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Noma: a forgotten disease

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Alarming reports from the World Health Organization (WHO) over the past 10 years have alerted the oral health/health communities that the frequency of noma, a hideous disease of poverty, is on the rise in parts of sub-Saharan Africa and in disaster-ridden areas [1,2]. Noma, also known as cancrum oris, is a devastating disease described as early as 1848 by Tourdes as a

> . . .gangrenous affection of the mouth especially attacking children in whom the constitution is altered by bad hygiene and serious illness especially from the eruptive fevers, beginning as an ulcer of the mucous membrane with edema of the face extending from within out, rapidly destroying the soft parts and the bone and almost always quickly fatal [3].

This description of noma is almost as valid today as it was in 1848. Although the introduction of antibiotics has changed the prognosis, the mortality rate is still reported as critically high, inferring that many children are not being treated. It is a disease with a multifaceted etiology and pathogenesis of known and suspected causes but also with missing links.

The name of the disease *noma* comes from the Greek word *nomein*, meaning "to devour," and the disease was reported already in the era of Hippocrates [3]. There are numerous reports of noma throughout history and from many parts of the world, primarily from poverty-stricken areas where the living conditions are deplorable, during periods of famine, and at times of catastrophe. The disease was common in both Europe and North America before the twentieth century [3] but was almost eradicated with the elimination of poverty and with improvement in health care after the industrial revolution. The disease, however, has resurfaced even in modern times in Europe in connection with war and other disasters. Noma was reported from the Nazi concentration camps in World War II. Acute

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necrotizing gingivitis (ANG)[a], a putative precursor to noma, was commonly seen in the trenches on the western front in World War I and was the disease from which the name *trench mouth* originated [4–7]. Noma could well occur anywhere if living circumstances become severely compromised and, thus, should not be regarded as "just another tropical disease" [1,3]. Although noma is believed to be noncontagious, it can occur after an epidemic of measles [1,3,5,6]. The last time multiple cases of classic noma occurred in the United States was after a measles epidemic in an orphanage in Albany, New York early in the twentieth century [1,3,8].

Noma has an estimated incidence in sub-Saharan Africa of about 100,000 to 140,000 cases per year, with a mortality rate of 70% to 90% and an estimated prevalence of 750,000 to 1 million cases. These numbers vary from report to report and there are no definitive accounts on its incidence and prevalence [1]. There are several explanations for the inconsistency. The disease most often occurs in poor, remote locations in developing countries of Africa where there is limited, if any, available means for transportation or communication. In some communities, noma is regarded as a curse, with a spell cast on a family or even an entire village [1]. Thus, the infected child might be hidden or ignored until she or he dies. Subsequently, the death may not be reported as a case of noma but referred to as any other childhood disease.

In a recent review of the noma literature for WHO, Tapsoba [9] reported that cases of noma have been observed in 64 countries, with most in developing countries and in the sub-Saharan region. This review, however, does not clearly distinguish between noma and ANG, and some of the literature references date back to the 1960s and 1970s. Thus, the report may not accurately describe the current situation, requiring additional epidemiologic research. Sporadic reports of solitary adult cases of noma from both the developing and the developed world seem to be a secondary disorder in individuals with an already medically complex situation such as HIV/AIDS and other diseases [10–18]. Recent literature references indicate that noma is almost exclusively found in sub-Saharan Africa and mostly in West Africa [19–21]. It has been inferred that noma occurs along the area stretching from Senegal across West Africa into Sudan and Ethiopia, coinciding with the so-called "meningitis belt."

The incidences of ANG, a suspected precursor to noma, may be higher in this area than in other areas such as South Africa and Kenya in East Africa [22,23]. Health care providers in Malawi report that about two to three cases are seen in a dental clinic in the latter parts of the dry season in August and September when malnutrition is rampant in rural

[a] The terms ANG and ANUG (Acute Necrotizing Ulcerative Gingivitis) are used synonymously in the reference material or combined as ANG/ANUG. To avoid confusion, the term ANG is used throughout this article.

communities (Mnthambala AT, personal communication, 1998). A survey of remote villages in the Phalombe district in southern Malawi indicated that the local people were aware of the disease but that it was relatively uncommon and had not been seen for several years (Naty Lopez, personal communication, 1998). These reports may not have provided the real picture because superstition and other beliefs may have influenced the willingness of the surveyed to discuss the disease. The situation in Malawi, however, has deteriorated over the last couple of years, with widespread famine and a serious HIV/AIDS situation that could have led to an increased prevalence of noma.

