Noma: an "infectious" disease of unknown aetiology

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Noma (cancrum oris) is a devastating gangrenous disease that leads to severe tissue destruction in the face and is associated with high morbidity and mortality. It is seen almost exclusively in young children living in remote areas of less developed countries, particularly in Africa. The exact prevalence of the disease is unknown, but a conservative estimate is that 770 000 people are currently affected by noma sequelae. The cause remains unknown, but a combination of several elements of a plausible aetiology has been identified: malnutrition, a compromised immune system, poor oral hygiene and a lesion of the gingival mucosal barrier, and an unidentified bacterial factor acting as a trigger for the disease. This review discusses the epidemiology, clinical features, current understanding of the pathophysiology, and treatment of the acute phase and sequelae requiring reconstructive surgery. Noma may be preventable if recognised at an early stage. Further research is needed to identify more exactly the causative agents.

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"Maladie dévoreuse de beauté et de vie" ("An illness devouring both beauty and life").

Edmond Kaiser, founder of the humanitarian organisation Sentinelles.

Noma (cancrum oris) is a gangrenous disease affecting the soft and hard tissues of the mouth and face. It predominantly affects children in less developed countries who live in conditions of poor hygiene and have debilitating diseases. From the severe disfigurement present in many of those who survive, noma has been called the face of poverty.

Although the disease has been known since antiquity and was present in Europe for several centuries, it is now seen mainly in Africa and occasionally in Latin America and Asia. After alarming reports from humanitarian organisations, WHO declared it to be a priority in 1994 and an action programme was initiated under a joint project involving WHO, the US National Institutes of Health, and the University of Maryland, Baltimore, USA. The first available data on the incidence and prevalence of noma are those reported by WHO in 1998, which estimated a worldwide incidence of 140 000 cases per year with a prevalence in 1997 of 770 000 people living with noma sequelae.[1]

Noma is thought to be an infectious disease but its cause remains unknown. Malaria, malnutrition, measles, and poor oral hygiene, present in most African children, all have roles in the pathogenesis of noma disease, and these pre-existing conditions are believed to be risk factors for the development of noma lesions. Better knowledge of the aetiopathology and epidemiology is needed for efficient preventive strategies to be implemented, but the necessary studies require substantial resources and are difficult owing to the remote areas involved and the idiosyncrasies of nomadic populations.[2] Moreover, since the victims of noma are the poorest among the poor of the world and many live in isolated conditions, the disease tends to be neglected by the scientific community and is overshadowed by higher-profile disorders such as cancer, cardiovascular disease, AIDS, and malaria.

Historical perspectives

The term noma originates from the Greek verb *numein* (to devour). The disease was first reported by Hippocrates in the 5th century BC; he described it as a destructive ulceronecrotic lesion in the mouth, face, and airways. As reviewed by Tourdes,[3] between the 16th and 19th centuries descriptions of the disease proliferated throughout Europe and became increasingly precise (Batthus 1620; Van der Voerde 1680; Lund 1728; Van Swieten 1744; Richter 1821; Coates 1826; Rillet and Barthez 1843; Meigs 1848). In 1848, Tourdes gave a definition of noma that is still valid today: "a gangrenous disease affecting the mouth and face of children living in bad hygiene conditions and suffering from debilitating diseases, especially eruptive fever, beginning with an ulcer on the oral mucosa rapidly spreading outside and destroying the soft and hard tissues of the face—and almost always fatal".[3]

With improvements in hygiene and nutritional status and the decline in outbreaks of measles and other eruptive fevers, noma disappeared from more developed countries. Among the earliest cases reported during the past century are in a 3-year-old child with acute myeloid leukaemia in

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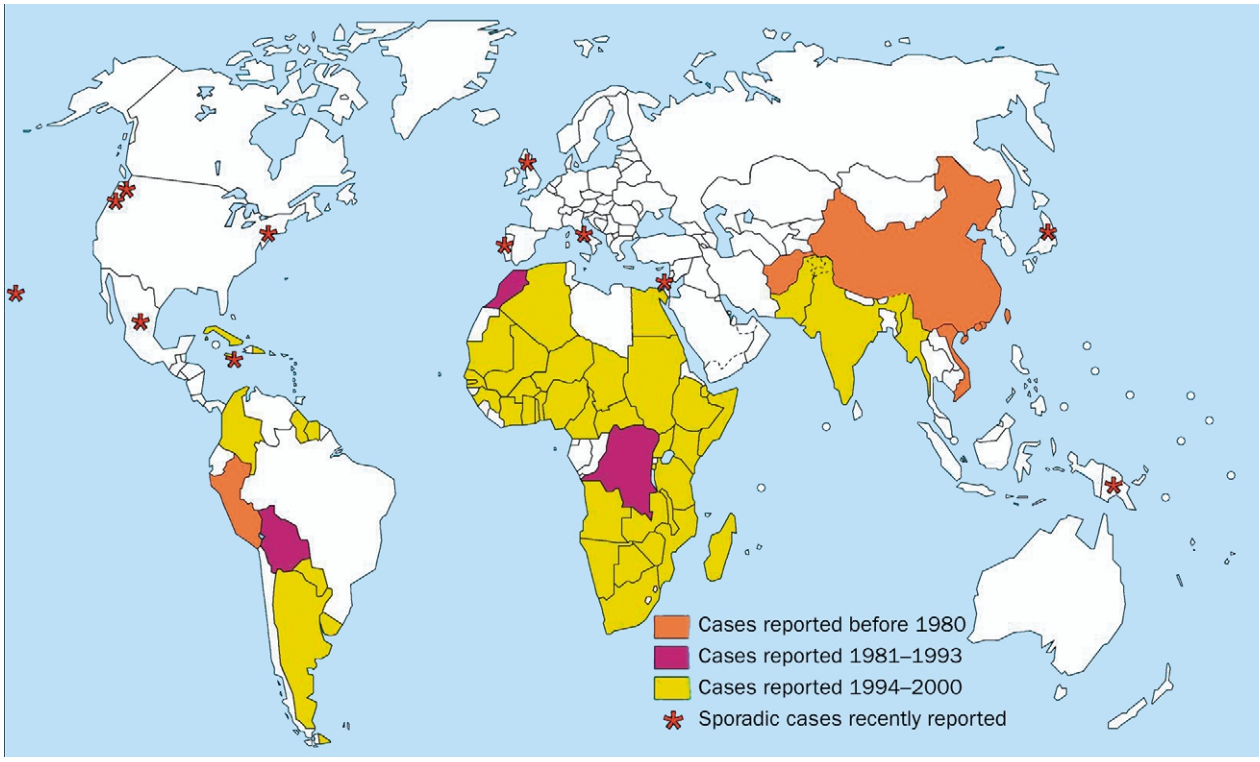

Figure 1. Noma cases reported worldwide before 1980 and until 2000 according to WHO. Reproduced with permission from WHO.

the USA in 1935,[4] and in two adults and a child in Germany in 1938, one with lymphoid leukaemia and two with agranulocytosis.[5] Eckstein observed 40 cases, all in children, in Ankara, Turkey, over a period of only 3 years (1936–38); 22 of these cases were observed during a malaria epidemic in 1938.[6] At the end of World War II, cases were reported from the concentration camps at Belsen[7] and Auschwitz.[8]

More recently, noma has been described in immunocompromised adults in more developed countries, especially among patients with blood dyscrasia.[9–13] Similar clinical features have lately been described in patients with AIDS.[14–18]

Clinical pictures of noma

Noma

The classic form of the disease affects children younger than 12 years, mainly between 2 and 6 years, living in less developed countries.

