SEVERE MEASLES

and

MEASLES BLINDNESS

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SEVERE MEASLES AND MEASLES BLINDNESS

Introduction

Blindness in children following a severe form of measles has been reported from Africa for many years. In pre-industrialized Western countries anecdotal accounts also reported a severe measles with consequent blindness, although such severe measles virtually disappeared from the advanced world prior to the widespread use of antibiotics or vaccination. In Africa severe measles and measles blindness continue to be reported to this day.

The origin of the severe form of measles and the etiology of the resulting blindness remain unknown. One theory states that the age and nutritional status of a child prior to measles infection dictate the outcome. Another suggests that severity (death) is the result of a synergistic effect of the measles virus and a secondary infection and is not related to nutritional status. The blindness associated with severe measles has been ascribed to vitamin A deficiency, a secondary bacterial or viral infection, or traditional practices. The objective of this paper is to summarize the available evidence regarding the origin of severe measles and the etiology of measles blindness in Africa by a literature review and subsequent exploration of these various hypotheses.
SEVERE MEASLES
AND
MEASLES BLINDNESS

Summary

Although clinical descriptions of measles similar to those recorded from developing countries today were reported in pre-industrialized Western countries, the decline in measles severity noted in the early part of this century in the Western world has not been paralleled in developing countries. Severe measles may be defined by two quantitative measures allowing for comparability:

1) Numbers of complications associated with measles.

Pneumonia and diarrhea are the two most common complications of severe measles and contributing factors in over 50% and 30% respectively of reported deaths of hospitalized measles patients in developing countries. Other complications associated with severe measles include a darkened rash, purulent conjunctivitis, laryngitis, otitis media and stomatitis.

2) Case fatality rates.

Case fatality rates ranging from 2.5 to 25% have been reported for measles patients from hospitals in East, West and Central Africa. Hospital reports from Asia and Latin America present similar case fatality rates - ranging from 5 to 23%. Community-based studies which include the population with mild as well as severe measles observe rates in the 6-10% range.

One theory to account for the observed measles severity prevailing in
developing countries states that the outcome of the illness is dictated by the condition of the individual prior to infection — young age and a poorly nourished state being important predisposing factors. Quantitative evidence in support of this theory are minimal. Although reports have shown that younger children are more likely to die unless protected by maternal antibodies or vaccination, several publications have also shown an increased risk of death in measles-infected adults over the age of 20. The impact of prior nutritional status on measles severity (death) as measured by anthropometry is controversial: While data from the Machakos Project of Kenya support the theory relating prior poor nutritional status to measles deaths, a recent study from Bangladesh found measles mortality unrelated to the prior nutritional state.

A second theory to account for measles severity suggests that measles and measles-complications (e.g. prolonged diarrhea/dysentery) determine severity (death) due to a synergistic effect of the two infections. Susceptibility to intercurrent infections depends on the immunological response of the measles patient, and is most often associated with the cellular-mediated immunity (CMI) known to be depressed with measles. As reduced immunity is common to all measles patients, a further predisposing factor, malnutrition, has been suggested for those with severe measles. Although evidence is indirect and conflicting, it is suggested that measles and malnutrition work synergistically to depress the CMI longer or to a greater extent, thus allowing for increased measles morbidity and mortality.

Hence, nutritional factors may play a role in predisposing an individual to severe measles, but the evidence to date are not convincing.

Measles-blindness, another complication associated with severe measles,
is most frequently reported from Africa, although it has been observed and reported also from Latin America, Asia, and pre-industrialized Europe. A quarter to half of blind children with corneal involvement from these countries claim association with measles. Studies of hospitalized measles cases report "damage to the eye" in the range of 0.8 to 2.8%, rates that are probably underestimated due to the possibly lengthy duration between measles onset and the resultant ocular damage.

The cause of measles blindness remains unknown. Although measles virus has been shown to replicate in the epithelium of the conjunctiva and cornea, the etiology of the ulcers involving the stroma of the cornea and the ensuing necrosis which permanently impairs vision has been variously ascribed to:

- vitamin A deficiency – xerophthalmia,

- infection by bacteria or viruses due to lowered corneal and systemic resistance (recently the herpes simplex virus has been implicated), and/or

- traditional medical practices.

Clinical diagnoses and laboratory analyses have supported both the vitamin A and herpetic infection theories, although the sequence of ocular changes widely associated with either xerophthalmia or herpetic keratitis have not been observed in these patients. Adding to this controversy is the unknown proportion of measles cases treated with traditional ophthalmic medications and the extent of damage that may ensue.
SEVERE MEASLES

A. Clinical Measles

An uncomplicated form of measles is now witnessed in the advanced industrialized countries. A child presents with a slight elevation of temperature, malaise and anorexia; the fever subsides for a day or two only to rise again as catarrhal signs appear—conjunctivitis with photophobia, coryza and a hacking cough. These symptoms may resemble a severe upper respiratory infection, but the distinguishing feature of Koplik spots followed 24 hours later by a rash make the clinical diagnosis of measles a certainty. Koplik spots are almost pathognomonic of measles. Bluish-gray specks on a red base resembling grains of sand, they appear on the buccal mucosa and may cover the entire mucous membrane of the mouth in severe cases. This enanthem persists for several days and begins to slough as the rash appears.

The rash usually begins on the face and proceeds down the body involving the extremities. During the healing phase the involved areas may desquamate. As it progresses it becomes confluent, especially on the face and neck. The rash usually lasts about 5 days and starts to clear on the skin first involved. The patient is usually most ill on day one or two of the rash, and begins to feel better as the fever abates several days after the appearance of the rash. The entire duration from the late prodrome to the resolution of rash and fever is 7–10 days.

A different picture of measles is seen in a proportion of children in Africa (72, 92, 129), Asia (47, 66) and Latin America (134). The child presents with similar symptoms as described above, but the rash
darkens to a deep red color and may even progress to a violet or purple hue. A few days after the appearance of this darkened rash, an intense desquamation begins. When the rash acquires a purple hue, large scales of skin are likely to separate. The coughing develops into bronchopneumonia, and the hoarseness into laryngitis. Soreness of mouth progresses into severe stomatitis and ulceration of the oral membranes making feeding painful and difficult. Diarrhea/dysentery ensue before, during, or after the onset of the rash and weight loss and dehydration become increasingly severe. Conjunctivitis becomes purulent with grossly evident punctate keratitis and the associated photophobia; corneal clouding may develop followed by ulceration. Illness continues longer than the norm with recovery seldom less than 10-14 days after the onset of the rash. In some cases, the primary viral infection appears to increase susceptibility to any combination of subsequent complications—chronic pneumonia, recurrent diarrhea, chancre of the oris, blindness, kwashiorkor, and finally death.

Severe measles was also reported in children living in the pre-industrial period: Rhazes described the illness in the 10th century as 'Measles which are of a deep red and violet color are of a bad and fatal kind' (119). Pneumonia following measles was reported as the possible cause of nine-tenths of the over 10,000 deaths due to measles during the 1839 epidemic in England and Wales (53). Creighton in describing the 1807-1808 epidemics of Glasgow and Edinburgh quotes an Aberdeen observer, 'There were troublesome symptoms on almost every case— a violent pain in the belly, frequently accompanied with diarrhea (and even with vomiting), and with the dysenteric symptoms of tenesmus and muco in the stools. This bowel complaint usually lasted three or four days and wasted the
patients remarkably' (28). And soreness of the mouth was described by Goodhart and Still as part of the English version of measles in 1921 as, 'The tongue and mouth become dry and ulcerated or covered with sores, and rapid emaciation takes place...' (50). Such complications of measles have become less frequent and less serious in industrialized countries since the 1920s, although other infrequent complications, such as encephalitis and subacute sclerosing panencephalitis (SSPE), continue to demand attention. Vaccine programs initiated in the early 1960s have helped maintain this low level of measles complications.

B. The Measles Infection

Measles virus, morphologically a member of the paramyxovirus group, is composed of a single-stranded RNA genome. Although labile to heat, acid, proteolytic enzymes, and strong light, it remains infective for several hours in droplet form in the air (46). This allows transmission via aerosol and the most infectious stage of the disease is associated with sneezing and coughing. There is no significant vector of measles virus and no animal reservoir.