This article is limited in scope and only discusses facial noma or cancrum oris; however, it is worth noting that there are uncharacteristic presentations of noma described in the literature. Noma neonatorum [24,25] is a rare form of noma affecting newborns in the first months of life. In this situation, the infants may already be medically compromised at birth. In a recent article, it was argued that noma neonatorum is a neonatal form of ecthyma gangrenosum and should not be classified as a form of noma [26]. Noma pudendi, another rare presentation of the disease, affects the anogenital (perineal) area and may lead to a necrosis and to amputating parts or all of the involved genitalia [26,27].

Clinical presentation

Noma affects children mainly after the weaning period and into their teens, even though there are an increasing number of reports of adults with the disease, albeit commonly as a complication of other medically complex situations. Noma, whether in a young child or in an adult, is rarely the primary condition [28].

The clinical presentation of the disease is typical in most cases. Ninety percent of the cases develop before the age of 10 years [29]. A child is at an increased risk after the mother stops breast-feeding when the best source of protein and protective antibodies are often replaced with a carbohydrate-rich diet and unsafe water, which may lead to malnutrition and diseases [30]. After a sibling is born, the newborn infant commonly receives total preference and, thus, the older child gradually becomes at risk for noma. The question of gender preference for noma is unclear, with some reports stating that girls are more at risk and other authors claiming that this is not the case.

A related debate is whether noma occurs with similar incidence throughout the year. It seems that the disease has a tendency to be more aggressive during the dry season in Africa, which often coincides with famine [8]. For still unknown reasons, it may affect only one child in a family living under the same circumstances.

Initial oral lesions that could develop into noma are ANG and other intraoral mucosal ulcerations of the gingiva. These lesions are often seen in

the premolar or molar region in either the maxilla or the mandible and are often accompanied by a swelling that will become massive over a short period of time. The infectious process will spread to the underlying bone, and ulcerations will progress to necrosis. At this stage, the process is very painful, with profuse salivation and strong odor.

Sequestrations of large bone fragments with teeth may now occur. Within days, a dark bluish/purplish furrow develops on the cheek that may involve the corner of the mouth or the lips. A necrotic mass is formed with a breakthrough onto the outside of the face. The lesion is commonly substantially larger on the inside than on the outside of the mouth and it may involve the tempomandibular joint, palate, infraorbital margin, nose, antrum, and virtually any part of the face. The gangrenous area is covered with bacterial masses and inflammatory cells (Fig. 1). If no intervention occurs, the process will continue and the child will perish. It is estimated that between 70% and 90% of the children, if untreated, will succumb to complications from infection such as septicemia, pneumonia, or diarrhea [20]. The child often is malnourished, apathetic, listless, and dehydrated and may suffer from underlying diseases such as malaria, HIV/AIDS, tuberculosis, or gastroenteritis, to mention just a few.

Only a small percentage, if any, of the cases in the initial stages will be seen by a health care worker. Noma victims may also be brought for care when it is already too late for successful intervention [18,31]. When a person is brought for care in the earlier stages of the infection, however, simple

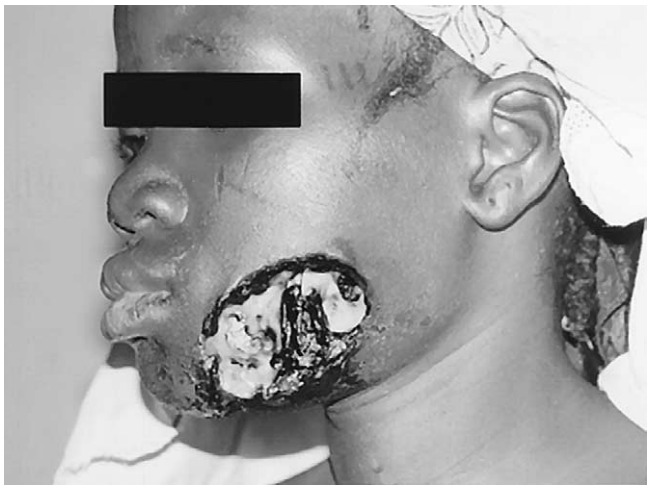

Fig. 1. Young female with noma in the invasive-destructive stage and with HIV disease. Patient was seen in Maradi Hospital, Niger in the fall of 2000. (*Case described in* Mamadou S, Kaka M, Montavon C, Noman Y, Maty M, Delaporte E, et al. A propos d'une association VIH et noma au Niger. Bull Soc Patho Exot 2002;2:76.)

antibiotic treatment with rehydration and dietary rehabilitation will halt the disease.