Noma of the debilitated adult

This typical, but less locally invasive, form of the disease occurs in immunocompromised adults with major debilitating diseases in both more and less developed countries. Knowledge of its aetiology and that of the classic form is limited. A more accurate approach could be to refer to noma in this category as a noma-like lesion.

Noma neonatorum

This condition has been called noma because of the similarity of the facial lesions but, in reality, it is a different disease affecting mostly premature babies. In addition to the facial lesions, necrosis of the perineal region is characteristic. The disorder is fatal in almost all cases because of irreversible septicaemia. *Pseudomonas aeruginosa* is known to be the causative agent.[19–21] We believe that noma neonatorum is a discrete pathological entity and should not be confused with the classic form of noma.

The panel summarises the three clinical pictures of noma.[19–21] This review focuses on the classic and most widespread form of the disease today, noma among children.

Epidemiology

Although noma has been known for at least seven centuries, it was designated as a priority for WHO only in 1994 after many alarming reports from humanitarian organisations working in Africa. The magnitude of the problem and the epidemiological trend are difficult to assess. Clearly, the number of noma cases does not compare to those of malaria or measles. However, the social impact of the disease is undeniable given the high mortality in children and the fact that survivors live hidden with little hope of social integration. Noma is reaching alarming proportions in Africa, especially among some populations of the Sahel region, the poorest area of the continent. Noma also affects children in Latin America (Argentina, Paraguay, and Uruguay)[22] and in Asia (India and China).[1] A few cases have been reported from Afghanistan, Pakistan, Vietnam, Philippines, New Guinea, and the Dominican Republic.[22] In

Table 1. Noma mortality in the 19th century in Europe (without drug therapy)

Author	Year	Cases	Deaths	Mortality (%)
Tourdes	1848	239	176	73
Barthez and Rilliet	1855	29	26	89
Bruns	1859	413	290	70
Springer	1904	88	83	94

Table 2. Noma mortality in the 20th century without drug therapy

Author	Year	Source	Mortality (%)
Fu Tang-Chu	1936	China	56
Osler	1938	Review	75
Stransky and Pecache	1941	Philippines	88
Stones et al	1954	Review	80
Durand	1959	Review	75

Africa, the incidence of noma varies within and between rural and urban areas.[23,24] Most cases are reported from sub-Saharan countries, particularly Niger, Nigeria, Burkina Faso, and Senegal, which is not surprising given the economic crises in many of these countries.

The only data available on the incidence and prevalence of noma are those obtained from WHO; however, we emphasise that these data are extrapolated from retrospective studies based on cases observed at the local health facilities in different African countries.[25] The exact prevalence and incidence of noma, and the true associated mortality, have proved difficult to establish for several reasons. First, WHO standardised the registration of noma only in 1992, and no cases were officially reported by the governments of less developed countries until 1994.[1] Second, owing to the high associated mortality, many cases of acute noma remain undiscovered. Third, in many regions noma is thought to be shameful or a curse, and affected children are hidden or isolated with animals.[22] Fourth, many affected people are nomadic, so are difficult to register, control, and follow up, or they live in remote areas where no transport is available or transport costs are high, so they cannot travel to medical centres to seek care.[2,26] According to recent reports, only 10% of patients seek medical care at the acute stage.[1,26]

Figure 1 shows the geographic regions in which noma has been reported before 1980 and until 2000 (according to WHO data).

The mortality associated with noma during both the 19th and 20th centuries was reviewed in 1966 by Tempest (table 1, table 2, table 3; adapted from his review).[27] For the 20th century, he distinguished between cases that were untreated and those treated with sulphonamides or penicillin. Table 4 summarises acute noma mortality reported from Africa in the most recent series.[2,25,27–30] The latest data from a 1998 WHO Delphi-type consultation showed a mortality rate without treatment of 90%.[1,22]

Characteristics

The sequelae of noma are well known, but the prodromes and the initial stages of the disease remain difficult to characterise because few patients seek medical care during the acute phase. According to our experience and that of non-governmental organisations dealing with the disease, many patients spend their entire childhood hidden and seek reconstructive surgery only when marriage is desired. For these reasons, clinical descriptions of the acute stage are rare and imprecise. Parents of some affected children mention fever and apathy, gingival bleeding, lesions of the oral mucosa, oedema of the face, and a fetid odour. Some researchers have also mentioned the presence of a spot or papule that rapidly forms an ulcer with subsequent bone exposure.[27,31]

In the early 1940s, Eckstein proposed a possible relation between acute necrotising gingivitis (ANG) and noma,[6] later followed by other investigators.[29] Bone exposure in the mouth was proposed as the passage-point between ANG and noma.[32,33] The present expert consensus is that ANG is a precursor of noma.[34–39]

Acute necrotising gingivitis

ANG is a generalised or localised gingivitis that begins with gingival oedema and is rapidly followed by necrosis and decapitation of the interdental papillae (figure 2). The clinical and pathognomonic signs are necrosis of the papillae with spontaneous gingival bleeding and pain. Less constant signs are the presence of greyish pseudomembranes, fetid odour, hyperscialorroea, and fever. Fetid taste has also been reported.[40,41]

In more developed countries, ANG mainly affects young adults with poor oral hygiene, stress, tobacco use, vitamin deficiencies, or pregnancy.[40,42,43] Worldwide, in a mixed population, ANG accounts for less than 1% of all periodontal lesions.[36] Lately, it has been deemed to be a marker of immune deterioration.[44] Generally, ANG regresses rapidly with professional oral hygiene treatment, but some cases show little response and antibiotic therapy is required.[36,40,41,45]

In less developed countries, however, ANG is especially common in children.[23,34,46] In studies in Africa, between 11% and 73% of children presented with ANG.[23,24,33,34,46–48] In India, ANG prevalence among children under 10 years of age has ranged from 54% to 58%.[32] In patients affected by immune disorders and children weakened by severe malnutrition or other diseases, appropriate dental hygiene is insufficient and antibiotics are needed to prevent the progression from necrotic gingivitis to necrotic stomatitis with alveolar bone resorption or even noma. Most investigators agree that the presence of ANG in young children in less developed countries can progress to noma if untreated; [32–34,36–39] whether systematic use of antibiotics in patients with ANG would lower the frequency of noma remains speculative.