Measles virus grows in tissues throughout the body, but the lymphatic and mucosal epithelial cells of the respiratory tract are the main source of disseminated virus. Infected cells continue to release virus for several days as they are not rapidly killed. Adjacent cells are often fused in syncytia and these may slough off.

With the onset of the prodromal period 10–12 days after infection, virus appears in the tears, nasal secretions, throat and urine. It can be isolated also from blood, and giant cells have been found in the lymph
nodes, tonsils and appendix. The Koplik spots appearing at the end of the prodromal period seem to be a direct manifestation of virus pathology. With the appearance of the rash, neutralizing antibodies become detectable and free virus is cleared from the blood although it remains detectable in leukocytes for 1 to 2 days longer. Once cleared from the blood, infectious virus does not reappear. Occasionally, measles virus antigens and recoverable virus in the brain of patients with SSPE indicate that the virus may persist in the body for long periods.

C. Measles Mortality

The importance of measles at different times or among different sites is inferred from mortality data, the only means available to make comparisons. Using mortality data is not without its limitations, however; these rates are affected by intercurrent problems such as malnutrition, the age of onset, other infectious diseases, as well as variations in the health care services and drugs available. Also, underestimates of measles mortality or case fatality rates are common if general hospital records are examined as deaths may have occurred with measles contributing to death, but not recorded as the underlying cause (113, 38). On the other hand, hospital studies specifically of measles may lead to overestimates of its mortality with respect to the general population.

There are several accounts of measles epidemics prior to the beginning of the twentieth century when routine reporting was initiated in Europe and America. Creighton (1894) gives several accounts of a high
mortality in epidemics of measles (28). In the orphanage Hospice des Enfants Assiste in Paris between the years 1867 and 1872, 612 deaths occurred among the 1256 children who developed measles (41). In the early 1900s, case fatality rates for children in their first and second years of life were reported as 11.7 and 14.2% respectively in Scotland (92). By the year 1960 these rates had decreased in England and Wales with the case fatality rate for under fives reported at approximately 0.02%. This decline in deaths is also reflected in the measles mortality rates from the United States: in 1913, 12.8 persons died per 100,000 population; in 1963 the figure was 0.2 per 100,000 (71), and between 1971-75 the average annual rate was only 0.017 per 100,000 population (37). Furthermore, rates had reached 1.0 per 100,000 by 1936, well before sulfonamides and antibiotics were available to control the secondary complications of measles associated with death.

Mortality from measles in developing countries has not shown this decline and continues to the present at the high levels seen in the pre-industrial period of the Western countries. Knowledge of this comes primarily from hospital data in the form of case fatality rates. These rates are probably high for the general population as hospitalized cases are usually severely ill with complications that arouse the parent's concern. Measles alone is thought to be an inevitable part of childhood (90), a visitation of a goddess (149) or the object of the malevolent work of a witch, sorcerer or the like (59), and would not usually warrant hospital care. Case fatality rates ranging from 3 to 25%, as have been reported from African hospitals over the last two decades, signify a disease with a major impact on children (Table 1). Although not so frequently reported, similar rates have been witnessed in hospitalized
patients in Asia and Latin America (Table 2). Even community-based studies which include measles in its mild form as well as the more severe form, have reported case fatality rates ranging from 1 to 42% in Africa, Asia, and Latin America (Table 3).
Table 1  Case Fatality Rates For Hospitalized Measles Patients – Africa

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Rate (%)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>1960-61</td>
<td>17.0</td>
<td>Primarily &lt; 5 yrs</td>
<td>2</td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagos</td>
<td>1959</td>
<td>22.7</td>
<td>?</td>
<td>42</td>
</tr>
<tr>
<td>Ilesha</td>
<td>1958-61</td>
<td>25.3</td>
<td>&lt; 5 yrs</td>
<td>94</td>
</tr>
<tr>
<td>’’W. Africa’’</td>
<td>1963-4</td>
<td>12.3</td>
<td>Review of 2164 patients in Ghana, Ivory Coast, Liberia, Nigeria, Niger, Mali. &lt; 5 yrs</td>
<td>96</td>
</tr>
<tr>
<td>Mali</td>
<td>1968</td>
<td>15.2</td>
<td>Age group NA</td>
<td>59</td>
</tr>
<tr>
<td>Central Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congo</td>
<td>1962</td>
<td>19.0</td>
<td>Age group NA</td>
<td>79</td>
</tr>
<tr>
<td>Cameroon</td>
<td>1975</td>
<td>---</td>
<td>Measles represents 25% of child hospitalization and 50% of all hospitalized infant deaths.</td>
<td>55</td>
</tr>
</tbody>
</table>

*Age group NA – age group not specified.
## Table 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Rate (%)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Africa</td>
<td>1963-64</td>
<td>5.7</td>
<td>Review of 2376 cases of measles in 96 hospitals</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sudan, Uganda, Kenya, Malawi, Zambia, Rhodesia, Tanzania</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 5 yrs</td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>1963-8</td>
<td>11.5</td>
<td>&lt; 5 yrs</td>
<td>18</td>
</tr>
<tr>
<td>Kenya</td>
<td>1943</td>
<td>2.5</td>
<td>&lt; 5 yrs</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>1968-70</td>
<td>10.0</td>
<td>&lt; 5 yrs</td>
<td>101</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1975-8</td>
<td>21.0</td>
<td>Age group NA</td>
<td>75</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1974-5</td>
<td>8.8</td>
<td>40% in year 1</td>
<td>56</td>
</tr>
<tr>
<td>Kenya</td>
<td>1974</td>
<td>22.0</td>
<td>Age group NA</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>1976-7</td>
<td>22.0</td>
<td>Age group NA</td>
<td>97</td>
</tr>
</tbody>
</table>
### Table 2 - Case Fatality Rates For Hospitalized Measles Patients – Asia, Latin America

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Rate (%)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delhi</td>
<td>1960</td>
<td>15.7</td>
<td>95% children ( \leq 5 \text{ yrs} )</td>
<td>47</td>
</tr>
<tr>
<td>India</td>
<td>1971–3</td>
<td>20.0</td>
<td>(&lt; 10 \text{ yrs} )</td>
<td>68</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1972–76</td>
<td>4.7</td>
<td>MOH data—primary cause of death only</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>1974–76</td>
<td>23.3</td>
<td>Surabaya Ped Dept—primary and secondary cause of death</td>
<td>38</td>
</tr>
<tr>
<td><strong>Latin America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td>1960</td>
<td>6.5</td>
<td>All reported cases nationwide</td>
<td>120</td>
</tr>
<tr>
<td>Colombia</td>
<td>1972–73</td>
<td>15.2</td>
<td>Average 36.6 mo. (5 \text{ mo} - 13 \text{ yrs})</td>
<td>33</td>
</tr>
</tbody>
</table>
### Table 3 Case Fatality Rates for Measles Patients – Community-based Studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Rate (%)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>1956-61</td>
<td>7.0</td>
<td>&lt; 5 yrs</td>
<td>94</td>
</tr>
<tr>
<td>Imesi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gambia</td>
<td>1961</td>
<td>14.3</td>
<td>&lt; 10 yrs</td>
<td>80</td>
</tr>
<tr>
<td>Keneba and Jali</td>
<td>21.6</td>
<td>&lt; 5 yrs (Assumes all children had measles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>1974</td>
<td>6.5</td>
<td>0-14 yrs</td>
<td>97</td>
</tr>
<tr>
<td>Machakos Project</td>
<td>1977</td>
<td>1.7</td>
<td>0-14 yrs</td>
<td>97</td>
</tr>
<tr>
<td>Zaire</td>
<td>1980</td>
<td>6.1</td>
<td>&lt; 5 yrs</td>
<td>61</td>
</tr>
<tr>
<td>Kasongo Project</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Latin America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guatemala</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santa Cruz</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balanya</td>
<td>1960</td>
<td>6.6</td>
<td>9.0%–preschool</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.4%–school children</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(control village)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1963</td>
<td>7.1</td>
<td>5 mo – 17 yrs</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>5 villages</td>
<td>1959-53</td>
<td>4.5</td>
<td>51</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sathuvachari</td>
<td>1969</td>
<td>1.5</td>
<td>&lt; 6 yrs</td>
<td>109</td>
</tr>
<tr>
<td>Ichag</td>
<td>1970-4</td>
<td>1.1</td>
<td>92% of cases</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 7 yrs</td>
<td></td>
</tr>
<tr>
<td>Melmonavoor</td>
<td>1977</td>
<td>14.0</td>
<td>&lt; 10 yrs</td>
<td>45</td>
</tr>
<tr>
<td>Country</td>
<td>Year</td>
<td>Rate (%)</td>
<td>Comment</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Bangladesh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matlab</td>
<td>1974-75</td>
<td>4.6</td>
<td>1-71 mos</td>
<td>66</td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lombok</td>
<td>1977</td>
<td>11.8</td>
<td>&lt; 10 yrs</td>
<td>38</td>
</tr>
<tr>
<td>Bangka</td>
<td>1978</td>
<td>15.9</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>1971</td>
<td>42.0</td>
<td>&lt; 5 yrs</td>
<td>154</td>
</tr>
</tbody>
</table>
D. What causes Severe Measles?

