# Aetiological doctrines and prevalence of pellagra: 18th century to middle 20th century

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Pellagra is characterised by dermatological, gastrointestinal and neuropsychiatric manifestations. Millions contracted the disease and hundreds of thousands died between the time it was first recorded until pellagra was finally recognised as a niacin-deficiency disease. Pellagra became epidemic when maize, with its limited bio-availability of nutrients such as niacin and tryptophan, became the staple food in the near-monophagic diets of the impoverished and institutionalised. By the mid-20th century, pellagra was all but eradicated in large parts. The decline in prevalence can largely be ascribed to a better understanding of the link between nutrition and disease, improvements in socio-economic conditions of workers and food enrichment. We briefly review aetiological doctrines on pellagra and the global spread of the disease from the early 18th century until the middle of the 20th century. In the final analysis, we examine the reasons for, and the legitimacy of, the persistent association between pellagra and the consumption of maize.

**Significance:**

- Almost two centuries have elapsed since the first description of pellagra and its general acceptance as a nutritional-deficiency disease.

- The link between maize and pellagra is primarily a reflection of the nutritional inadequacies of a near monophagic diet over-dependent on a grain deficient in bioavailable niacin and tryptophan.

- We refute the concept of nixtamalisation as the main reason for the apparent absence of pellagra in early pre-Columbian North American, Mesoamerican and South American cultures.

## Introduction

Pellagra is a nutrition-deficiency disease characterised by dermatological, gastrointestinal and neuropsychiatric manifestations. The symptoms are commonly referred to as the three D's: dermatitis, diarrhoea and dementia, which may not necessarily present in that order. Although the symptoms of pellagra are defined as dermatitis, diarrhoea and dementia, a wide range of gastrointestinal and neuropsychiatric symptoms may present.[1,2] The skin lesions appear primarily on those parts exposed to sunlight, such as the dorsum of the hands and feet, with the typical 'Casal's necklace' of rough skin in exposed areas around the neck and upper chest.[1]

Pellagra is the classical syndrome of a severe deficiency of the water-soluble vitamin niacin.[2] Niacin, also known as nicotinic acid or vitamin B3, and its amide derivative nicotinamide, are precursors of the co-enzyme nicotinamide adenine dinucleotide (NAD) which can be phosphorylated (NADP) and/or reduced (NADH and NADPH).[3] As NAD and its derivatives are involved in a multitude of oxidation-reduction as well as non-redox reactions, severe niacin deficiency can lead to death with multi-organ involvement.

Niacin is abundant in a number of different foods – dairy products, cereals, nuts, leafy vegetables, yeast, fish, and meat products.[4] However, the form in which it occurs and its bio-availability differ. Some foods contain niacin in the free form that is highly bio-available. Cereal grains, as a source of niacin, vary depending on the type and the processes involved in food preparation. In addition to dietary intake, niacin can also be synthesised from the essential amino acid tryptophan via the kynurenine pathway.[5] Such *de novo* synthesis of niacin decreases with a deficiency in iron, riboflavin (vitamin B2) or pyridoxine (vitamin B6).[6] Several factors may have pellagragenic effects, either through their influence on the absorption of niacin and/or tryptophan, or through their effects on the conversion of tryptophan to niacin. These factors include excessive leucine intake[7], chronic alcoholism[1,2], anti-tuberculosis drugs[8], immunosuppressive drugs[9], eating disorders and a variety of gastrointestinal disturbances[2].

Today, the name pellagra has become virtually synonymous with the term niacin deficiency. However, many aetiological theories were explored and almost two centuries elapsed between the first description of the condition and its general acceptance as a nutritional-deficiency disease. We briefly review the main proposed aetiological doctrines, the global spread of the disease from the early 18th century until the middle of the 20th century and the association between pellagra and maize.

## Aetiology of pellagra: From vampires to nutritional deficiency

Up until its formal recognition as a dietary deficiency, pellagra has been blamed on various phenomena. It is even believed by some to be the origin of the vampire myth on which Bram Stoker's blood-sucking Transylvanian vampire, Count Dracula, was based. This association was perhaps largely because of the sunlight sensitivity of pellagrins and the belief that vampires were said to avoid sunlight in order to maintain their strength, but also because of shared psychological traits such as insomnia, anxiety, aggression and depression. Similarities between the physical and psychological characteristics of pellagrins and that attributed by folklore to vampires are described in an intriguing overview by Hampl and Hampl[10] based on early 1700s European literature and folklore.