Table 3. Noma mortality in the 20th century with drug therapy

Author	Years	Country	Mortality (%)	Treatment
Eckstein	1940	Turkey	8	Penicillin, sulphonamide
Tupas	1946	Philippines	6–7	Penicillin
Struthers	1947	China	5–10	Penicillin, sulphonamide
Reynaud	1950	Afghanistan	48	Penicillin
Boulnois	1950	Madagascar	25	Penicillin, ascorbic acid
Phan-Dinh-Tuan	1960–62	Vietnam	12	Penicillin

Table 4. Acute noma mortality in Africa, after 1950, with drug therapy

Author	Years	Country	Cases	Mortality (%)	Systemic treatment
Boulnois and Rabedaoro[28]	1950	Madagascar	73	0	Penicillin, ascorbic acid
Jelliffe[29]	1949–51	Nigeria	53	30	Penicillin
Tempest[27]	1962–65	Nigeria	250	8	Antibiotics, sulphonamide
Adekeye and Ord[2]	1978–82	Nigeria	13	0	Antibiotics
Bourgeois et al[25]	1981–93	Senegal	73	10	Not specified
Oginni et al[30]	1982–96	Nigeria	133	0	Not specified

Acute stage

The prodromic phase of noma and its duration are unknown.[34] Fever and apathy are mentioned later but are often misdiagnosed as malaria by the parents, and medical care is never sought at this stage. The first-recognised and well-known sign of acute noma is oedema of the cheek, gingiva, or both. Necrotising stomatitis may be observed (figure 3), generally starting at the alveolar margin in the premolar-molar region and extending to the mucosal surface of the cheek. The evolution is very rapid (24–48 h).

Within the next few days, a discoloured, greyish-black area appears on the external surface of the cheek opposite to the original intraoral lesion. It rapidly becomes necrotic and remains remarkably well defined. The necrotic zone turns black and acquires a typical cone shape (named the *cône gangréneux* by the first French clinicians who observed the disease) indicating that the internal destruction of tissue is greater than the external loss of skin. The necrotic matter, which generally includes both soft and hard tissue, rapidly sloughs away. Inside the mouth, the bone is exposed with exfoliation of teeth. Large sequestra of bone may form, but sometimes the necrosis is so profound that both mandible and maxilla are totally destroyed.[27,29,34]

Introduction of nutritional rehabilitation, local disinfection, and antibiotic treatment at the earliest stage could halt the disease but, for reasons already discussed, parents seek medical help for early noma only in a minority of cases.[34] Early reports mention the use of sulphonamides,[6,27] penicillin,[6,27,49] or a combination of both,[7] as well as chloramphenicol.[27] Broader-spectrum antibiotics covering gingival flora including aerobes and anaerobes are now recommended, but the treatment has to be started as soon as possible.

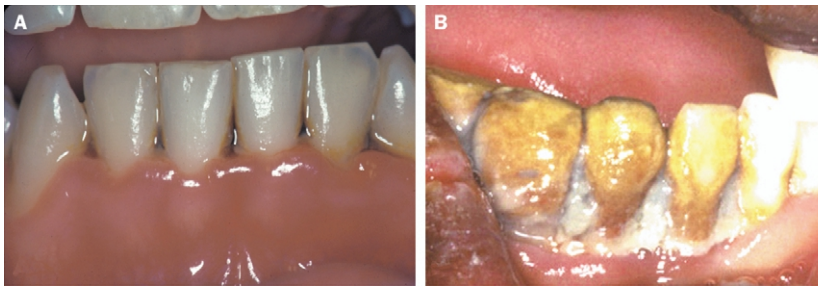

Figure 2. Examples of ANG. (A) A young white adult patient; note the oedema of the gingiva and the decapitation of the interdental gingival segment (papillae). (B:) An African child; note the oedema of gingival tissue, decapitation of papillae, the greyish pseudomembranes, and the amount of calculus. Property of the Plastic and Reconstructive Surgery Unit, University of Geneva Hospitals. Reproduced with permission.

Noma is unilateral in most cases, but bilateral lesions are sometimes observed. General signs are anorexia, prostration, fetid odour, excessive salivation, and occasionally local adenopathy; pain and fever can also occur.[27,34,50] Secondary infection occurs very rapidly, and most children die at this stage because of starvation, aspiration pneumonia, or sepsis. The course of the disease is very rapid and death can occur only a few days after the onset of oedema.

When the gangrenous process has led to perforation of the cheek, antibiotic treatment can lower the risk of death but will not permit a return to the normal state before the illness.[6,27] Sadly, in many cases this is the stage at which parents seek medical care.

Sequelae

The healing of noma lesions is characterised by fibrous scars that apparently reduce the cutaneous defect but often lead to definitive stricture of the mouth.[2,26,31,51–56] Other consequences are severe dental malposition and salivary incontinence. When the maxilla is lost, there may be defective speech and nasal regurgitation.[57] The only possible treatment at this stage is reconstructive surgery.

There have been many attempts to classify the lesions of noma on the basis of the cutaneous defect. The classification that seems to be both the simplest and the most useful for the surgeon is that of Montandon and colleagues (figure 4),[52] which has been adopted by WHO as the standard to describe defects caused by noma.[56]

Type I, localised cheek and commissural defect, is the most common appearance of noma sequelae and is so typical that the origin of the mutilation can be diagnosed immediately. In occasional cases, it seems to be a very minor problem, but surgeons should be aware that after the mouth has been opened, the contracture released, and the defect corrected, the tissue loss can be much more extensive than initially assessed because the wound has healed by contraction. Type I is bilateral in some cases.

Type II includes the upper lip and in many cases the nose, the alveolar border, and the palate. More rarely, an isolated nasal defect with loss of septum is observed.

Type III is mostly located on the lower lip and can sometimes include the complete mandible and floor of the mouth.

Type IV covers major defects that may include the whole cheek, lips, the

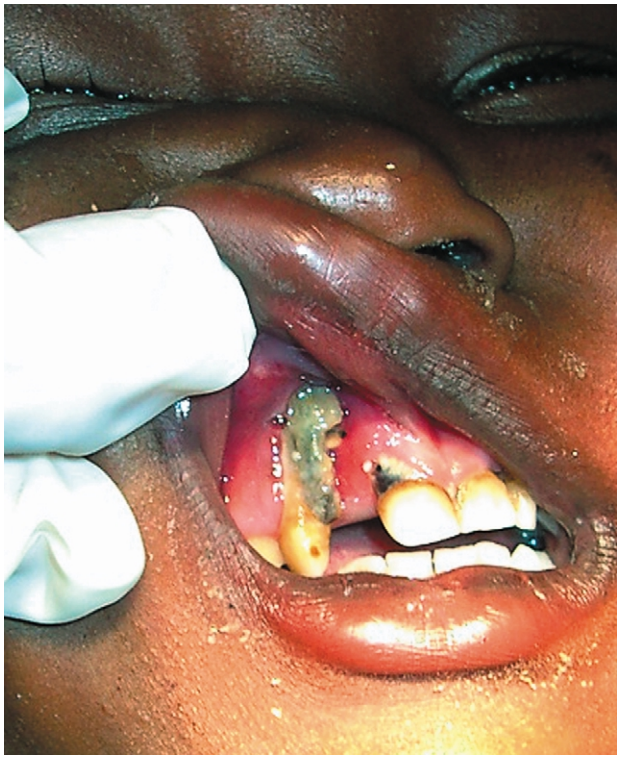

Figure 3. Necrotising stomatitis, which commonly precedes or accompanies oedema and represents the passage point between ANG and noma. Property of the Plastic and Reconstructive Surgery Unit, University of Geneva Hospitals. Reproduced with permission.

