local

physicians, Cristoforo Belloli, Leopoldo Pilati, Francesco Ortalli, and Francesco Ballotta. Alessandro Colla, in particular, is appreciated and cited by Alibert in his comprehensive treatise on skin diseases.

The disease would not have been endemic in Comacchio, but may have been brought by sea through trade routes. A lazaret was provided in Comacchio, while for hospitalization of the sick, the reference was Bologna.

A historical investigation was conducted in this first phase. It is in our purposes a clinical evaluation of the evidence reported by nineteenth-century authors in order to assess the actual correspondence to cases of leprosy in the light of current knowledge.

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