Theories on the aetiology of pellagra can broadly be divided into maize-based theories and those based on factors other than the consumption of maize. The latter includes theories that claimed pellagra was caused by a blood-

sucking insect, the ingestion of semi-dried edible oils and the retention of mineral salts, or was an inherited disease, a race-dependent disorder, a type of scurvy, a disease related to leprosy and, perhaps the view with the most far reaching consequences, a communicable condition caused by infectious agents.[11-14] A more comprehensive treatise on these early aetiological doctrines can be found in a 1912 document by Niles[15]. Probably most important among the theories that attributed pellagra to factors other than maize is Sambon's infectious paradigm that shaped the early American investigations and hampered investigations and the correct treatment of pellagrins in the USA during the early 1900s.[16] Louis Westenra Sambon (1867–1931) was born in Milan, obtained an MD from the University of Naples and after some award-winning work on cholera moved to England where he spent the major part of his career at the Liverpool School of Tropical Medicine. In line with his groundbreaking theories on sleeping sickness, malaria and yellow fever, Sambon was convinced that pellagra was an infectious disease caused by a protozoan parasite and transmitted by an insect (*Simulium*). This parasitic theory of Sambon's was first introduced in 1905 at the meeting of the British Medical Association.[12,16]

The most enduring theories about the aetiology of pellagra were based on the consumption of maize, to the extent that an association can still be found in modern medical textbooks.[1] There were several variations of the hypothesis that maize consumption was the cause of pellagra. A theory given prominence by the Italian psychiatrist Cesare Lombroso in 1892, was that pellagra was caused by a toxin in deteriorating maize.[13,17] Lombroso's toxico-chemical approach, also referred to as the toxic zeist or spoiled maize theory, stated that inadequately dried, stored maize, under the influence of microorganisms, undergoes certain changes with the formation of one or more toxic chemical substances that could lead to pellagra. Lombroso's theory was more explicitly articulated in a 1905 pamphlet by Alpago-Novello, president of the Pellagrological Commission of the Province of Belluno and close friend and follower of Lombroso: 'he who eats safe corn does not develop pellagra, but he who eats rotten corn does'[18]. Scores of microorganisms were subsequently tested in various countries in an attempt to find the causative agents.[13] Two further views developed as outflows of the toxic maize theory, i.e. the belief that good uncontaminated maize itself carries toxic substances, and the view that when spoiled maize is ingested certain toxic substances are formed within the body.[19]

In contrast to hypotheses based on the toxic-maize theme, many investigators suspected nutritional deficiencies, rather than toxicity, to be the causal link between maize and pellagra. The Spaniard Gasper Casal (1650–1759), who first officially documented pellagra, in observing the prevalence of the disease in those subsisting on maize as a staple food, recommended the inclusion of vegetables and cow's milk to their diets. This concept of a nutritional inadequacy was more explicitly defined in 1810 by the Italian Giovanni Marzari who attributed pellagra to an unknown deficiency in diets over-dependent on maize.[20] Filippo Lussana (1820–1897), an Italian medical practitioner and clinical neurophysiologist, was more specific, and in a 1856 publication Lussana and Carlo Frua described a proteinaceous insufficiency as the cause of pellagra, declaring the protein content of maize to be far below that required for health.[21] In 1914, the specific 'nitrogenous substance' referred to by Lussana and Frua, and today known as the substrate for *de novo* synthesis of niacin, was identified as tryptophan by Mendel and Osborne. Lafayette Mendel, a professor of physiological chemistry with an interest in the relative values of various proteins for growth and health, and his co-worker at Yale, Thomas Osborn, a chemist interested in the amino acid composition of plant proteins, demonstrated the low availability of tryptophan and lysine in zein, the major protein of maize.[22] During these early years of the study on protein chemistry, several workers were involved in the pursuit of what was deemed 'micronutrients that could prevent disease'. The Polish biochemist Casimir Funk (1884–1967), working successively in Paris, the Lister Institute and the USA, is generally accredited with being the first to use the name vitamins (vitamines) in 1912 and to propose among others an 'antipellagric' vitamin.[23] In a paper, largely ignored at that time, Funk suggested that a change in the method of milling maize was contributory to the prevalence of pellagra.[24] As discussed in later paragraphs, this suggestion was, in fact, correct. The so-called 'vitamine hypothesis',

inferred by Funk in early 1912 was later that year articulated by Fleming Sandwith and Rupert Blue, members of the American Clinical and Climatological Association.[25]

Despite these early observations[17,19,20], formal recognition of the disease as a nutritional deficiency only happened at the beginning of the 20th century[26]. There was some opposition to this recognition, which should largely be seen against the background of the then prevailing knowledge of clinical medicine. The concept of nutritional deficiencies as causes of disease, despite being implied more than a century earlier by individuals such as Italian Giovanni Marzari,[20] was in its infancy and the general belief was that good nutrition consisted of proteins, fats and carbohydrates as the essential elements. It is also important to remember that the decisive work that led to confirmation of pellagra as a nutritional deficiency was performed not long after Robert Koch's identification of *Bacillus anthracis* in 1875 – therefore during a period when many diseases of unproven aetiology were suspected of being of bacterial origin. Thus, the commonly held opinion by the early 20th century was that pellagra was an infectious and communicable disease.[26] Two theories contributed to the persistence of the germ theory: the spoiled maize theory of Lombroso[13,18] and Sambon's theory of pellagra as a vector-borne infectious disease[12,25].