Diagnosis of advanced lesions is usually not difficult to reach; Mead commented in 1946 that "there is nothing else like it" [3]. A history of recent fever (ie, measles or other disease), signs of malnutrition, excessive salivation, foeter ex oris, and sore mouth with or without facial swelling all point to noma. Among the differential diagnoses that should be considered, however, are mucocutaneous leishmaniasis, with disfiguring and destruction of nose, throat, and mouth; lupus erythematosus, which is a slowly progressing disease; syphilis, oral cancer, yaws (an infectious tropical disease caused by the bacterium *Treponema pertenue*), and leprosy agranulocytic ulcerations, none of which is common in younger ages; and physical trauma including burns [3,20,29]. In the era of HIV/AIDS, however, opportunistic infections and diseases may make a differential diagnosis more difficult.

Survivors, whether due to a successful intervention or not, suffer from severe facial disfigurement and functional difficulties in terms of speech and food intake. Trismus, a common complication, severely limits food intake and oral hygiene and can rarely be treated without surgery. Other complications based on level of tissue destruction include saliva leakage, nasal regurgitation of food, and impaired vision (Fig. 2).

Etiology and pathogenesis

Some of the poorest parts of the world (primarily the western parts of sub-Saharan Africa, including but not limited to Niger, northern Nigeria, Mali, and Burkina Faso) are areas where noma occurs. The 2000/2001 World Development Report [32] indicators for health, poverty, and quality of life are among the lowest in the world for these countries. Life expectancy at birth in 1998 for males was 44 years in Niger and 52 years in Nigeria compared with 77 years in Sweden and Japan and 74 years in the United States. The mortality rate (per thousand) for children under 5 years of age in 1998 was 250 in Niger (second to Sierra Leon) and 119 in Nigeria compared with 5 in Sweden/Switzerland/France and Finland. Finally, the percentage of the population with access to adequate sanitation in 1996 was 15% for Niger and 36% for Nigeria. Western European countries reported 100% and the United States reported 98% access in 1985.

In 1999, 300 million people in sub-Saharan Africa were estimated to live on less than one US dollar per day. Sub-Saharan Africa is the only continent where there is an increasing trend of poverty, with an estimated 345 million people projected to live on less than one US dollar per day in 2015 [33].

These downward trends in health, poverty, and quality of life forecast a gloomy future for sub-Saharan Africa. Political, ethnic, and religious strife and the HIV/AIDS pandemic are just some of the factors leading to difficult living circumstances. In addition, the current global economic situation