Table 5. Accompanying disorders in a series of 98 noma cases, 1807–43 (adapted from Tourdes 1848)[3]

Disorder	Number of cases
Eruptive fever	
Total	47 (48%)
Measles	39
Scarlatina	5
Variola	3
Respiratory-tract infections	
Total	12 (12%)
Pertussis	6
Tuberculosis	3
Pneumonia	2
Bronchitis	1
Digestive-tract illness	
Total	8 (8%)
Enteritis	5
Dysentery	2
Oral diphtheria	2
Other disorders	
Intermittent fever	8 (8%)
Typhoid fever	7 (7%)
Calomel (mercurialism)	7 (7%)
Scrofula	4 (4%)
Scorbut	2 (2%)
Syphilis	2 (2%)
Cerebral congestion	1 (1%)

maxilla, the palate, and the malar bone and which can in some cases extend to the eyelid and the nose. The frequency of this type is difficult to assess because most of the affected children die from meningitis or septicaemia.

Risk factors

Early descriptions of noma have cited malaria, malnutrition, measles, and poor oral hygiene as determinants in the aetiology of the disease (table 5). All these factors have a role in its pathogenesis (figure 5), and one or more may be found in most African children.

Malnutrition

The gingiva is a barrier to the penetration of pathogens. It is weakened by inflammation, particularly by necrotising ulcerative gingivitis. The tissues most affected by food deficiencies are those characterised by high turnover, such as

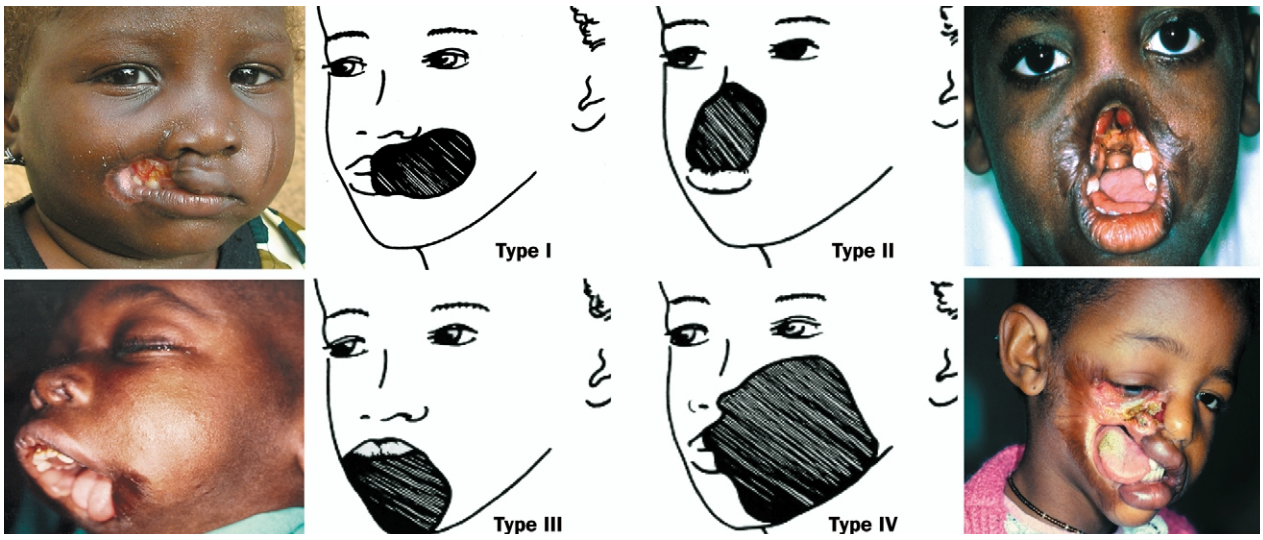

Figure 4. Classification of noma sequelae with corresponding clinical cases. Diagrams reproduced with permission from LWW (reference 52).

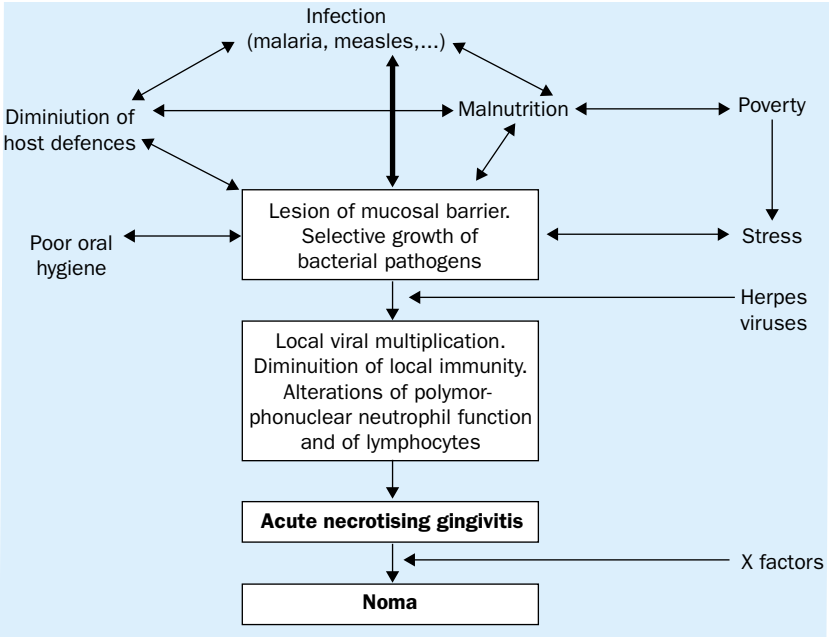

Figure 5. Summary of risk factors implicated in the aetiology of ANG and noma. Double arrows show the interdependence of all factors. Factor X represents the unknown element facilitating the passage point between ANG and noma. Adapted from reference 57.

the gingival mucosa. Protein-energy malnutrition or vitamin deficiencies can thus lead to increased tissue permeability and the entry of oral pathogens (figure 5).

Even in the earliest descriptions, malnutrition was judged to be one of the most important risk factors for noma because of the well-known consequences for the immune system. Protein-energy malnutrition causes atrophy of lymphoid tissues on T-dependent areas of the thymus, spleen, Waldeyer ring, and lymph nodes, with a striking reduction in numbers of all lymphocytes and T cells positive for CD4 and CD8,[58,59] particularly in children. The efficacy of immunoglobulins becomes inadequate when antibody production requires the presence of antigen-presenting T lymphocytes.[60,61] This feature is important because the gingival inflammatory response in children is characterised by the presence of T lymphocytes,[62] which may explain why periodontal tissue in malnourished children is more susceptible to periodontal diseases or noma. Furthermore, numbers and activity of polymorphonuclear neutrophil leucocytes are diminished in malnutrition,[63] as observed in individuals with cyclical neutropenia, agranulocytosis, or Chediak-Higashi disease, who show many severe gingival lesions.[64]

The importance of malnutrition in the aetiology of noma was recognised by several researchers during the past century.[29,33,49] In a series of 250 noma patients, Tempest found that 55% had severe and 28% moderate malnutrition; only 18 (7·2%) were in good nutritional condition.[27] In a series of 1068 Nigerian children, Enwonwu found a high prevalence of protein-energy malnutrition and vitamin deficiencies among those affected by ANG and noma.[34] Among the 69 children affected by noma, albumin and globulin concentrations were almost normal, but a severe deficiency of ascorbic acid was observed. Furthermore, conversion of folic acid into its active form (folinic acid) was lower than normal.