In 1914, Joseph G. Goldberger confirmed pellagra as a nutritional-deficiency disease by managing to cure, prevent and induce it through dietary manipulations in institutionalised humans.[26,27] By then, several groups – including the physician Claude Hervey Lavinder, assigned in 1909 to pellagra investigation by the USA Public Health Service – had already shown that pellagra could not be transmitted from humans to other animals.[25] Goldberger confirmed that pellagra was not contagious by injecting himself, his wife and his associates with blood from pellagrins. In his quest to demonstrate pellagra as a nutritional deficiency, he showed, in children in an orphanage, that pellagra could be cured by improving their diets. These findings were corroborated when pellagra was induced by inadequate maize-based diets in inmates of the Rankin Prison Farm who participated in the study in return for early release.[26,27] Goldberger named the causative deficient factor pellagra-preventative-factor, the substance earlier described by Funk as an 'antipellagric vitamine'. The pellagra-preventative-factor was eventually, in 1937, identified as nicotinic acid (niacin) by an American biochemist, Conrad Elvehjem, and his colleagues. This investigation was done in dogs, in which the deficiency presents as black tongue.[28] Spies, Blankenhorn and Cooper subsequently showed that niacin also cured pellagra in humans, for which *Time Magazine* dubbed them its 1938 'Men of the Year in Comprehensive Science'.[29] The work of Goldberger, Elvehem, Spies, Blankenhorn and Cooper underlined the role of nutritional deficiencies in disease and paved the way for niacin enrichment of certain foodstuffs. It should be mentioned that similar contributions were made in Italy between 1937 and 1940, in which Frontali, Visco and others demonstrated the therapeutic effects of nicotinic acid. However, as a consequence of the general political situation of the period and publication in Italian and German journals, their papers were less accessible to the international scientific community.[18]

While the conundrum surrounding the aetiology of pellagra was, for practical purposes, now resolved, general acceptance of the concept of pellagra as a nutritional deficiency was, particularly in the USA, hampered by two factors. One of these was the findings of the influential US Thompson McFadden Pellagra Commission of Carolina that studied pellagra over the period 1912 to 1914.[30] The Commission erroneously concluded that pellagra was an infectious disease and that it was not possible to explain pellagra from the viewpoint of a deficient diet alone.[30] The other obstacle was socio-political. The association of pellagra with poverty-linked malnutrition, coupled to the high prevalence in the southern states, presented an embarrassment to southern pride with subsequent public denial of the connotation by politicians.[31]

## Spread and prevalence of pellagra

### Pellagra in Europe

The earliest records on pellagra appeared during the first half of the 18th century in Spain, but by the second half of the 19th century it had also been described in France, Italy, Romania, and Great Britain, with

incidences of pellagra reported for Portugal, Austria, Bulgaria, Serbia, Croatia, Bosnia, Turkey, the Ionian Island of Corfu and Poland.[15]

The symptoms of pellagra were first documented in 1735 in poor peasants of the Asturian region of Spain by the Spanish court physician, Don Gasper Casal.[32] At that stage it was referred to as *mal de la rosa*. Casal not only noted the typical dermatological symptoms, but also the gastrointestinal and neurological features and the association with maize-based diets. His findings were published posthumously in 1762 as a chapter in the '*Historia Natural y Medica de el Principado de Asturias*'.[18] By then, a French physician, Francois Thiery, had, after an earlier visit to Casal, already in 1750 published a description of the disease.[18,31] The formal naming of the disease as pellagra, in 1771, is ascribed to an Italian physician, Francesco Frapolli.[18,32] However, the term 'pellagra' – which means 'rough skin' – is derived from the Lombard dialect of Northern Italy and may have been in popular use long before its introduction into medical literature.[18] In 1784, a special hospital for pellagrins and for study of the disease, the Joseph II Pellagra Asylum, was established in Legnano (Milan) by warranty of Emperor Joseph II of the Hapsburgs.[15] The Italian physician Gaetano Strambio (1752–1831), head of the asylum, is said to have written, not only an excellent treatise on the physical symptoms, but also one of the best on the neuropsychiatric manifestations of pellagra.