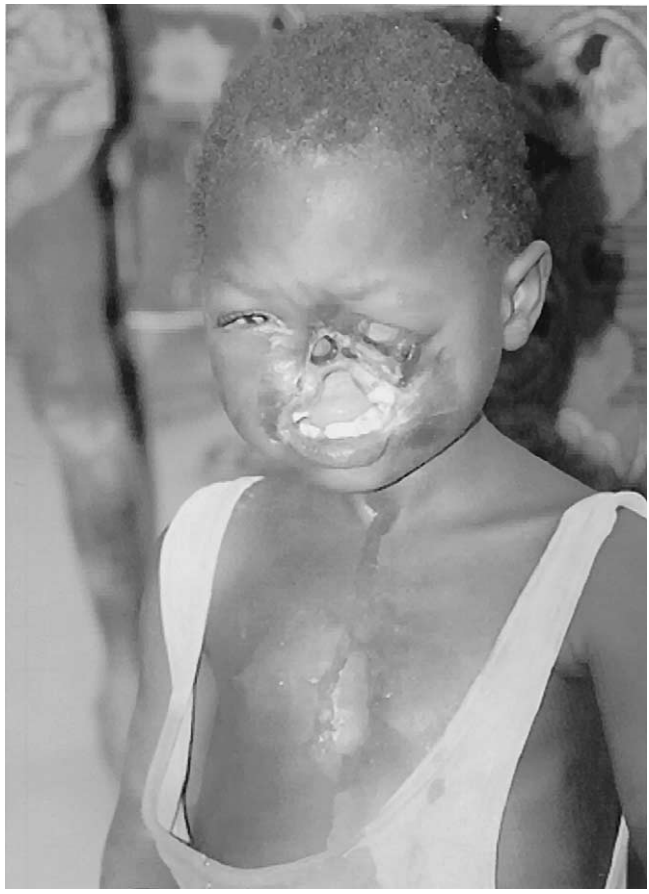

Fig. 2. Child from village in Zinder area, Niger. Severe case of noma in a chronic stage. Note the saliva streaming down the girl's chest.

cannot be disregarded. In recent articles related to oral health in Africa and other developing countries, Hobdell [34,35] argued that "many local oral health issues (including noma) cannot be fully understood unless seen in the context of the global economy." It seems clear that the move toward a global economy has resulted in both good and bad outcomes. For many developing countries, however, there is not much good news, with a widening gap between the rich and the poor, both between countries and within countries [34]. The large and poorest group of the world's population (2.8 billion people) is living on less than two US dollars per day. This group could become even more marginalized, with dire consequences for individuals and, in particular, for children and women.

Considering this discussion, it is obvious that one of the major risk factors for acquiring noma is the society into which a child is born. It is not

only geographic location that matters but also social class and culture. Obiechina et al [36] discussed the increased risk of growing up in societies and cultures where the educational level is low and where polygamy with large families living in poverty is common. Poverty itself breeds many of the risk factors for noma, including chronic malnutrition, poor environmental sanitation, poor oral hygiene, unsafe water, close living situations with domestic animals, exposure to animal and human fecal products, and exposure to viral and bacterial infections [20,37]. The stress on children living under these circumstances should not be overlooked. It is suspected that through a cascade of reactions, the level of circulating cortisol is increased, thereby weakening the immune system [20].

Among the major risk factors for noma, measles must be regarded as one of the most dangerous factors next to poverty [3,6,38]. Severe measles is a dreadful curse on children in the developing world but is rare in the developed world because of mandatory child vaccination programs. Measles, however, is not the only disease that has been implicated in the noma pathogenesis. Malaria, tuberculosis, chicken pox, herpes infection, bronchopneumonia, and gastroenteritis also are mentioned [20].

ANG is believed to be a substantial risk factor and even a precursor of noma. It is most commonly found among disadvantaged children and is identified as a socioeconomic problem [39–41]. Aggressive necrotizing gingivitis can be an oral manifestation related to HIV but studies have shown that ANG is on the rise in several African countries independently of the current HIV/AIDS epidemic [41,42].

Chronic malnutrition is a clear predisposing factor in the pathology of noma [6,43–45] and both noma and ANG are reported to be more prevalent when food is scarce [20,22,23,46]. Insufficient intake of essential nutrients in combination with a viral infection (measles, herpes infections) will impair the mucosal immunity, allowing trigger bacteria (see later discussion) to enter the tissue. Enwonwu et al [44] recently reported that the majority of a group of Nigerian children with noma showed a marked depletion of plasma retinol, zinc, albumin, and ascorbate, which is suggestive of malnutrition. It must be mentioned, however, that changes in plasma levels of some of these nutrients reflect acute-phase response due to infectious inflammation. Vitamin A and zinc deficiencies may lead to reduced cell-mediated immune function and an early breakdown of epithelial tissue, with pathologic changes of the oral mucosa resulting in invasion of pathogens. Difficulties in eating due to the infection would aggravate the precarious situation already at hand.

Although noma has been studied for over 150 years, its etiology and pathogenesis have not been convincingly discussed until recently. In a series of articles, Enwonwu, Falkler, and Idigbe with co-workers [20,37,44,47] hypothesized about the mechanisms involved in the noma disease process. They suggested that the process has three stages involving nutritional, bacterial, viral, and cultural components.

