REVIEW ARTICLE

BJD
British Journal of Dermatology

Pellagra: a review with emphasis on photosensitivity

P. Wan, S. Moat* and A. Anstey†

Department of Dermatology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China
**Department of Medical Biochemistry, University Hospital of Wales, Cardiff University, Cardiff, U.K.*
†*Academic Dermatology, St Woolos Hospital, Aneurin Bevan Health Board, Newport, U.K.*

Summary

Niacin has recently been demonstrated to lower blood pressure in hypertensive patients and to reduce cardiovascular events when combined with a statin. As a consequence, niacin has been elevated from being of historical interest as the treatment for pellagra, to being a compound with possible relevance to contemporary therapeutics. In spite of this, niacin deficiency leading to pellagra continues to be a health problem in some countries. Characterized by an exposed-site hyperpigmented dermatitis, pellagra is generally accepted to have been the first photosensitivity syndrome described. At its worst, pellagra manifests as one of the most striking examples of systemic photosensitivity. This is the only photosensitivity syndrome where death is included as a cardinal clinical feature (the often quoted four 'Ds': dermatitis, diarrhoea, dementia and death). However, the pathogenetic mechanism for the photosensitivity caused by niacin deficiency has yet to be determined. This review seeks to update the classification and phenotypic characterization of the various forms of niacin-deficient photosensitivity. Previous speculation about possible mechanisms for the pathogenesis of photosensitivity due to niacin deficiency is reviewed in the context of advances in the understanding of the photochemical basis of photosensitivity reactions. The review concludes by highlighting research required to advance the understanding of this photosensitivity syndrome.

Correspondence
Pengjie Wan.
E-mail: fof2007@126.com

Accepted for publication
19 November 2010

Funding sources
Nevill Hall Hospital, Thrombosis and General Research Fund, U.K., Academic Dermatology, St Woolos Hospital, Newport, U.K. and Department of Dermatology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, China.

Conflicts of interest
None declared.

DOI 10.1111/j.1365-2133.2010.10163.x

Niacin is currently the focus of renewed interest due to recent research demonstrating a role in lowering blood pressure in hypertensive patients.[1] Furthermore, niacin has been shown to decrease carotid intima–media thickness producing fewer clinical cardiovascular events when combined with a statin.[2] In stark contrast, World Health Organization data from 2004 confirm that pellagra, a niacin-deficiency syndrome, remains a health problem in some parts of the developing world.[3] The population group most susceptible to pellagra is probably malnourished children. Recent data from UNICEF includes India and China at the top of the table of clinically malnourished children under the age of 5 years, with 60·8 million and 12·3 million affected, respectively.[4] Furthermore, pellagra is one of a number of clinical syndromes seen in populations subjected to prolonged war or famine.[5,6] First described nearly 250 years ago, photosensitivity due to niacin deficiency remains an enigma. As a cause for photosensitivity, niacin deficiency is not infrequently omitted from modern dermatology text books, or referred to as a 'photoaggravated disorder'. Published photographs of patients with pellagra from these same books typically reveal a striking photosensitivity dermatitis on all exposed skin with a clear cut-off at the margins of clothing. Photoprotected skin is usually unaffected. Such clinical features place photosensitivity due to niacin deficiency at the severe end of the spectrum of photosensitivity disorders. Pellagra has almost disappeared from developed countries, which may explain why it has yet to be the focus of rigorous photobiological research. As a consequence, the clinical features of the condition remain poorly characterized, the action spectrum for the photosensitivity has not been established and its pathomechanism remains unknown. This review seeks to address these issues by updating the literature on niacin deficiency syndromes in general; epidemiological and clinical papers on niacin-deficient photosensitivity in both developed and developing countries are analysed. We have reviewed the biochemical consequences of niacin deficiency and speculate about photochemical mechanisms that could explain this striking clinical phenotype.

Methods

The search strategy was developed over several phases. The initial search, focused on peer-reviewed literature, was conducted using OVID-hosted databases. These were Medline

(1996 to current) and Embase (1950 to current). Other online databases used were the Cochrane Library, PubMed and Google Scholar. The Google Scholar search provided many of the pre-1950 articles. Each strategy was adapted according to the database, using an appropriate combination of subject heading and free-text terms.

The second phase of the search was based on MD and PhD dissertations and these from Venezuela, South Africa, India and Brazil, where the disease remains prevalent, and the university libraries are of good quality and freely accessible. In order to locate dissertations from these four countries, a list of universities was compiled using Google, and links within websites. Each university site had a library catalogue which was also searched.

The third phase concentrated on the grey literature from these four countries, using online search engines, such as the Virtual Health Library and other international resources. This included reports, statistics and other corporate and unpublished or unofficially published information. Additionally *ad hoc* references were also obtained by scanning the reference lists of retrieved literature. In addition, the same search strategy in Mandarin was used to search pellagra in Chinese databases.

History

The first medical report of pellagra is credited to Gaspar Casal in Spain in 1735.[7] He described an exposed-site dermatitis on the dorsum of the hands and feet with a collar-like rash on the upper part of the neck in Asturian peasants.[7] He speculated that the origin of this disease was poor diet and 'atmospheric influences' in the area.[8] These proved to be astute deductions, preceding both the discovery of ultraviolet (UV) radiation and proof of the dietary cause for pellagra by more than 100 years. Casal's writing was compiled and posthumously published by his friend Juan Sevillano in 1762 with the title '*Historia Natural y Medicina del Principado de Asturias*'.[8] Casal's published report on pellagra preceded Willan's report of 'eczema solare' in 1798 by 36 years;[9,10] as such, it was the first description of a photosensitivity syndrome in modern medicine. It is now recognized that pellagra is a potential complication of diet dominated by cornmeal, a cheap energy-rich food source that fails to provide adequate levels of niacin. Cornmeal was introduced into Europe after the voyages of Columbus in the late 15th century and rapidly became the staple diet of the poor.[11–13] The spread of cornmeal as a food source was followed by the spread of pellagra across the continent from Spain to Italy, France, central Europe, Romania, Bulgaria, Turkey, Greece, southern Russia, Hungary and Austria;[11,14] it eventually spread to Egypt, central and southern Africa and Ethiopia.[6,13] Pellagra rapidly became a worldwide health problem.[15]

Francesco Frapolli[16] was the first to coin the term 'pellagra'. In the 19th century, the French physician Roussel eradicated pellagra by a public health campaign that persuaded the government to restrict the cultivation of maize in France.[17] However, pellagra remained endemic among the maize-eating poor population of southern Europe for nearly two centuries. It was not until early in the 20th century that an American public health doctor, Joseph Goldberger, dedicated his life's work to demonstrating that pellagra was not an infectious disease, as was widely believed at the time, but was caused by a deficient diet.[18,19] Goldberger carried out a variety of experiments including the induction of pellagra in six of 11 prison inmates by changes in their diet.[14,20,21] Goldberger was correct in establishing that pellagra was caused by a nutritional deficiency factor, but did not discover that it was due to deficient vitamin B_3.[14] Nicotinic acid was first discovered by Huber in 1867;[22] however, its role in the prevention of pellagra was not identified until 1937.[23] Conrad Elvehjem was the first to show that niacin cured pellagra when attempting to treat 'black tongue' (the canine version of pellagra) in dogs.[24,25] Krehl subsequently discovered that tryptophan dietary supplements were also effective in the treatment and prevention of pellagra.[15] The outcome of this body of research was that niacin became a routine additive to staple foods such as flour and bread in both developed and developing countries.[13] In 1945, Wisconsin researchers found that corn significantly increases the body's niacin requirement, while milk reduces it.[26] In 1956, a new congenital metabolic syndrome characterized by a pellagra-like exposed-site dermatitis was reported; the name 'Hartnup disease' derives from the index family surname.[27] Hartnup disease is caused by impaired neutral amino acid transport in the kidneys and intestine; amino acids, such as tryptophan, are excreted in the urine.[28,29] The 'Hartnup' gene, *SLC6A19*, has now been identified, cloned and sequenced.[29–31] Highlights in the history of pellagra are summarized chronologically in Table 1.