Pellagra remained endemic for over 200 years in those regions of Italy over-dependent on maize as a staple crop for peasants.[18,33] In certain areas, up to 3% of agricultural workers were affected. The highest prevalence of pellagra was seen in the North – especially Veneto and Lombardy.[33] For Italy as a whole, the highest prevalence appeared to have been over the period 1871 to 1884 with 104 067 officially reported pellagra cases out of an estimated total population of about 290 107.[15] Records suggest that a progressive decline occurred towards the end of the 19th to the beginning of the 20th century, coinciding with improvements in the socio-economic conditions of the peasantry.[18,33]

The disease was first reported in France in 1818 in the vicinity of Arcachon in Gascony.[15] Numerous reports appeared during the early 19th century which referred to pellagra among poor peasants in the provinces of Gironde, the Landes, the Haute-Garonne, and areas adjacent to the Pyrenees.[34] These reports coincided with a widespread increase in the cultivation of maize, with maize becoming the staple food of poor peasants, especially those in the land tenure system.[34,35] Hospitals were established at Auch, Montpellier and Pau, for what Marie referred to as 'the terrible pellagrous insanity'.[36] Pellagra was a major subject of interest in scientific and sociologic thought and literature from 1829 to1880 and subsequent social reforms and agricultural changes led to a dramatic decrease in the prevalence of pellagra among the population, with asylums for pellagrins becoming vacant. It is suggested that pellagra was virtually eradicated from large parts of France by 1880.[15,34,35] The French physician Roussel, who later entered politics, was instrumental in bringing the disease to the attention of physicians, legislators and the French public, and contributed to bringing about legislation to improve the living conditions and diets of the rural poor, to diversify crop cultivation and to increase animal husbandry.[15,34,35]

The first case in Romania was reported in 1810.[15,19] By the 1930s, the number of cases had steadily increased until, by 1932, a total of 55 000 cases with 1654 deaths had officially been recorded in the estimated population of about 184 300. Pellagra occurred mainly in poor farm and other labourers for whom about 75% of calories were provided by whole yellow maize. A permanent medical committee was appointed in 1888 to study the aetiology and means of combatting pellagra and many prestigious Romanian doctors and major university centres were involved in the study of pellagra.[19] However, implementation of the findings appears to have been hampered by financial constraints and the fact that authorities were more interested in other diseases.[19]

Pellagra apparently never reached epidemic proportions in Great Britain. The first confirmed case was seen in 1863 by Dr James Howden, superintendent of the Montrose Royal Asylum.[37] In 1909 a young woman from the Shetlands was admitted to the Royal Edinburgh Asylum and was seen by Drs Brown and Cranston.[37] The first officially recorded death

as a result of pellagra in England occurred in 1912 in a boy admitted to St Thomas' Hospital in London with obscure nervous symptoms.[38] Three more cases of pellagra in children were described by Box over the period 1913–1914; two of these cases were fatal and, in 1923, two more cases were reported by Hutchison and Paterson[39]. A small number of other isolated cases are mentioned in a 1913 paper by Sambon who believed pellagra to have been endemic, if not in Great Britain, than at least in Fifeshire, Forfarshire, Aberdeenshire and the Shetland Islands.[37] Although documented evidence does not support the idea that pellagra ever reached endemic proportions, it is possible that many cases may have been overlooked as a result of medical inexperience. This view is supported by papers from a number of doctors in Great Britain. For instance, in 1934, Stannus and Gibson wrote:

> Pellagra is certainly a rare disease in Great Britain: owing to the fact that it is an affection that perhaps very few have learned to distinguish and there can be little doubt that a proportion of the cases go unrecognised.[40]

By 1941 a similar report appeared in the *British Medical Journal*.[41] The low incidence is inexplicable as at least three major famines occurred in Great Britain over the period of the early history of pellagra: Irish Famine of 1740–1741, Great Irish Famine of 1845–1853 and the Highland Potato Famine of 1846–1856. Malnutrition-related diseases are also indicated by a British Army Medical Service report on the rejection, on medical grounds, of about 40% of volunteers for the Boer War (1899 to 1902).[42]

