PELLAGRA

and its prevention and control
in major emergencies

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                   Centre, Kuito, 1999

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Pellagra

A disorder due to inadequate dietary intake of niacin and/or tryptophan, manifested by a characteristic dermatitis on areas of the skin that are exposed to the sun, beginning as an erythema with pruritus that may lead to vesticulation but more frequently becomes chronic, rough, scaly, and hard with the formation of crusts as the result of haemorrhage; a broad band of this dermatitis frequently encircles the neck. The digestive tract and nervous system may be involved, with glossitis, stomatitis, gastroenteritis, diarrhoea with profuse watery and sometimes bloody stools, anxiety, depression, tremor, and reduced or absent tendon reflexes; encephalopathy may occur in severe cases. The disease is classically associated with a diet based on non-alkali-treated maize.

Synonyms: alpine scurvy; Casals collar (in part); Casals necklace (in part); chichism; disease of the 3 Ds; elephantiasis asturiensis; elephantiasis italica; erythema endemicum; Lombardy erysipelas; Lefula-pone (Lesotho); mayidism; niacinamidosis; niacin deficiency; pellagra sine pellagra; pseudopellagra (in part); psilosis pigmentosa; St Ignatius itch; typhoid pellagra (in part).

Notes.
1.   The term "pseudopellagra" has been applied to pellagra occurring in those whose diet is not based on maize or millet, and "typhoid pellagra" has been applied to pellagra with sustained fever; both terms are deprecated. The typical band of dermatitis encircling the neck has been referred to as Casals collar or necklace (these terms are not recommended). The term "disease of the three Ds" (for dermatitis, diarrhoea, and dementia) is misleading since diarrhoea is not always present and dementia is relatively rare (though depression is common). On rare occasions pellagra may not show the characteristic dermatitis; this condition has been referred to by the confusing term "pellagra sine pellagra".

2. The disorder may be secondary to certain other conditions, such as adrenal phaeochromocytoma and the administration of certain drugs (e.g. Isoniazid); in this case, the term "nicotinic acid deficiency due to ..." is recommended.

Linguistic note. The name pellagra is derived from the Italian pelle agra, sharp [i.e., rough] skin.

Source: *International nomenclature of diseases*. Vol. IV. Metabolic, nutritional, and endocrine disorders. Geneva, World Health Organization, 1991, p. 279.

Introduction and scope

This document is a review of pellagra. Pellagra results from a niacin and/or tryptophan deficient diet. Earliest recorded reports of pellagra were made almost 250 years ago. The condition quickly became associated with maize-based diets and was seen to spread throughout Europe following the introduction of maize as a staple crop from its original home in the New World.

The disease was still considered a public health problem in many maize-consuming African and Asian countries throughout the 1960s and 1970s. In South Africa more than 100 000 cases were reported each year during the 1970s. More recently, apart from sporadic cases reported in rural health centres during times of drought and food shortage, the condition has only been observed as a significant problem among food-aid dependent populations during food emergency and refugee programmes.

Numerous outbreaks of pellagra have occurred among refugees (see Table 1). More than 22 000 cases have been reported among 900 000 Mozambican refugees in southern Malawi since 1989. In 1990 alone, at least 18 000 cases were reported and attack rates in certain camps were as high as 13% (Centers for Disease Control, 1991). Cases of pellagra were also reported among refugees in Zimbabwe (1988 and 1989), Swaziland (1989), the former Zaire (1989), Angola and Nepal (1994) (Toole, 1994; ACC/SCN, RNIS Report Nos 5 & 8, 1994).

Large-scale outbreaks have also occurred among refugee returnee populations. This occurred in Mozambique where in one location in Tete province the prevalence of pellagra at the end of 1995 was estimated at 1.4%. This outbreak followed a large influx of refugees from Malawi whereby the population of Mutarara district increased from 50 000–200 000 (ACC/SCN, RNIS Report No.14, 1996). The most recent large-scale outbreak occurred among conflict-affected populations in Angola at the end of 1999 (ACC/SCN, RNIS Report No. 30, 2000).

The focus of this review will be on the occurrence of pellagra during emergencies with an analysis of risk factors and preventive and alleviation measures. It will begin with an historical overview of pellagra outbreaks leading up to the most recent outbreaks in refugee and emergency programmes. The next section will review the signs and symptoms of the disease and means of diagnosis. A subsequent section will detail the role of niacin in the etiology of pellagra and current consensus on RDAs of niacin. This will be followed by a section on sources of niacin. The final two sections of the review will provide detailed information on recent pellagra outbreaks, remedial strategies employed during these emergency programmes, and recommendations on strategies to prevent and combat future outbreaks of pellagra.

Table 1. Pellagra outbreaks in emergency-affected populations

Year	Location	Population	Prevalence (%)
1988[a]	Zimbabwe	-	1.5%
1989[b]	Malawi (11 camps)	285 000	0.5%
1990[c]	Malawi (all camps)	900 000	2.0%
1991[d]	Malawi (Nsanje district)	300 000	0.2%
1994[e] (June)	Nepal (Bhutanese refugees)	85 000	0.5/10 000/day (incidence)
1994[e] (September)	"	85 000	0.005/10 000/day (incidence)
1995	Mozambique [f]	200 000	1.4%
1999 (November)	Angola [g]	240 000	2.6/1000/week

[a] Berry-Koch et al. Alleviation of nutritional deficiency diseases in refugees. Food and Nutrition Bulletin, 12 (2):106-112.
[b] Moren A, Le Moult D. Pellagra cases in Mozambican refugees [Letter]. Lancet 1990, 335:1403-1404.
[c] Centers for Disease Control. Outbreak of pellagra among Mozambican refugees, Malawi, 1990. MMWR 1991, 40:209-213.
[d] UNHCR, unpublished report.
[e] RNIS Report Nos 5 & 8. ACC/SCN News. June 1994, December 1994.
[f] RNIS February 1996, Report No. 14.
[g] MSF/ICRC Rapid Nutritional Assessment, Kuito province of Bie, Angola. December 1999.

History of pellagra

Outbreaks

The earliest description of pellagra was that of the Spanish physician Don Gaspar Casal in 1763. Casal recorded all the clinical characteristics and ascribed the disease to the unbalanced diets, based on maize, of poor peasants in the Asturia region of Spain. The next description of the disease came from Italy in 1771 when pellagra was given its name, meaning "rough skin". The disease continued to be widespread in Italy throughout the nineteenth century, e.g. data from 1862 report 39 000 cases in Lombardy in a population of 2.5 million (Carpenter, 1981).

Pellagra outbreaks followed the introduction of maize into Europe from its original home in the New World. It spread through Europe from Spain to Italy, France, central Europe, Romania, Turkey, Greece and parts of southern Russia. It also followed in the wake of maize introduction into Egypt

and later into central and southern Africa. (WHO, 1970). There has been no evidence of pellagra among the indigenous peoples of North, Central and South America where maize was domesticated and has been the staple cereal for thousands of years. The main reason for this is the traditional practice of eating maize treated with lime or wood ashes, a treatment which increases the bioavailability of the niacin in maize (see section on niacin). Carpenter (1981) made the following observation:

> *It seems possible that if the traditional method of processing corn—developed in America by those who had used it as a safe staple food for millennia—had been brought back to the Old World by Columbus along with the grain itself, and generally adopted, pellagra might never have developed, and the suffering of hundreds of thousands in southern Europe would have been avoided.*

After 1900, pellagra decreased greatly in Italy for reasons that are unclear, and by 1916 the disease had almost disappeared in the country. However, it remained a serious problem in parts of south-eastern Europe until World War II. In Romania, over 55 000 cases were officially recorded with 1654 deaths in 1932. A study made in four villages in the province of Moldavia revealed that almost 10% of the population suffered from the deficiency disease every spring; in these villages about 75% of total calories were provided by whole yellow maize.

After 1906, pellagra also became a serious problem in many southern parts of the United States, affecting tens of thousands of people. The great majority of the cases were women, mostly housewives, and typically with previously good health. The disease occurred mostly among poorer people whose diet consisted mainly of the cheapest available food, maize, supplemented with salt pork, lard, and molasses. Records showed that there were nearly 16 000 cases in eight states of the South from 1907 through 1911, with a death rate of 39.1%. It was the leading cause of death in hospitals for the insane. Pellagra declined sharply between 1930 and 1933 mainly due to improved agricultural and economic conditions in the country. In the 1960s and 1970s pellagra was still considered a public health problem in many countries: Egypt (Barret-Connor, 1967; Hanafy et al., 1968); southern Africa in countries like Lesotho and Malawi during the 'hungry' season from October until February, affecting up to 15% of the population (Aykroyd, 1971); South Africa where 50% of the Bantu who were examined in clinics for a number of diseases presented with skin manifestations of pellagra (Pretorious, 1968); Angola (Adrian et al., 1973); in the deltas of some rivers in China (Barret-Connor, 1967); and India (Gopalan, 1969; Aykroyd, 1971).