Epidemiology

Pellagra has been a worldwide health problem in the recent past. Public health statistics from the U.S.A. in the early 20th

Table 1 Summary of the history of pellagra

Year, reference	Event
1735[7]	The first description of pellagra was made by Gaspar Casal in Spain
1762[8]	Casal's writing on pellagra was published by his friend Juan Sevillano
1771[16]	Francesco Frapolli was the first to coin the term 'pellagra'
1926[14]	Joseph Goldberger established that pellagra was caused by a nutritional deficiency factor
1937[25]	Conrad Elvehjem discovered the role of niacin in the prevention of pellagra
1945[15]	Krehl discovered tryptophan could protect people from pellagra
1956[27]	Baron recognized Hartnup disease as a congenital niacin-deficient syndrome
2004[29,30]	*SLC6A19* was identified as the causative gene for Hartnup disease

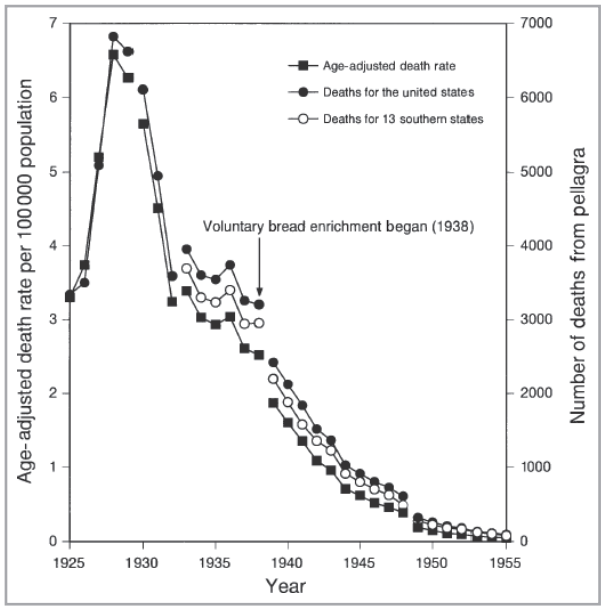

Fig 1. Pellagra deaths in the United States from 1929 to 1955.[38] Permission to use this figure granted by E.A. Yetley (pers. comm., 10, Mar 2010).

century provide the best quality epidemiological data on pellagra. The first case of pellagra in the U.S.A. was reported by Gray in New York in 1864.[32,33] Initial sporadic reports of pellagra before 1906 were followed by a pellagra epidemic in the southern U.S.A. among the poor, especially in black people.[21] Incidence and mortality statistics from the state of South Carolina recorded 30 000 cases of pellagra by 1912, with a case fatality rate of 40%.[34,35] From 1915 to 1925, the first decade of systematic reporting, 27 648 deaths from pellagra were recorded in the U.S.A.[36] Reported deaths exceeded 7000 between 1928 and 1930; there were probably more than 200 000 patients suffering from pellagra in the U.S.A. at this time.[14] At its peak, pellagra was the eighth highest cause of death, exclusive of accidents, between 1928 and 1929;[37] the rise and fall in pellagra deaths in the U.S.A. from 1929 to 1955 are summarized in Figure 1.[38] Thus, the pellagra epidemic lasted for over 30 years from 1906 to 1940.[21] It resulted in an estimated three million cases, with at least 100 000 deaths in the reporting states.[36] The pellagra epidemic resolved rapidly once research had revealed niacin deficiency as the cause and dietary niacin fortification was introduced.

In the 21st century, pellagra is now rare in developed countries, having been largely eradicated by niacin fortification of food. Despite this, sporadic cases continue to occur. Niacin deficiency may still occur in subjects with severe alcoholism,[39] patients with anorexia nervosa[40] and severe malabsorption disorders,[5] and as a drug-induced condition.[41] Recently the Chinese literature confirmed that the majority of patients with pellagra from China were male chronic alcoholics.[42,43] In economically poor countries, or in economically deprived areas of developing countries, pellagra remains a problem if the diet is restricted to corn or maize and where foods such as bread and flour have not been fortified with niacin.

Recent outbreaks of pellagra

Recent major outbreaks of pellagra have been described in association with humanitarian emergencies in Malawi, Mozambique, Angola, Zimbabwe and Nepal.[5,13,44] While affecting both children and adults, pellagra was more generally common in female than in male subjects; the risk of pellagra increased with age.[45,46] Young children and infants were rarely affected.[46,47] In Angola, 10% of the population in displaced camps around Kuito and 30% of the inhabitants in Camacupa showed signs of pellagra. Although niacin levels were not measured throughout the population, it was speculated that many had subclinical niacin deficiency which could develop into pellagra over time.[48] Seal *et al.*[5] reported that the incidence of clinical pellagra in Angola had not decreased since the civil war in 2002. Clinical pellagra was reported in 0·3% of women and 0·2% of children while niacin deficiency was noted in 29·4% of women and 6% of children. Of relevance was the reliance on untreated corn as the major food staple. The highest prevalence in recent times has probably been in South Africa. A report from South Africa suggested that 50% of patients seen at a clinic in the Transvaal had some evidence of pellagra, and that the majority of adults admitted to the mental hospital in Pretoria had the disease.[49] World Health Organization data on pellagra cases in 2004 also showed that South Africa had the most deaths (2·28 deaths per 1 million people), with Venezuela and Brazil ranking second and third, respectively.[3]

Biochemical basis for pellagra

Pellagra occurs as a result of a deficiency in niacin (also known as nicotinic acid or vitamin B_3). This water-soluble vitamin is essential for maintaining cell function and more than 100 enzymes in the human body require nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) to act as hydrogen ion donors and acceptors. NAD is involved in the catabolism of carbohydrates, fats, proteins and alcohol. NADP functions in anabolic reactions, for the synthesis of fatty acids and cholesterol. The reduced form NADP is converted to NADPH and is used in reactions to detoxify reactive oxygen species and drugs. In addition, NAD is also involved in nonredox reactions such as cell signalling and DNA repair.[50]

The metabolic pathway for conversion of tryptophan to niacin is summarized in Figure 2.[15,51–54] The *de novo* synthesis of niacin from tryptophan involves a series of eight different reactions and this supplies most of the body's niacin requirements. The reason that a poor diet can produce a deficiency in niacin is that the pathway is dependent upon an adequate intake of tryptophan, niacin and the B vitamin cofactors required for this pathway. Furthermore, the conversion of

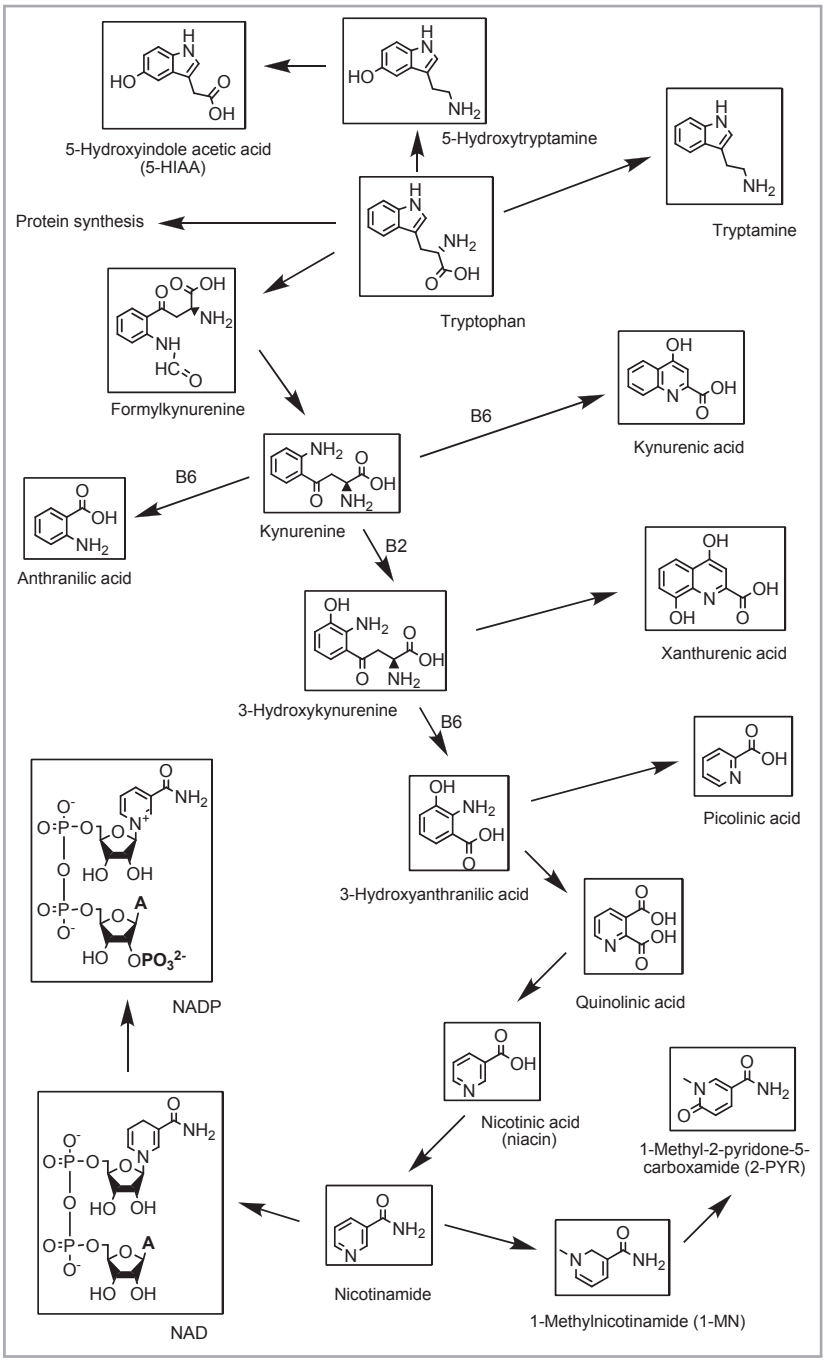

Fig 2. Metabolism of tryptophan to niacin.[15,51–54] NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; B_1, thiamine; B_2, riboflavin; B_6, pyridoxine.