Reports triggering concern for the continued presence of severe measles in developing countries came from Africa in the early 1960s. At that time it was postulated that the severity of measles was not due to any variation in the virus, but to factors in the host – primarily early age of infection and poor nutritional status prior to measles attack. It was theorized that a young, malnourished child suffering from measles would become still further wasted and more susceptible to other infections. Secondary invaders would then overwhelm the body and the child either would die or have a prolonged recovery. This sequence of events has been rarely challenged, although quantitative evidence to support it are minimal. The following is a review of the literature exploring viral and host factors in severe measles.

D. 1. The Virus

Epidemic behavior of a disease is often partially explained on the basis of a change in virulence of the organisms. Such altered virulence of the measles virus can be brought about during laboratory preparation of vaccines. Variants have also been isolated from virus populations – temperature sensitive mutants, defective interfering (DI) particle (a particle containing only a part of the viral genome), and non-interferon-inducing particles (89). Just how these variants can affect or modify virulence remains to be established along with any role they may play in establishing and/or maintaining persistent or severe measles infections.
In its natural or wild state, the measles virus is considered a stable agent with variation in its antigenicity non-existent for all practical purposes (78). Strains of measles virus from different countries have been found to be indistinguishable and antibody in sera from diverse populations shows identical specificity (11). To confirm this non-variation of the virus in clinical measles, Scrimshaw et al report the existence of both the mild and severe forms of measles in Guatemala — implying that they occur simultaneously. A survey of pediatricians caring for well-nourished children living under good social and economic conditions observed a mortality no different from that seen in the industrialized countries at the time (0.2 per 100,000 population, 1963), whereas a mortality rate of 693 per 100,000 was observed in a rural Guatemalan village (134).

D. 2. The Host Response

a. Age

Virtually all persons contract measles unless vaccinated, and practically no one has the disease more than once. All ages seem equally susceptible to infection beyond the first birthday. Up to six months of age, maternal antibody derived from a natural illness usually confers immunity against measles to infants and the disease may be modified by marginal levels of maternal antibody remaining during the latter part of the first year. After one year, the age at which measles is most commonly contracted depends on human habit, population density and population isolation (11). This observation is borne out in populations having no history of measles or suffering epidemics at widely spaced
intervals. Susceptibles in every age group may develop measles as illustrated by the experience in two island societies — the Faroe Islands where attack rates were 97/1,000 for all exposed persons in the 1846 epidemic (106), and in Greenland a century later with a rate of 976/1000 (23). In most countries adults are spared because they are immune, not because they are adults, and age of itself has no direct influence on the contraction of the disease.

Since the age distribution pattern of measles morbidity is determined by a critical mass of susceptibles and their exposure to the virus (7), most children in Western societies contract measles when entering school with a subsequent smaller peak of secondary cases among contacts (siblings and others) in their preschool years. In developing countries, most measles occur in children in the preschool years. In West African societies, Morley attributes this to an increased number of close contacts for the young over that of similarly aged children in Western society (92).

Mortality from measles is closely correlated with age. In the Greenland outbreak (23), the highest age specific death rates were for persons aged more than 55 years, with that for infants under one year next in order. In England and Wales and in the U.S., the highest case fatality rates are in children under one year, decreased in persons up to the age of 15 (6) or 20 (37, 8) and then increased again. In the developing countries of Asia, Africa, and Latin America, case fatality rates reported from hospital data remain high throughout the 6 month to 3 year range (45 47, 56, 59, 88, 92, 120). Community-based studies in these areas report that the age specific rates continue to be high to the
age of 5 (51) or 6 years (66). Data on measles mortality in adults in developing countries were not available.

Although the common age of measles infection in developing countries includes an age group most at risk to death in developed countries, factors other than age may be involved in predisposing the child between 1-6 years to the severe form of measles.

2.b. Premorbid Nutritional Status

In the early 1960s, it was postulated that malnutrition predisposed a child to the severe form of measles. The basis for this argument was a questionnaire survey of doctors in several countries that resulted in the statement - 'the areas where measles is severe are also areas where kwashiorkor is prevalent' (91). Supporting evidence came from a one-year clinical study in East African hospitals (95) where the mean weight of hospitalized children with fatal measles was found to be in the third percentile compared with the average weights (by age) for healthy East African village boys (156). Most hospital and community-based studies from developing countries give anecdotal information suggesting this same trend, but few present quantitative nutritional data. Even hospital studies that do present quantitative nutritional and measles severity data (29, 44, 47, 56, 129) only infer nutritional status of the patient prior to illness.

More appropriate to examining this hypothesis of a predisposing nutritional factor are longitudinal field studies that collect nutritional measurements routinely. Suggestive evidence came from a
study in rural Kenya (97) where measurements of mid-upper arm 
circumference (UAC) routinely collected on children (0-4 years of age) 
showed that the mean UAC for age (percent) (162) for measles patients who 
died (81.0% for n=21) was just significantly lower than the mean UAC of 
those who survived (84.8%, n=35). The two groups were matched for age, 
residence, and diagnostic score (probability of having measles based on 
the clinical and laboratory findings). Comparative anthropometric 
measures made during the two measles epidemics observed in the period of 
this project are also supportive. The mean percent weight for age* 
measured less than three months prior to contracting the disease was 
higher (88.4%, n=24) during the second epidemic period when the case 
fatality rate was 1.7% than during the first period (79.4%, n=28) when 
the case fatality rate was 6.5%.

Should prior nutritional status play a role in measles mortality 
and/or related morbidity, it is anticipated that a feeding program would 
decrease the severity of measles infection. And this is what is reported 
from a Guatemalan study in the mid-1960s when children were offered a 
protein-rich supplement providing 15 grams of 'good - quality protein' 
and approximately 450 calories (134). Measles mortality per annum for 
the 0-4 year olds decreased from 0.97% (12 deaths over the 9 years 
preceding the study) to 0.3% (2 deaths over the 5 year study period) in 
the study village, whereas the rate stayed near 0.7% (14 and 8 deaths in 
the prestudy and study periods respectively) in a control village not

*All anthropometric measures refer to the Harvard Standards (60) unless 
otherwise specified.
offered the supplement. The attack rate in the control village was nearly double that of the supplemented population during the 5 year study and case fatalities were 6.8% (8 deaths) and 4.3% (2 deaths) respectively. Although supportive of the nutritional hypotheses, these findings are based on few measles deaths. No individual nutritional data are presented and only 27% of the families in the study village with 6 mo - 5 year old children actually received the supplement more than three-quarters of the time.