The virtual disappearance of pellagra as an endemic health problem in recent years can be attributed mainly to a general rise in the standard of living of small farmers, accompanied by greater diversification of the diet. While pellagra is historically a maize-eater's disease, it has also been reported in people eating jowar (*Sorghum vulgare*). Pellagra in an endemic form among sorghum eaters was described among poor agricultural labourers in Hyderabad (Gopalan and Srikantia, 1960). *Sorghum vulgare* is widely consumed, particularly in Africa, and it was extensively cultivated in Europe in the 18th century. However, there does not seem to be any record of the occurrence of pellagra in sorghum eaters, apart from the outbreak referred to above. Pellagra, in conjunction with other micronutrient deficiencies was also recently recorded and reported among Bhutanese refugees in Nepal consuming a diet based on polished rice. For a description of the most recent outbreaks in emergency-affected populations, see the section on **Recent outbreaks of pellagra and lessons learnt** beginning on page 18.

Prevention and treatment

While no striking differences in the nutritive properties of maize and those of other cereals were revealed by laboratory analysis in the 1800s and early 1900s, some authorities advocated reducing the production of maize and replacing it with wheat, barley and other cereals on the grounds that in some way maize caused pellagra.

Historically, one of the prevalent beliefs was that maize contained a toxin which caused pellagra. In 1910, the Italian authorities set up rural bakeries, in order to make cheap wheat bread available to people whose staple was maize. These rural bakeries undoubtedly made a significant contribution to pellagra prevention in Italy (WHO, 1970).

There was a marked tendency for pellagra to recur year after year in the same individuals. This occurred mostly in the late spring and early summer, which suggested an association with poverty and insufficiency of nutritious foods as diet was most likely to be restricted during the winter season; those affected consumed little milk, meat, and other foods of animal origin. In addition, the seasonal appearance of pellagra in spring and summer was often ascribed to stronger sunlight causing the outbreak of the skin rash.

Although a number of theories about the cause of pellagra prevailed, there were rarely disagreements about appropriate treatment of the disease. A good varied diet containing plenty of milk and meat was universally regarded as an essential part of treatment.

Pellagra

Signs and symptoms

Clinical manifestations of pellagra

Pellagra is a multiple-deficiency disease associated with diets providing low levels of niacin and/or tryptophan and often involving other B vitamins resulting in changes in the skin, gastrointestinal tract, and nervous system. The characteristic manifestations appear as dermatitis, diarrhoea and dementia ("the three Ds") and can lead to death (the fourth D). The description of the clinical manifestations of pellagra given below is taken principally from the following source: World Health Organization, *Nutrition in Preventive Medicine*, WHO Monograph Series No. 62, 1976.

Skin lesions

The dermatological changes, called "pellagra", are usually the most prominent. The lesion starts with erythema resembling sunburn, which is symmetrically distributed on the parts of the body exposed to direct sunlight—the backs of the hands and forearms up to the rim of the sleeves ("pellagra gloves"), the feet and legs up to the edge of the trousers or skirt, the forehead, and on the nose and cheeks in a butterfly distribution. The front side of the upper part of the neck shadowed by the chin escapes, but the lower part of the neck and the upper part of the chest are affected according to the width and shape of the neck of the shirt ("Casals necklace"). The genitals and pressure points may

also be affected.

Pellagra dermatitis is characterized by a clear zone of demarcation between the affected and normal skin. The erythema is accompanied by burning and itching; scaling and exfoliation follow in the rims, beginning from the centre of the lesion and spreading towards the periphery. The affected skin is hyperpigmented.

Gastrointestinal lesions

Pellagra patients usually complain of nausea, excessive salivation, a burning sensation in the epigastrium, and diarrhoea. The mouth is sore and the tongue is brilliant or beef red in colour and swollen. Cheilosis and angular stomatitis are seen in niacin deficiency, although these may, in part, be a result of a simultaneous riboflavin deficiency. Inflammation spreads through the gastrointestinal tract, with chronic gastritis and diarrhoea; bacterial infections may aggravate the diarrhoea and may also cause anaemia.

Nervous lesions

Early neurological symptoms associated with pellagra include anxiety, depression, and fatigue; later symptoms include apathy, headache, dizziness, irritability and tremors. In early cases the manifestations are psychoneurotic; later, lesions affect the nerves. Peripheral neuritis has been reported in some pellagra cases and this could not be cured by niacin alone, suggesting a secondary deficiency of thiamine or vitamin B_{12}. Mental aberrations may pass to dementia: about 4-10 % of chronic pellagra patients develop mental symptoms. In acute niacin deficiency an encephalopathy is found which closely resembles Wernicke's syndrome.

Early symptoms/mild niacin deficiency

Loss of weight, strength, and appetite precede the appearance of any diagnostic dermal lesions. During this early stage, ill-defined disturbances of the alimentary tract, including indigestion, "dyspepsia", diarrhoea or constipation, as well as weakness, lassitude, irritability and distractability develop without obvious reason.

Diagnosis of pellagra

Pellagra is usually a complex disease often involving deficiencies of protein, and other members of the vitamin B-complex besides niacin, i.e. riboflavin and pyridoxine. Niacin nutrition is further complicated by the ability of the amino acid, tryptophan, to serve as a precursor of nicotinic acid, and by the variable biological availability of bound forms of the vitamin in foods. The main criteria for diagnosing pellagra are:

- A history of dietary inadequacy of available niacin and of the amino acid, tryptophan, a precursor of nicotinic acid. However, dietary surveys can be misleading with respect to niacin nutrition if not all the factors are considered.

- Clinical manifestations characteristic for pellagra (Table 2 summarizes the main symptoms).

- Biochemical indices, i.e. levels of urinary excretion of products of niacin metabolism, most commonly N^1-methylnicotinamide (N^1-MN) and 2-pyridone.

Table 2. Clinical manifestations of pellagra in adults

Body system	Typical lesion
Skin	Initial change: temporary redness like that of sunburn
	Hyperpigmentation, hyperkeratosis, and thickening of skin
	Dark red or purplish eruption followed by desquamation
	Lesions are usually bilateral and symmetrical involving areas of friction and exposure, i.e. face, neck, hands and feet; there is usually a clear demarcation of the lesions from the normal skin
Mouth	Gingivitis, stomatitis and a fiery glossitis, the tongue being swollen and beefy red
Intestinal tract	Diarrhoea
Central nervous system	Progressive dementia, with apprehension and confusion in the early stages progressing to severe derangement with maniacal outbursts

The clinical diagnosis of pellagra is usually clear in people with dermatosis. However, the skin lesions may be minimal or absent if the skin has not been exposed to sunlight or minor trauma. In addition, niacin deficiency is commonly associated with deficiency of other nutrients, i.e. protein, riboflavin, pyridoxine, thiamine, folic acid, vitamin A, magnesium, potassium, iron, and zinc (Feldman, 1988) which can further complicate the clinical assessment of pellagra. These associated deficiencies contribute to some of the following clinical findings in pellagra: cheilosis, stomatitis, glossitis, encephalopathy, peripheral neuritis. In Malawi in 1989/1990, in addition to dermatitis (rash on two or more different areas of the skin exposed to sunlight), approximately 60% of cases had stomatitis, 19% had diarrhoea, and 8% had mental disorders.

The classical symptoms of pellagra are usually only seen in adults and are generally not well developed in infants and children. Anorexia, irritability, anxiety, and apathy have been observed frequently in young children who have pellagra (Nelson, 1960). Like adults, children who have pellagra often have evidence of other nutritional deficiency diseases. Pellagra has very frequently been incorrectly diagnosed in patients having malnutritional lesions simulating pellagra. The three main dermatoses that have been confused with pellagra are shown in Table 3 (WHO, 1976;

McLaren, 1988). The diagnosis of pellagra should rest primarily on the specific skin lesions with their typical distribution and characteristic zone of demarcation. The dietary history of the people and an investigation of food habits will assist the diagnosis of pellagra.

Table 3. Malnutritional dermatoses simulating skin lesions in pellagra

Dermatosis	Symptoms	Contrast to pellagra
Subacute dermatosis ("chapped" skin)	Fissured, hyperkeratotic, hyperpigmented skin on the dorsum of hands, wrists, forearms, feet and legs Very common in children and adolescents Seen particularly in winter	No clear area of demarcation, no rim scales, no denudation Can be cured with a glycerine lotion
Skin xerosis	Thin and atrophic epidermis Generalized dryness and bran-like desquamation Usually seen on legs	No clear zone of demarcation Due to chronic nonspecific malnutrition
"Flaky paint" dermatosis of kwashiorkor	Areas of desquamation and pigmentation, usually extensive, often bilateral Occurs in young children and infants Lesions characteristically found on the buttocks and backs of the thighs	Lesions occur on skin mostly unexposed to the sun Affected area has no clear line of demarcation Age incidence not typical for pellagra

Apart from the clinical signs of pellagra, a few laboratory methods are available for assessing niacin status. The general procedure is to measure one or more **urinary excretion products of niacin metabolism**, most commonly N^1-methylnicotinamide (N^1-MN) and 2-pyridone according to one or both of the following parameters:

- Urinary excretion of N^1-methylnicotinamide (mg per g creatinine) or (mmol per 24 hour urine)

- Ratio of niacin metabolites in urine:

$$\frac{\text{2-pyridone}}{N^1\text{-methylnicotinamide}} < 1$$

The interpretation of the biochemical parameters cited above is rather equivocal, but in the absence of other available tests, provisional criteria are suggested in Table 4. An excretion rate per g of urinary creatinine in random samples of fasting urine that exceeds 1.6 mg for adults and 2.5 mg for pregnant women in the third trimester has been thought to indicate adequate niacin nutritional status.