tryptophan to niacin is an inefficient process in humans as 1 mg of niacin is obtained from 60 mg of tryptophan.[53]

Pathogenesis of photosensitivity in pellagra

The pathogenetic mechanism of photosensitivity in pellagra remains unclear. Four theories have been proposed: (i) cutaneous deficiency in urocanic acid;[54,55] (ii) accumulation of kynurenic acid;[51,55] (iii) deficiency of NAD/NADP;[56] and (iv) altered porphyrin metabolism.[57] Each of these theories and their proposed mechanism of action are summarized below.

Defective photoprotection due to skin deficiency in urocanic acid resulting in ultraviolet B-mediated photosensitivity

Urocanic acid in the stratum corneum of the epidermis is believed to play an important role in the protection of the epidermis against the damaging effects of UVB radiation.[58] Vasantha[59] measured histidase activity, histidine and urocanic acid in eight patients with pellagra and 12 normal adults. On admission, histidase enzyme activity and concentration of urocanic acid and histidine were low in skin from patients with

pellagra compared with normal subjects. After treatment with nicotinic acid, there was a rise in histidase enzyme activity, as well as in urocanic acid and histidine content. They concluded that deficiency in the skin of urocanic acid leads to the loss of the photoprotective effects of this epidermal compound, leading to photosensitivity induced by UVB.[59] Recent research by Barresi *et al.*[60] has demonstrated decreased UVB absorption capacity and increased DNA damage in a mouse model of histidinaemia characterized by decreased urocanic acid concentrations. In contrast, it appears that individuals with histidinaemia, an inborn error metabolism due to histidase deficiency, resulting in decreased concentrations of urocanic acid in blood and skin, do not have an increase in sensitivity to sunlight.[61,62] Further studies assessing urocanic acid concentrations in the skin of patients with pellagra are required to clarify the possible role of low urocanic acid levels in producing photosensitivity in pellagra.

Phototoxicity to ultraviolet A mediated by accumulation of kynurenic acid

Kynurenic acid, a by-product of the tryptophan–kynurenine–nicotinic acid pathway (Fig. 2), has a ring structure with alternating double bonds; this structure makes it a candidate for inducing photosensitivity reactions when irradiated with appropriate radiant energy. In 1973, Swanbeck *et al.* identified kynurenic acid as a potential photosensitizer by analysis of fluorescence and excitation spectra in patients with actinic reticuloid.[63,64]

When present in excess, kynurenic acid leads to photohaemolysis *in vitro* cell culture studies. It was proposed that kynurenic acid might act as a photosensitizer leading to a phototoxic reaction when irradiated by UV radiation between 350 and 380 nm.[63,64] In the tryptophan–kynurenine–nicotinic acid pathway, nicotinic acid deficiency leads to accumulation of kynurenic acid.[51]

Cellular photosensitivity secondary to deficiency of nicotinamide adenine dinucleotide (NAD) and NAD phosphate

Niacin is a precursor of NAD and NADP (Fig. 2). Both NAD and NADP are cofactors important to the repair of UV-induced damage in the epidermis. Thus, deficiency in NAD and NADP reduces this photorepair mechanism with a resultant susceptibility to photosensitivity.[56] Rapaport[65] attributed photosensitivity in pellagra to a reduction of epidermal repair process due to NAD and NADP deficiency and regarded this process to be phototoxic in origin. Another possible explanation from relatively minor damage to the skin may arise from the fact that both NAD and NADP are obligatory for cellular energy transfer reactions. It might be expected that tissues with a high energy requirement, such as the brain, or those with a rapid cell turnover, such as skin, mucosa and intestine, would be the sites of major metabolic derangement if cellular energy transfer was impaired.[54,66]

Altered porphyrin metabolism leading to photosensitivity to visible light

Porphyrin accumulation was suggested by Gillman *et al.*[57] as a possible mechanism for the clinical photosensitivity observed in pellagra. However, no supporting biochemical evidence was presented to support this concept.

Phototesting in patients with pellagra

Initial uncertainty about the role of sun exposure in the pathogenesis of pellagra was addressed by a number of authors with clinical photoprovocation studies (Table 2).[7,67–71] These studies confirmed that sun exposure played a central aetiological role in the exposed-site dermatitis of pellagra.[69]

No research group has attempted formal *in vivo* phototesting studies to establish the action spectrum of the photosensitivity reaction in pellagra. Only four papers have included reports of phototesting in pellagra (Table 3). The first of these, from 1935, used a quartz mercury vapour lamp for phototesting in 10 patients.[70] This study reported increasing pigmentation of UV-irradiated nonpellagrous skin. The author concluded that pellagra was a systemic disorder and sunlight was not the primary cause. They did, however, state that sunlight may act as 'an irritant and precipitate the cutaneous lesions'. Phototesting in a Japanese patient with pellagra secondary to chronic alcoholism was reported as normal to UVB, UVA and visible light.[71] Phototesting using a broad-spectrum 'solar simulator' light source in a patient with pellagra due to anorexia nervosa was reported as being normal.[65] Finally, a single case report with monochromator light testing showed sensitivity in drug-induced pellagra to UVA.[72] This is the only published report of monochromator light testing for pellagra (Table 3).

Clinical variants of niacin deficiency

Niacin deficiency may develop as a consequence of a wide variety of clinical conditions. This section describes the main features of the single congenital form of niacin deficiency and the multiple acquired variants (Table 4).[27,41,55,72–94]

Hartnup disease

Hartnup disease, first described in 1956, is an autosomal recessive defect named after the English family in whom the condition was first recognized and described.[27] It results from impaired transport of neutral amino acids across epithelial cells in the intestinal mucosa and proximal renal tubules.[29] The clinical manifestations include a pellagra-like rash on exposed areas, cerebellar ataxia and psychosis. As with pellagra, there is wide clinical variation from case to case. The exposed-site dermatitis is the most constant feature of Hartnup disease, and usually precedes other features.[95,96] The rash is worse during the spring and summer months; as in pellagra, the skin is dry, scaly, hyperkeratotic and

Table 2 Photoprovocation with sunlight in patients with pellagra

Year	Authors	Experiments	Results or comments
1905	Gherardini[67]	Limits of the eruption varied according to displacement of clothing	This was the earliest report of photoprovocation testing in patients with pellagra
1905	Hameau[67]	Variety of photoprovocation outline according to variation in fenestration in gloves worn for experimental studies	Pellagra was provoked by the action of the sun's rays
1911	Tucker[68]	30 patients with pellagra were exposed to the sun	21 out of 30 had positive photoprovocation tests
1935	Spies[70]	The areas of pellagrous dermatitis in 8 patients were exposed to direct sunlight. In 6 of these patients, normal (nonpellagra) skin was also exposed to sunlight	Normal skin became reddened and swollen, then desquamated and became pigmented. Pellagrous skin showed similar changes
1935	Spies[70]	Two pellagra patients with normal-appearing skin and 2 normal controls were exposed to the sun for 5 days	Photoexposed skin in both patients and normal subjects became reddened, swollen and desquamated. No difference was observed between patients with pellagra and the normal controls
1937	Smith and Ruffin[69]	35 pellagra patients on a pellagra-inducing diet with normal skin and some controls (number unspecified) were exposed directly to the sun with gradual increase in exposure time	13 out of 35 pellagra patients developed typical skin lesions of pellagra. It was concluded that exposure to the sun precipitates acute pellagrous dermatitis
1985	Kojima *et al.*[71]	One pellagra patient and 6 controls with similar skin type were exposed to 8 MED of UVB (dosage not specified)	No pellagra-like rash was observed in pellagra patient. The cutaneous reaction was reported as bright erythema that turned purplish-red colour; later small blisters appeared. No reaction was recorded for the 6 controls

