

## An outline of the history of pellagra in Italy

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**Summary** - During the 16th and 17th centuries maize, a New World cereal deficient in niacin (vitamin B<sub>3</sub> or PP), replaced cereals of higher economic and nutritional value in the staple diet of the poor in Southern Europe. As a consequence of quasi-monophagic maize porridge-based diets pellagra, a lethal new disease due to severe niacin deficiency, spread dramatically among the Southern European peasantry. For over 200 years, between the 18th and the 20th centuries, pellagra was endemic in those parts of Italy whose agrarian economy depended on maize as a staple crop. The disease, first discovered in Spain, took its name from the Lombard dialect and was intensively studied in Italy during the latter part of the 18th and the 19th century. This led to a quick recognition of its association with maize as a staple and with poverty, stimulating heated debates and the emergence of a social conscience among Italian scientists. During the first half of the 20th century international research efforts clarified the biochemical and physiopathologic bases of deficiency diseases. In 1937 this led to the discovery by Elvehjem and collaborators in the USA of niacin, the pellagra-preventing factor. Between 1937 and 1940 field studies on pellagrins conducted in endemic areas of Northern Italy by the Institute of Biology of the National Research Council gave a key contribution to the demonstration of the curative effect of niacin. In Italy pellagra is now a disease of the past but it teaches an enduring lesson on the impact that social structure, cultural adaptation and environmental/economic change have on human health.

**Keywords** - Pellagra, Italy, Nutrition, Disease, Niacin, Maize, Monophagy.

### An introduction to the disease

Pellagra is caused by a severe dietary deficiency of niacin (also referred to as vitamin B<sub>3</sub> or "PP", from "pellagra-preventing factor") and its key metabolic precursor, tryptophan (whose intake reflects the overall quantity and quality of dietary protein). This vitamin deficiency disease is a consequence of quasi-monophagic diets based on cereals poor in tryptophan and niacin, used generically for both nicotinic acid and its amide, nicotinamide (Scrimshaw, 1975; Cannella & Solinas, 2006). Maize (corn, *Zea mays*) in Europe, the Americas, parts of Africa

and East Asia, and millet (*Sorghum vulgare*), in South-East Asia and sub-Saharan Africa, are the two major cereals implicated in pellagra (Roe, 1973; Scrimshaw, 1975). Concurrent endemic diseases such as intestinal parasites, infections, and other dietary deficiencies, combined with gender-, age- and ethnicity-related factors, influence the disease phenotype, so that pellagra may be present with individual, ethnic or regional differences (Scrimshaw, 1975; Hegyi *et al.*, 2004).

The heterogeneous clinical manifestations of pellagra are all reducible to an interference on protein synthesis and cell replication due to disturbances in the tryptophan-nicotinamide

adenine dinucleotide pathway, which plays a key role in cellular energy metabolism and DNA repair (Cannella & Solinas, 2006). The consequences of these disturbances are most prominent in tissues that have higher self-renewal or protein turnover. Pellagra is always characterized by cutaneous signs, most evident in sun-exposed areas. At an early stage skin involvement takes the shape of cutaneous inflammation similar to sunburn, while later changes include thickening, scaling, hyperpigmentation and hyperkeratinization. The general clinical symptomatology initially consists of lassitude, anorexia and digestive disturbances, combined with psychic and emotional changes; and progresses to dysphagia and diarrhea with gastrointestinal bleeding. This is associated with various pathological signs that reflect anemia and inflammation of internal mucous epithelia. The non-specific neurologic symptoms also evolve in severity, proceeding to hallucination, schizophrenic delirium and lethargy, reflecting increasing encephalopathy. If untreated the disease leads to death within four or five months because of disease complications, unless these are preceded by suicide (Scrimshaw, 1975; Hegyi *et al.*, 2004).

#### **Maize monophagy: impact of the post-Columbian dietary revolution on Mediterranean frugality**

Before 1492 the agricultural societies of the Old and of the New Worlds had developed parallel but distinct cereal-based dietary models that relied on wheat and other minor cereals on one side and on maize and tubers (potato, sweet potato, and manioc/cassava) on the other. In both cases nutritional balance was low in terms of intake of energy and essential nutrients, particularly for the lower classes of society (Mariani-Costantini & Ligabue, 1992).

In Mediterranean countries, and in particular Italy, which sustained a relatively large population, frugality had always represented a necessity in relation to the scarce food production. In areas with less diversified food availability this tended to result in monophagy (Mariani-Costantini, 2006).