A study in Bangladesh reported recently on measles deaths in a rural population. The 5775 children, aged 1 mo - 10 years, were followed for 12 months for occurrence of measles, diarrhea and dysentery, changes in nutritional status, and cause of all deaths (66). Mortality from measles-associated illness (death within 30 days of measles onset) was found unrelated to the nutritional status as measured by weight and height within the previous two months. This conclusion was derived from a case-control study comparing the percent weight for height amongst the 32 children who died of measles-associated illness with two controls - children who had not had measles and those who survived measles matched with measles deaths for age, sex, and in the case of the former control, also for neighborhood. The mean pre-morbid nutritional level of all measles-associated deaths (85.7% weight for height) was comparable to the matched healthy controls (88.2%) and measles survivors (87.3%) (67) and these were not significantly different from the group dying of measles complicated by prolonged diarrhea/dysentery (82.1%). The authors did find, however, that prolonged diarrhea/dysentery (>7 days) acted synergistically with measles to increase mortality four-fold over the combined mortality rates of measles alone (without prolonged
diarrhea/dysentery) and prolonged diarrhea/dysentery alone.

2.c. **Secondary Infections**

i. **Pneumonia**

The findings of the Bangladesh study (66) conflict with the original hypothesis that prior nutritional status dictates the outcome of measles infection. Their results suggest that measles and measles-complications determine severity (death) due to a synergistic effect of the two infections, in this case measles with prolonged diarrhea/dysentery. Pneumonia is the most common complication of hospitalized measles patients in the developing countries. As seen from Table 4 it has been variously reported as concurrent in 28–87% of measles patients of whom 9–28% died. Looking at these same studies from the point of total measles deaths, pneumonia is a complicating feature in over 50%. In the few community-based studies presenting such data, pneumonia is also considered a common complication of measles (45,80) although its attendance with measles deaths may be less prevalent, averaging 33%.

The etiology of the pneumonia associated with measles remains relatively unresearched. If pneumonia occurs early in measles prior to the fading of the exanthem, it is theorized that the cause is the measles virus itself; if its appearance is after the initial measles symptoms, it is thought to be due to a secondary bacterial or viral infection (65). In an Ugandan study, 65% of the lung tissues examined from young children who died of measles-pneumonia within seven days of measles onset were histologically diagnosed as suffering from a true measles pneumonia (29);
the other 35% showed a characteristic bacterial infection. A Colombian study (33) also showed low bacterial infection (13%) of the lung during acute measles complicated with pneumonia. Yet in another study histological examination detected evidence of measles virus in the lung tissues and fluids of 28% of children who died of measles-pneumonia up to 4 weeks post-measles onset (65). Herpes virus (type 1) (22%) and adenovirus (33%) were also isolated from these tissues while the percentage of secondary bacterial infection diagnosed histologically was 50%.

The impact of the nutritional status of the child suffering with measles-associated pneumonia is confusing. Whereas the Bangladesh community-based study (66) found that children dying with measles-associated pneumonia had significantly better pre-morbid nutrition (mean weight for height, 91.8%) than the average of those dying of measles with any complication (85.7%), data from a South African study (104) show the nutritional status (weight for age) upon admission and susceptibility of measles patients to pneumonia to be inversely related. Measured within 5 days of onset of measles rash, all children with a percentage weight for age equal to or less than 80% of standard and/or with low serum proteins were classified as malnourished. Of those found to have pneumonia (12) or to have died with respiratory disease (2) three months after measles, 79% were malnourished upon initial hospital admission; of those with a clear chest, only 25% were malnourished.

2.o.ii. Diarrhea/Dysentery

Diarrhea/dysentery is often an attendant of measles infection if not
a stimulant with measles virus for the ensuing mortality (66). Although not as prevalent as pneumonia, it is associated with 4-52% of measles cases and implicated in an average of 32% of the hospital—reported measles deaths (Table 4). Community-based studies also report it to be frequently associated with measles and as a contributory factor to death in 32-67% of the cases.

Acute measles has been shown to increase the incidence of diarrheal episodes in patients (66,134) as well as the duration of measles-related episodes (66). These episodes may be protracted or recurrent for up to 5 weeks (66) starting before, during or after onset of the rash (66, 94, 134).

Etiologic agents are not known. The stools often contain mucous, and in persistent cases may be bloody (55, 66, 80, 94, 96), a sign associated with an increase in mortality (96). Shigella spp has been cultured from measles-related diarrheal episodes in an uncontrolled sample of patients; other common intestinal pathogens such as enterotoxigenic E. coli or rotavirus may be present also but have not investigated (66). Measles virus is known to infect the intestinal epithelium (137) and is associated with substantial protein losses from the gut (31); hence it may itself be a viral agent of diarrhea. Evidence for the direct involvement in the gut by measles virus comes from reports of multinucleate giant cells found during the prodromal period in the intestinal lymphoid tissue (27, 121), and in jejunal biopsy specimens (155), and during acute infection in the stools (129).

Nutritional information related to measles-associated diarrhea/dysentery is minimal. One report from Guatemala did state that
Measles-diarrhea occurred three times more frequently in patients less than 75% of 'normal' weight for age than in patients within 10% of normal weight (standard not specified) (126). As pointed out previously, in one Asian study death from measles-associated diarrhea has not been found to correlate with the premortid nutritional status by anthropometry (66).

2.d. **Immunological Status**

The susceptibility to secondary infections in children with measles is often ascribed to the suppression of the cell mediated immune (CMI) responses. That measles virus itself causes impairment to the CMI was first recognized by Pirquet in 1908 when a previously positive patient gave a temporary negative tuberculin reaction after measles infection (111). This transient loss of delayed cutaneous hypersensitivity to tuberculin and other antigens was confirmed years later by Starr and Berkovich who demonstrated that this 'anergy' frequently occurred in the incubation period of the disease, was almost uniformly present in the first four days of the rash, and lasted for an average of 18 days after the onset of the rash (145).

Some insight into this phenomenon in well-nourished measles patients has been provided by *in vitro* studies. Lymphocytes infected with measles virus or obtained from measles patients are unreactive, as determined by their inability to mount a proliferative response to stimulating antigens, such as phytohemagglutinin (PHA), and this may persist for 3 to 12 weeks (25, 164). The T, B and null cells were shown to be reduced (26) and an absolute lymphopenia obtained during the acute phase. Six
weeks after measles onset, the B and null cell counts were still significantly diminished. Functional assessment of the T cells by lymphocyte responsiveness to PHA and in vivo delayed skin hypersensitivity (DHR) to dinitrochlorobenzene (DNCB) showed a depression in activity which persisted for at least six weeks (158). The ability to produce antibody in response to an antigen stimulus can be reduced in measles, resulting not only from immunoparesis of helper T cells but also from a direct depression of the B cell function (25). However, studies on the immunoglobulins themselves have reported normal, raised or decreased levels (26, 158). During the rash, complement components and hemolytic function were not significantly different from controls.

The cell-mediated immune response is not only affected by the measles virus, but it is also considered the key defense to the disease (17). Clinical observations have shown children with thymolymphatic deficiency (98), malignancies, or receiving chemotherapy that depress the CMI (36, 86), often have severe fatal measles characterized by persistent viral infection without the typical rash, whereas the disease runs its normal course in children with hypogammaglobulinemia (49), a disease which generally does not compromise the CMI.

As protein energy malnutrition (PEM) results in immunodeficiency, particularly depression of the CMI (17, 21, 62, 84, 99, 115, 139, 140), it has been suggested that the cellular immune response may be more depressed in a child with measles and malnutrition than with either illness alone (126, 130, 140, 157). Studies of the physiological indices of the CMI have not borne this out consistently. Although Sellmeyer et al have demonstrated a lowering in the PHA response in lymphocytes from
children both malnourished and infected with acute measles over that from children either malnourished or with measles alone (135), Smythe et al (140) found thymolymphatic depletion less marked in children dying of PEM with measles as compared to those without measles.

Indirect evidence supporting this theory of synergism came from a Kenyan study where duration of measles infection measured by excretion of giant cells was correlated with severity of the infection (degree of skin staining) and nutritional status (weight for age) (129). Giant cells formed as a result of alteration in cellular membranes by the measles virus have been shown to contain viral particles (146) and are used as evidence of continued infection. In the average North American case of measles, giant cells and free virus disappear within two days of the appearance of the rash and recovery occurs soon thereafter. In highly immunocompromised leukemic patients, measles virus has been isolated up to one month post rash (86, 114, 122). The prolonged giant cell excretors in the Kenyan study remained sick until evidence of viral infection stopped whereupon recovery followed in two-three days. The authors hypothesize that prolonged infection means an impaired immune response to measles and showed that as the percentage of standard weight for age decreased, the giant cells persisted longer, skin staining was more extensive, and numbers of other viral complications increased (129).