In the first stage, the host's resistance is lowered, often due to malnutrition, viral infections and, most commonly, measles. Other diseases such as herpes viral infections (including cytomegalovirus infection), malaria, and tuberculosis could also be precursors to noma. Mucosal resistance becomes impaired and oral ulcers combined with poor oral hygiene allow for easier access of infectious agents to enter the system.

In the second stage, the causative agents invade the tissue, and the child's condition allows for massive bacterial growth and rapid disease progress.

In the final stage, the invasive-destruction stage, the disease rapidly advances, with severe intraoral and extraoral tissue destruction leading to a serious situation. Unless intervention takes place, the disease will progress to death or it will become self-limiting and the child recovers from the acute phase but with irreversible tissue destruction. The mechanisms for noma to become self-limiting are not yet understood.

It has been difficult to pinpoint a specific trigger agent in the complex microbiota of the acute noma lesion, although many have studied this and have suggested a critical involvement of different bacteria. It was speculated by Hicken and Eldridge [48] that a symbiotic relation between fusiform bacilli with nonhemolytic streptococci and *Staphylococcus aureus* was necessary for noma to develop. Others have reported the occurrence of *Borrelli vincenti* and *Fusiformis fusiformis* as prominent bacteria in the lesions [5,49]. These early studies suffered from several obstacles: difficulty in obtaining specimens from early lesions, problems with large numbers of microorganisms that could not be adequately cultured according to modern standards, lack of an animal model to study the disease, and a confusing taxonomy [47].

It was not until the reports by Falkler et al [47,50] and Paster et al [51] that potential trigger organisms were suggested. Falkler et al [47] studied the predominant microbial flora from active noma lesions in eight patients (3–15 years of age). Standard anaerobic culturing techniques were used to cultivate the specimens, and *Fusobacterium necrophorum* was isolated in over 87% of the specimens. *Fusobacterium necrophorum* has most commonly been associated with necrotic disease with foul odour in animals and has also (but infrequently) been isolated from infections in humans and from diseases such as necrotic tonsillitis, brain abscesses, and oral and dental infections [47]. Numerous other microorganisms were also identified and, among those, *Prevotella intermedia* was found in 75% of the cases. This second most common isolate (*P intermedia*) is a gram-negative anaerobic organism that forms black pigmented colonies on blood agar. Whether this is a previously reported black pigmented microorganism (*Bacteroides melaninogenicus*) found in noma lesions has not been established [52]. *P intermedia* has been recognized as a putative pathogen in ANG and also in progressive periodontal lesions. Falkler et al [47] proposed in 1999 that *Fusobacterium necrophorum* might be one such trigger bacteria that could enter the system through mucosal surfaces in the oral cavity damaged by malnutrition and

vitamin deficiencies. It was also proposed that children who live in close quarters, share water sources with domestic animals, and come in contact with animal fecal matters may get infected through these pathways. After the microorganism is established, it could trigger the infection either alone or in a multimicrobial process. *Fusobacterium necrophorum* produces a toxin and substances that are destructive to the tissue, explaining the rapid progression of the disease. *P intermedia* has the ability to break down lipid structures that could add to the tissue destruction. It also produces proteolytic enzymes capable of breaking down IgG, with a negative effect on the elimination of microorganisms. Several antibiotics were tested and these strains were sensitive to all of them, except for one strain of *P intermedia* that was resistant to penicillin. These findings could be further evidence that these strains are part of the pathogenesis due to their potential of inducing severe pathology and also because noma infections respond to antibiotic treatment. This is an intriguing hypothesis and additional research should be done to either accept or discard the hypothesis.

In a recent article, Paster et al [51] studied the bacterial multiplicity of noma lesions using culture-independent molecular methods. Four of the samples they studied came from the same collection of eight specimens used by Falkler et al [47] in their article in 1999. The molecular technique revealed 67 bacterial species, of which 25 had never been cultured in vitro. A number of these species are not commonly found in the oral cavity, although this is not surprising because noma lesions are open to the environment. Several species previously implicated as noma pathogens (spirochetes and *Fusobacterium*) were detected in at least one subject. Comparing results from these two studies using the same specimens raises some concern because two different outcomes are seen. These contradicting results even further emphasize the importance of additional research to elucidate the microbiology of noma.