MED, minimal erythema dose; UV, ultraviolet radiation.

pigmented.[96] Of note is the absence of reports of either mucosal involvement or skin hyperkeratosis over bony prominences.[97,98] Both of these features have been reported for dietary variants of pellagra cases.[69,99]

Inadequate diet

Pellagra occurs in association with extreme poverty, occurring in communities that subsist on maize and rarely eat niacin-rich foods such as meat, eggs, milk or fish.[100] Maize contains niacin, but in a tightly bound, unusable form, as determined from bioassays with rats.[101] Alkaline hydrolysis unbinds niacin from maize, which explains why pellagra is rarely seen in Central America and Mexico where corn is routinely washed with lime water before consumption.[22,82,102] Lime water is a cheap and efficient way to remove the husks from kernels of corn.[103,104] Pellagra also occurs in jowar-eating populations.[105] Jowar (*Sorghum vulgare*) has adequate levels of usable niacin but also contains leucine which inhibits the conversion of tryptophan to niacin.[82,91,106] This may also be important in individuals who are on other high leucine diets including gelatin, yogurt and beef.[107]

In patients with chronic alcoholism, malnutrition is common.[108] Klauder and Winkelman[109] reported 100 patients with cutaneous pellagra, all of whom were chronic alcoholics. Currently, alcoholism is the most common cause of pellagra in developed countries.[77] Pellagra also occurs in populations subjected to prolonged starvation as a result of war and famine.[5]

Malabsorption

Gastrointestinal disease characterized by malabsorption may result in deficiency of tryptophan and niacin. Crohn disease,[15,80] coeliac disease,[41] subtotal gastrectomy,[55] gastroenterostomy,[82] jejuno-ileitis,[82] chronic colitis,[41] severe ulcerative colitis,[41] regional ileitis[82] and tuberculosis of the gastrointestinal tract[41] may all cause pellagra: such patients respond rapidly to parenteral supplementation with niacin and tryptophan. Pellagra may also complicate long-standing hepatic cirrhosis, although this is rare.[84]

Metabolic 'steal'

Tryptophan and niacin deficiency may rarely complicate the carcinoid syndrome. Carcinoid syndrome results from excessive neuroendocrine secretion of amines and peptides including serotonin (5-hydroxytryptamine). Serotonin is derived from tryptophan (Fig. 2).[110,111] In normal subjects, just 1% of absorbed tryptophan is metabolized to serotonin; in carci-

Table 3 Phototesting in patients with pellagra

	1935, Spies[70]	1985, Kojima *et al.*[71]	1985, Rapaport[65]	1999, Darvay *et al.*[72]
Patients	10 patients with pellagra	1 patient	1 patient with anorexia nervosa	1 patient with drug-induced pellagra
Light source	Quartz mercury vapour	Fluorescent lamps FL20SE, FL20BLB, FL20B	Solar simulator	Monochromatic irradiation source
Type of radiation	Broad spectrum: UVB, UVA, visible light	UVB, UVA, visible light	Broad spectrum: UVB, UVA, visible light	Wavelengths: 300–400 nm
Experiment	Irradiation of pellagra rash and protected skin. Control was covered skin on opposite side of body	UVB irradiation of front chest and UVA, visible light irradiation of abdomen skin. No controls	Irradiation of the back	Unaffected skin of the patient's back was irradiated with a series of increasing doses
Result	Normal skin reddened and became tanned. Pellagrous skin became darker. UV did not prevent pellagrous change from healing	MED was in normal range	MED > 100 s (in the authors' normal range)	Photosensitivity to UVA with reduced minimal erythemal doses recorded at 340 and 360 nm
Comment	Protected skin reacted normally to increasing doses of UV with erythema and tanning, as would be expected with a light source which was primarily UVB. Sensitivity to UVA with this light source would not be apparent due to dominant cutaneous effects of high doses of UVB	Anterior chest was tolerant to UVB. The dosage of radiation was not stated	This is not greatly different from other subjects and patients. Use of this light source for phototesting is not ideal as the effects of UVB dominate and obscure effects of UVA and visible light. Dosage of irradiation was not given	The action spectrum for drug-induced pellagra due to isoniazid is primarily UVA and is maximal at 340 and 360 nm

MED, minimal erythema dose; UV, ultraviolet radiation.

noid syndrome, up to 99% of tryptophan can be catabolized to serotonin.[112,113] Shah *et al.*[112] found that 10 out of 36 patients with carcinoid syndrome suffered from niacin deficiency at an early stage of the disease. Bell *et al.*[113] showed that five out of 25 patients with advanced malignant carcinoid syndrome developed signs of pellagra and described the diversion of this pathway away from production of niacin and NAD/NADP (Fig. 2).

Drug induced

Several drugs interact with compounds in the tryptophan–kynurenine–niacin pathway leading to inhibition of NAD and NADP synthesis. Isoniazid, a structural analogue of niacin, can cause suppression of endogenous niacin production, and subsequent pellagra. Slow acetylators may be more susceptible to drug-induced pellagra.[114] Ishii sand Nishihara[92] reported eight patients with pellagra among 106 necropsy cases from isoniazid-treated tuberculosis. Other drug-induced cases of pellagra are explained by inhibition of the conversion of tryptophan to niacin; such drugs include 5-fluorouracil, pyrazinamide, 6-mercaptopurine, hydantoin, ethionamide, phenobarbital, azathioprine and chloramphenicol.[15,115,116] In addition, 6-mercaptopurine, whose structure resembles adenine, may substitute for adenine in NAD, making it nonactive.[15]

Human immunodeficiency virus

Pellagra may be observed in patients with human immunodeficiency virus (HIV).[84,116] It has been shown in cell culture models that HIV infection induces intracellular niacin deficiency, which is reversed by the administration of nicotinamide.[117] Monteiro *et al.*[118] showed that all of five patients with acquired immune deficiency syndrome (AIDS) with diarrhoea had reduced urinary excretion of a niacin metabolite when compared with seven patients with AIDS without diarrhoea. In contrast, a 3-year prospective study of 108 patients with pellagra between 1996 and 1998 included six patients with HIV. The authors commented that the incidence of HIV infection in patients with pellagra and pellagra-like erythema was not higher than in the general population.[119] Tremeschin *et al.*[120] showed that HIV-positive

Table 4 Medical conditions that cause niacin deficiency

Type/variant	Factors
Congenital	Hartnup disease[27]
Acquired	
Inadequate diet	Malnutrition[73]
	Maize diet[55]
	Jowar (sorghum) diet[55]
	Chronic alcoholism[74,75]
	Anorexia nervosa[76–78]
	Dietary restriction in atopic dermatitis[79]
Malabsorption	Crohn disease[80,81]
	Jejuno-ileitis[55,82]
	Gastroenterostomy[55,82]
	Subtotal gastrectomy[55]
	Chronic colitis[41]
	Severe ulcerative colitis[41]
	Regional ileitis[83]
	Hepatic cirrhosis[84]
	Gastrointestinal tract tuberculosis[41]
	Coeliac disease[41]
Metabolic 'steal'	Carcinoid syndrome[85,86]
Drug-induced	6-Mercaptopurine[82]
	5-Fluorouracil[82,87]
	Azathioprine[88]
	Carbamazepine[89]
	Chloroamphenicol[93]
	Ethionamide[41]
	Hydantoin[90,91]
	Isoniazid[72,92]
	Phenytoin[84]
	Phenobarbitone[93]
	Protionamide[91]
	Pyrazinamide[94]

children showed normal niacin metabolism compared with HIV-negative controls.

Cutaneous manifestations of pellagra

Generations of medical students in the English-speaking world have remembered the features of pellagra as 'four Ds': dermatitis, diarrhoea, dementia and, if left untreated, death. Cutaneous, gastrointestinal and neuropsychiatric manifestations are generally observed, but not invariably appearing in this order.[121] Early symptoms are usually nonspecific, with weakness, loss of appetite, vomiting, abdominal pain and irritability.[39,41] Cutaneous features are often an important clue to the diagnosis of pellagra.[84,122] Skin signs become evident in spring and summer, and may present initially as sunburn-like erythema.[51] A number of different forms of skin and mucous membrane features have been described for pellagra.[51,69] These include photosensitivity dermatitis on exposed sites; perineal, genital and mucosal skin lesions; skin thickening and pigmentation over the bony prominences; and sebaceous gland changes. The nails are rarely affected.[123] These four variants of cutaneous pellagra are now summarized in more detail.