## Pellagra in Africa

Pellagra has not only been recorded in the normal population in Egypt, but also among prisoners of war (POW) and refugees. Although definitive statistics of the incidence among the general population in Egypt are not available, pellagra is said to have been prevalent in certain country districts with at least 55% of pellagrins being agricultural workers.[43] A 1937 report on clinical investigations of inhabitants of villages in the Nile Delta showed a 34% incidence of pellagra. Three-quarters of these pellagrins were subsisting on pure maize bread and parasitic infections of the gastrointestinal tract were almost invariably present. The disease was less common in Upper Egypt, where the diets were also more varied.[44] According to Miller and Ismail[43], millet was the staple food in Upper Egypt, while maize was the staple food in Lower Egypt. The first documented institutionalised pellagrins were probably the 40–50 'pellagrous lunatics' reported in 1892.[15] Miller and Ismail's 1920 paper describes a further 757 cases of pellagra admitted to the Khanka (Khānkah) Mental Hospital in Egypt over the period 1912–1920.[43] The fatality rate for these patients, whom they referred to as 'insane Egyptian pellagrins', was 32%. Significant numbers of pellagrins were also admitted to the Kasr el Ainy Hospital, as well the Abbassia (Abbāsiyya) Asylum for the Insane in Cairo.[45] The prevalence of pellagra among POWs and refugees in Egypt was high. During the winters of 1916–1918, the number of pellagrins among the Ottoman POW in Egypt reached epidemic proportions, while much lower rates were observed among the German and Austro-Hungarian prisoners – the difference ostensibly because of the 'European diet' provided to the latter, whereas the Ottoman POWs received a 'non-European diet' of lower nutritional value.[46,47] Pellagra was also prevalent among the 1916–1917 Armenian refugees at Port Said.[48]

Pellagra is said to have become a problem in South Africa following the outbreak of rinderpest in 1897, which killed most of the cattle, leading to a marked deterioration in diets.[49] The first quantitative documentation of pellagra in South Africa seems to be in 1906: 150 pellagrins were diagnosed among the 3000 Zulu rebel prisoners, captives of the Bambatha uprising led by Bambatha kaMancinza against British rule and poll tax in KwaZulu-Natal.[50] It is said that that the prisoners received mainly maize while in captivity, but that inadequate diets before captivity may have contributed.[50] Based on published reports and their own research, Gillman and Gillman[51] estimated that about 2000 cases of pellagra were documented over the period 1906–1945. In scrutinising the original papers, it is evident that pellagra was predominantly found in black populations with inadequate diets (with maize and maize flour as

the main sources of calories). Beyond the time frame of this paper, but of interest, is the observation that the incidence of pellagra increased until the late 1970s whereafter a decline was seen.

Isolated reports on pellagra in the rest of Africa are available leading up to 1945. According to papers referred to in a 1951 book by Gillman and Gillman[51], two cases were reported in the Gold Coast (Ghana), six cases in Kenya, five cases in Tanganyika (Tanzania), and seven cases in Uganda, while estimates varied from endemic for Rhodesia (Zimbabwe and Zambia) and Sudan to between endemic to epidemic in Nyassaland (Malawi), Basutoland (Lesotho) and Swaziland. In view of periods of starvation as a consequence of natural disasters and population displacements, and in examining later (post-1945) reports on pellagra in Africa, especially among food aid dependent populations, it is feasible to suspect the prevalence to have been much higher than that concluded from official reports.

### Pellagra in Asia

The first official records of pellagra in China appear to be in 1923 when six cases were reported in Shanghai and one in Wuhu and, in 1926, with one reported case in Peking (Beijing).[52,53] Forty more cases of pellagra were reported 14 years later from a hospital for the Shanghai War Refugee Camps.[54] Wilkinson[55], in a 1944 publication in *The Lancet*, referred to a high prevalence of nutritional diseases in China, with pellagra having a much higher incidence in the South than in the North. It is possible that the extensive use of soya beans popular in the North, but not in the South, may have accounted for the lower prevalence of pellagra in the North.[52] Wilkinson blamed pellagra on poverty and a diet of polished rice.[55] Some support for his suggestion came years later when an outbreak of pellagra (0.57/10 000/day) was seen in March 1994 in Bhutanese refugee camps in Nepal where polished rice formed the emergency food aid.[56] Suggestions that pellagra was not as rare in China as would be implicated by the sparse available literature are also supported by a limited number of meta-analyses of earlier case histories.[57]

For India, as for China, nothing appears to be known about pellagra before the 20th century. Lowe[58] reported in 1931 on what may be the first officially recorded cases: 40 pellagrins among inmates of a leper hospital. Over the ensuing decade, isolated cases were reported by Lowe in 1933, Raman in 1933, Manson-Barin in 1935, Rogers and Megaw in 1935, Panja in 1935, Raman and Rau in 1936, Harris in 1939, Gupta et al. in 1939, Bajaj in 1939 and Goodall in 1940,[59] with most authors suggesting pellagra to be rare in India. Carruthers[59], who reviewed 10 representative cases from a larger cohort of patients admitted to the Miraj Hospital in Bombay (Mumbai) over a period of 2 years, hypothesised that pellagra was a common condition in the Bombay Deccan and possibly endemic in India; supporting evidence is, however, lacking.