Table 4. Guidelines for the interpretation of urinary excretion of niacin metabolites by individuals

Parameter/ Population group	Deficient	Low	Acceptable	High
N^1-methylnicotinamide *mg per g* Creatinine, in 24-hr sample:				
Adults (men; women, non- pregnant or 1st trimester)	<0.5	0.5-1.59	1.6-4.29	4.3
Pregnant: 2nd trimester	<0.6	0.6-1.99	2.0-4.99	5.0
3rd trimester	<0.8	0.8-2.49	2.5-6.49	6.5
2-pyridone:N^1-methylnicotinamide <1	<0.5	<1.0	1.0-4.0	
Dietary intake of niacin-equivalents *(mg/day)*	<5	5-9	10	

Sources: First two rows (boxes) : Sauberlich et al., op. cit., 1974. Last two rows: Dillon JC et al. Annals of Nutrition and Metabolism, 1992, 36: 181-185,   Malfait P et al. International Journal of Epidemiology, 1993, 22: 504-511.

It should be noted that the above-mentioned assays are reliable tests for the dietary intake of niacin and tryptophan, but not necessarily a diagnosis of pellagra. Nonetheless, a study of 10 Mozambican women living in refugee camps in Malawi and displaying clinical symptoms of pellagra found a good correlation between the ratio of 6-pyridone (similar to 2-pyridone) and N^1-MN and clinical symptoms of niacin deficiency (Dillon et al., 1992).

More recently, high-pressure liquid chromatography (HPLC) techniques have been applied to plasma and urine samples to measure nicotinic acid, nicotinamide, and their metabolites. There have been reports on the use of modified microbiological assay procedures for determining the biologically active forms of niacin in plasma and blood. For laboratories lacking appropriate chromatography equipment, an extremely sensitive fluorometric procedure has been reported for the measurement of N^1-MN and nicotinamide in serum (Sauberlich, 1984).

In practice, however, laboratory assessment of niacin nutritional status is still limited to the measurement of niacin metabolites in urine. The availability of HPLC simplifies the process and enhances the speed, accuracy, and sensitivity of determinations of 2-pyridone and N^1-MN in urine.

An attempt has been made to define mild, moderate and severe public health problems in terms of percentages of a population with clinical or biochemical signs of niacin deficiency and in terms of dietary intakes of niacin equivalents (see Table 5). However, these criteria have not been officially or formally endorsed by any recognized scientific or public process.

Table 5. Provisional criteria for severity of public health problem of niacin deficiency

Indicator	Severity of public health problem*		
	Mild	**Moderate**	**Severe**
Clinical signs:	1 clinical case; <1%	1–4%	= 5%
Urinary N^1-methylnicotinamide mg per g creatinine: <0.50	5-19%	20-49%	= 50 %
Ratio $\frac{2\text{-pyridone}}{N^1\text{-methylnicotinamide}}$ <1.0	5-19 %	20-49 %	= 50 %
Dietary intake of niacin-equivalents <5mg/day	5-19 %	20-49 %	= 50 %

Source*: Management of nutrition in major emergencies,* World Health Organization, Geneva, 2000.
*Percentage of population in age group concerned.

Niacin

Discovery of the role of niacin and tryptophan in pellagra

Pellagra was considered to be an infectious disease until the early 20th century. It was only in 1917 that Joseph Goldberger succeeded in proving that the disease was caused by nutritional deficiency (Jukes, 1989). Dogs, used as experimental animals, developed a deficiency disease called "black tongue" when fed diets similar to those consumed by people with pellagra, and it was the cure of the "black tongue" in dogs that eventually led to the identification of the "anti-pellagra" vitamin. In 1937, Professor C. Elvehjem discovered that dogs with "black tongue" responded dramatically both to nicotinic acid and to nicotinamide which was isolated from liver extracts that had previously been found to have relatively high anti-pellagra activity. The acid and the amide were tested with pellagrins and gave similarly dramatic results, commonly including almost complete relief of the irritation of the mucous membrane of the mouth and digestive tract and the disappearance of acute mental symptoms within 48–72 hours (Spies et al., 1939).

The studies carried out showed that the typical inadequate diets on which pellagra developed were deficient in other vitamins as well. For instance, peripheral neuritis shown by some pellagrins responded only to thiamine while a characteristic angular stomatitis of the lips and a more general feeling of ill health and weakness could be corrected with riboflavin.

However, there was still confusion about the precise cause of pellagra as analyses of the diets of poor rice-eaters in India, among whom pellagra was not a problem, found nicotinic acid values even lower than in the diets of Romanians who had pellagra (Aykroyd and Swaminathan, 1940).

It was later established that the mixed proteins of maize are particularly low in tryptophan, and that it is this amino acid, which is present at higher levels in other cereals and in animal proteins, that spares the requirement for nicotinic acid. In a controlled trial, the addition to the diet of 30 molecules of tryptophan was found to be roughly equivalent to that of 1 molecule of nicotinic acid, or 60:1 in terms of weight (Goldsmith et al., 1961). This explained the high pellagra-protective value of milk and other animal products—and the 'inferiority' of maize to other cereals.

Properties

Chemistry

Niacin is the generic descriptor for pyridine 3-carboxylic acid and derivatives which exhibit qualitatively the biological activity of nicotinamide. The term niacin may therefore refer to either nicotinic acid or sometimes, more vaguely, to the total of nicotinic acid and nicotinamide in the diet. Both compounds are stable, white crystalline solids. Nicotinamide is more soluble than nicotinic acid in water, alcohol, and ether.

Because several forms of niacin are available to the body, and tryptophan can be converted to niacin at the ratio of 60 mg of tryptophan to 1 mg niacin, the term "niacin equivalent" is used to describe the contribution to dietary intake of all active forms of niacin. Niacin is a member of the B-vitamin complex group.

Physiology

Both acid and amide forms of the vitamin are readily absorbed from the small intestine. In the tissues, most of the vitamin is present in the metabolically active forms of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are formed in the blood, kidney, brain, and liver. The main storage organ, the liver, may contain a significant fraction of the bioavailable vitamin, but there is little storage of niacin as such (Jacob, 1990).

The vitamin is absorbed nearly completely at pharmacological concentrations. The presence or absence of food in the gut appears to have no effect on niacin absorption. The drugs Rifampin and Isoniazid (for tuberculosis) inhibit the absorption of niacin. Niacin is excreted as a variety of water-soluble metabolites; the major ones being N^1-methylnicotinamide and 1-methyl-6-pyridone 3-carboxamide. Humans normally excrete daily up to 30 mg of total niacin metabolites of which 7–10 mg are N^1-methylnicotinamide (Combs, 1992).   At high rates of niacin intake, the vitamin is excreted predominantly (65–85% of total) in unchanged form.

The metabolically active forms of niacin—NAD and NADP—are synthesized from three precursors: nicotinic acid, nicotinamide and tryptophan. The conversion efficiency of tryptophan to niacin is reduced under conditions of pyridoxine (*vitamin B6*) deficiency. It has also been suggested that deficiency of *zinc* and *copper* which are essential cofactors of key enzymes, may impair tryptophan-niacin conversion.

Metabolic functions

Niacin is vital to oxidation of all living cells, where, as a functional group of the coenzymes NAD and NADP, it is involved in the release of energy from carbohydrate, fat and protein, and the synthesis of proteins, fats, and pentoses for nucleic acid formation. Tissues with a high respiration rate, such as the central nervous system, are therefore the most extensively affected by deficiency.

Nicotinic acid also has a pharmacological role in which it is an effective hypolipidaemic agent. It is particularly effective, at levels of daily consumption of the order of 1 g, in lowering the concentrations in the blood of low and very low density protein (LDL and VLDL) cholesterol and in increasing the concentration of high density lipoprotein (HDL) cholesterol.

Recommended daily allowance (RDA)

Calculating RDA for niacin

Intakes of less than 7.50 mg niacin per day have been associated with occurrence of pellagra but these studies were made before the contribution of tryptophan to the formation of niacin was fully acknowledged (WHO, 1967). It has been shown that 60 mg of tryptophan can be converted by the human body into approximately 1 mg of nicotinic acid (Goldsmith et al., 1961). In recognition of the contribution of tryptophan to niacin nutriture the term "niacin equivalent" was introduced, which permitted the calculation of the combined effects of both niacin and tryptophan.

Essentially all the information used in estimating niacin requirements comes from studies conducted more than 30 years ago on adult men and women who were fed diets deficient in niacin equivalents but which were otherwise complete (Goldsmith et al., 1952; Horwitt et al., 1956). The studies compared the intake of niacin equivalents to the incidence of pellagra and showed that 4.4 niacin equivalents per 1000 kcal or 9.2 to 12.3 niacin equivalents daily for 38 to 87 weeks was the minimum requirement for the prevention of the clinical deficiency in adults (Annex, Table A). Depletion-repletion studies further showed that an intake of 5.5 niacin equivalents per 1000 calories per day was an intake at which no clinical signs were observed and at which some of the subjects showed an increase in urinary excretion of niacin metabolites. The inclusion of a factor to account for individual variation led to a recommended intake of 6.6 niacin equivalents per 1000 kcal per day.