Vitamin A deficiency causes atrophy of lymphoid tissues with a reduction in circulating lymphocytes and antibody production.[59,61,65] The protective effect of vitamin A against infection was known before the advent of antibiotics, and it was used as treatment against infections such as pneumonia, puerperal fever, and scarlatina. Deficiencies of vitamins B6 and E are known to impair cell-mediated immunity and antibody formation.[61] Vitamin C deficiency does not directly affect cell-mediated immunity or antibody production but is associated with decreased bactericidal capacity of neutrophils and macrophages.[61] However, vitamin C deficiency could affect immunity by its effect on plasma cortisol concentrations.[66,67]

Among the most important deficiencies of trace elements and aminoacids influencing the efficacy of the immune system are iron, zinc, cysteine, methionine, serine, and glycine. In addition to causing anaemia, iron deficiency impairs the activity of neutrophils and lymphocytes and also the response to certain antigens, particularly those of herpes simplex virus.[61] Zinc deficiency leads to atrophy of lymphoid tissues, diminution of cell-mediated immunity[68] and phagocytosis, and impairment of tissue-repair processes.[61] Protein synthesis is affected by severe deficiencies in essential aminoacids that occur in malnutrition.[59,63]

Protein-energy malnutrition is also characterised by adrenal hyperfunction with an increase in serum cortisol concentrations.[69] Concentrations of this hormone in malnourished children have been reported to be twice as high as those in well-nourished children of the same age. Moreover, the plasma cortisol concentration increases as malnutrition becomes more severe; notably, it is higher in marasmus than in kwashiorkor.[63] In addition to the depression of cell-mediated immunity,[63] hydrocortisone causes a reduction in cell turnover in epithelial tissues, a reduction in collagen synthesis,[70] and an increase in serum hyaluronidase,[71] which has a role in bone loss.[72] Noma-like lesions have been produced in the oral mucosa of rats subjected to repeated injections of cortisone and simultaneous mechanical gingival injuries.[73] Furthermore, corticosteroids can be used nutritionally by certain bacteria. *Prevotella intermedia*, which has a major role in the development of ANG,[42] can use steroid hormones for growth in place of vitamin K.[74] A study of 1000 Nigerian children at risk of noma found low plasma concentrations of zinc, retinol, ascorbate, and essential aminoacids, and increased concentrations of cortisol.[75]

Both general and local immunity are affected by malnutrition with direct consequences on the periodontal tissues and oral flora.[76] Undernourished children show a predominantly anaerobic flora and, particularly, the presence of Gram-negative rods. In Nigeria, spirochaetes are present in 88% of malnourished children but not in well-fed children.[76]

The negative effects of malnutrition are aggravated by various ethnic traditions in weaning. For example, African children are normally breastfed for 2 years; breastfeeding is then stopped abruptly, without a gradual transition to a solid diet. This change can cause children rapidly to become deficient in vitamins, immunoglobulins, essential aminoacids, and minerals.[77] Around this age children can develop kwashiorkor as well as suffering their first attack of malaria, measles, or other childhood diseases—and acute noma. The term kwashiorkor in certain African dialects translates as "the disease of the child whose brother will come soon". This is also true of noma.

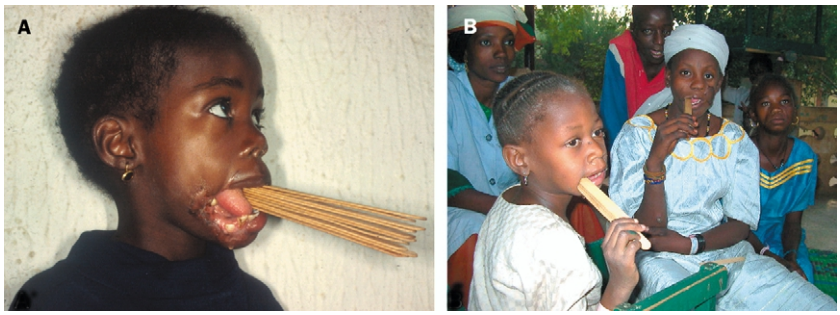

Figure 6. Effects of physiotherapy. (A) Preoperative physiotherapy for the prevention of contracture of the mouth. (B) Postoperative physiotherapy for the same reason at the noma centre of "Sentinelles" at Zinder, Niger. Property of the Plastic and Reconstructive Surgery Unit, University of Geneva Hospitals. Reproduced with permission.

Some researchers believe that malnutrition, although important, is not the main determinant in the aetiology of noma. Eckstein found that the children who came to hospital in the late phase of the disease were malnourished, but those who attended during the early stage were in a good nutritional state.[6] In his opinion, certain infectious diseases may predispose to noma more than malnutrition does.

Poor oral hygiene

The role of poor oral hygiene in the aetiology of ANG (figure 5) has been studied intensively in children in less developed countries, where the toothbrush is largely unknown.[23,24,32,34,78–81] Only a fifth of Nigerian children, mostly in urban centres in the south of the country, use a toothbrush. In the north, the poorer and more rural part of the country, children use "chewing sticks" or just their fingers.[24] Taiwo observed that ANG was present in 28% of 438 Nigerian children under the age of 12.[81] She stratified the children into three groups according to their standards of oral hygiene (good, inadequate, and very bad) and found that only 2·4% of the children in the first group had ANG but that the proportion was 62% in the second group and 70% in the third. She also pointed out that, since ANG was present in more than 2% of the children with good oral hygiene, other factors could play a part in the aetiology of the disease.

Malaria

When noma was still prevalent in Europe, xanthomatous fevers, particularly measles, were recognised risk factors.[3,82] In less developed countries, malaria has often been described as a risk factor for noma.[6,50] However, there is some debate about the importance of its contribution. Eckstein thought that malaria was the usual precursor of noma.[6] He postulated that the major involvement of the reticuloendothelial system characterising chronic malaria causes the loss of immunity that could lead to noma. By contrast, Tempest believed measles to be more important, and he found little evidence to suggest malaria as a risk factor for noma in west Africa.[27] Enwonwu mentioned malaria as a risk factor but, like Tempest, judged measles to be the most important debilitating disease preceding noma.[57] In a survey of the living conditions of children at risk of noma in Nigeria, the disease was found to be prevalent in the northern area of the country where the frequency of measles was higher, but no significant difference was seen in the frequency of malaria in the northern and southern regions.[24]

Measles

Measles causes the death of more than a million children each year in less developed countries[83] and has a major role in malnourished children.[27,34] Despite WHO measles vaccination programmes, in Niger only 25% of children are covered by vaccination (http://www.unicef.org/statis/country_1Page127.html; March 22, 2001). Children with measles have a lower than normal energy intake and show low mobilisation of hepatic vitamin A. In less developed countries, the disease can rapidly transform moderate undernutrition into kwashiorkor or marasmus with a fatal outcome in most cases.[84] African children affected by measles also present with ulcerative lesions of the oral mucosa, which can be so destructive that they have been termed "noma-like post-measles ulcerations".[85] These can easily progress to noma owing to impaired tissue repair resulting from vitamin A deficiency.[57]