Photosensitivity dermatitis on exposed sites

Prominent skin changes involving exposed sites are the most common and characteristic cutaneous feature of pellagra.[41,55,124] The rash is typically bilateral, symmetrical and limited to exposed sites of solar exposure.[11] It is well-defined and usually most prominent on the dorsum of hands, 'V' of the neck, face, radial aspects of the forearms, and exposed skin on legs and feet.[125] These sites initially become red and swollen; patients may complain of burning and pain.[51] The clinical features at this stage closely resemble sunburn with erythema and skin oedema as dominant signs;[51] the initial clue to the diagnosis of pellagra may only arise following recognition by the patient that the threshold for sunburn has reduced significantly.[70] Vesicles may occur in acute and severe attacks of pellagra.[41,51,126] Persistent erythema and scaling are sequelae of the acute eruption. In contrast to sunburn, where skin erythema and swelling typically fade within days, in pellagra the skin becomes darker with prominent hyperpigmentation.[84] Skin healing and repair in pellagra is delayed fourfold or longer compared with acute sunburn.[127] In long-established disease, hyperpigmentation increases and becomes the dominant cutaneous sign, in association with skin thickening, dryness and roughness.[99] Painful fissures may complicate involvement of palms and soles.[126]

The dorsa of the hands is one of the most commonly affected sites with up to 97% of patients with pellagra having skin features showing involvement.[41] Skin changes on the arms may extend proximally with a characteristic line of demarcation at the distal margin of clothing to form the 'glove' or 'gauntlet' of pellagra.[126] Feet and legs up to the distal edge of trousers or skirt are also commonly affected sites. The sharply demarcated hyperpigmentary changes of pellagra on the lower legs and feet have been likened to 'boots'.[126] Symmetrical eruption on the face is frequently observed in pellagra, involving the nose, cheeks, chin and lips; less commonly, eyelids and ears are affected.[128] A broad hyperpigmented band or collar-like appearance has been reported for pellagra on the neck. This is commonly referred to as 'Casal's necklace' (Fig. 3) in recognition of the first doctor to describe this characteristic sign of pellagra.[51,55] Malfait *et al.*[129] reported a sample of 992 patients with pellagra in 1990 of whom 76% had 'Casal's necklace'. Differences in the degree of photoprotection afforded by clothing are thought to explain the variability of skin changes of pellagra on the neck and upper chest. Neck changes can sometimes extend down over the sternum.[126]

Perineal, genital and mucosal skin lesions

Scrotal and perineal erythema with erosions have been reported in pellagra.[13,69,127] A variety of genital skin signs have been reported in pellagra including perineal erythema with maceration and secondary bacterial infection. The vaginal mucosa may become inflamed and exudative. About one-third of patients with pellagra have involvement of the lip, tongue and oral mucous membrane.[41] The tongue in pellagra shows marked erythema, swelling and dryness followed by pseudo-

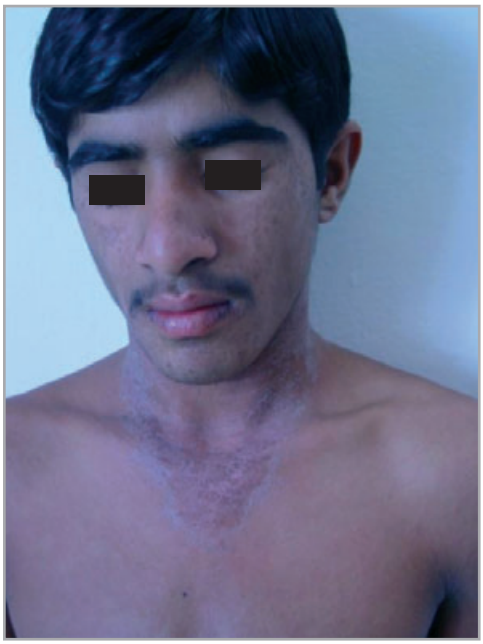

Fig 3. Clinical image showing the broad hyperpigmented band or collar-like appearance of pellagra on the neck. This is commonly referred to as 'Casal's necklace'.

membranous furrows, erosions or ulcers; later, it becomes atrophic with diminution of its papillae.[11] There is also tenderness, swelling and fragility of gum and oral mucous membranes. Cheilitis, or angular stomatitis, may also occur.[41] In 1937, Sydenstricker and Armstrong[130] reported that 96·5% of 440 patients with pellagra had glossitis and stomatitis. Of note is the absence of reports of genital and oral mucosal involvement in Hartnup disease and drug-induced pellagra.

Skin thickening and pigmentation over the bony prominences

Bilateral symmetrical skin lesions over the bony prominences of the body sites include the knees, ankles, elbows and spinous processes.[51,69] These lesions are hyperkeratotic and hyperpigmented. In contrast to the exposed-site photosensitivity skin changes, these skin changes are slow in onset.[69] As with the genital, perineal and oral mucosal lesions of pellagra, case reports of Hartnup disease and drug-induced pellagra do not include skin thickening and pigmentation over bony prominences as clinical features.[85,131,132]

Sebaceous gland changes

Patients with pellagra may develop sebaceous gland hyperplasia and prominent seborrhoea.[133] Sebaceous gland prominence in pellagra has been described on the alae nasi, forehead, scalp, face and neck.[15] There are fine, yellow scales over the follicular orifices. The eruption resembles seborrhoeic dermatitis except for its location.[127] This dysfunction of the sebaceous glands appears to be confined to the face and seems to be independent of sun exposure.[133] The plugs of abnormal inspissated sebum may project from the dilated orifices of the sebaceous follicles giving the skin surface a rough appearance and feel.[85,131,132]

Discussion

This review confirms pellagra to be a complex, multisystem disease that may arise in a variety of different situations and conditions. The best recognized of these is pellagra developing due to inadequate diet. In developed countries pellagra is now rare, but may still occur in alcoholism, severe malabsorption syndromes, and rarely, as a side-effect of drug therapy. As with many rare metabolic conditions with multisystem manifestations, the key to diagnosis is clinician awareness of the disorder. Once recognized, the diagnosis is easily established; treatment is inexpensive and the therapeutic response is fairly rapid over a few days. In most developing countries pellagra is also rare. However, it is unclear how rare, as countries with low gross domestic product and high rates of poverty tend to have poorly developed public health services, including unreliable or absent public health morbidity and mortality data. This review includes an attempt to collate public health data on pellagra from both developed and developing countries. Data from the World Health Organization from 2004 reported higher death rates of pellagra in South Africa, Venezuela and Brazil.[3] Pellagra may also arise where chronic starvation affects populations affected by famine or war. Sporadic reports from famine and war zones indicate that the rate of pellagra is often high.[44,129]

The cutaneous features of pellagra have been described in medical publications over the past 200 years. The most consistent clinical feature is exposed-site dermatitis. The clinical features are consistent with a primary photosensitivity syndrome and do not suggest a photoaggravated disorder. The associated oral and genital mucosal changes are more difficult to assess from the literature. They are clearly not features of photosensitivity and it is unclear from the literature if they are related to niacin deficiency. In the absence of conclusive evidence to confirm a causal relationship, it is more likely that accompanying vitamin deficiencies are responsible. Possible compounds include thiamine, riboflavin, pyridoxine, vitamin C and zinc.[108,121] The absence of mucosal involvement in drug-induced pellagra and Hartnup disease is consistent with this explanation.[97,98] Similarly, the thickening of skin over bony prominences is an inconsistent feature of pellagra that appears to be limited to niacin deficiency caused by an inadequate diet. Chronic malnutrition leads to skin, muscle and subcutaneous fat atrophy which makes skin on bony prominences particularly vulnerable to trauma. Thus, chronic trauma with hypertrophic repair is a more likely explanation for this cutaneous feature of pellagra rather than niacin deficiency itself. As with mucosal involvement, this explanation is supported by the absence of this cutaneous feature in drug-induced pellagra and Hartnup disease.[97,98] Occasionally, sebaceous gland changes in pellagra patients are independent of

sun exposure and resemble seborrhoeic dermatitis, raising the possibility of riboflavin deficiency.[108,121]

The case report by Darvay *et al.*[72] concluded that the action spectrum for photosensitivity in drug-induced pellagra in the patient reported was in the UVA range.