RDA for adults

The niacin recommendation for adults of all ages is 6.6 niacin equivalents per 1000 kcal and not less than 13 niacin equivalents at caloric intakes of less than 2000 kcal (WHO, 1967; National Research Council [U.S.], 1989). The adequacy of this allowance has recently been confirmed in young men (Jacob et al., 1989). On the basis of calorie requirements for adults, the recommended intake would provide 21.1 niacin equivalents for the "reference man" (3200 kcal) and 15.2 niacin equivalents for the "reference woman" (2300 kcal).

RDA for pregnant and lactating women

There is no evidence that the requirement for niacin equivalents is increased in pregnancy and lactation above that satisfied by the recommended intake of 6.6 niacin equivalents per 1000 kcal per day (WHO, 1967). The United States National Research Council, however, recommend an additional 5.0 niacin equivalents daily for lactating women based on an increase in energy expenditure to support lactation as well as the loss of 1.5 mg niacin/850 ml breast milk.

Despite the possible involvement of a biological mechanism that enhances the ability of pregnant women to convert tryptophan to niacin derivatives (Wolf, 1971), an increased niacin intake during pregnancy is recommended because of increased energy requirements. An absolute increase of 2 niacin equivalents daily is recommended on the basis of an increased energy requirement of 300 kcal/day (National Research Council [U.S.], 1989).

RDA for infants and children

The recommended intake of 6.6 niacin equivalents per 1000 kcal daily is accepted for children of 6 months or older. For infants up to 6 months, it is accepted that breastfeeding by well-nourished mothers will supply adequate niacin equivalents to fulfil the needs of this age group, i.e. 8 niacin equivalents/1000 kcal (WHO, 1967). Table 6 shows the daily intakes of niacin equivalents for different age groups recommended by the Joint FAO/WHO Expert Group (1967) and based on the average daily calorie intakes.

Table 6. FAO/WHO recommended daily allowances for niacin equivalents

		Energy intake (kcal/day)	Niacin equivalents *
Infants	(0–6 mths)	-	Breastfeeding by a well-nourished mother
	(7–12 mths)	1000	6.6
Children	(1 yr)	1150	7.6
	(2 yrs)	1300	8.6
	(3 yrs)	1450	9.6
	(4–6 yrs)	1700	11.2
	(7-9 yrs)	2100	13.9
	(10–12 yrs)	2500	16.5
Adolescents (13–15 yrs)			
Girls		2600	17.2
Boys		3100	20.4
Adolescents (16–19 yrs)			
Girls		2400	15.8
Boys		3600	23.8
Adults			
Women		2300	15.2
Men		3200	21.1

* A niacin equivalent is 1 mg niacin or 60 mg tryptophan.

Factors affecting requirements for niacin

The following factors have been found to influence niacin requirements:

• Composition of the diet

Pellagra is a multi-factorial dietary deficiency rather than a disease of insufficient intake of niacin *per se*. It is most often found in people who consume maize, which is deficient in *tryptophan* and in which the niacin is in a form of low bioavailability (see section on food sources of niacin). Reports suggest that when tryptophan is a limiting factor, the usual conversion to niacin may not occur. In addition to tryptophan and *pyridoxine* supplies being important determinants of niacin status, it has been suggested that excess intakes of the amino acid *leucine* may antagonize niacin synthesis and/or utilization and, thus, also may be a precipitating factor in the etiology of pellagra (Srikantia, 1978). However, more recent work does not support this view. Leucine supplements fed to rats did not aggravate their niacin-deficient condition. Another amino acid, *isoleucine*, has also been implicated in the pathogenesis of the disease, and it has been suggested that the leucine–isoleucine ratio in the diet is connected etiologically with pellagra.

• Climate

Although the skin lesions of pellagra are nearly always more easily seen in areas of the skin exposed to sunlight, climate *per se* has not been associated with changes in the requirement for niacin (WHO, 1967).

• Body weight

Niacin requirement will vary with body weight to the extent that calorie requirement is related to body weight. Table 7 shows the recommended niacin intakes for adults of different body weights based on the "reference man" and "reference woman" (WHO, 1967).

Table 7. Recommended daily intakes of niacin equivalents for adults of different body weights

Men*	45	50	55	60	65	70	75	80
(mg/day)	16.3	17.5	18.7	19.9	21.1	22.3	23.5	24.6
Women*	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**
(mg/day)	11.0	12.1	13.2	14.2	15.2	16.2	17.2	18.2

* Body weight (kg)

- ## Physical activity

It has been noted that pellagra is more frequently observed among agricultural workers. While this may be associated with an increased calorie intake without a proportional increase in niacin intake, it seems probable that this association is due to the aggravation of dermal lesions by exposure to sunlight. No adjustment in the basic recommended intake (6.6 niacin equivalents per 1000 kcal) is suggested for physical activity (WHO, 1967).

- ## Chronic conditions

There are rare cases when patients in good nutritional circumstances present with pellagra. The main factors responsible for such cases of secondary pellagra are the following: (a) *malabsorption*: malabsorption is usually associated with jejuno-ileitis, gastroenterostomy and Crohn's disease. Gastrointestinal changes play an important part in the production or deterioration of pellagra (Stratigos & Katsambas, 1977); (b) *chronic alcoholism*: pellagra in chronic alcoholics is usually due to a combination of their diets being very limited in niacin and tryptophan, and due to an incomplete absorption of the already poor diet (Valyesevi, 1989); (c) *abnormalities of tryptophan metabolism*: in Hartnup's disease there is a block in the tryptophan–nicotinic acid pathway which can lead to pellagra due to nicotinic acid deficiency (Castiello & Lynch, 1972; DesGroseilliers, 1976); (d) *chemotherapeutic agents*: the chemotherapeutic agents known to provoke pellagra are the following: Isoniazid, 6-Mercaptopurine, 5-Fluorouracil and Chloramphenicol (Stratigos & Katsambas, 1977).

Niacin toxicity

In general, the toxicity of niacin is low. There are, however, side effects that have been seen in the clinical use of high doses of the vitamin. These include (Combs, 1992; Pfeiffer, 1975; Doyle et al., 1993):

- flushing, i.e. severe redness in the blush area;

- itching urticaria (hives);

- severe gastrointestinal discomfort, i.e. heartburn, nausea, vomiting;

- hyperuricemia (nicotinic acid may precipitate an attack of gout because it competes with the excretion of uric acid; and

- altered glucose tolerance.

Clinical trials have shown no adverse reactions at 500 mg nicotinic acid/day, but with significant reactions at 1000 mg/day (gastrointestinal effects for unmodified nicotinic acid, and mild liver toxicity for slow-release nicotinic acid). Liver toxicity and serious gastrointestinal effects occur in a significant fraction of persons consuming 1000 mg or more per day of nicotinic acid. Gastrointestinal side effects may include indigestion, nausea, vomiting and diarrhoea. More severe reactions may produce jaundice, fatigue, or, rarely, fulminant liver failure (Shrimpton, 1997).

Supplementation for prevention and treatment

Prevention

An average intake of 15–20 mg of niacin per person daily prevents pellagra for all age groups. Mass administration of niacin as a preventive measure is not practical as niacin, like all water-soluble vitamins, is not stored in the body and would only be effective if administered daily.

Treatment

The administration of niacin has a dramatic curative impact on pellagra. The daily recommended dose is 300 mg of nicotinamide in divided doses, and treatment should continue for 3–4 weeks. Large therapeutic amounts of niacin should be provided in the form of nicotinamide, which does not produce the side effects encountered when nicotinic acid is administered. Acute inflammation of the tongue and mouth, as well as diarrhoea, subside in a few days. The dementia and dermatitis usually improve significantly within the first week of therapy. In chronic cases, a longer recovery period is required, but appetite and general physical health improve rapidly. It is also recommended to administer a vitamin B complex preparation or a yeast product since patients with pellagra very often have a deficiency of other B vitamin compounds.

Sources of niacin and its stability in foods

Availability in foods

Niacin is widely distributed in plant and animal foods. Good sources are bakers' yeast and meats (including liver), cereals, legumes and seeds but significant amounts are also found in many other foods such as milk, green leafy vegetables, and fish, as well as coffee and tea. Niacin occurs in plants mostly as nicotinic acid and in animal tissues mostly as nicotinamide.

In plants niacin is found mostly in a bound form (sometimes referred to as niacytin or niacinogen) affecting its availability in the diet. In maize, niacin is present in covalently bound complexes with small peptides and carbohydrates and is therefore unavailable when eaten. The bioavailability of the bound form of niacin can be improved substantially by hydrolysis with a mild alkali. It has long been a tradition in Central America to soak maize in lime-water prior to the preparation of tortillas. This practice effectively liberates the bound niacin and appears to be responsible for effective protection against pellagra in that part of the world. In other plant foods, the bound niacin is heat-labile and the niacin can be released by heating. Thus, the roasting of coffee beans increases the available nicotinic acid content in coffee from 20 to 500 mg/kg coffee beans (Combs, 1992). This practice might have contributed to the prevention of pellagra in South and Central America along with the regular consumption of beans that are good sources of bioavailable nicotinic acid.