Traditionally, disease risk factors do not include the social and cultural aspects of a society where a specific disease occurs. It is this author's belief, however, that those factors need to be part of the equation. In a recent but unfortunately unpublished fascinating study of the Hausa people in Niger, the sociocultural situation's influence as a risk factor and on disease patterns was reported by Trudeau [53] in 1999 to the WHO. Issues such as cultural values, decision-making processes, traditional healer's impact, and a village's political structure must be regarded as important as the medical attention of the disease. We must take the following statement by Trudeau [53] to heart if we are to make progress in prevention strategies: "health and illness are not only biological manifestations, but have social and cultural significance as well."

Treatment

The treatment can be divided into two major phases: intervention in the acute stage and surgical reconstruction of sequelae.

Acute intervention should consist of administration of appropriate antibiotics [6,28], rehydration, correction of electrolytic imbalances, administration of nutritional supplements that often can be done through the mouth, and addressing other diseases such as malaria, tuberculosis, parasites, and skin disorders. The literature agrees that there are no indications for "heroic" surgery in the acute phase, although older literature emphasizes such an approach [3,29,54]. Surgical intervention at this stage should only be recommended if secondary hemorrhaging occurs. Local wound care includes irrigation of the oral cavity, frequent wound dressing, and excision of necrotic tissue. Fully sequestered bone fragments and loose teeth may also be removed. During the period of healing, extensive scarring with constrictions occur both inside and outside the mouth. Ankylosis of affected bone structures leading to trismus is a severe complication that is commonly seen and where surgical intervention is needed (Fig. 3); however, a slow and gradual forceful opening of the mouth and "break" of the constricting structures (Fig. 4) may be partially successful in restoring limited but nevertheless important function in less severe cases where bone fusion may not have occurred (P.B., unpublished data, 2000).

Reconstructive surgery techniques are complicated and not part of this review. The interested reader is directed to the many excellent articles that can easily be found in the literature.

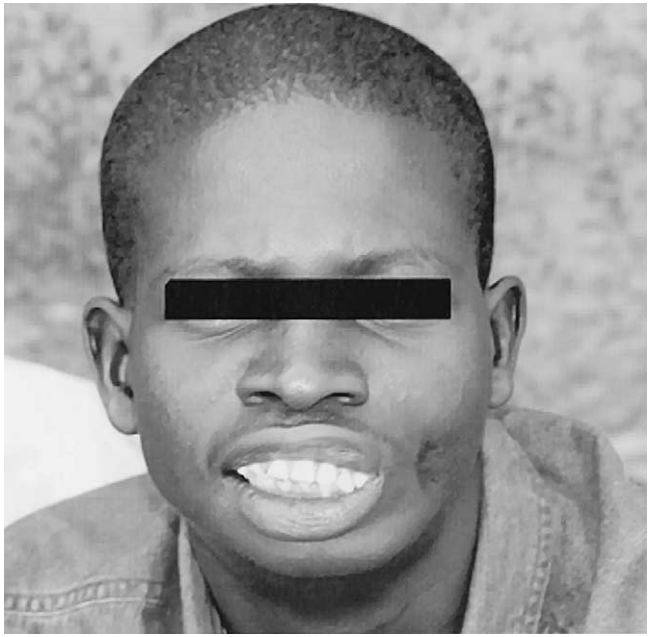

Fig. 3. Young man recovered from noma but with complete trismus.

Fig. 4. Treatment of trismus. As many tongue blades as possible are inserted between the teeth. One additional tongue blade is slowly pushed in between the others, increasing the opening.

Reconstructive surgery may be done both locally "in country" and in some European countries including Holland, France, Switzerland, and Germany. The German Hilfsaktion and the Swiss Sentinelles are two of the European organizations that send surgery teams to affected areas to assist local surgery teams. This assistance has an advantage in that a relatively large number of children can be evaluated and have reconstructive surgery. In more complicated cases, several surgeries must be done before an acceptable result can be obtained. A second advantage with visiting surgery teams is that local surgeons can get "continuing education" on site, become more advanced in their skills, and later could assume increased responsibility for those in need of reconstructive surgery. An increasing number of noma cases are now being treated by local teams of surgeons (Fig. 5). Some of the most severe cases, however, are still referred to plastic surgery clinics in Europe at a staggering cost. The child will be under the care of specialists but away from his/her home country and village for long periods at a time, which could create a new set of problematic social issues such as reintroducing the child into village life after treatment, which is a complicated process that has not always been successful (P.B., personal observation, 2000). The major problem is that the child would have been used to a living situation at a European hospital that is dramatically different from village life.