Of note, in Tourdes' review of 98 cases between 1807 and 1843, he reported that measles was the most important disease accompanying noma.[3] Noma after measles was reported in Germany in 1900, when 33 of 133 children with measles developed the disease.[82] During a severe epidemic in the USA in 1901, 16 cases of noma developed among 173 children with measles. In France in 1904, 41 of 46 cases of noma occurred after measles. The last reported case of noma after measles in a more developed country was that of a Turkish boy in Germany in 1981; the child had no other risk factors apart from measles.[86] These historical clinical observations are now supported by some scientific evidence. In-vitro investigations have proved that the presence of morbillivirus in mononuclear cells diminishes cell-mediated immune

Figure 7. Intervention to prevent malnutrition. (A) Amputation of nose and upper lip in a 1-year-old child with marasmus who weighed 4 kg on admission. (B) Condition after spontaneous healing; the mouth and upper lip have closed by contraction. (C) Result a year after opening of the mouth and reconstruction of the nose. The child has returned to his family. Reproduced with permission from LWW (reference 52).

response and has a temporary effect that is similar to the definitive immunosuppression occurring in AIDS.[83,87] The measles virus can act by direct cytotoxic effect on activated T cells[88] and reduces the production and activation of interleukins, particularly interleukin 12.[89] Immunosuppression during measles can also result from additional and combined mechanisms;[90] whether they can facilitate the occurrence of noma remains unclear (figure 5).

Although measles is believed by some to be an important risk factor for noma, many cases of noma have been documented among children with no recent history of measles. The causal relation and physiopathological pathways linking measles, immunology, and ANG or even noma remain speculative.

Debilitating diseases

Any debilitating disorder can facilitate the progression of a buccal lesion into noma (table 5). Other infectious diseases have been considered as predisposing factors, such as chickenpox, smallpox, typhus, typhoid fever, diphtheria, visceral leishmaniasis (kala-azar), pneumonia, tuberculosis,[27,34,57] and more recently, AIDS.[50,77,91]

Pathophysiology

Vascular theory

Given that the cutaneous necrosis in noma is very well demarcated and self-limiting, an ischaemic mechanism with localised arterial thrombosis or capillary microthrombosis could be the explanation. However, the importance of the facial vascularisation and the striking separation between deep and superficial networks exclude a hypothesis such as an arterial thrombosis. Moreover, there is no anatomical relation between the lesion observed and the vascular topography. Capillary microthrombosis could have a role but is probably secondary to infection.[92,93]

Bacterial theory

A bacteriological aetiology of noma has long been postulated because of the type of necrosis and the odour of the lesions. However, both early and recent studies have been hampered by the rarity and geographic distribution of the disease, the difficulty of observing acute stages, the rapidity of necrosis and secondary infection, and the difficulties encountered in both culturing anaerobic species and reproducing the disease experimentally.

Recent microbiological techniques have allowed improved identification and characterisation of the flora present in noma lesions: *Prevotella melaninogenica, Corynebacterium pyogenes, Fusobacterium nucleatum, Bacteroides fragilis, Bacillus cereus, Prevotella intermedia*, and *Fusobacterium necrophorum* have been identified. The last two are judged by some investigators to play a key part in the aetiology of noma.[39,50,57,75,94–96]

However, comparison of the flora present in diseased and healthy subgingival plaques, and more generally in the oral cavity, does not formally establish the microbial aetiology of noma, but this could be due also to technical limitations. The vast majority of microbial life is resistant to cultivation in the laboratory. Molecular genetic tools have estimated that 60–80% of the organisms present in human

microflora have not been cultivated.[97] Large-scale sequencing[98] or broad-range amplification techniques[99] confirmed that 50–60% of gingival bacteria were distinct from all those previously described at the species level.

By means of molecular phylogenetic techniques, Paster and colleagues[100] investigated the flora present in advanced noma lesions of four Nigerian children. From only 212 clones, they reported a broad diversity of 67 bacterial species or phylotypes, of which 16 were novel, from eight bacterial phyla. 19 were present in two or more children. Fusobacteria and spirochaetes, major candidates for the role of noma causative agents, were minor constituents of the bacterial population and *F necrophorum* was not detected.[100]

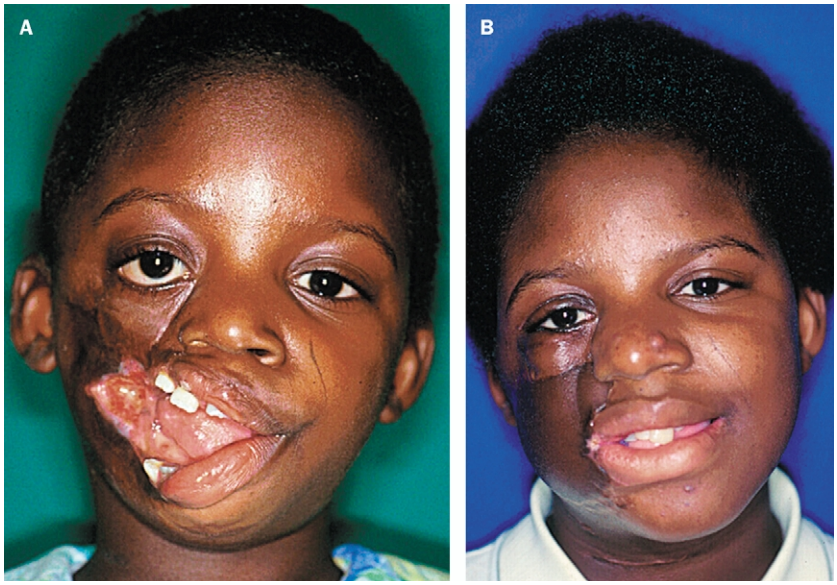

Figure 8. A patient with noma sequelae type I. (A) Before surgery. (B) 3 months after the last surgical procedure. Reproduced with permission from reference 118.