The nutritional adequacy of diets with respect to niacin involves not only the level of the preformed vitamin, but also that of the essential amino acid, tryptophan. A substantial amount of niacin can be

synthesized from tryptophan, although the efficiency of that process is relatively low (60 mg tryptophan produce 1 mg equivalent of niacin). The degree to which *de novo* synthesis of niacin from tryptophan supplements dietary niacin intake depends on the quantity and quality of the protein ingested. With protein deprivation tryptophan is used preferentially to maintain nitrogen balance, and only thereafter utilized for niacin synthesis (Vivian et al., 1958). Because most proteins contain about 1% tryptophan, it is theoretically possible to maintain adequate niacin status on a diet devoid of niacin but containing >100 g protein.

Table B in the Annex shows the niacin equivalents (one niacin equivalent is equal to either 1 mg niacin or 60 mg tryptophan) of several foods. It is now known why milk, which contains little niacin, prevents pellagra, and why consumption of rice, which contains less niacin than maize, as a staple crop, does not lead to pellagra. Milk and rice both have proteins with a higher tryptophan content than maize, and the niacin present is in a more bioavailable form. Maize has a low tryptophan content and a relatively low niacin content which, in addition, is in the bound form so that only about 30% is bioavailable.

Stability in food processing and food preparation

Both nicotinic acid and nicotinamide are stable in the presence of atmospheric oxygen, acids, light and heat, and also have a marked resistance to ionizing radiation. In normal food preparation, niacin is hardly destroyed at all, e.g. 5% niacin is lost during baking. However, it can be washed out by water, e.g. during blanching and boiling, when up to 40% of the niacin is lost. If the cooking water is not discarded, the overall losses remain minimal. Negligible amounts are lost in the pasteurization, sterilization or drying of, for example, milk.

However, nicotinic acid losses during the milling and processing of cereals can be large. Milling of wheat to produce a white flour reduces to a minimum the content of bran and germ. These are valuable sources of nicotinic acid and other micronutrients. Whole wheat bread contains five times more nicotinic acid than does white bread. The degermination of maize before milling reduces the weight of the maize meal by only 18%, but reduces both the tryptophan and the niacin to about one half of the original values (see Table 8).

Table 8. Changes in niacin and tryptophan contents produced by degermination of maize

	Total weight (g)	Tryptophan (mg)	Niacin (mg)*
Whole maize	100	75	1.5
Maize meal (degermed)	82	30	0.82
Germ	12	36	0.52
Bran	6	8	0.18

* Niacin mainly in the bound form.
Source: adapted from Carpenter, 1981

The stability of niacin in food is good compared to vitamins like vitamin C, A , and B12. Losses of

niacin, e.g. in a milk-based fortified drink powder after 12 months or in a multivitamin tablet after 30 months is in the order of 10% compared to over 30% for the other vitamins (Berry Ottoway, 1993).

Fermentation

Fermentation is the result of the activity of microorganisms (yeasts, moulds or bacteria) as they utilize the organic components of food to obtain energy for growth. It increases protein content and improves its quality and digestibility; increases vitamin levels and mineral bioavailability; and reduces certain toxic substances. Fermented foods usually belong to the categories of cereal products, dairy products, and beverages. They constitute important components of diets in many parts of the world, for example South-East Asia and parts of Africa.

Increased nutritive value (increases in the biologically available amino acids including tryptophan, and improved amino acid balance) of maize meal is achieved by fermentation with yeasts (Wang and Fields, 1978). The niacin content and the bioavailablity of the niacin in the fermented product was, however, not analysed in this study. Studies carried out by Murdoch and Fields (1984) showed no differences between the niacin content of natural lactic acid fermented whole maize meal and unfermented whole maize meal. However, other studies showed that the fermentation of whole grain maize in West Africa resulted in an increase in niacin and other vitamins as well as an increase in tryptophan and lysine (Umoh and Fields, 1981). Akinrele (1970) also reported that niacin levels increased during the traditional method of *ogi* preparation (fermented maize using lactic acid bacteria and yeasts) in Nigeria. The contradiction in findings can be attributed to the difference in substrates and microflora used in the fermentation processes.

Van Veen and Steinkraus (1970) reported that niacin increased nearly 7-fold during the preparation of Indonesian *tempeh,* i.e.from 0.9 mg niacin/g soybeans to 6.0 mg niacin/g *tempeh. Tempeh* is made by fermenting dehulled, partially cooked soybeans with molds of the genus *Rhizopus*. Beverages prepared from cereals or fruit that are left to ferment naturally, usually have high yeast contents, e.g. palm wine, the fermented sap of palm trees, has a naturally high yeast (therefore also niacin) content, and in Nigeria it is even used in the manufacture of local bread (Uzogara et al., 1990).

Germination

Germination is the sprouting of cereal and legume grains brought about by soaking in water, which stimulates metabolic activity as the seed starts to grow. As soon as the seed is hydrated a number of complex chemical changes occur, including the synthesis of vitamins, the most important ones being niacin, riboflavin and vitamin C (Chen et al., 1975; Lay and Fields, 1981).

Studies carried out by Lay and Fields (1981) showed that sprouts of germinated maize were significantly higher in niacin, riboflavin and ascorbic acid than non-germinated maize. Niacin increased 3-fold and 1.8-fold in sprouts and de-sprouted maize after germination. The niacin content increased from 2.46 mg niacin/100 g in non-germinated maize to 4.38 mg niacin/100 g in germinated de-sprouted maize and to 7.51 mg niacin/100 g in the sprouts after germination.

Other studies found that after 5–6 days germination of oats, wheat, barley and maize, the content of niacin increased 6, 2, 2, and 4 times, respectively. Wang and Fields (1978) and Taur et al. (1984)

reported an increase in the amino acids tryptophan, lysine and methionine in maize and sorghum germinated for 5 days at 25°C when compared to the non-germinated products. The brewing of beer involves a germination as well as a fermentation process—usually of barley.

Adding niacin to foods

The fortification of food with micronutrients is a public health measure to prevent overt and subclinical deficiencies of vitamins, minerals and trace elements. According to the Codex Alimentarius Commission 1987, essential nutrients may be added to foods:

- to replace losses that occur during manufacture, storage and handling of food (restoration);
- to ensure nutritional equivalence in imitation or substitute foods;
- to compensate for naturally occurring variations in nutrient levels (standardization);
- to provide levels higher than those normally found in a food (fortification); and
- to provide a balanced intake of micronutrients in special cases (dietetic foods).

In the United States, a policy of fortifying white wheat flour and subsequently maize meal, with niacin, thiamine and riboflavin was adopted in 1941 and has been standard practice in the United States and many other countries ever since. The greatly reduced incidence of pellagra in the United States has sometimes been attributed to the fortification of cereals with niacin.

Fortification of cereals was proposed in South Africa at the end of the 1970s. As consumer preferences are crucial in any fortification programme, acceptability trials were carried out in 1983 to assess whether consumers would discriminate against maize meal that had been fortified with niacin, riboflavin and folic acid. No significant discrimination against the fortified product was detected and the authors of the study recommended immediate, government-enforced fortification of maize meal in South Africa (Walker et al., 1983). A number of countries currently add niacin, among other micronutrients, to cereal products such as white rice, maize meal, corn grits, pasta products, bread, and breakfast cereals. Table C in the Annex shows the levels of niacin added to wheat flour in different countries. Niacin is relatively stable and theoretically any food can be fortified with the vitamin, e.g. soft drinks, fruit juices, biscuits (Bauernfeind & LaChance, 1991).

Recent outbreaks of pellagra and lessons learnt

Populations consuming maize or sorghum and little else are at risk of pellagra. Large numbers of poor people living in southern and eastern Africa may therefore be said to be at risk. Yet there is hardly any literature on recent pellagra cases in non-refugee populations although checks on rural health centre records in these regions frequently show cases of pellagra particularly during the 'hungry season'. Furthermore, micronutrient deficiency diseases may well occur in many populations who are consuming diets similar to those of refugees but who do not benefit from the same degree of nutritional surveillance.

Individual cases of the deficiency disease are occasionally found in chronic alcoholics, elderly widowers who have an improper food intake, and inpatients suffering from malabsorption. Tubercular patients who are on poor diets and on long-term treatment with the drug Isoniazid, may

sometimes show clinical signs of the deficiency. Pellagrous skin lesions have also been reported in the rare Hartnup disease, in which there exists a defect in the transport of tryptophan across mucosal cells resulting in malabsorption and renal loss of this amino-acid.