It is clear that further studies are needed to elucidate fully the biochemical basis of pellagra before an adequate explanation can be given for the mechanisms of pellagra-induced photosensitivity. Previous biochemical studies undertaken to investigate the biochemical basis of pellagra have used subjects with chronic alcohol abuse, individuals from a background of poor nutrition and animal models with dietary restriction of niacin/tryptophan. While these studies have been useful, they have not fully assessed the impact of the essential nutritional cofactors that play a crucial role in the functioning of this pathway. Further biochemical investigation of this pathway is now needed to assess the interplay of the essential cofactors under different conditions of niacin/tryptophan status. Such studies should include subjects with pellagra caused by nutritional deficiencies, and patients with Hartnup disease. Additionally, cell culture model systems will be required in order to identify the biochemical basis of pellagra.

It is currently not possible to give a concise explanation for the pathogenesis of the photosensitivity eruption of pellagra. Such an explanation will require good quality phototesting studies to establish the action spectrum for the disorder. *In vitro* studies using cell culture techniques could then be used to assess cell survival in selectively depleted media of relevance to the tryptophan/niacin pathway. Finally, *in vivo* cellular studies on the effects of skin irradiation in patients with pellagra with relevant wavelengths can then be used to characterize the nature of the cutaneous damage and the immunological and repair response that is elicited.

In conclusion, this review of the literature confirms pellagra as a primary photosensitivity disorder which may sometimes be severe. Mucosal changes and skin changes over bony prominences are probably unrelated to niacin deficiency. Clinical studies on phototesting in pellagra have yet to establish the action spectrum for this photosensitivity disorder, but preliminary data in a single patient suggest this will be within the UVA spectrum. This review includes a detailed analysis of the niacin/NADP/NADPH biochemical pathway which has revealed many unresolved issues and a lack of contemporary research. Further biochemical studies are needed to understand how biochemical changes in this pathway lead to the striking clinical pathology that characterizes pellagra. Only then will the pathogenesis of this photosensitivity disorder be established.

What's already known about this topic?

- Pellagra was the first photosensitivity disorder to be reported in the medical literature nearly 250 years ago.
- The biochemical and photobiological features of pellagra have not yet been analysed using contemporary techniques.

What does this study add?

- This study is the first to identify systematically relevant clinical, epidemiological, biochemical and photochemical literature on pellagra with the aim of establishing a clearer understanding of this photosensitivity disorder.
- The review concludes by highlighting potential areas for future research.

Acknowledgments

We thank Anne Dixon, Maureen Williams and Hannah O'brien for the help with literature searches; we thank Professor Rex Tyrrell and Professor Paul Smith for the helpful advice on photochemistry mechanisms; we thank Jiannan Guo for the help with biochemistry.

References

1 Lindsay AC, Halcox JP. Niacin compared with ezetimibe. *N Engl J Med* 2010; **362**:1046–8.
2 Taylor AJ, Villines TC, Stanek EJ *et al.* Extended-release niacin or ezetimibe and carotid intima–media thickness. *N Engl J Med* 2009; **361**:2113–22.
3 Mortality statistics. Niacin deficiency (pellagra) (most recent) by country, 2004. Available at: http://www.nationmaster.com/graph/mor_nia_def_pel_percap-niacin-deficiency-pellagra-per-cap-ita (last accessed 10 January 2011).
4 Pada G. Putting the smallest first: why India makes a poor fist of feeding the young, and how it could do better. *Economist* 2010. Available at: http://www.economist.com/node/17090948 (last accessed 10 January 2011).
5 Seal AJ, Creeke PI, Dibari F *et al.* Low and deficient niacin status and pellagra are endemic in postwar Angola. *Am J Clin Nutr* 2007; **85**:218–24.
6 Berry-Koch A, Moench R, Hakewill P *et al.* Alleviation of nutritional deficiency diseases in refugees. *Food Nutr Bull* 1990; **12**. Available at: http://www.unu.edu/unupress/food/8f122e/8F122E04.htm (last accessed 10 January 2011).
7 Casal G. The natural and medical history of the principality of the Asturias. In: *Classic Descriptions of Disease* (Major RH, ed.), 3rd edn. Springfield, IL: Charles C Thomas Publisher, 1945; 607–12.
8 Menéndez A. Casal Julian, Gaspar. In: *Dictionary of Medical Biography* (Bynum WF, Bynum H, eds). London: Greenwood Press, 2007; 312–13.
9 MacCormac H. Tradition in dermatology. *Br J Dermatol Syph* 1924; **36**:235–44.
10 Bateman T. Eczema solare. In: *A Practical Synopsis of Cutaneous Diseases according to the Arrangement of Dr Willan* (Bateman T, ed.). London: R. and A. Taylor, 1819; 253–5.
11 Hampl JS, Hampl WS 3rd. Pellagra and the origin of a myth: evidence from European literature and folklore. *J R Soc Med* 1997; **90**:636–9.
12 Leng ER, Tavcar A, Trifunovic V. Maize of southeastern Europe and its potential value in breeding programs elsewhere. *Euphytica* 1962; **11**:263–72.
13 World Health Organization. *Pellagra and Its Prevention and Control in Major Emergencies. WHO/NHD/00.10*. Geneva, Switzerland: World Health Organization, 2000.