These labour-intensive methods provide a comprehensive inventory of the microorganisms, but only in a few individuals.[98] The information derived by sequencing should be transferred to more parallel techniques to enable the screening of a broader population of diseased and control individuals. Microarray technology will probably help to decipher the composition of complex microbial flora, since it provides simultaneous detection of thousands of genes or target DNA sequences on the same slide.[101–104]

Viral theory

An interesting viral theory of noma aetiology suggests that infection with herpesvirus could lower local immunity, thus facilitating the development of pathogenic bacterial flora (figure 5).[33,105] This hypothesis was originally concerned with the aetiology of ANG but later extended to noma.[37,39]

Among the herpesviruses, cytomegalovirus is the most frequently associated with periodontal diseases.[37,38,105–107] At the time of primary cytomegalovirus infection, the ratio of CD4-positive to CD8-positive cells is inverted, which may explain the weak immune response and the high frequency of secondary bacterial or fungal infections.[108–110] Cytomegalovirus can also directly infect polymorphonuclear neutrophils and interfere with their function.[87] Cytomegalovirus infection can cause an increase of interleukin 1β,[111] a potent bone-resorptive cytokine which is thought to have a role in periodontal diseases.[112] In less developed countries, cytomegalovirus infection occurs at the same age as the appearance of ANG and acute noma.[37,105] A study in Nigeria examined 22 children with ANG and 40 children without.[37] Of the latter group, 20 children were malnourished and 20 were in good general condition. In the ANG group, 59% of the children were seropositive for cytomegalovirus. By contrast, in the ANG-free group, only 5% were seropositive, with no difference between malnourished and well-fed children. The researchers found a high prevalence of cytomegalovirus in the gingival fluid of children with ANG and concluded that there was a relation between cytomegalovirus and ANG. A herpetic oral lesion clearly reflects damage to the mucosal barrier and reduced local immunity, which could lead to the proliferation of pathogenic bacteria and, possibly, to the development of ANG in an undernourished child.[37,38,106,113]

Taking into consideration previously mentioned features, elements of a plausible noma aetiology could include: a predisposing condition with all the above-mentioned risk factors; a primary infection with cytomegalovirus or another herpesvirus; a lesion of the gingival mucosal barrier, the postulated one being ANG; and an unrecognised bacteriological factor acting as a trigger for the development of the noma lesion (figure 5).[57,95]

Transmissibility and recurrence

Since a bacterial factor could be implicated in the aetiology of noma, the possibility that the disorder is transmissible has to be considered. In some African countries, noma is believed to be contagious and affected children are often rejected for this reason. At the beginning of the 20th century there were reports of noma epidemics among children in institutions or admitted to hospital for measles.[82] However, as in the ANG epidemics reported in soldiers during World War I (trench mouth), these probably reflected a common experience of risk factors and poor living conditions rather than true transmission. For example, there are no reports of children contracting noma at the same time as their siblings or other children living in the same village. Our group has personal experience of twins, each of whom was affected by noma but not at the same time, with the second twin developing the disease a year after the first. Several cases in a particular village have been observed but, again, never at the same time.

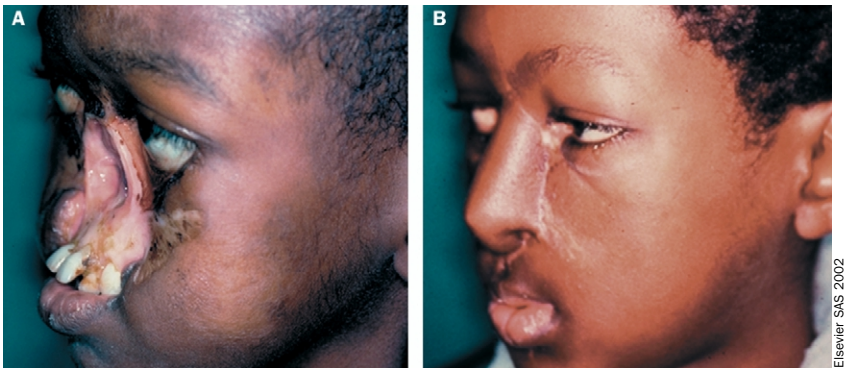

Figure 9. A patient with noma sequelae type II. (A) Before surgery. (B) after several surgical procedures for total nose reconstruction. Reproduced with permission from reference 118.

Experimental transmission of necrotic gingivitis in animals has been attempted in several studies. However, the injection into healthy dogs of dental plaque taken from gingival lesions gave rise to necrosis only when the injection was accompanied by injections of corticosteroids.[114]

There is no consensus about the recurrence of noma. Tempest affirmed that noma does not recur.[27] Emslie[33] reported only one case of recurrent disease but Adekeye and Ord[2] reported that four of 13 cases of acute noma were recurrences of episodes some years earlier. Whether the first episode was observed by the same team or was only recalled by the parents or patient is not clear; therefore the possibility that it could have been a severe necrotising gingivitis rather than a florid noma cannot be excluded. In a cohort of more than 580 children referred to the noma centre in Zinder, Niger, and followed up regularly since 1992, no case of recurrent disease has been observed (P Joly, personal communication). Similarly, among a series of 148 African children with noma sequelae operated on by our team since 1985 with regular follow-up, no recurrence has been observed.[56]

Treatment of acute phase

Management at this stage consists of attempts to improve overall health status by rehydration, nutritional rehabilitation, administration of vitamins (especially vitamin A), and treatment with antibiotics. Broad-spectrum antibiotic therapy covering mostly aerobic and anaerobic periodontal and oropharyngeal flora is generally recommended in the absence of definitive data on specific pathogens. Improved oral hygiene has to be introduced as soon as local conditions permit, and the adverse effects of poor hygiene have to be gently removed.[17,27,49,115] However, invasive intraoral intervention has to be avoided because of the risk of precipitating evolution of the lesion. In particular, extractions are possible only for teeth that are already loose. Reconstructive surgery is also prohibited in the acute phase and cannot be undertaken until lesions are well demarcated and healing is complete.[17] Importantly, during the healing phase characterised by fibrous scarring leading to definitive stricture of the mouth, physiotherapy should be started promptly and should continue after surgery to prevent recurrence of the stricture (figure 6).[2,56]

Surgical treatment

The correction of deformities after noma is one of the most challenging problems for plastic and reconstructive surgeons. The children and young adults affected by the disease can later show all kinds of disfigurements; each case requires an individual approach, and there is no standard surgical procedure.[56]

At the end of the acute phase, the necrotic tissues may slough spontaneously, but in many cases debridement of the wound is necessary to avoid secondary infection and to accelerate the healing process. Wound contraction can lead to mouth stricture, which can progress to complete closure of the mouth aperture with intertwining teeth and bony fusion between the maxillomalar complex and the mandible, a condition extremely difficult to correct surgically. Prevention of these contractures by conservative measures can greatly contribute to the final outcome (figure 6).

Reconstructive surgery is rarely considered earlier than a year after the

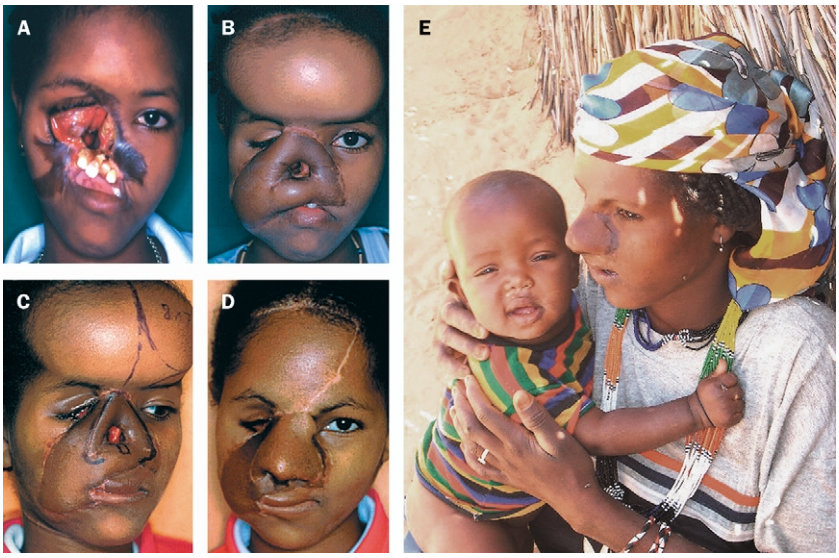

Figure 10. A patient with noma sequelae type IV. (A) Before surgery. (B) Reconstruction of cheek and lip soft tissue by means of a musculocutaneous flap and placement of a frontal expander. (C) Reconstruction of the upper lip with a local flap and preparation for nose reconstruction. (D) Final result with total nose reconstruction with a pre-expanded frontal flap and a rib graft. Reproduced with permission from reference 118. (E) The same patient, now a wife and mother, in her home village in Niger, several years later. Property of the Plastic and Reconstructive Surgery Unit, University of Geneva Hospitals. Reproduced with permission.