Mozambican refugees in Malawi

In 1989 the distribution of groundnuts in the general ration for Mozambican refugees in Malawi stopped and the level of available niacin in the food basket dropped. In addition, even though the distributed general ration had included beans as a source for tryptophan, the quality was often so poor that excessive cooking was necessary to make the beans edible which was often not feasible because of fuel shortages (Berry-Koch et al., 1990). Cases of pellagra appeared four months after groundnut distribution ceased and declined once groundnuts were returned to the food basket. Outbreaks occurred when the mean daily per capita quantity of niacin equivalents (NE) in the food distributed to the refugees was 7.9 mg NE per day (or <4.0 mg per 1000 kcal energy intake) instead of the daily amount of 12 mg niacin equivalents recommended by FAO/WHO (or 6.6 mg NE per 1000 kcal) (see Table 9b). The previously recommended ration with 60 g of groundnuts would have contained 11.4 mg NE per day which would still not have covered the basic requirements for the vitamin (see Table 9b). It should be noted that only 30% of the niacin in the maize was available so the available niacin equivalent (ANE) of maize and therefore of the whole ration was considerably less than the above mentioned NE. This is reflected in Table 9a.

Table 9a. Niacin, niacin equivalent (NE)[1] , and available niacin equivalent (ANE)[2] of daily recommended ration for Mozambican refugees in Malawi*

Food item	Quantity (g)	Niacin (mg)	NE (mg)	ANE (mg)
Maize flour	400	5.6	6.9	3.0
Beans, dried	60	1.4	1.4	1.4
Groundnuts	60	3.1	3.1	3.1
Sugar	20	-	-	-
Total			**11.4**	**7.5**

* recommended by UNHCR.
[1]The sum of niacin and 1/60 of the tryptophan (by weight).
[2]The total amount of niacin biologically available; in maize, this is calculated by adding 30% of the niacin and 1/60 of the tryptophan. All niacin in beans and groundnuts is bioavailable.

Table 9b. Niacin, niacin equivalent (NE)[1], and available niacin equivalent (ANE)[2] of daily rations distributed to Mozambican refugees in Malawi in 1990

Food item	Quantity (g)	Niacin (mg)	NE (mg)	ANE (mg)
Maize flour	400	5.6	6.9	3.0
Beans dried	40	1.0	1.0	1.0
Groundnuts	0	-	-	-
Sugar	20	-	-	-
Total			**7.9**	**4.0**

Source: Tables 9a and 9b adapted from Table 1 in CDC (1991).
[1]The sum of niacin and 1/60 of the tryptophan (by weight).
[2]The total amount of niacin biologically available; in maize, this is calculated by adding 30% of the niacin and 1/60 of   the tryptophan. All niacin in beans and groundnuts is bioavailable.

Most of the pellagra cases registered in the outbreak in Malawi in 1990 were adults aged 15–44, the incidence rate being highest among women, i.e. the female:male ratio was almost 8:1. The overall attack rate was 11.5 per 1000, the attack rate on persons > 5 years of age was almost ten times that in children < 5 years.   It was argued that as women were more likely to work outside than men, exposure to sunlight may have contributed to the higher incidence of clinical pellagra among women.

The following risk factors were identified in the 1990 outbreak of pellagra in Malawi (Toole, 1992; Centers for Disease Control, 1991):

- female sex;
- having an unemployed head of the household;
- residence in a closed camp rather than an integrated village;
- absence of groundnuts or fish in the daily diet;
- lack of a home vegetable garden or domestic poultry;
- home maize milling.

As an immediate response to the pellagra problem in Malawi, groundnuts were reintroduced into the general ration, nicotinamide was used to treat the clinical cases, and vitamin B complex tablets were distributed as a preventive measure to refugees living in camps (Centers for Disease Control, 1991).

When it became clear that dietary diversification in the form of increased groundnuts in the general ration was not being effective in eliminating pellagra in Malawi, bean meal was fortified at a level providing 100 mg of nicotinamide per 20 g of bean meal and distributed to the refugees in the general ration. Subsequently, in 1991, maize meal was fortified at local commercial mills so that approximately 70% of all maize flour distributed in the general ration in Malawi was fortified with nicotinamide, providing an average intake of 55 mg per person per day or, after cooking losses, approximately 40–45 mg per day (Toole, 1994).

Lessons learnt

- *Emergency affected populations dependent upon a maize-based diet should be provided with at least one niacin-rich food commodity in the general ration.*

- *The niacin content of the food basket for maize-dependent emergency-affected populations should be carefully monitored and if found to be low or marginal, a surveillance system for pellagra and other micronutrient deficiency diseases should be established.*

- *A longer-term solution for the complete eradication of pellagra may be the fortification of maize or bean flour with nicotinamide.*

Bhutanese refugees in Nepal

An outbreak of pellagra occurred among Bhutanese refugees in Nepal in 1994. Surprisingly this was a rice-eating population. The food basket at the outset of the refugee programme consisted of polished rice, dal, oil, salt and sugar, and fresh vegetables. This provided an adequate food basket in terms of calories and wasting among this population rapidly declined to 5%.

However, despite the regular supply of these food commodities and well managed water, health, and sanitation services in the camps, cases of beriberi were reported in September 1993 (Field Exchange, 1998). Following these reports, a surveillance system for micronutrient deficiencies was established. Within a short time cases of pellagra and scurvy were also reported (ACC/SCN, RNIS, Report Nos 5&8, 1994). Investigating teams identified several factors which were likely to result in micronutrient deficiencies in the camps. Some of these were:

- consumption of polished rice;

- provision of vegetables that had perished and lost much of their micronutrient content;

- unfavourable exchange rates for general ration commodities.

After the emergence of micronutrient deficiencies, the general food basket was modified to include micronutrient-enriched blended food at the rate of 40 g per day. This meant that the food basket was adequate for all nutrients except calcium, riboflavin, and vitamin A. The peak of the pellagra outbreak occurred in March 1994 when a rate of 0.57/10 000/day was recorded. This declined to zero in January 1995 and there were no reported cases thereafter (ACC/SCN, RNIS Report No. 10, 1995).

Lessons learnt

- *Pellagra can occur among food-aid dependent populations consuming rice as their main staple.*

- *Provision of fortified blended foods in the general ration, e.g. corn–soy blend (CSB), can completely eradicate pellagra.*

Refugee returnees to Mozambique

An outbreak of pellagra occurred among the population of Mutarara in Tete province in Mozambique between August 1995 and early 1996. The outbreak mostly affected refugee returnees from Malawi. The population of Mutarara district increased from 50 000 to at least 200 000 due to the returnee influx. A survey in November 1995 found a prevalence rate of pellagra of 1.4%. This meant that the number of cases of pellagra in the district in November was
between 1600 and 5400 (ACC/SCN, RNIS Report No 14, 1996). By May 1996 the number of cases had dropped considerably. This was believed to be due in part to the good rains and the long-awaited micronutrient-enriched corn–soy blend that was distributed via hospitals and nutrition centres to food-aid beneficiaries (ACC/SCN, RNIS Report No 16,1996).

Lessons learnt

- *Pellagra outbreaks can occur among maize-dependent non-refugee populations in the early phases of rehabilitation.*

- *Provision of fortified blended foods can have a marked impact on the outbreak.*

Emergency-affected population in Angola

The most recent large-scale outbreak of pellagra occured in Kuito, the capital of Bie province in the central highlands of Angola in the last half of 1999. The province had been engulfed in continuous civil conflict since June 1998. Almost half the population were Internally Displaced Persons (IDPs) sheltered in various sites around the town. The purchasing power of the resident population had rapidly decreased due to inflation, and the activities of most traders had been reduced due to the war. Food was being supplied by the international agencies to specific target groups, i.e. the IDPs and some categories identified as vulnerable (children under five, pregnant and lactating women and disabled persons). By November 1999 families with malnourished children, and families with pellagra cases were also categorized as vulnerable and in receipt of an emergency general ration (Field Exchange, 2000).

According to health professionals, pellagra had sporadically occurred at very low levels in the province prior to the outbreak. But in July 1999, an increase was seen and the phenomena became epidemic from August (Graph 1). The daily general ration distributed by international agencies comprised maize, peas, oil and salt providing 7.5–9.5 mg of niacin. The recommended daily intake is 12 mg. The case definition used for pellagra diagnosis was dermatitis on two different and symmetrical sites exposed to sunlight, or typical Casals necklace. Once the diagnosis was confirmed, patients were referred to the supplementary feeding centre where they received a standard protocol of nicotinamide 50 mg (adults = 3x2 tablets/day for 15 days; children = 3x1 tablet/day over 15 days), vitamin B complex tablets and a supplementary ration of CSB and dried fish (Field Exchange, 2000).