Another approach to the some of the concerns related to surgery is to establish a local specialized hospital for reconstructive surgery. This approach would be more beneficial in terms of cost and care and diminishes the reintroduction issue. The Noma Children's Hospital in the heart of the "noma belt" in Sokoto, Nigeria is just such a hospital. It is owned by the

Fig. 5. Girl with self-limiting noma. She was a candidate for reconstructive surgery at the Noma Pavilion in Niamey Hospital, Niger.

Sokoto State Government but receives substantial funding from the federal government of Nigeria and from international foundations.

The World Health Organization noma network

It was in the early 1990s that a wider interest for noma began, following new reports of an increase of cases seen primarily in West Africa. The need for updated and reliable survey data and other strategies to address noma became obvious. The WHO in collaboration with nongovernmental organizations conducted surveys and Delphi-type consultations from 1992 to 1994. Since then, limited surveys in a few West African countries have been conducted. Previous reports often dealt with isolated cases and not with the broader picture, giving the impression that the disease was almost eradicated.

Sporadic cases have been reported from other parts of the world. There are many reasons for the poor epidemiologic data, similar to the reasons why access to care is so limited: lack of official monitoring, remote rural areas, high mortality rate, incorrect death diagnosis, lack of disease knowledge among primary health care workers, and sociocultural obstacles. The WHO launched The International Action Network Against Noma on the World Health Day in 1994. A five-point program was established to address the growing concerns about noma. The outline of the program as listed in Box 1 originates from the WHO Noma Website and with the following URL: http://www.who.int/ncd/noma/noma_whostrategy.htm.

The WHO activities are ongoing, with an evaluation mission to Niger in 2000 and a strategic planning meeting in Harare, Zimbabwe in 2001. Numerous organizations such as Nongovernmental Organizations (NGOs),

Box 1. WHO noma action agenda

1. Prevention. Set up information and educational program to make parents, especially mothers, aware of the signs of noma and the urgent need to act. Train health care workers to detect the disease and provide the emergency care needed.
2. Epidemiology and surveillance. Organize and finance epidemiologic research on the occurrence and prevalence of the disease. Introduce appropriate preventive actions based on the epidemiologic research.
3. Etiologic research. Promote research to study the cause or causes of noma and why it develops in some children but not in others.
4. Primary care. Arrange for health services for local treatment of patients. Establish availability of necessary antiseptics, drugs, and nutritional supplements.
5. Surgery and rehabilitation. Refer children who are severely disfigured and require complex surgical treatment; organize transport; provide after-care and rehabilitation; assist in reintegration of treated children into their society. Train local health workers to assist noma sufferers. Set up a specialized regional center in West Africa for complex treatment of noma patients.

universities, foundations, WHO Collaborating Centers, and the media are participating in the project. The National Institute for Dental and Craniofacial Research (NIDCR) at the National Institutes for Health lists noma as a high-priority issue for international collaborative research. NIDCR also has produced a video (*Science Knows No Borders*) from the mission to Niger in 2000. That is available from NIDCR to schools and organizations.

One other sign of an increased interest and willingness to address the noma situation was a United States Congressional Hearing, with testimonies in the Congressional Human Rights Caucus in the spring of 2002.

Summary

According to recent reports from the WHO, noma (or cancrum oris), a hideous, ancient disease primarily affecting children living in poverty in parts of sub-Saharan Africa, is increasing. Noma often starts as an ulcer on the oral mucosa or as ANG and commonly after a bout of measles or other disease. It quickly develops into a massive necrosis, moving from the inside outward, often involving major portions of the face. Early treatment with

antibiotics, rehydration, correction of electrolytic imbalances, and administering nutritional supplements will halt the disease. The high mortality rate, however, indicates that many children are not given care or brought for care in time. Surviving victims often display severe facial deformities that demand extensive reconstructive surgery. Current research has elucidated parts of the pathogenesis of noma. The WHO started the International Action Network Against Noma in 1992, with its official launch on the World Health Day in 1994; a five-point action plan was presented and current work follows that plan.

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