Plinius the Elder had observed that the Ancient Romans used to live on porridges (“puls”), obtained by boiling ground cereals in water and/or milk, rather than on bread: *pulte Romanos longo tempore vixisse* (Pucci, 1989). In fact wheat, commonly used for bread manufacture, was scarcely cultivated in ancient Latium where the most diffuse cereals were instead barley and *far* (*Triticum dicoccum*) together with spelt (*Triticum spelta*), which constituted the basis of the Roman *puls*. To stress the relevance of these ancient foods it is noteworthy that *puls* and *far* are the Latin roots of the Italian terms for porridge, *polenta* and flour, *farina*, respectively (Mariani-Costantini, 2006). While the foods available in Italy increased in quantity and variety following improvements in agriculture, animal husbandry and exchanges within the Mediterranean region and with Asia, the hierarchical stratification of the society based on census determined a profound divergence between the varied and excessively abundant diets of the wealthy few and the extreme frugality, tending to seasonal starvation, of the lower classes. However, due to the nutritional value of the Old World cereals, the pre-Columbian Italian diets do not appear to have been associated with specific nutrient deficiencies and pellagra was unknown, in spite of widespread hunger and malnutrition (Mariani-Costantini, 2006).

In the 16th century the development of trans-Atlantic exchanges sparked off a dietary revolution which in the long run amalgamated the diets of the Old and New Worlds and thus shaped the modern food system (Braudel, 1979). The allegoric paintings of Giuseppe Arcimboldo (1527-1593) attest to the early Northern Italian diffusion of maize and other vegetable food items of New World origin, such as potatoes, beans, string beans, tomatoes, pepper, *etc.* (Fig. 1). However the wider dietary choices (and the consequent qualitative variation in foods) that followed the discovery of the Americas was destined to remain for a very long period an almost exclusive privilege of the wealthy. This is exemplified by the fact that as late as the 19th century the consumption of tomatoes, today regarded as a typical component of the popular Mediterranean diet, was still low

in Southern Italy (Mariani-Costantini, 1996). Only maize and potatoes spread to the lower classes because they could be produced more easily and at a lower cost than wheat and other native Old World cereals. Thus in a comparatively short time these two new American foods became dietary staples of the poor in those parts of Europe that were suitable to their cultivation, *i.e.*, Northern Europe for potatoes and Southern Europe (mainly Spain, Portugal and Italy) for maize (Mariani-Costantini, 2006). Unfortunately, the traditional alkali preparation methods of maize developed by native peoples of the New World (e.g., the use of nixtamalization by Mesoamericans) which required treatment with slaked lime or some other alkaline products like plant ash, was not adopted (Brenton, 2004). This alkali treatment makes niacin, biochemically bound in corn, nutritionally available and thus reduces the severity of niacin deficiency in maize-based diets (Kodicek *et al.*, 1956).

In Italy, the diffusion of maize as a staple allowed for at low cost sustained peasant populations that were harshly exploited for

their labour, particularly in the Northern flood plains, suitable for intensive agriculture. Wheat, a preferred grain source for flour and bread, sold at almost double the price of corn and was therefore almost entirely reserved for the market, together with other economically valuable food items (Mancini, 1954). Thus during the 16th and 17th centuries porridge (*polenta*), the central component of the poor diet of the Northern Italian peasantry, became almost exclusively based on maize flour prepared without the traditional New World indigenous alkali treatment (Brenton, 2004). This quite abrupt socio-economically-driven switch in dietary habits, combined with the lack of cultural culinary adaptation, led to the development of the terrible scourge of pellagra in the Italian countryside (Mancini, 1954).

Literature and memoirs attest to the impact of the disease in those areas of Italy that are now among the most affluent in Europe and that were also in the past fertile, with richly cultured and developed cities. Goethe, in his voyage in Italy (1786-1788), descending from the Brenner pass into the Venetian plain noted the abrupt change in the facial features and skin color of the population and the pitiful appearance of the children. He concluded that this was due to the continuous use of maize as food. Much later, in his memoirs, the economist Felice Guarneri, born into a noble family of Northern Italian landowners and later Minister of Foreign Exchange, sketches the lifestyle of the peasants that cultivated the Cremonese countryside during the second half of the 19th century. He noted that their staple diet was maize porridge, accompanied only by seasonal green salads dressed with linseed oil. As a consequence of this poor diet, “pellagra, the disease of misery harvested...” (Guarneri, 1953).