Graph 1. Number of Pellagra Cases admitted in the Supplementary Feeding Centre (SFC), Kuito, 1999
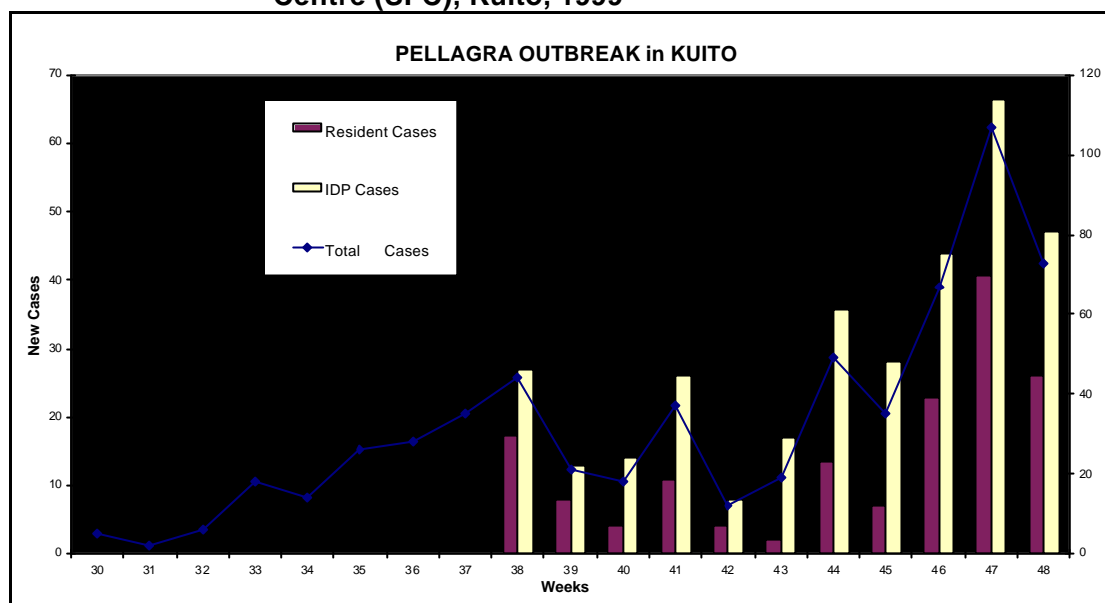
Source: Médecins sans Frontières, 1999

Week 48, the total number of cases (616) represented an attack rate in the town of 2.6 /1000 inhabitants (if estimated at 240 000).

The data showed that 83% of pellagra cases were female and that 85% of cases were over 15 years of age. Sixty-six percent of cases were IDPs (Table 10a). The attack rates at the end of November were 2.6/1000 inhabitants. Attack rates by age and sex are given in Table 10b.

Table 10a. Distribution of pellagra cases per main demographic characteristic, n = 571 cases, 1999

Distribution by sex	Male:	98	(17 %)
	Female:	473	(83 %)
Distribution by age	< 15 years:	86	(15 %)
	≥ 15 years:	485	(85 %)
Distribution by residential status	Resident:	196	(34 %)
	Displaced:	375	(66 %)

Source: Médecins sans Frontières, 1999.

Table 10b: Attack rates per main demographic groups, n = 571 cases, 1999

		IDP's n = 110,000 IDP's	Resident n = 130,000 inhab.	Total population n = 240,000 pop.
Male	< 15 y	0.8 / 1,000	0.5 / 1,000	0.65 / 1,000
	≥ 15 y	1.4 / 1,000	0.6 / 1,000	1.0 / 1,000
Female	< 15 y	1.2 / 1,000	0.4 / 1,000	0.8 / 1,000
	≥ 15 y	10.2 / 1,000	4.5 / 1,000	7.1 / 1,000
Total		3.4 / 1,000	1.5 / 1,000	2.4 / 1,000

Note: First cases of the epidemic have not been included, as data are not available.
Source: Médecins sans Frontières, 1999.

In view of the fact that the general food distribution did not provide enough niacin, and other sources

like CSB were not yet available, a distribution of vitamin B complex tablets to all women aged 15 and over was organized as an emergency response by humanitarian agencies present at the time. Thirty tablets were distributed to each woman. A nutritional survey conducted in December 1999 assessed compliance with intake of vitamin B-complex tablets by counting the number of tablets left in the distributed bag after a set number of days.

The survey found that 44.5% of women were compliant in the town and 42% in camps. Low compliance was due to a number of factors including confusion between vitamins and contraceptive tablets, the perception that intake of the vitamin increased feelings of hunger, and lack of understanding of the concept of prevention. Furthermore, 20% of women presented fewer tablets than expected, either due to sharing with other members of the family or because they took more than recommended.

The survey concluded that a vitamin B tablet distribution campaign does not seem to be the most effective solution to control a pellagra outbreak. Furthermore, targeting women with tablets was an emergency measure, but not a satisfactory option, as all strata of the population were probably deficient in niacin (MSF/ICRC, 1999). By January 2000, a number of important issues and lessons about the outbreak and response had been identified at multi-agency meetings (WFP/ICRC/MSF/UNICEF, 2000) held in Luanda and through discussion with knowledgeable experts.

- Although an average intake of 15–20 mg of niacin per person per day prevents pellagra for all age groups, the majority of the population in Kuito were exposed to malaria, diarrhoea, and an increased risk of other infections and therefore may have had a greater requirement.

- The fact that the general ration was deficient in many nutrients including all those implicated in pellagra, led to the conclusion that CSB would be the best food supplement to improve the intakes of a wide range of nutrients. Groundnuts and beans, although rich in niacin, have relatively low levels of riboflavin and pyridoxine, which are both required to convert tryptophan to niacin.

- Although the case definitions used ensured that the diagnosis was not in doubt, the actual numbers with niacin deficiency in the population were grossly underestimated. Children would be eating the same diet as adults and have the same proportionate requirements for niacin, but would not necessarily show the skin lesions of pellagra—although they may get diarrhoea. Classical signs are much less common in young children than in adults. There were many possible explanations for the high prevalence of pellagra among females over 15 years of age: demographic profile; differential health seeking behaviour; different sunlight exposure (men go bare-chested so will not get Casals necklace in sunlight); real dietary differences; different clinical expression of illness.

- In the longer term, a more appropriate solution should be found than supplementing the general ration with fortified CSB. Strategies used in similar situations have included fortification of the maize in local mills, and commercial fortification of maize in the country where needed or in the country of origin.

- A second vitamin B distribution targeted to everyone in Kuito was conducted at the end of

February/March 2000, because CSB had not yet been included in the general ration. The number of cases of pellagra began to decline markedly in February and March. This was probably due to a combination of factors—distribution of the vitamin tablets and a diversified WFP ration (including groundnuts). However, pellagra cases were beginning to reappear again by the end of April. Although WFP had been promising the delivery and addition of CSB to the general ration since early 2000, none had been distributed in the general ration by the end of May 2000 (Field Exchange, 2000).

Lessons learnt

- *Vitamin B tablet distributions can be used as a short-term measure to moderate a pellagra outbreak when it is impossible to improve the general ration. However, full compliance with a vitamin distribution may be problematic.*

- *Although groundnuts are niacin rich, they lack other nutrients which may also be implicated in a pellagra outbreak, e.g. pyridoxine and riboflavin. Fortified blended foods may be a more effective commodity to include in the general ration.*

- *Diagnostic criteria for pellagra based upon dermatological symptoms may mask a high prevalence in males and young children.*

- *Targeting niacin-rich foods only to families with pellagra cases or malnourished children is not a preventive strategy and may have limited impact in preventing further outbreaks of the deficiency disease.*

- *Where logistical difficulties associated with the general ration prevail and where such difficulties are likely to be exacerbated by the addition of an extra (niacin-rich) food commodity to the general ration, it may be more appropriate to concentrate resources on fortifying one of the existing ration commodities with nicotinamide.*

Strategies to prevent pellagra in large populations affected by emergencies

Background

There are currently no published guidelines on strategies to prevent pellagra in large populations affected by emergencies. Although the theory of how to prevent outbreaks of pellagra and other micronutrient deficiency diseases is well documented and understood (ACC/SCN, 1995), each emergency situation presents a unique context and set of factors which may predispose the success of one strategy over another. It is therefore crucial that an initial assessment examine the feasibility and likely success of each available strategy. A pragmatic scenario-based analysis is therefore often necessary.

The main strategies available to prevent outbreaks of pellagra are outlined below. Each strategy is considered on the basis of context. However, there are only a limited number of

published/documented experiences of interventions to draw upon so that this brief overview cannot be seen as exhaustive in terms of identifying relevant factors and context. It is nevertheless presented in a manner to encourage the reader/programme decision-maker to consider each situation separately and the type of variables that may influence the final choice of strategy.

Main approaches

The main approaches to preventing the onset of pellagra in emergency situations affecting large populations are as follows.

Provision of food rations containing adequate amounts of bioavailable niacin (niacin equivalents) by diversifying the general ration:
- a maize-based general ration should always contain a commodity rich in bioavailable niacin, e.g. legumes (especially groundnuts), pulses, meat/fish;
- have two staples in the general ration, e.g. maize and sorghum/rice/millet, or add a fortified cereal–legume blend to the food basket.

Fortification of relief commodity with niacin especially when major staple in ration is maize:
- the fortification of maize meal with niacin.

Allocation of surplus foods:
- provision of surplus food in the ration to allow the affected population to sell or exchange for another food commodity.

Supplementation:
- provision of niacin in the form of tablets (vitamin B-complex) for prevention and treatment of pellagra.

Cultivation and production of foods by affected population:
- encourage and facilitate, where feasible, the cultivation of home gardens or keeping of domestic livestock.

Diversification of diet

Pellagra is most common in populations who consume maize as the principal cereal. The prevention of pellagra is best achieved by providing pulses (especially groundnuts) and fish or meat in sufficient quantities in all rations where maize is the principal cereal. However, fish or meat are unlikely to be available in sufficient quantities to be included in the food basket and they are usually too expensive. Furthermore, the ration may be deficient in other nutrients that are essential for niacin metabolism, e.g. riboflavin and pyridoxine. Groundnuts do not contain large amounts of these nutrients.