14 Sydenstricker VP. The history of pellagra, its recognition as a disorder of nutrition and its conquest. *Am J Clin Nutr* 1958; **6**:409–14.
15 Stratigos JD, Katsambas A. Pellagra: a still existing disease. *Br J Dermatol* 1977; **96**:99–106.
16 Frapolli F. The natural and medical history of the principality of the Asturias. In: *Classic Descriptions of Disease* (Major RH, ed.), 3rd edn. Springfield, IL: Charles C Thomas Publisher, 1945; 612–15.
17 Semba RD. Théophile Roussel and the elimination of pellagra from 19th century France. *Nutrition* 2000; **16**:231–3.
18 Goldberger J. The etiology of pellagra. *Public Health Rep* 1914; **90**:373–5.
19 Goldberger J. The cause and prevention of pellagra. *Public Health Rep* 1914; **29**:2354–7.
20 Rajakumar K. Pellagra in the United States: a historical perspective. *South Med J* 2000; **93**:272–7.
21 Elmore JG, Feinstein AR. Joseph Goldberger: an unsung hero of American clinical epidemiology. *Ann Intern Med* 1994; **121**:372–5.
22 Shibata K, Tayuchi H. Nicotinic acid and nicotinamide. In: *Modern Chromatographic Analysis of Vitamins* (De Leenheer AP, Lambert WE, Van Bocxlaer JF, eds), 3rd edn. Basel: Marcel Dekker Inc, 2000; 325–64.
23 Mariani-Costantini R, Mariani-Costantini A. An outline of the history of pellagra in Italy. *J Anthropol Sci* 2007; **85**:163–71.
24 Middleton J. Pellagra and the blues song 'Cornbread, meat and black molasses'. *J R Soc Med* 2008; **101**:569–70.
25 Elvehjem CA, Madden RJ, Strong FM *et al.* Relation of nicotinic acid and nicotinic acid amide to canine black tongue. *JACS* 1937; **59**:1767–8.
26 Akst D. The forgotten plague. *Am Herit* 2000; **51**:72–9.
27 Baron DN, Dent CE, Harris H *et al.* Hereditary pellagra-like skin rash with temporary cerebellar ataxia. Constant renal aminoaciduria. And other bizarre biochemical features. *Lancet* 1956; **2**:421–8.
28 Azmanov DN, Kowalczuk S, Rodgers H *et al.* Further evidence for allelic heterogeneity in Hartnup disorder. *Hum Mutat* 2008; **29**:1217–21.
29 Kleta R, Romeo E, Ristic Z *et al.* Mutations in *SLC6A19*, encoding B(0)AT1, cause Hartnup disorder. *Nat Genet* 2004; **36**:999–1002.
30 Seow HF, Broer S, Broer A *et al.* Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. *Nat Genet* 2004; **36**:1003–7.
31 Bröer S, Cavanaugh JA, Rasko JEJ. Neutral amino acid transport in epithelial cells and its malfunction in Hartnup disorder. *Biochem Soc Trans* 2005; **33**:233–6.
32 Ozarin L. The case of the vanishing diagnosis. *Psychiatr News* 2005; **40**:28.
33 Gray JP. Case of pellagra of the insane. *Am J Insanity* 1864; **21**:223–7.
34 Morabia A. Joseph Goldberger's research on the prevention of pellagra. *J R Soc Med* 2008; **101**:566–8.
35 Elvehjem CA. Relation of nicotinic acid to pellagra. *Physiol Rev* 1940; **20**:249–71.
36 Bollet AJ. Politics and pellagra: the epidemic of pellagra in the U.S. in the early twentieth century. *Yale J Biol Med* 1992; **65**:211–21.
37 Dekleine W. Control of pellagra. *South Med J* 1942; **35**:992–6.
38 Park YK, Sempos CT, Barton CN *et al.* Effectiveness of food fortification in the United States: the case of pellagra. *Am J Public Health* 2000; **90**:727–38.
39 Pipili C, Cholongitas E, Ioannidou D. The diagnostic importance of photosensitivity dermatoses in chronic alcoholism: report of two cases. *Dermatol Online J* 2008; **14**:15.
40 Prousky JE. Pellagra may be a rare secondary complication of anorexia nervosa: a systematic review of the literature. *Altern Med Rev* 2003; **8**:180–5.
41 Hegyi J, Schwartz RA, Hegyi V. Pellagra: dermatitis, dementia, and diarrhea. *Int J Dermatol* 2004; **43**:1–5.
42 Han YS, Liu GY, Xu DY. Clinical analysis on 42 cases of pellagra (in Chinese). *J Chinese Village Med Pharmacy* 2004; **11**:14–15.
43 Cui Y, Cao M, Li CT *et al.* Meta-analysis of 23 case reports of pellagra in China (in Chinese). *Pract J Clin Med* 2009; **6**:34–6.
44 Baquet S, Wuillaume F, Van Egmond K *et al.* Pellagra outbreak in Kuito, Angola. *Lancet* 2000; **355**:1829–30.
45 Moren A, Lemoult D, Brodel A. Pellagra in Mozambican refugees. *Lancet* 1990; **335**:1403–4.
46 Centers for Disease Control. Outbreak of pellagra among Mozambican refugees – Malawi, 1990. *MMWR Morb Mortal Wkly Rep* 1991; **40**:209–14. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00001945.htm (last accessed 10 January 2011).
47 Prinzo ZW, de Benoist B. Meeting the challenges of micronutrient deficiencies in emergency-affected populations. *Proc Nutr Soc* 2002; **61**:251–7.
48 Golden M. *A Report on the Investigation into Recurrent Epidemics of Pellagra in Kuito, Angola*. Washington, DC: Food and Nutrition Technical Assistance Project, Academy for Educational Development, 2002.
49 Latham MC. Pellagra. In: *Human Nutrition in the Developing World*. Food and Nutrition Series no. 29, Chapter 17. Rome: FAO. Available at: http://www.fao.org/docrep/w0073e/w0073e05.htm#P4008_468640 (last accessed 11 January 2011).
50 Oliver FJ, Menissier-de Murcia J, de Murcia G. Poly(ADP-ribose) polymerase in the cellular response to DNA damage, apoptosis, and disease. *Am J Hum Genet* 1999; **64**:1282–8.
51 Hendricks WM. Pellagra and pellagra-like dermatoses: etiology, differential diagnosis, dermatopathology, and treatment. *Semin Dermatol* 1991; **10**:282–92.
52 Brown TM. Pellagra: an old enemy of timeless importance. *Psychosomatics* 2010; **51**:93–7.
53 Horwitt MK, Harper AE, Henderson LM. Niacin–tryptophan relationships for evaluating niacin equivalents. *Am J Clin Nutr* 1981; **34**:423–7.
54 National Institute of Nutrition. Histidine, urocanic acid and histidase activity in the stratum corneum in pellagrins. National Institute of Nutrition Annual Report, Hyderabad, India, 1969; 56–8.
55 Karthikeyan K, Thappa DM. Pellagra and skin. *Int J Dermatol* 2002; **41**:476–81.
56 Buchness MR. Photoexacerbated dermatoses. In: *Clinical Photomedicine* (Lim HW, Soter NA, eds). New York: Marcel Dekker Inc, 1993; 277–8.
57 Gillman J, Gillman T, Brenner S. Porphyrin fluorescence in the livers of pellagrins in relation to ultra-violet light. *Nature* 1945; **156**:689.
58 Rhodes LE, Lim HW. The acute effects of ultraviolet radiation on the skin. In: *Photodermatology* (Lim HW, Hönigsmann H, Hawk JLM, eds). New York: Informa Healthcare, 2007; 76–89.
59 Vasantha L. Histidine urocanic acid and histidine alpha-deaminase in the stratum corneum in pellagrins. *Indian J Med Res* 1970; **58**:1079–84.
60 Barresi C, Stremnitzer C, Mlitz V *et al.* Increased sensitivity of histidinemic mice to UVB radiation suggests a crucial role of endogenous urocanic acid in photoprotection. *J Invest Dermatol* 2011; **131**:188–94.

61 Levy HL, Taylor RG, McInnes RR. Disorders of histidine metabolism. In: *The Metabolic and Molecular Bases of Inherited Disease* (Scriver CR, Beaudet AL, Sly W, Valle D, eds). New York, NY: McGraw-Hill Companies, Inc., 2001; 1827–20.

62 Baden HP, Hori Y, Pathak MA *et al.* Epidermis in histidinemia. *Arch Dermatol* 1969; **100**:432–5.

63 Swanbeck G, Wennersten G. Evidence for kynurenic acid as a possible photosensitizer in actinic reticuloid. *Acta Derm Venereol* (Stockholm) 1973; **53**:109–13.

64 Wennersten G, Brunk U. Cellular aspects of phototoxic reactions induced by kynurenic acid. *Acta Derm Venereol* (Stockholm) 1977; **57**:201–9.

65 Rapaport MJ. Pellagra in a patient with anorexia nervosa. *Arch Dermatol* 1985; **121**:255–7.

66 Harber LC, Bickers DR. Pellagra. In: *Photosensitivity Diseases: Principles of Diagnosis and Treatment* (Harber LC, Bickers DR, eds), 2nd edn. Toronto: B.C. Decker, 1989; 303.

67 Sambon LW. Remarks on the geographical distribution and etiology of pellagra. *BMJ* 1905; **2**:1272–5.

68 Tucker BR. Pellagra, with the analytical study of fifty-five non-institutional or sporadic cases. *JAMA* 1911; **56**:246–51.

69 Smith DT, Ruffin JM. Effect of sunlight on the clinical manifestations of pellagra. *Arch Intern Med* 1937; **59**:631–45.

70 Spies TD. Relationship of pellagrous dermatitis to sunlight. *Arch Intern Med* 1935; **56**:920–6.

71 Kojima T, Okamoto S, Fujita M *et al.* Pellagra – photo-induction of lesions by UVB irradiation (in Japanese). *Nippon Hifuka Gakkai Zasshi* 1985; **95**:949–53.

72 Darvay A, Basarab T, McGregor JM *et al.* Isoniazid induced pellagra despite pyridoxine supplementation. *Clin Exp Dermatol* 1999; **24**:167–9.

73 Mayer J. Tropical malnutrition. 3. Pellagra and other syndromes of malnutrition. *Postgrad Med* 1966; **39**:A127–31.

74 Vannucchi H, Mello de Oliveira JA, Dutra de Oliveira JE. Tryptophan metabolism in alcoholic pellagra patients: measurements of urinary metabolites and histochemical studies of related muscle enzymes. *Am J Clin Nutr* 1982; **35**:1368–74.

75 Saracibar N, Ferrer I, Arbizu T *et al.* Pellagroid encephalopathy in chronic alcoholism. Clinicopathological study (author's transl). *Med Clin (Barc)* 1980; **75**:151–5.

76 Jagielska G, Tomaszewicz-Libudzic CE, Brzozowska A. Pellagra: a rare complication of anorexia nervosa. *Eur Child Adolesc Psychiatry* 2007; **16**:417–20.

77 MacDonald A, Forsyth A. Nutritional deficiencies and the skin. *Clin Exp Dermatol* 2005; **30**:388–90.

78 Cleary MJ, Cleary JP. Anorexia nervosa: a form of subclinical pellagra. *Int Clin Nutr Rev* 1989; **9**:137–43.

79 Ladoyanni E, Cheung ST, North J *et al.* Pellagra occurring in a patient with atopic dermatitis and food allergy. *J Eur Acad Dermatol Venereol* 2007; **21**:394–6.

80 Pollack S, Enat R, Haim S *et al.* Pellagra as the presenting manifestation of Crohn's disease. *Gastroenterology* 1982; **82**:948–52.

81 Abu-Qurshin R, Naschitz JE, Zuckermann E *et al.* Crohn's disease associated with pellagra and increased excretion of 5-hydroxyindolacetic acid. *Am J Med Sci* 1997; **313**:111–13.

82 Miller SJ, Diego S. Nutritional deficiency and the skin. *J Am Acad Dermatol* 1989; **21**:1–30.

83 Eisenstadt HB. Regional ileitis, a review. *Am J Gastroenterol* 1965; **43**:560–4.

84 Nogueira A, Duarte AF, Magina S *et al.* Pellagra associated with esophageal carcinoma and alcoholism. *Dermatol Online J* 2009; **15**:8.