onset of the disease, except when sequelae prevent an adequate nutritional intake (figure 7). Since most patients live in very poor countries with inadequate medical facilities, an initial selection has to be made between the cases with a minor deformity that can be corrected on site by local surgeons or during surgical missions, and severe cases for which a sophisticated surgical environment will be needed to obtain a satisfactory result and avoid severe and even life-threatening complications. This selection can generally be made by an expert surgical team using records that include a photograph of the patient, the degree of mouth aperture, age, general condition, and comorbidities.

When first seen, the patient undergoes a thorough clinical and, if necessary, radiological examination so the stage of the disfigurement, the amount of true bone and soft-tissue loss, dental state, and degree of mouth stricture can be assessed. An action plan is drawn up by the surgical team, which includes the choice of procedures to be carried out, the type of intubation, and the time schedule of the various interventions. Most operations have to be done under general anaesthesia, and intubation is required. For mouth stricture, tracheostomy can be avoided by the use of fibroscopic intranasal intubation.[116]

Moreover, since most patients are children, special care and planning are indicated. Although the pathology is very varied, the treatment strategy includes the following. First, the mouth contracture must be released by removal of scar tissue. Excision of a hypertrophic coronoid process of the mandible may be necessary. In the case of maxillomandibular synostosis, a horizontal large bone fragment must be removed to release the constriction. Second, if bone has been destroyed, a vascularised bone flap is generally necessary and the problem should be addressed initially. Third, soft-tissue reconstruction and aesthetic refinements are carried out during subsequent operative steps. When required, a flap can be prefabricated,[52] or a skin expander inserted under the forehead[117] as a first procedure.

No precise guideline can be advocated for each type of noma sequela, because every case differs.[56,118] However, according to the extent of the defect, we believe that adherence to certain recommendations, published recently in a review of a series of 148 patients treated by the same team in which 275 flaps were used during 440 interventions, is important.[56] In type I, mouth constriction occurred in 67% of cases. The soft-tissue defects to be reconstructed included the inner side or full thickness of the cheek, part of the upper lip, and in some cases a nostril (figure 8). In type II, the centrally localised lesion does not induce any mouth contraction in most cases. The defects to be reconstructed include the upper lip, the nose, and, in some, the alveolar bone and the palate (figure 9). Type III sequelae are less frequent. Only 17 cases have been treated by our team (ten in Africa) by a one-step procedure. Mouth constriction was present in three cases without osseous bridge. Partial lower-lip defects are corrected by the mobilisation of soft tissue and local flaps. Type IV sequelae represent 50% of patients treated in Geneva. Most are associated with mouth constriction (70%), including osseous bridge (77%). Soft-tissue defects similar to the type I lesion are generally more important and even though the same principles of reconstruction are applied, they require more flaps and procedures (figure 10). Since the onset of noma generally occurs during early childhood, local bone defect and adjacent contractile scar impair normal facial growth.[119] In three cases, bone distraction to correct a secondary underdeveloped mandible has been used.

As in any type of surgery, reconstruction for noma sequelae may involve complications such as wound infection and flap necrosis, as well as those that can follow extensive and complex surgical procedures under general anaesthesia. If not chosen and treated correctly, the donor sites of flaps or grafts may be more disfiguring than the original lesion. In all cases, follow-up for at least 2 years is necessary for assessment of the result of the surgical treatment. Furthermore, the long-term benefit of surgery cannot be guaranteed without a close collaboration with noma centres in less developed countries to ensure postoperative physiotherapy and social reintegration, and to coordinate on-site visits by the surgical team.

The main objective of reconstructive surgery of noma sequelae is to restore a human face and to allow noma victims to reintegrate into a normal social life. Common examples are the ability to attend school, to get married, or to learn a skill (figure 10).

Search strategy and selection criteria

Data for this review were identified by searches of Medline, references from relevant book articles and chapters, and unpublished reports from research laboratories and public-health agencies. Many articles were identified through searches of our own extensive files. Search terms included "noma", "noma and malnutrion", "noma and measles", "noma and herpesviruses", "noma and fusobacterium", "noma and necrotising gingivitis", "necrotising gingivitis and malnutrition", and "noma and adult". Papers published in English, French, German, or Italian were reviewed.

Conclusion

Improved knowledge of the epidemiology, aetiology, and physiopathology of noma is urgently needed so that appropriate treatment and possibly prevention can be achieved. Factors to prevent noma and its sequelae include early recognition, appropriate diagnostic approaches, correct understanding of the disease process, and attempts at directed preventive and therapeutic strategies. Most importantly, a multidisciplinary team approach is needed for optimum research and management strategies. Adequate funding is urgently required for both basic and clinical research if a long-term solution is to be achieved, perhaps even the development of a vaccine if the disease proves to be of infectious origin.

Nowadays, noma could be preventable. If the disease could be detected and recognised at an early stage, would simple and low-cost care stop the evolution of the gangrene and avoid disfigurement? Can noma be controlled with improved management of conditions thought to be major factors of the disease, such as measles, malaria, and poor nutritional status? Would antimicrobial therapy at the

earliest phase of the disease solve the problem? These questions and many others remain to be answered by use of advanced epidemiological and investigational tools.

Acknowledgments

This work is dedicated to Edmond Kaiser, 1914–2000, founder of the Swiss humanitarian organisations Terre des hommes and Sentinelles, and to those who continue to pursue his work at the noma centres at Zinder, Niger, and in other African countries. Sentinelles was created in 1980 and is dedicated to combating the "destruction of innocence" in the world, especially the sexual mutilation, prostitution, and slavery of children in less developed countries, and including those who are outcast owing to disfigurement such as noma. We especially thank Martina Rusconi for her contribution as dental hygienist to the research programme of GESNOMA on the aetiology of noma in Niger. We thank the health-care workers and the administration of the University of Geneva Hospitals for their dedication to care of patients and logistic support in humanitarian medicine, Gertrude Hirzel for support and encouragement, and R Sudan for editorial assistance. The research programme on the aetiology of noma conducted by GESNOMA is currently funded by the Hirzel Foundation. DB-M is supported by GESNOMA. Surgical missions are conducted in Africa by the Plastic and Reconstructive Unit of the University of Geneva Hospitals under the direction of DM and BP and supported by the Association d'Entraide pour les Mutilés du Visage and Sentinelles.

Conflicts of interest

None declared.

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