Even less information is freely available on pellagra in trans-continental Russia. Although it is claimed that pellagra was common among prisoners of the Soviet labour camps (the Gulag) that existed between 1923 and 1961,[60] no official records seem to be available. Nevertheless, from a paper in a Soviet medical journal, describing the eradication of pellagra in the USSR,[61] it is feasible to assume that the disease was prevalent – at least to some extent.

### Pellagra in the United States of America

The USA has perhaps the best statistics on the prevalence of pellagra. Mortality data were gathered by each state department of health and compiled by the National Centre for Health Statistics (NCHS) of the US Department of Health and Human Services.[62] Pellagra is generally said to have first officially been reported in the USA in 1902 in a farmer presenting with dermatological symptoms, severe melancholia and suicidal ideation.[26] However, it has been suggested that endemic pellagra was already present after the Civil War, but that the spread of information was suppressed for political reasons.[31,63] Further evidence that pellagra was known in the USA earlier than 1902 comes from excerpts of the *Transactions of the National Conference on Pellagra*, held under the auspices of the South Carolina State Board of Health at

the State Hospital for the Insane, Columbia, South Carolina, in 1909, in which it was suggested that pellagra had already been discussed at a meeting of asylum superintendents in Washington as far back as 1864.[64] Furthermore, retrospective analyses showed that practitioners in the Spartanburg area had seen patients with pellagra-like symptoms as early as 1885, and when the case records of the South Carolina Hospital for the Insane were reviewed, it appeared that pellagra-like symptoms had been present among the inmates as early as 1834.[26]

It is estimated that about 3 million people, out of a reported total population of about 120 million, were affected and 100 000 might have died in the USA over four decades – the majority in the American South.[26] This number is believed to be an underestimation as some states may not have reported their pellagra cases.[31] Pellagra in the USA occurred predominantly in the poor who subsisted on maize as a staple food, such as sharecroppers, tenant farmers, cotton mill workers, residents of orphanages and inmates of state penitentiaries, and was reported, above all, in mental institutions. In 1906, 88 cases of pellagra were cited in the Mount Vernon Hospital for the Coloured Insane with a case fatality rate of 64%. Similar outbreaks were seen over the period 1909 to 1911 in Illinois mental hospitals, with case fatality rates of 50% in Peoria, 40% in Kankakee and 33% at the Elgin State Hospital.[55] Statistics are available for at least two orphanages – the Methodist Orphanage in Jackson with a pellagra prevalence of 32% and the Baptist Orphanage at Jackson with a prevalence of 60%.[31]

The number of deaths in the USA peaked at about 7000 per year in 1928 with much higher death rates for female than for male individuals and for non-white than for white individuals.[65] A sharp decline in mortality rates occurred between 1928 and 1932 in the USA, and again from 1939 onwards.[57,65] Various factors contributed to the decline in the incidence, including a greater awareness of the nutritional values of foods, voluntary bread enrichment by bakers, and food fortification through federal regulation.[65] Nutrition programmes in the USA were accelerated in the 1940s when it came to the attention of the authorities that 25% of draftees were rejected from military service as a result of evidence of some or other form of malnutrition. However, the more permanent eradication of pellagra occurred only with improvements in the socio-economic status of the workers.

## Pellagra and maize

Maize is said to have been domesticated in Mesoamerica around 3500 BC, from where it spread to the American continent and, after European contact in the late 15th and early 16th century, to the rest of the world.[66] Maize was introduced to Europe in the early 16th century[67] and, during the 16th and 17th century, largely replaced several other foods as the staple food for the poor and as a cheap source of food for those confined to mental institutions and orphanages in Southern Europe and the USA. Several reasons exist for the preferential cultivation of maize. Maize, when introduced into the Old World, increased the yield of food calories per acre well beyond that previously provided by rye and wheat.[31] In addition, cultivation was less labour intensive and large areas could be planted more economically – all contributing to maize becoming a cheaper staple crop,[33] affordable to impoverished populations and the institutionalised on inadequate low cost diets. Historically, outbreaks of pellagra were seen, largely, when maize took over as staple food. Whether pellagra made its first appearance only after the introduction of maize into the Old World is perhaps questionable. To quote from a writing dated more than a century ago (1912):

> *…it is probable that pellagra appeared in Europe long before its scientific description, but was classed as either gastrointestinal, or nervous, or mental, or leprous, or scorbutic diseases. It is, therefore, somewhat difficult to determine whether or not pellagra appeared in Europe before the advent of Indian corn as a food.*[15]