Another study (32) confirmed that malnourished children with measles had persistent evidence of virus but showed no significant correlation with nutritional status, number of secondary infections and mortality when compared with malnourished measles infected children without persisting virus; the only significant difference was in the severity of
the rash. However, from experiments on the CMI response to Candida antigen in malnourished and well-nourished measles patients, the authors concluded that the former 'probably' have a poorer cell mediated immunity 'due to viral persistence' and hence, are more susceptible to secondary infections; malnourished children without measles were not examined. Although these authors were able to culture measles virus from well-nourished children with acute measles (1 day post onset), they were unable to do so from malnourished children with giant cells 13 days post rash onset.

Another study (160) exploring the interaction of nutrition and the immune system in response to measles infection found that the peripheral blood monocytes from malnourished children (6 with kwashiorkor, 6 with marasmus-kwashiorkor) with no history of measles yielded significantly greater amounts of measles virus when infected than those from well-nourished children (>80% weight for age). The yield was inversely correlated with serum albumin levels. The quantity of interferon produced was similar from both groups of children. This author suggests that faulty macrophage function may allow this increased viral multiplication in malnourished children, although macrophage were not tested. As in other studies, humoral responses to measles virus were normal in the malnourished child. Whittle concluded that if the peripheral blood monocytes from malnourished children are more susceptible to infection and they are resisted by a normal cellular and humoral immune response, extensive allergic damage would result. He hypothesizes that lyses of these cells may generate immunosuppressive factors in the patients' plasma which lead to the high incidence of secondary infections.
Alternatively it may be surmised that the extensive damage done to the epitheliol (129) and lymphocytic system (32) by persistent measles viral infection itself allows for the susceptibility of secondary infections. In support of this latter argument, it is known that measles virus shares with other paramyxoviruses the ability to establish persistent infections in vitro. Although measles infection usually results in widespread cellular destruction, surviving cells can be selected and subcultured and are often found to be persistently infected. One feature that is common to most persistent infections is that cultures are usually refractory to superinfection with measles virus, but are readily infected with other unrelated virus (85, 100, 124).
Table 4 Secondary Infections as Percent of Measles Cases and Deaths in Hospital and Community-based Studies

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Secondary Infections</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Measles Cases</td>
<td>% Measles Pneumonia Cases That Die</td>
<td>% All Measles Deaths</td>
<td>% Measles Cases</td>
<td>% Measles Diarrhea Cases That Die</td>
</tr>
<tr>
<td>Hospital-based</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania (56)</td>
<td></td>
<td>30</td>
<td>12</td>
<td>41</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Uganda (18)</td>
<td></td>
<td>—</td>
<td>—</td>
<td>51</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kenya (101)</td>
<td></td>
<td>59</td>
<td>17</td>
<td>70</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>E. Africa (95)</td>
<td></td>
<td>45</td>
<td>9</td>
<td>70</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Nigeria (93)</td>
<td></td>
<td>47</td>
<td>28</td>
<td>52</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>South Africa (72)</td>
<td></td>
<td>28</td>
<td>13</td>
<td>50</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>India</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delhi (47)</td>
<td></td>
<td>87</td>
<td>—</td>
<td>—</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>Madurai (68)</td>
<td></td>
<td>70</td>
<td>—</td>
<td>—</td>
<td>39</td>
<td>—</td>
</tr>
<tr>
<td>Chile (120)</td>
<td></td>
<td>42</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

| Community-based  |         |         |         |         |         |         |
| Studies          |         |         |         |         |         |         |
| Nigeria-Imesi (94)| —       | —       | 27      | —       | —       | 33      |
| India -Vellore   |         |         |         |         |         |         |
| – Patha (45)     | 58      | 8       | 33      | 52      | 18      | 67      |
| Bangladesh-Matlab|         |         |         |         |         |         |
| (66)             | 14      | —       | 22      | —       | —       | —       |
| Guatemala (134)  |         |         |         |         |         |         |
|                  | —       | —       | 83      | —       | —       | —       |
F. Conclusion - Severe Measles

For decades malnutrition and young age have been postulated as the primary factors predisposing an individual to an increased severity in measles. Age of itself may be most important in the under ones as they experience a high measles mortality world-wide. Children between one to six years in developing countries continue to be vulnerable to severe measles; they are also prone to malnutrition. Because of this coincidence, a theory of cause and effect has developed: a poor nutritional status prior to infection dictates a more severe outcome to measles in young children. Routine anthropometric measures taken during field studies investigating this thesis report conflicting results. Whereas arm circumference data in relationship to measles fatality tend to support the theory, mean weight-for-height measurements show no significant impact of the prior nutritional status on measles mortality.

Children are assumed to die from measles by succumbing to complicating illnesses, primarily pneumonia or diarrhea/dysentery. The mechanism by which malnutrition has been assumed to operate in causing increased fatality among measles-infected individuals is by depressing the cellular immune response, already depressed by measles, and hence increase the susceptibility of the patient to other infectious agents, or to allow the measles virus to persist. The etiological agents of the complicating illnesses are not well-researched, and it is not known which agents, or combinations thereof, are more involved in the increased morbidity and mortality seen with severe measles. Anthropometric measures, clinical categories of malnutrition, and physiological indices of the CMI used in studies to date have not provided a clear statement of
the relationship between nutrition and immunology in response to measles. In light of this lack of evidence supporting the nutritional theory of severe measles, it may be wise at this point to re-open the question of what causes severe measles.
A. Ocular Involvement With Measles

Measles, an essentially benign disease with regard to the eyes in advanced countries, is a major cause of blindness in developing countries. The viral infection is typically accompanied by conjunctival injection and photophobia resulting from superficial punctate keratopathy in the early stages of the disease. This was described by Trantas (152) in the early 1900s and has since been reported in both developed and developing countries (30). This mild blepharo-kerato-conjunctivitis regresses rapidly without sequelae in healthy children. In some children the inflammatory signs persist rather than regress and secretions develop along with an extreme photophobia causing the child to close his eyes. When the eyes are opened by an examiner, a grayish dull cornea may be seen. The cornea may deteriorate rapidly, 'within a few hours', with the formation of marginal or central ulcerations and ending in perforation and panophthalma. Although some studies have reported the rapid appearance of corneal ulcers within days of measles onset (8, 142), the more common picture appears to be a course that is prolonged by a few weeks or even months after the measles infection (12, 40, 58, 127, 142, 148).

B. Prevalence of Measles-Associated Corneal Lesions

In surveys of childhood blindness in developing countries, corneal ulceration is a significant cause of blindness with measles reported as
its antecedent in approximately one-fourth to one-half the cases. An early report from Zambia estimated 81% (110) of blindness was caused by measles, although a later report (3) found 80% corneal blindness with half of these associated with measles. In Malawi, the estimate of 44% was made (22). Only 14% of childhood blindness was ascribed to measles in a southern Nigerian hospital (102) although examination of children in a blind school in the same area of Nigeria showed 33% of the inmates and 79% of the new admissions were blind from measles (1). In El Salvador (143) and Haiti (144), 57% and 16% respectively of children with corneal scarring claimed their active disease had been accompanied by measles. And in Indonesia 36% of cases of activo corneal disease claimed to have had measles during the past month. When the question was phrased differently, 64% of all corneal cases claimed the onset of their ocular disease had been preceded within 1-4 weeks by measles (142).