In the absence of sufficient vitamin B-rich foods in the ration, the provision of fortified cereal–

legume blends could help to increase the niacin, riboflavin and pyridoxine intake of the affected population. However, as recently occurred in Angola where a large proportion of the population were said to be at risk from pellagra, the logistical difficulties and cost of providing a fortified blended food to all those at risk may be prohibitive so that priority groups need to be identified and targeting employed.

Another means of diversifying the diet may be to introduce a second staple into the ration, e.g. rice or wheat. However, this may create problems of acceptability if the population has little experience of consuming another staple. Furthermore, it may be difficult to access large quantities of alternative staples locally or regionally, resulting in long delays before a second staple can be introduced into the ration.

Fortification of relief commodity with niacin especially when the major staple in the ration is maize

Addition of a vitamin pre-mix to a food commodity is technically and logistically feasible in most situations. However, this type of intervention is best undertaken when it is clear that the emergency or risk of pellagra is long term, or that for logistical or cost reasons it may not be possible to add an extra niacin-rich commodity to the general ration. Furthermore, technical and logistical factors also need to be carefully appraised before deciding which food vehicle to use and where fortification should take place. A food vehicle should be chosen on the basis that it is consumed by all demographic groups and that it is not significantly exchanged for other food and non-food commodities. The decision whether to fortify at the central level or closer to a camp or emergency-affected population will need to be taken on the basis of a thorough assessment of milling capacity at different levels (Beaton, 1995; Harrell-Bond, 1989; Mears & Young, 1998; Nagy, 1996, USAID, 1999).

Allocation of surplus foods

This strategy assumes that beneficiaries are able to exchange a 'surplus' commodity for a micronutrient- (niacin/tryptophan) rich food. However, the success of this strategy will depend on access to markets and the exchange values of the surplus commodity. Market analysis is required in order to be able to anticipate the likely effect on prices of a surplus commodity being sold in large quantities and the per capita income raised by the exchanged surplus ration. An estimate of how much niacin/tryptophan would be made available by exchange of the ration would be needed.

Other issues to consider are the likely impact (positive and negative) on traders or local producers. Furthermore, some donors may not approve of this strategy. Donor attitudes to sale of emergency food aid by beneficiaries are varied and not always explicit. There have been instances where evidence of ration sale has led donors to argue for a reduction in overall general rations on the basis that beneficiaries are selling food because they are receiving excess to requirements. It may be necessary to advocate among donors a strategy of allocating surplus food for exchange (Field Exchange, 1998).

Supplementation

Supplementation through distribution of tablets has rarely proven to be an effective method of preventing or curing micronutrient deficiency outbreaks. Experiences of scurvy among Ethiopian refugees in Somalia in the mid-1980s where vitamin C tablets were distributed (WFP/UNHCR, 1985) and more recently the pellagra outbreak in Angola (MSF/ICRC, 1999), have shown how a major problem is that of compliance, especially for water-soluble vitamins which are not stored by the body and so require daily intake.

However, in situations where circumstances preclude other strategies involving additional food commodities, a tablet distribution may be a short-term expedient. Furthermore, certain measures may maximize impact, e.g. publicity/education campaigns and utilizing local information networks to increase compliance.

Cultivation and production of foods by affected population

A key objective of emergency food-aid provision is to encourage self-sufficiency (UNHCR/WFP/ENN, 2000). Encouraging home garden and small-livestock production in refugee camps are strategies that are often implemented with this objective in mind. However, while such initiatives will enhance access to micronutrients, these are not always feasible options. For example, in many camp situations there is insufficient land to allow home garden production for each household.

Furthermore, camps are often established in inaccessible and inhospitable environments. There may therefore be a high risk of drought, so that dependence on home garden production for part of the micronutrient intake is unwise. In other (non-refugee) situations, insecurity may also preclude dependence on cultivation and production as a means of ensuring access to sufficient micronutrient intake.

Variables to be assessed in order to devise a strategy to prevent or combat an outbreak of pellagra

It can be seen from the above that choice of strategy to prevent pellagra must be preceded by a thorough assessment that examines a number of variables. Assessed variables should include:

- access to niacin- and tryptophan-containing foods and amounts of these nutrients in distributed maize;

- access to other nutrients (riboflavin and pyridoxine) which influence niacin metabolism;

- groups most at risk of developing pellagra (probably defined in terms of

socioeconomic rather than demographic status);[1]

- feasibility of introducing another staple, i.e. acceptability and logistical considerations;

- likely longevity of emergency;

- food consumption habits and implications for choice of food vehicle for fortification;

- milling capacity at different levels;

- market prices for niacin rich foods and market sensitivity to large quantities of food-aid commodities being sold;

- donor attitudes towards sale of food-aid commodities; and

- existence of information networks for sensitizing beneficiaries to vitamin tablet consumption.

Conclusions and recommendations

There have only been a handful of pellagra outbreaks over the past 10 years. Each of these events has occurred among emergency-affected populations dependent upon food aid, e.g. refugees, returnees and internally displaced people. With hindsight, it was theoretically possible to predict these outbreaks based on the niacin content of the emergency general ration available to the affected populations. The fact that these outbreaks were not predicted or prevented demonstrated the inadequacy of food security monitoring and assessments at the time.

However, in many emergency programmes general rations fail to provide sufficient micronutrients yet populations do not go on to develop overt clinical signs of micronutrient deficiencies. The obvious reason for this is that populations obtain access to other food sources. A critical point is that it is not always possible to determine accurately whether other (non-general ration) sources of food are available to an emergency-affected population. Thorough needs assessments may be difficult due to insecurity or population dispersal. It may therefore be difficult to judge whether a population is wholly dependent upon the general ration and therefore at risk of micronutrient deficiency disease. The WFP/UNHCR Memorandum of Understanding (WFP March, 1997) states that fortified blended foods should be made available to emergency-affected populations wholly dependent on food aid.

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[1] In many emergency situations, scarcity of resources and/or difficulty of access to populations may lead to pressures to target food aid to those most at risk. In the Angola case, agencies agreed a set of priority groups for distribution of CSB depending on availability and logistical considerations. While it is probably not feasible to target food aid in a refugee camp situation, targeting is more of an option (and often more necessary given the large numbers involved and logistical difficulties) in non-camp emergencies. However, in order to target effectively there is a requirement for information about which groups are most at risk. Clearly epidemiological analysis should be carried out in order to identify at risk groups. Given the similar proportionate niacin requirements for different demographic groups it is likely that socioeconomic circumstances will be the major determinant of risk. Identifying means of classifying socioeconomic risk factors may therefore provide a rational basis for targeting scarce food aid resources in order to prevent pellagra.

The difficulty appears to be in determining the degree of dependency and the point at which a population is at risk from micronutrient deficiency disease, or in this case pellagra. Furthermore, the risk may only be seasonal (ACC/SCN/RNIS, 1996).

This review therefore strongly recommends the following course of action for those agencies responsible for providing adequate emergency food rations.

• Basic rations (general rations plus additional sources of food) should be routinely monitored for niacin content where maize is the staple cereal being consumed. This would necessitate household level (post-distribution) food basket monitoring.

• Where the basic ration is clearly deficient in niacin and a risk of deficiency is indicated, micronutrient deficiency surveillance systems should be established immediately .

• Different options for improving niacin status should be explored based upon the types of variable and context discussed in the above section (see Table 11).

Table 11. Options for the prevention of pellagra deficiency in an emergency

A. Natural sources of niacin available locally

Natural sources available immediately

1. Provide adequate amounts of pulses (especially groundnuts) or meat/fish

2. Include a second staple e.g. sorghum, rice, millet, in a maize-based general ration

3. Encourage barter or purchase by providing 10% extra ration

Natural sources not available immediately

4. Encourage household food production of pulses, coarse grains

   (maize, millet), and for example keeping of domestic poultry

B. Natural sources not available locally

EITHER

Provision of commodities fortified with niacin

5. Provide fortified cereal–legume blends in the general ration

6. Provide fortified maize in a maize-based general ration

OR

Provision of niacin supplements

7. Provide niacin supplements

Each of the above options/interventions will have merits and weaknesses depending on prevailing circumstances.

It is clear that the type of pellagra outbreak which recently occurred in Angola is eminently preventable given forward planning and pre-emptive intervention. There can be no legitimate excuse for such outbreaks occurring. However, there are areas where further clarification of practice and policy in regard to prevention of pellagra is warranted. These include the following:

- The appropriateness of diagnosis of pellagra based upon dermatological criteria only.

- The strategy of relying upon fortified blended foods to prevent micronutrient deficiency disease outbreaks should be reviewed in light of recurring evidence that provision of adequate supplies of these foods is often problematic. The reasons for these difficulties should be assessed and if necessary the strategy revisited or at least qualified on the basis of context. It may be that in some situations fortification of maize should be considered in preference to this strategy.

- Donor policies on the bartering or exchange of food aid should be clarified. This review argues that barter/exchange should be permitted. However, there is a lack of a clear policy statement among bilateral and multilateral donor agencies regarding this important issue.