## Pellagra, maize and niacin deficiency

Since confirmation of pellagra as a nutritional deficiency – often caused by an inadequate diet over-dependent on maize – the term pellagra has become synonymous with niacin deficiency. Maize is, however, not totally devoid of niacin. The problem is partially to be found in the bio-availability of niacin in mature maize. Depending on the type of maize, up to 99% of the niacin in hard mature, but not immature, maize is present as niacytin, which is niacin bound up in a complex with hemicellulose that is nutritionally unavailable to humans.[68] This property is, however, not unique to maize as the niacin in sorghum, wheat, rice and barley has also been shown to be in chemically bound form[68] – which may, in theory, have contributed to isolated reports of pellagra in populations in which sorghum or rice were consumed[69]. Part of the problem with maize as a staple food appears to reside in the process of food preparation. Boiling of maize is arguably said to not have a significant effect on the availability of niacin, but nixtamalisation (preparation of maize or other grain by soaking and cooking in an alkaline solution), roasting and fermentation of maize have been shown to render the niacin more bioavailable.[68,70,71] In fact, nixtamalisation, as in the preparation of tortillas, is by many considered the main reason for the apparent absence of pellagra in early pre-Columbian North American, Mesoamerican and South American cultures. However, there are many reasons to doubt this assumption. Although nixtamalisation releases niacin, at least 30%, but probably considerably more, of niacin is destroyed by nixtamalisation as performed by pre-Columbian Mesoamerican cultures.[70-72] In addition, other practices and dietary habits known to influence niacin intake also existed. Fermentation of maize was, for instance, performed in the preparation of Pozol (in the form of a dough or drink) which is said to have a higher nutritional quality than either raw maize or tortillas[70,71], while huitlacoche, a maize fungus rich in amino acids, formed part of the diet of pre-Columbian Mesoamerican culture[73]. Furthermore, various types of maize exist and indications are that floury maize with a soft, nutritionally more bio-available endosperm, was preferentially used in Mexico, Guatemala and the Andean countries.[70] However, the most important motive for doubting the assertion of nixtamalisation as the main reason for the ostensible absence of pellagra is that these populations were by no means monophagic populations over-dependent on maize – as evidenced by the many books and papers on Pre-Columbian cuisine.

Beyond the limited bioavailability of niacin in unprocessed mature maize, another, probably even more important, factor that could contribute to the pellagragenic potential of maize is the amino acid imbalance of zein, the main protein of maize.[70] Although the total protein quality of common maize is not significantly different from that of most other cereals, zein is deficient in the essential amino acids lysine and tryptophan[70] – substrates for the *de novo* synthesis of niacin. The tryptophan levels do, however, vary in different types of maize and are influenced by environmental conditions.[70] In addition, maize contains considerable amounts of the amino acid leucine[74] which, when present in high concentrations, interferes with *de novo* synthesis of niacin from tryptophan by inhibiting quinolinate phosphoribosyl transferase and, in addition, lowers the body's tryptophan levels[7]. Preliminary indications are that leucine in itself could exacerbate the mental derangements associated with pellagra.[75]

Besides the low bio-availability of niacin and the deficiency of tryptophan in unprocessed maize, these nutrients may be lost in the milling process whereby the aleurone and germ is removed to form the refined product.[68] Up to 80% of niacin and the two vitamins necessary for *de novo* synthesis of niacin from tryptophan (i.e. riboflavin and pyridoxine) may be removed by milling, not only from maize, but also from rye, wheat, barley, rice and sorghum.[76] Indications are that degerming may also remove considerable amounts of tryptophan from maize, but not from other cereals.[76] Crude stone-grinding processes, instead of the newer industrialised milling, has been suggested as the reason for what seems to be a relatively low incidence of pellagra in the early 20th century in South Africa.[50]

## Erstwhile competing theories on the pellagra–maize link

From an aetiological point of view, the association between maize and pellagra was predominantly sustained by two competing theories:

Lombroso's spoiled maize theory and the nutritional deficiency theory usually associated with Goldberger. Although the nutritional theory on pellagra is now generally accepted, the spoiled maize theory of Lombroso contributed to the persistence of the association between maize and pellagra even after pellagra was confirmed to be a nutritional-deficiency disease.[71] Not generally acknowledged is the fact that both theories were anticipated by others long before the work of either Lombroso or Goldberger. Front-runners to the work of Goldberger were mentioned in the section on the aetiology of pellagra. Similarly, disease as a result of the ingestion of mould-infested grain was known long before Lombroso's work on microorganisms such as *Aspergillus glaucus, Eurotium herbariorum, Oidium lactis maidis, Penicillium* spp*., Sporisorium maidis* and *Sporotrichum maidis* as potential producers of a pellagra-inducing toxin.[74,77] It is feasible to accept that Lombroso was familiar with ergotism, which is caused by the ingestion of the alkaloids produced by the *Claviceps purpurea* fungus that infects rye and other cereals. He might also have known about the association between mould-infested maize and pellagra*,* earlier described by investigators such as Guerreschi and DeRolandis in 1814 and 1824, respectively, and in 1845 by Balardini who suggested *Sporisorium maidis* as the causative fungus.[13]

The idea of an association between pellagra and spoiled maize was not totally abolished by the confirmation of pellagra as a nutritional deficiency. Several continued to study the link, not only with regard to maize, but also with sorghum and other grains, and some even came to consider pellagra as a mycotoxicosis.[69,72] Various factors contributed to the endurance of Lombroso's spoiled maize theory, not least socio-political motives. Admitting pellagra to be a nutritional deficiency would have reflected poorly on the political and social issues of food availability to the lower social classes in Europe.[18] In the American South, recognition of pellagra as a poverty-associated nutritional deficiency would have been an embarrassment to Southern pride.[31] The spoiled maize theory on pellagra was also reinforced by evidence of pellagra outbreaks when, under conditions of food emergencies, spoiled maize was imported to areas previously not associated with the disease, such as the outbreak on the Island of Corfu (1858 and 1866), and epidemics in Yucatan, Mexico when maize was shipped under unfavourable conditions of humidity and temperature, first from New York in 1882, and again in 1907 from New Orleans.[15,67]

Although the concepts of pellagra as a nutritional deficiency and pellagra as the result of spoiled maize are generally seen as two separate theories, it is impossible to overlook potential interactions between them. Spoiled maize, and therefore mycotoxin exposure, is generally more likely to have occurred in populations for which improper methods of food handling and storage are common and malnutrition was already a problem.[78] Furthermore, toxins from contaminated stored maize could have had devastating effects on agriculture and on livestock, further contributing to poverty and malnutrition,[78,79] and by implication to the prevalence of pellagra. Of interest is the fact that, although not related to pellagra per se, both the association between spoiled maize and disease, and the association between nutritional deficiencies and disease, have now evolved into major scientific disciplines.

In summary it can be said that the link between maize and pellagra cannot be denied. From an historical point of view, a major reason for the strong association between the disease and maize is that pellagra was often observed when maize, with its limited bio-availability of niacin, as well as its amino acid imbalance and tryptophan deficiency, replaced other more nutritional foodstuffs as staple for peasants and other impoverished populations subsisting on near monophagic diets. More recent evidence of an association between pellagra and the nutritional deficiency of maize, is to be found in the fact that pellagra was until recently still reported in sub-Saharan Africa (Mozambique, Malawi, Zimbabwe, Swaziland) in food aid dependent populations, in food emergencies, in refugee camps and among refugee returnee populations.[80] Pellagra prevalences of up to 13% were reported and supplementation of the maize-based food aid rations with peanuts, and on occasion niacin, was seen to bring about significant relief.[80] Enormous efforts went into the early studies on the aetiology of pellagra. Although dermatological symptoms were probably

the major diagnostic indicators during the early history of pellagra, gastrointestinal and neuropsychiatric symptoms were well recognised and diagnosed. Today the diagnosis of pellagra and estimates of niacin deficiency are mainly based on the dermatological symptoms. Niacin is the precursor of the all-important coenzyme NAD and we are starting to understand the mechanisms through which niacin and NAD deficiencies can influence virtually all physiological processes, from cerebral functions to genomic stability. Yet, the levels of niacin and its precursor for *de novo* synthesis (i.e. tryptophan) are still rarely measured for diagnostic purposes or in nutritional surveys.

## Conclusions

Pellagra seems to have followed wherever maize became the staple food. This persistent association between maize and pellagra is not unwarranted. It is, however, largely the result of the socio-economic circumstances and near monophagic diets of the underprivileged and the spread of maize, with its limited bioavailable niacin and tryptophan, as a staple food. Largely, two theories sustained the dogged association between maize and pellagra. Although pellagra is now generally accepted as a nutritional deficiency, spoiled maize could have contributed indirectly through its effects on food production.

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## Authors' contributions

M.V. was responsible for the conceptualisation, data collection, writing the initial draft and revisions. P.B. was responsible for data collection and reviewing the writing and revisions. J.L.R. was responsible for critically reviewing the writing and revisions. All authors read and approved the final manuscript.

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