Studies of hospitalized measles cases in Africa report 'damage to the eye' in the range of 0.8 to 2.8% (Table 5). These rates are probably on the low side due to the possible lengthy interim between measles onset and the resultant ocular damage mentioned earlier. The rubric 'damage to the eye' is used because of the variety of ocular symptoms included in the studies: opacity and ulcers which may be amenable to treatment are listed in some reports while others refer to partial or complete blindness.
Table 5  Prevalence of Damage to the Eye in Measles Patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Hospital-based Reference</th>
<th>Damage to the Eye</th>
<th>Percent of Measles Cases</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria</td>
<td>1</td>
<td></td>
<td></td>
<td>Blindness</td>
</tr>
<tr>
<td></td>
<td>159</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Corneal ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanga District</td>
<td>56</td>
<td></td>
<td>2.8</td>
<td>Corneal opacity and ulceration</td>
</tr>
<tr>
<td>-Mwanza</td>
<td>63</td>
<td></td>
<td>0.8</td>
<td>Keratitis and blind</td>
</tr>
<tr>
<td>S. Africa</td>
<td>72</td>
<td></td>
<td>1.0</td>
<td>Frank corneal ulcers</td>
</tr>
<tr>
<td>E. Africa</td>
<td>95</td>
<td></td>
<td>0.75</td>
<td>Damage to one or both eyes</td>
</tr>
<tr>
<td>W. Africa</td>
<td>96</td>
<td></td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India-Delhi</td>
<td>47</td>
<td></td>
<td>1.8</td>
<td>Corneal ulcers</td>
</tr>
<tr>
<td>-Madurai</td>
<td>68</td>
<td></td>
<td>2.6</td>
<td>Partially or completely blind</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

Community-based Studies

Gambia                     | 80                       |                   | 0.9                      | Permanently damaged eyes               |
C. Agents Involved in Measles-Blindness

Measles virus, isolated from the conjunctiva (36, 128) and corneal scrapings (128, 159) by immunofluorescence or viral culture, is assumed to be the cause of the punctate keratopathy affecting the epithelium of the conjunctiva and cornea in the normal measles case (30). However the etiology of the ulcers involving the stroma of the cornea and leading to measles blindness has been variously ascribed to xerophthalmia (vitamin A deficiency), infection by bacteria or viruses due to lowered corneal and systemic resistance, or traditional practices. The controversy over the primary etiological agent continues as the clinical picture recorded for the corneal ulcers post-measles is comparatively unique: the sequence of pathological changes widely associated with either xerophthalmia or herpetic keratitis have not been observed in children with post-measles corneal ulcers. And the extent of use and damage by traditional ophthalmic medications is unknown.

This literature review will examine the arguments for each of these possible agents with emphasis on African studies where the problem of measles blindness has been most publicized.

C.1. Xerophthalmia

a. Post-Measles Xerophthalmia and Serum Vitamin A and RBP Levels

Although conjunctival symptoms of xerophthalmia are not significantly associated with measles, the numbers of patients with clinically severe corneal ulceration and necrosis have been shown to
significantly increase following measles (141). These corneal lesions have been diagnosed as xerophthalmia by pediatricians and ophthalmologists in Africa (3, 15, 39, 77, 103, 128, 141, 147, 153), as well as in Asia (58, 117, 142, 148), and the Middle East (83, 107). In Europe up to the time of recovery from World War I, diarrhea and measles were mentioned as companions or precursors of manifest xerophthalmia (13, 52). As recently as 1955 in Liepzig, Germany, five cases of post-measles corneal ulcers were reported (12). Although these children were very ill, xerophthalmia was ruled out by the absence of any significant clinical response to vitamin A therapy; no other explanation could be found for their genesis. Sommer concludes that little viable corneal tissue may still have been present as the therapy was given late in the course of the corneal disease. Also, it was administered as an oily injection later shown to be relatively ineffective (142).

In support of the clinical diagnosis of xerophthalmia, serum levels of vitamin A have been reported extremely low in association with post-measles corneal ulcers (3, 83, 142). A Nigerian study (70) found that children with measles and keratomalacia had a mean level of serum vitamin A (11.3 µg/dl) consistent with others' findings for children with corneal xerophthalmia, but there was no statistical difference between this value and the mean for children with measles without "keratomalacia" (13.9 µg/dl). No definition of "keratomalacia" was given and it is not known if children "with measles only" suffered mild xerophthalmia also.

In another Nigerian study (127), the authors claim vitamin A deficiency is probably not the primary etiological agent in the post-measles corneal ulcers as they found half the corneal ulcer cases had
normal total retinol-binding protein (RBP) levels (≥ 15 µg/ml).

Indirectly serum (total) RBP level is a measure of the serum vitamin A status, although it is only that portion bound with vitamin A that accurately measures the vitamin level. As the free and bound forms of RBP were measured together in this study, their claim may not be valid. The ratio between the two forms cannot be taken as a constant; 10–20% of the total RBP is in the apo form in normal subjects (48), but this ratio was not considered to hold in malnourished children (118). What is of interest in this Nigerian study is the tendency for more severe ulceration to be seen in the more malnourished children after measles.

1.b. Primary Xerophthalmia in Africa - Does it exist?

If the corneal ulcers occurring post-measles are due to xerophthalmia, these children must have a prior borderline vitamin A status made deficient with acute measles. Other factors may also affect such borderline cases, and a normal distribution of xerophthalmic symptoms would be expected in such populations with or without measles. Yet for many decades, it has been postulated that primary xerophthalmia is rare among African peoples. The milder symptoms of vitamin A deficiency—night blindness, conjunctival xerosis, and Bitot’s spots—are not often witnessed, although corneal ulceration and necrosis similar to that seen in severe xerophthalmia are reported. These corneal lesions are most noted in very ill children in malnutrition or pediatric wards of hospitals (35, 69, 132, 161) where the rapid deterioration of the cornea in South African children with kwashiorkor has been described as "perforation of one or both eyes developing within 12 hours of noticing the first indication of dryness and haziness of the cornea" (132).
Prior conjunctival involvement as might be anticipated in vitamin A deficiency was not noted with these kwashiorkor cases leading the author to suggest that the corneal lesions may be attributable to a "'nutritional gangrene'" of ocular tissues, or infection due to some dysfunction of the lacrimal gland. However, laboratory analyses of swabs from eyes of kwashiorkor patients revealed a wide range of organisms (Pneumococcus, Staph. pyogenes, Staph albus, Staph. aureus, B. proteus, Koch-Weeks bacillus, hemolytic streptococci, and Strept. pyogenes) identical in patients with eye lesions and those without (69). Carotene levels were found significantly reduced in these kwashiorkor patients as compared to well-nourished controls, although no significant difference was seen between the malnourished children with eye lesions and those without (69). On the other hand, serum vitamin A levels of the malnourished group with corneal ulceration and necrosis were significantly lowered to one-third the value of normal or malnourished controls (69).

Numerous studies have associated hypoproteinemia and xerophthalmia, especially the blinding form (13, 14), and it has even been asserted that protein malnutrition, not vitamin A deficiency, is responsible for corneal xerophthalmia (35, 69, 163). The significance of vitamin A-protein interaction is generally ascribed to the importance of retinol-binding protein (RBP) synthesis for retinol transport, although this may be one of many means of interaction needed to achieve adequacy of vitamin A metabolism in target tissues. Using serum albumin and transferrin as indices of basic protein status, Indonesian data revealed both these proteins to be relatively normal in a substantial proportion of xerophthalmic children, including some of the severe cases. Mean albumin
levels were inversely related to the severity of corneal disease but the
trend was found not statistically significant. The transition between
local and total corneal necrosis was however (142). Hence, the
significance of vitamin A-protein interaction in the development of
clinical xerophthalmia is apparent for cases of corneal necrosis only.
The wide variation in frequency of ocular involvement reported in
kwashiorkor patients (108) may be explained by a more normal vitamin A
status in those without eye lesions.

Although not frequent, reports from rural Africa do present evidence
of the occurrence of mild forms of primary xerophthalmia. In an area of
Zambia known as the "Valley of the Blind" (24), frank kwashiorkor was
not prevalent, but preschool and school children were seen suffering from
night blindness, as well as conjunctival and corneal xerosis (3).
Bitot's spots, although reported a rare phenomenon by several
investigators (3, 7, 82, 147), were used as an index of xerophthalmia in
Ruanda-Urundi (123) and reported among the nomads as well as urban school
children in Niger (73). In a study in Kenya (128), signs of primary
xerophthalmia from night blindness to keratomalacia were observed in many
parts of the country.

These few studies reporting primary xerophthalmia are descriptive
and no estimate of the magnitude of the problem can be made. The age
range observed to be affected (1-5 years) (35, 69, 147, 153) compares
well with results obtained in a nationwide survey of xerophthalmia in
Indonesia (142). Most affected children are described as poorly
nourished although quantitative nutritional data are lacking.