**Fig. 1 - An allegoric painting of the Summer, by Giuseppe Arcimboldo, dated to 1573, attests to the early diffusion of maize in Northern Italy. A maize cob is well evident in the mixed variety of vegetable food items of European and American origin (Paris, Louvre).**

### **Disease identification and emergence of pellagra as a medical and social problem**

The term “pellagra”, literally meaning “rough skin”, derives from the Lombard dialect of Northern Italy and clearly highlights the

most readily evident clinical sign of the disease, easily recognizable even by illiterate peasants. According to Maggioni (1976, 1984), who analysed the earliest pellagra literature, this descriptive designation was introduced in the medical literature by Francesco Frapolli in a treatise entitled "*Animadversiones in morbum vulgo pelagram*" (1771), but had clearly been of wide popular use in the Padan plain well before then. However, in spite of the North Italian origin of its designation, pellagra appears to have been first discovered by the Spanish physician Gaspar Casal in the Asturias region of Spain around 1735. In his posthumously published encyclopaedic treatise on the "*Historia Natural y Medica de el Principado de Asturias*" (1762), there is a chapter on "*De affectione quae vulgo in hac regione mal de la rosa nuncupatur*", where Casal refers to pellagra using a Spanish designation that reflected the characteristic sunburn-like skin erythema. Casal also correctly noted and described the gastrointestinal and neurologic manifestations of the disease and made the very first important observation of its association with a corn-based diet.

In Northern Italy, where the socio-economic and humanitarian burden of pellagra was heaviest, several studies on the disease soon followed during the last quarter of the 18th century (Odoardi, 1776; Zanetti, 1778; Gherardini, 1780; Strambio, 1789; Videmar 1790). These are brief monographic publications related to particular areas of Lombardy and Veneto. Besides clinical symptoms, they describe the dietary habits and the socio-economic conditions of pellagrins, most notably highlighting the non-infectious nature of the disease (Strambio, 1789). Then, in the first half of the 19th century, the social basis of pellagra became a major focus of attention as shown in the studies of Liberali (1831) on the manic dementia of pellagrins. The work of Zecchinelli (1818) on public health-political issues raised by the disease (Fig. 2) denounces in particular "the social responsibility of landlords", hoping that "the increasingly rapid progress that pellagra is making among peasants may open their eyes on their true and stable interest and because

of this, if not for humanity, may persuade them to consider the peasants that work their lands at least as important tools strictly necessary to the land itself" that should be cared for "at least as work animals". Later, to highlight the agrarian question underlying pellagra, Flarer (1849) used as a disease synonym the term "*malattia del padrone*" (*i.e.*, illness due to the landlord).

In a charming little travel book which considers the influence of climate and residence on health and disease, entitled "Change of air or the philosophy of traveling" (1831), British physician James Johnson noted the widespread presence of pellagra in the Padan plain, highlighting the notable fact that the disease was not seen in other even poorer parts of Southern Italy, heavily afflicted with malaria and hunger. He states that at this time the general opinion that he gained by talking with "the medical men of the Milanese" was that pellagra resulted "from the extreme poverty and low unwholesome diet of the peasantry".

The strict link between maize and pellagra was becoming generally recognized. This is clearly apparent in the study on the causes of



*Fig. 2 - Title page of the Riflessioni sanitario-politiche sullo stato attuale della pellagra nelle due provincie di Belluno e di Padova by Giovanni Maria Zecchinelli, a work which as early as 1818 strongly denounces the social basis of the disease.*

malnutrition in the lower social classes promoted by the Pontanian Academy of Naples in 1861, soon after the unification of Italy. Here the “adversion towards maize consumption” typical of the Neapolitan food culture was regarded as providential “because its use (i.e., the use of maize) is probably the true reason for which pellagra rages in the North of Italy” (Ottini *et al.*, 2001). The first enquiry that statistically demonstrated an association between pellagra and consumption of porridges and flat bread made from ground maize was promoted by the Italian Society for Anthropology and Ethnology between 1872 and 1878 in the Italian regions that harboured endemic pellagra, then including Veneto, Lombardy, and Piedmont in Northern Italy, Emilia, Marche and Umbria in Central Italy (Raseri, 1879).