85 Reichman O, Sobel JD. Vulvovaginal pellagra and lichen sclerosus complicating carcinoid syndrome. *Obstet Gynecol* 2009; **113**:543–5.

86 Castiello RJ, Lynch PJ. Pellagra and the carcinoid syndrome. *Arch Dermatol* 1972; **105**:574–7.

87 Stevens HP, Ostlere LS, Begent RH *et al.* Pellagra secondary to 5-fluorouracil. *Br J Dermatol* 1993; **128**:578–80.

88 Jarrett P, Duffill M, Oakley A *et al.* Pellagra, azathioprine and inflammatory bowel disease. *Clin Exp Dermatol* 1997; **22**:44–5.

89 Heyer G, Simon M, Schell H. Dose-dependent pellagroid skin reaction caused by carbamazepine. *Hautarzt* 1998; **49**:123–5.

90 Pitche PT. Pellagra. *Sante* 2005; **15**:205–8.

91 Lyon VB, Fairley JA. Anticonvulsant-induced pellagra. *J Am Acad Dermatol* 2002; **46**:597–9.

92 Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48**:628–34.

93 Ozturk F, Koca R, Aydin M *et al.* Pellagra: a sporadic pediatric case with a full triad of symptoms. *Cutis* 2001; **68**:31–4.

94 Das R, Parajuli S, Gupta S. A rash imposition from a lifestyle omission: a case report of pellagra. *Ulster Med J* 2006; **75**:92–3.

95 Sarkany RPE, Breathnach SM, Seymour CA *et al.* Metabolic and nutritional disorders. In: *Rook's Textbook of Dermatology* (Burns T, Breathnach S, Cox N, Griffiths C, eds), 7th edn. Oxford: Blackwell Science Ltd, 2004; 57.1–124.

96 Halvorsen K, Halvorsen S. Hartnup disease. *Pediatrics* 1963; **1**:29–38.

97 Zheng Y, Zhou C, Huang Y *et al.* A novel missense mutation in the *SLC6A19* gene in a Chinese family with Hartnup disorder. *Int J Dermatol* 2009; **48**:388–92.

98 Sander CS, Hertecant J, Abdulrazzaq YM *et al.* Severe exfoliative erythema of malnutrition in a child with coexisting coeliac and Hartnup's disease. *Clin Exp Dermatol* 2009; **34**:178–82.

99 Crutchfield ED. Pellagra: with special reference to the skin and mucous membrane. *Arch Dermatol Syph* 1928; **17**:651–8.

100 Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. *Annu Rev Nutr* 2008; **28**:115–30.

101 Carter EC, Carpenter KJ. The available niacin values of foods for rats and their relation to analytical values. *J Nutr* 1982; **112**:2091–103.

102 Brenton BP. Pellagra and nutrition policy lessons from the Great Irish famine to the New South Africa. *Nutr Anthropol* 1998; **22**:1–11.

103 Manuel JR, Roberto C, Francisco A. Continuous production of an instant corn flour for arepa and tortilla, using an acid-cooking. US patent no. 6322836, 2001. Available at: http://www.patentstorm.us/patents/6322836/fulltext.html (last accessed on 11 January 2010).

104 FAO. Processing of whole maize: lime-cooking. In: *Maize in Human Nutrition*. Rome: FAO, 1993. Available at: http://www.fao.org/docrep/T0395E/T0395E05.htm#Processing%20of%20whole%20maize:%20lime-cooking (last accessed on 11 January 2011).

105 Belavady B, Madhavan TV, Gopalan C. Production of nicotinic acid deficiency (blacktongue) in pups fed diets supplemented with leucine. *Gastroenterology* 1967; **53**:749–53.

106 Magboul BI, Bender DA. The effects of a dietary excess of leucine on the synthesis of nicotinamide nucleotides in the rat. *Br J Nutr* 1983; **49**:321–9.

107 Beretich GR Jr. Do high leucine/low tryptophan dieting foods (yogurt, gelatin) with niacin supplementation cause neuropsychiatric symptoms (depression) but not dermatological symptoms of pellagra? *Med Hypotheses* 2005; **65**:628–9.

108 Vannucchi H, Favaro RM, Cunha DF *et al.* Assessment of zinc nutritional status of pellagra patients. *Alcohol Alcohol* 1995; **30**:297–302.

109 Klauder JV, Winkelman NW. Pellagra among chronic alcoholic addicts: a clinical and laboratory study. *JAMA* 1928; **90**:364–71.
110 Barakat MT, Meeran K, Bloom SR. Neuroendocrine tumours. *Endocr Relat Cancer* 2004; **11**:1–18.
111 Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**:934–59.
112 Shah GM, Shah RG, Veillette H *et al.* Biochemical assessment of niacin deficiency among carcinoid cancer patients. *Am J Gastroenterol* 2005; **100**:2307–14.
113 Bell HK, Poston GJ, Vora J *et al.* Cutaneous manifestations of the malignant carcinoid syndrome. *Br J Dermatol* 2005; **152**:71–5.
114 Cohen LK, George W, Smith R. Isoniazid-induced acne and pellagra: occurrence in slow inactivators of isoniazid. *Arch Dermatol* 1974; **109**:377–81.
115 Rabinowitz SS, Reddy S, Rajakumar K. Pellagra. Available at: http://emedicine.medscape.com/article/985427-overview (last accessed on 11 January 2011).
116 Hegyi V, Schwartz RA. Pellagra. Available at: http://emedicine.medscape.com/article/1095845-overview (last accessed on 11 January 2011).
117 Murray MF, Nghiem M, Srinivasan A. HIV infection decreases intracellular nicotinamide adenine dinucleotide (NAD). *Biochem Biophys Res Commun* 1995; **212**:126–31.
118 Monteiro JP, da Cunha DF, Filho DC *et al.* Niacin metabolite excretion in alcoholic pellagra and AIDS patients with and without diarrhea. *Nutrition* 2004; **20**:778–82.
119 Pitche P, Kombate K, Tchangai-Walla K. Prevalence of HIV infection in patients with pellagra and pellagra-like erythemas. *Med Trop (Mars)* 1999; **59**:365–7.
120 Tremeschin MH, Cervi MC, Camelo Junior JS *et al.* Niacin nutritional status in HIV type 1-positive children: preliminary data. *J Pediatr Gastroenterol Nutr* 2007; **44**:629–33.
121 Weismann K. Nutrition and the skin. In: *Rook's Textbook of Dermatology* (Burns T, Breathnach S, Cox N, Griffiths C, eds), 8th edn. Oxford: Wiley-Blackwell Ltd, 2010; 9.58–81.
122 Isaac S. The 'gauntlet' of pellagra. *Int J Dermatol* 1998; **37**:599.
123 Cakmak SK, Gonul M, Aslan E *et al.* Half-and-half nail in a case of pellagra. *Eur J Dermatol* 2006; **16**:695–6.
124 Ormsby OS. Pellagra. *J Cutan Dis* 1912; **30**:589–607.
125 Spivak JL, Jackson DL. Pellagra: an analysis of 18 patients and a review of the literature. *Johns Hopkins Med J* 1977; **140**:295–309.
126 Jen M, Shah KN, Yan AC. Cutaneous changes in nutritional disease. In: *Fitzpatrick's Dermatology in General Medicine* (Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds), 7th edn. New York: McGraw Hill, 2007; 1201–18.
127 James WD, Berger TG, Elston DM. Nutritional disease. In: *Andrews' Disease of the Skin: Clinical Dermatology*, 10th edn. Philadelphia: Elsevier, 2006; 479–86.
128 Dreizen S. The butterfly rash and the malar flush. What do these signs reflect? *Postgrad Med J* 1991; **89**:225–8.
129 Malfait P, Moren A, Dillon JC *et al.* An outbreak of pellagra related to changes in dietary niacin among Mozambican refugees in Malawi. *Int J Epidemiol* 1993; **22**:504–11.
130 Sydenstricker VP, Armstrong ES. A review of four hundred and forty cases of pellagra. *Arch Intern Med* 1937; **59**:883–91.
131 Okan G, Yaylaci S, Alzafer S. Pellagra: will we see it more frequently? *J Eur Acad Dermatol Venereol* 2009; **23**:365–6.
132 Prakash R, Gandotra S, Singh LK *et al.* Rapid resolution of delusional parasitosis in pellagra with niacin augmentation therapy. *Gen Hosp Psychiatry* 2008; **30**:581–4.
133 Fred HL. 'Dyssebacia' – a fifth D of pellagra. *Pract Gastroenterol* 2003; **27**:41–2.