The presumed rarity of primary xerophthalmia in Africa . . . be based
not on its lack of prevalence, but on its prevalence not being observed.

1.c. Post-Measles Nutritional Status

Similar to kwashiorkor, measles appears to precipitate corneal ulcers without the prior conjunctival involvement usually seen in classic xerophthalmia. This may be due to a sharp decrease in adequate levels of vitamin A at target tissues in a child with already low vitamin A stores. That measles has a devastating effect on the nutritional status of the individual is attested to by hospital records of kwashiorkor cases with a recent history of measles (18, 31, 42). In Uganda 50% of kwashiorkor cases were associated with measles (18) while 34% were reported from a Nigerian hospital (31).

The initial weight loss seen with measles is probably due to anorexia as well as the common practice of withholding solid foods and fluids from infected children (59, 92, 107). Mouth ulcers so frequently seen during and after measles (47, 55, 92, 97) compound the feeding difficulties. Fever by itself can increase protein breakdown in excess of synthesis resulting in a negative protein balance (43). Poskitt measured serum albumin levels before, during, and 6 weeks after measles in children with suboptimal nutrition and found a significant decrease during acute measles with recovery 6 weeks later (112). Fecal protein loss has been reported (4, 31) suggesting that protein loss from the gut may reach significant levels and contribute to the serum albumin decline. With diarrhea accompanying measles, urinary nitrogen excretion and decreased nitrogen absorption are exaggerated (133). Lactose intolerance has been reported also in some children with measles (19, 31).
This decreased nutrient intake, malabsorption, excretion as well as increased catabolism and excretion results in weight loss and long recovery periods. In West Africa (96), a quarter of the measles-infected children lost 10% of their former weight with a small proportion losing over 20%. The delay in weight catch-up after measles associated with diarrhea has been correlated to the initial weight loss and age (66). Children with measles and diarrhea of at least seven days duration initially lost twice as much weight as other measles cases. If less than two years of age, these children sustained a persistent weight loss of approximately 10 percentage points even after the initial two months of accelerated growth. In the age group of 2-4 years, the trend was similar but not as striking. Children older than 4 years did not sustain a persistent weight for height deficit despite the combination of measles and prolonged diarrhea.

The undernutrition or even malnutrition following measles probably affects the release and transport of vitamin A via RBP as well as the utilization of vitamin A in its target tissue. The accompanying or subsequent diarrhea and respiratory diseases impair vitamin A absorption and increase its excretion. It is conceivable that these combined effects of measles could precipitate the corneal ulcers and necrosis in a child already in a borderline vitamin A status without first exhibiting the slow keratinizing effects of a more chronic vitamin A deficiency.
C.2. Infection of the Cornea

The possibility of a significant bacterial or viral secondary infection of the cornea due to the lowered immune response in measles patients has long been suspected, but until recently evidence of this has been inconclusive. Pneumococci have been implicated in the post-measles corneal ulcers since 1902 (20, 57) and more recently other microorganisms commonly found in the conjunctiva have been detected (116). In another study, swabs from corneal ulcers post-measles produced only a few gram-positive cocci and diphtheroids when cultured and it was concluded that any bacterial infection would seem a minor secondary factor (40). Although all patients in this Haitian study were severely malnourished, the lack of any noncorneal signs of vitamin A deficiency precluded the diagnosis of xerophthalmia and the rubeola infection itself was implicated from histopathologic findings. Syncytial cells present in the cornea of one patient were similar to those described for rubeola infections of the tonsil and nasopharyngeal mucosa.

The presence of measles virus has been recently confirmed in the corneal scrapings of 12% of patients suffering with corneal ulcers post-measles although the herpes simplex virus (HSV type 1) proved even more prominent in this Nigerian study: HSV type 1 was detected in 47% of the corneal scrapings by immunofluorescence or viral cultures (159). In Israel another measles patient with corneal ulcers proved positive for herpes simplex upon laboratory analyses (125). Herpetic corneal lesions have been clinically diagnosed in children with concomitant measles and malnutrition (128), measles and mild malnutrition (30) or with malnutrition only (69) elsewhere in Africa.
The patients with the proven herpetic eye lesions post-measles were young — first or second year, malnourished (37.5% <60% weight for age (159) and described as suffering a severe form of measles (complicated with pneumonia, gastroenteritis, and high fever) (125, 159). The onset of the ulcers averaged two-three weeks post-measles and in most cases were bilateral (125, 159). In the Nigerian study, eye lesions were preceded one week by mouth ulcers assumed of herpetic origin in two-thirds of the patients. Recovery was slow — two to six weeks—with treatment of vitamin A, high protein diet and systemic and local antibiotics. Most of the affected eyes resulted in scars that impaired vision (159). In the case of the Israeli patient, neither systemic vitamin A nor idoxuridine treatment, commonly used to treat ocular herpetic lesions of epithelial tissue, proved helpful and mechanical debridement was performed.

2.a. Measles, Herpes, and Malnutrition

That measles and herpes are not infrequent companions is attested to by reports of:

- fatally disseminated herpes infection following measles (64),
- stomatitis of HSV origin during acute measles (104, 159),
- HSV isolation from lung tissue of children who died of measles-pneumonia (65),
- herpes isolation from the oropharynx of post-measles patients suffering chronic pulmonary disease (26), and
cultured HSV from nasal aspirants of malnourished patients two weeks post-measles (32).

The high prevalence of herpes infection with measles is possibly due to two characteristics of the HSV virus:

1. Between 7 and 24 months of age, the incidence of susceptibles to HSV infection is greatest (16, 131), and adult levels of neutralizing antibodies to herpes obtain by the age of 5 years in a U.S. outpatient population (131) and 4 years in Bantus in South Africa (10). Also the greatest reservoir of herpes infection has been found among young children with an inapparent infection. Twenty percent of apparently healthy children aged 7-24 months shed virus, whereas only 2.5% of those over 15 years of age were carriers (106). Children in the age range most prone to shed HSV as well as be infected by it are also most susceptible to severe measles.

2. Following primary infection, HSV may become latent within sensory nerve ganglion sites. Various immunologic and biochemical theories of this latency and reactivation have been proposed but remain unproven (74). The cellular immune system is postulated to play the major role in maintaining the latency as neutralizing antibodies are present in the body after the primary infection (76). When the CMI is depressed as with measles, herpes is more likely to be expressed.

Herpes infection usually runs its course in 10-14 days with no sequelae. Further dissemination of the disease may be due to immune incompetence as fatally disseminated HSV is known to occur in infants with immature immune mechanisms, immunosuppressed patients, malnourished
children, as well as children with measles infection (64, 81, 150). In a South African study, measles preceded or coincided in 17% of children with the fatal illness while 7% suffered from other infectious diseases. A study from Senegal found 100% of the 13 children who died of disseminated herpes simplex had been measles patients; nine had also been malnourished (64).

Stomatitis seen with measles could be ascribed to herpes simplex, measles virus, Candida infection or vitamin B deficiency (63). Rates ranging from 1 to over 50% have been reported for stomatitis in measles patients in hospital (18, 47, 56, 63, 72, 95, 96, 159) and community-based studies (80, 97). The rate of association may increase with time post-measles onset: 1.7% of measles-infected children were seen with mouth or lip ulcers within the first 7 days of rash, but 13.9% were seen in the second or more weeks post-measles onset (159). In a Nigerian study (159), HSV was isolated from 68% of the ulcerated patients whereas about 10% of the controls (children who had had measles but no mouth or lip ulcers) shed virus (about half the level of healthy carriers seen in the U.S. (76). Most of these infected children were between 60-80% of average weight for age.

In this same Nigerian study, patients suffering with proven herpetic corneal ulcers post-measles were even more malnourished than those with HSV caused stomatitis; 37.5% of these 16 patients were marasmic i.e. <60% weight for age (159). Since two-thirds of them suffered oral lesions as well as corneal ulcers, it is suggested that the herpes infection spread from the mouth ulcers which occurred a week earlier. As all patients already had detectable herpes simplex antibody, the eye ulcers were
considered a recurrent herpetic infection, a common clinical finding of ocular herpetic lesions.