In spite of this, medical action against pellagra was hampered by the fact that the very concept of deficiency disease had not yet emerged. The experimental approach as developed by Claude Bernard in his “Introduction to the Study of Experimental Medicine” (1865) was rarely applied to disease. Only the prevention of scurvy was empirically practiced with the introduction of lemon juice in the food rations of ships during long sea travels, based on the observations of Lind of its protective value (1753). Otherwise, the only nutrition-related disease whose physiopathology could be understood and cured was starvation.

### **The debate on the etiology of pellagra**

The association between a poor socio-economic context and maize diets stimulated a heated debate on the etiopathogenesis of pellagra. In Italy, two distinct hypotheses clashed one against the other. The first one, which we now know was on the right track, had been already advanced by Marzari at the beginning of the 19th century (Marzari, 1810; 1815) and attributed the disease to a poorly understood deficiency connected with maize-based diets, which resulted in an inadequate ability to “tissue repair”, as stated by Lussana

(Lussana, 1872). However, no hard experimental evidence could be provided in support of this theory. The other hypothesis, first advanced by Balardini (Balardini, 1845) but then very authoritatively advocated by the famous and eclectic neuropsychiatrist, criminologist and anthropologist Cesare Lombroso in his prophylactic and clinical treatise on pellagra (Lombroso, 1892), held the view that the disease was caused by “toxic” substances generated in rotten maize by the presence of molds. Between the end of the 19th and the beginnings of the 20th century one of the main advocates of this “toxic” theory was Alpago-Novello, president of the Pellagrological Commission of the Province of Belluno, close friend and follower of Lombroso. In a pamphlet published in 1905 he stated that the person that “eats safe corn does not develop pellagra, but he who eats rotten corn does” (Alpago-Novello, 1905). The “toxic” theory can be understood when situated in a historic context in which the pathogenetic role of micro-organisms and their toxins was becoming increasingly apparent. From the socio-economic aspect, this theory was also less disruptive than a nutritional deficiency one, because on its basis pellagra prophylaxis could be limited to improvements in the practices of maize desiccation and storage, without calling into question the politically and socially sensitive issue of food availability to the lower classes. The question remained open in the first decades of the 20th century, with contributions by several eminent personalities, including Tizzoni (1907, 1909), Sanarelli (1909), Rondoni (1919), Boschi (1927) and others. Thus in those critical years the Italian approach, even if starting from sound hypotheses which were ahead of their times, was not realized in the design of experimental approaches adequate to the solution of the problem of disease etiology. Nonetheless, between the end of the 19th century and the first quarter of the 20th century the general improvement in socio-economics conditions and health of the peasantry resulted in a progressive decline of the disease in endemic areas (Tab. 1).

### Discovery of nutritional deficiency diseases and identification of niacin as the pellagra preventing factor

At the very end of the 19th century a crucial change in the understanding of nutrition-related diseases was sparked off by the seminal studies of Christiaan Eijkman on beri-beri, a degenerative disease of nerves due to thiamine (vitamin B<sub>1</sub>) deficiency, once frequent in South East Asia (Eijkman, 1897). Eijkman clearly showed that beri-beri was associated with diets based on polished rice and hypothesized that the polishing process caused the loss of an anti-toxic component protective against beri-beri. Soon after (1898) studies on voluntary Javan prisoners provided a full experimental demonstration that beriberi was due to a dietary deficiency (Funk, 1922). Thereafter, in 1912, Funk gave a full theoretical interpretation of vitamin deficiency diseases and identified thiamine as the individual nutrient whose lack caused beri-beri (Funk, 1912). The supposed amine nature of this factor inspired the term “vital amin”, hence “vitamin”, thereafter applied to a diversified series of essential micronutrients discovered in the first half of the 20th century (Funk, 1922).

The turning point in the history of pellagra came in 1937 in the United States when Elvehjem and collaborators demonstrated that niacin administration cured the black tongue disease of dogs, an experimental model of the human disease obtained by feeding dogs with a corn-based diet (Elvehjem *et al.*,

1937). As a consequence niacin treatment was successfully tested in pellagra patients both in the USA (Spies *et al.*, 1938) and in Italy (Frontali, 1938), as documented in historic photographs (Fig. 3). However in these first studies the patients were hospitalized and, even if they were kept on diets deprived of pellagra preventing factor (which was administered in a controlled fashion), their overall lifestyle changed. To address this limit, as early as May 1937 the Institute of Biology of the then newly established Italian National Research Council (CNR) decided to test the efficacy of nicotinic acid administration in the course of field studies which the Institute conducted on pellagra in Veneto (after World War II it became the National Institute of Nutrition, INN, and today it is known as the National Institute of Research on Foods and Nutrition, INRAN). It was decided that treatment had to be performed on pellagrins that remained in their habitual conditions and followed their usual lifestyle and diet (Visco, 1938). The results of these investigations can be synthesized as follows:

- 1) Lesions on the tongue and oral mucosae and gastrointestinal manifestations disappeared totally after the second or third intravenous injection (200 mg of nicotinic acid), more slowly after intramuscular and oral administration.
- 2) Cutaneous lesions in the erythematous phase regressed in 2-3 days, chronic dermatitis resolved in 12-15 days;

**Tab. 1 - Pellagra cases ascertained in Italy, 1879 to 1909, from censuses of the Ministry of Agriculture, Industry and Commerce (1879-1909) and the Ministry of Internal Affairs (1905, 1909), as reported in Mancini & Fiorentini (1957).**

Year	1879	1881	1899	1905	1909
Population	28.437.061	28.45.628	32.242.220	33.441.484	34.269.828
Pellagra cases	97.855	104.067	72.603	46.984	41.768
Prevalence/100,000	344	366	225	140	122

- 3) Anorexia and fatigue disappeared after 70-80 days from treatment inception, with weight increase in about two-thirds of the subjects.

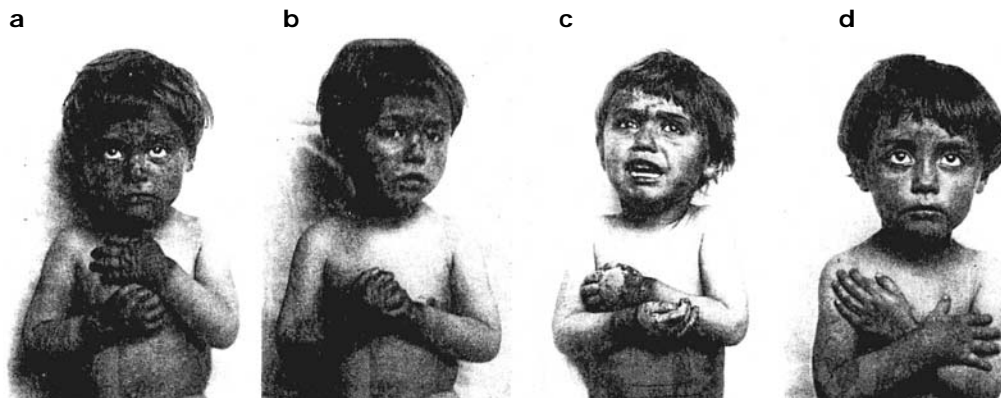
Therefore the field research conducted in Italy between 1937 and 1940, in which Frontali, Visco and collaborators (Fabriani, Fiorentini, Maggioni, and Mancini among the others) were pioneers, unequivocally demonstrated that nicotinic acid was curative in pellagrins, since its administration brought about the only change introduced in the trials. The impact of this research suffered from the general political situation of the period and from publication in Italian and German journals scarcely accessible to the international scientific community (Frontali, 1938; Visco, 1938; Visco, 1940; Mancini & Fiorentini, 1957).

As a consequence of economic growth and of specific and effective prevention, pellagra in Italy disappeared completely between 1950 and 1960 (Tab. 2) and is now an often forgotten disease of the past. However, it is still seen in parts of Africa and its very presence teaches us an enduring lesson on the impact that social

**Tab. - 2. Regional distribution of pellagra cases reported in Italy in 1954 (from Mancini & Fiorentini, 1957).**

Region	Cases
Piedmont	1
Lombardy	4
Veneto	18
Friuli-Venezia Giulia	1
Emilia-Romagna	1
Other regions	---
Total	25

structure, cultural adaptation and environmental/economic change have on human disease (Roe, 1973; Brenton, 1998; Brenton, 2004). These factors will always influence the balance between health and disease in human societies and need to be addressed and controlled in ever changing contexts, in light of scientific knowledge and social justice, combined with economic, cultural and public health development.



**Fig. 3 - Original sequence of photographs from the outline on pellagra written by Maggioni for the Italian Medical Encyclopedia (USES Edizioni Scientifiche, Florence, 1984). These photographs were taken by G. Frontali during the first studies on treatment of pellagrins with nicotinic acid (1937-1940) and depict improvements of skin lesions in a child (A, pretreatment; B, day 6 of treatment; C, day 8 of treatment; D, day 16 of treatment).**

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Associate Editor, Rita Vargiu