2.b. Measles and Herpetic Keratitis

Infection with herpes simplex is the single most frequent cause of corneal opacities in the United States (151), although bilateral corneal HSV is relatively uncommon (0.5 to 9.5%) (34). The frequent bilaterality of the proven ocular herpetic lesions post-measles suggests immune incompetence. However, the increased risk to labial herpes observed in acute measles patients in a South African hospital - 43% as compared to 20% in tuberculosis patients- did not correlate with nutritional status or to the degree of immunosuppression (105). Patients with percentage weight for age greater than, and less than or equal to 80%, showed an equal chance of having HSV infection. Children treated for measles as outpatients did exhibit a significant relationship between malnutrition and HSV infection but their numbers were small. Functional assessment of cell mediated immunity was found equally depressed in the measles-infected children who contracted and those who failed to contract oral herpetic infection. This study implies that depression of the CMI, known to occur with measles and malnutrition, may not be the determining factor in herpetic manifestations. Ocular herpes, as herpetic disease elsewhere in the body, is triggered by specific mechanisms, including exposure to sunlight, menstruation, psychiatric disturbances and fever - the latter being the possible "'trigger'' during measles.

The description of the ocular herpetic lesions in the Nigerian measles patients implicate two or possibly even three complicating
agent(s). Deficiency of tear production was observed in 5 of the 16 measles-herpes patients and the typical picture of bilateral keratomalacia presented in one of the patients (159). The mean total serum RBP levels of the patients with post-measles corneal ulcers proved lower than those of the well-nourished post-measles controls, although not as low as in post-measles malnourished children suffering no ocular lesions (127). It may be that the ocular lesions result from the combination of the effects of the measles virus, vitamin A deficiency and herpes virus on the cornea.
C.3. Traditional Medical Practices

As the cause of measles is considered spiritual in many countries (9, 38, 47, 59), Western medicine is assumed to have little to offer in the way of a cure. Yet this disease may create such alarm that in Mali, for example, a pseudonym meaning "good mother" is used for fear that uttering any of the proper names for measles would cause the disease in one's family (59).

During the prodromal period, spiritual leaders may be requested to aid with charms and special concoctions. Thereafter their assistance may be invoked if the situation deteriorates. Although the cause is spiritual, non-spiritual treatment may be used to treat the symptoms of measles. The rash is given a great deal of attention in several countries (9, 38, 59) as it has been observed that the other symptoms, cough, headache, fever, photophobia and coryza, improve with its onset. Anything which impedes the exanthem is avoided and attempts are made to facilitate its development. Purges may be given to drive it out of the intestinal tract, and ophthalmic treatments may be applied to prevent the rash from getting into the eyes.

In Mali (59), the possibility of a child with measles suffering subsequent impaired vision is well recognized and feared. The specific ophthalmic preparations used to prevent this corneal scarring are considered innocuous for the most part and cause mild reactions or none. However, others, such as a solution of sourwood (Parkia biglobosa), may cause severe chemical conjunctivitis (59). In one tribe in Northern Rhodesia (Zimbabwe), 53 different concoctions were produced and each tribe had its own preparations (110). Solutions, suspensions, infusions
and powders may be manufactured from a choice of leaves, roots, bark, flowers, grasses, berries, tubers (110), cowrie shells (82), copperstone (110), honey, goats, or human milk, and crushed onions, (59) using saliva, urine or oil as solvents (110).

Damage to the eye depends on the chemical and physical properties of the preparations, the dosage, and the pathogenic state of the eye. The susceptibility of children with measles may be increased as they suffer a depressed immune response, as well as viral keratitis in the cornea and conjunctiva. Powders may act as mechanical abrasives, and acidic or alkaline solutions may result in what appears as "burns" (5). Some of the plants used contain substances with known toxicity to the eye (30).

Registration of the blind in one African country led the investigator to conclude that these traditional preparations instilled in the eyes of measles patients were the major cause of corneal lesions (110). However, an ophthalmologist elsewhere in Africa diagnosed children hospitalized with ulcerated eyes after traditional treatment as suffering from vitamin A deficiency primarily (82). Just how widespread and how damaging these practices are cannot be said.

Perhaps the most serious aspect of the traditional practices in the treatment of measles is the withholding of foods - both animal meat and vegetable - due to the fear of bringing on diarrhea (59, 67), a complication equated with a poor prognosis. In Mali, intake is reduced as fluids are believed to worsen the rash (59). These practices can only contribute to the deteriorating nutritional state of the measles patient.
D. Conclusion - Measles-Blindness

Corneal ulceration following measles contributes significantly to childhood blindness in African countries, and probably in other developing countries as well. The etiology of these ulcers remains controversial. Although traditional practices may play a role, the extent of use or damage of such treatments is not known. Vitamin A deficiency has been proposed as a causative agent and recently herpes simplex virus has been implicated. One factor held in common by these diseases in developing countries is the age range most affected: Children between the years of 1-5 are more prone to incur measles, malnutrition, vitamin A deficiency and/or herpes simplex infections.

That primary xerophthalmia is rare among African peoples has been used as an argument against vitamin A deficiency being a major causative agent in the wide-spread measles blindness. Reports indicating the observation of primary xerophthalmia are published, including observations made from areas known for measles blindness, but the extent of the problem remains unknown.

Another factor used to argue against vitamin A deficiency involvement in measles blindness is the rapid deterioration of the cornea without manifestation of the mild xerophthalmic symptoms - Bitot’s spots and conjunctival xerosis. In Indonesia, children with Bitot’s spots had history of recent measles at a rate similar to that of their matched controls or other normal children. However cases of active corneal disease claimed to have had measles during the past month at a rate several times that of the rest of the population (142). Sommer proposes that measles acutely decompensates vitamin A status resulting in the more
severe corneal disease (142) similar to the clinical description of corneal lesions in kwashiorkor patients. Both serum vitamin A and total RBP levels are known to be decreased in the measles patients suffering corneal lesions.

Malnutrition figures prominently in the genesis of the corneal ulcers following measles. Most children who develop these lesions are malnourished, whether it be during the acute phase of measles or several months post-infection. Children with underlying malnutrition are more likely to be vitamin A deficient, and interference with protein metabolism will prove catastrophic to those in borderline vitamin A balance. Sweet (145) traced a case of classical conjunctival xerosis and bilateral corneal ulceration to an episode of measles 3 months earlier. The measles had led to severe diarrhea, poor dietary intake and weight loss. One month prior to admission, the now severely malnourished child developed a chronic cough and finally, ocular disease. At autopsy keratizing metaplasia was present in a wide variety of epithelial-lined organs.

Malnutrition is known to depress the cell-mediated immune response, and hence, it is theorized that the susceptibility to herpes simplex infection would be increased. Although the immune system in well-nourished children who have suffered measles recovers within a 6-12 week period post-infection, a child malnourished from measles and further so by associated infections would not be expected to regain immunological competence so quickly. Hence, it may be reasonable to assume that herpes infection could occur in immunocompressed children a few weeks or months post-measles - if immunological compromise were the only trigger needed
for manifestation of herpes which is not apparently the case.

The two studies reporting proven herpetic corneal ulcers found the interim between measles onset and the ensuing ulcers to be two weeks. It may be that the measles virus, known to invade the cornea during the acute infection, predisposed the cornea to the type of herpetic ulceration observed. And it may be that only within a brief period post-measles is the cornea susceptible to herpes infection. However children of 5 years of age in the U.S. and in Africa have similar levels of herpes antibodies, and hence latent herpes. Yet no reports of such corneal deterioration were found for American children post-measles. Malnutrition and the accompanying depressed cell-mediated immunity are again summoned as further predisposing factors, although not found to be significant factors in the susceptibility to oral HSV ulcers in one study. Alternatively, the corneal ulcers described within two-three weeks post-measles suggest herpes and vitamin A deficiency may combine efforts in a cornea predisposed by the invading measles virus.

From the present state of research on the corneal ulcers resulting after measles in developing countries, it is not clear what factor or combination of factors is involved in measles blindness.
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