Current Practice

MEDICINE IN THE TROPICS

Severe Measles in the Tropics.—I

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In 1965 800 children died in the wards of the Lusaka Central Hospital. Of these, one-third died from measles.[1] A survey in West Africa showed the mortality in children admitted to hospital with measles to be 12·3%, but in two hospitals in which paediatricians admitted only the children who were most seriously ill the mortality was respectively about two and four times as great as this overall figure.[2 3] Measles is clearly a severe disease in tropical countries.

Beliefs about the Cause and Treatment of Measles

The delay in recognizing the severity of measles in many developing countries has been to some extent due to the strong beliefs about the disease held universally by the villagers and poorer city dwellers. Such beliefs have not, of course, been confined to tropical countries.

Europe.—In Europe, for more than 1,000 years, measles was ascribed to the failure of the mother to menstruate during pregnancy. The retained "bad blood" was believed to enter the foetus and appear later as the rash of measles. Laymen and doctors shared this belief, which is found in the writing of Willis.[4]

Africa.—Measles is generally believed to be due to sorcery, though heat and eating certain foods such as snails or beniseed are thought in some areas to be responsible. For treatment, all medicines, both traditional and scientific, are avoided, and injections which may prevent the rash coming "out" are feared. Two dangerous customs are the restriction of fluids during the course of the disease in many areas, and in the Zambesi valley the application to the eyes of an astringent fluid made from roots or herbs.

Asia.—These proverbs collected from West Asia suggest the respect in which measles is held.

"A child that gets out of measles is a child that is reborn." (Arabic)

"Count your children after the measles has passed." (Arabic)

"Smallpox will make your child blind. Measles will send him to his grave." (Parsee)

In Asia, measles is often considered to be due to a malignant goddess. Given this aetiology, parents may hide the child from neighbours and feel that it is useless and dangerous to bring a child suffering from measles to hospital. If a child in hospital for some other condition develops measles he is likely to be promptly removed by his parents.

Treatment in Asian countries is generally by special foods; those that are "cold" according to ancient medical systems are considered most suitable.

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Distribution of the Severe Forms of Measles

West Africa.—Measles is not a newcomer to the area. A description of the disease in Accra over 100 years ago, given by Daniell,[5] a naval surgeon, indicates that it was then severe and particularly attacked small children. During a three-year period at Ilesha, Nigeria, measles accounted for 16% of 4,475 admissions to the children's ward in the Wesley Guild Hospital, and 22% of 849 deaths.[6]

The severity of measles throughout West Africa is now well documented. In the Gambia, McGregor[7] recorded a mortality of 14% and 15% in all the children under 12 in two villages respectively during the period of a measles epidemic. In Mali, Imperato[8] recorded 78 deaths among 213 cases in a village. Hendrickse and Sherman[9] have drawn attention to the severity of the disease as seen in the University College Hospital, Ibadan. Some 14 papers have been written about measles in this region; these are referred to in my previous papers.[2 9]

The rest of Africa, except North Africa.—In a review of some 2,376 children with measles admitted to 36 hospitals in the Sudan, Uganda, Kenya, Malawi, Zambia, Rhodesia, and Tanzania,[3] the case fatality was found to be only 5·7%. From South Africa, Leary[11] records a case fatality of 5%. These rates differ from that of Savage,[1] who experienced a 21% mortality among hospital patients in Lusaka, Zambia, and suggest a wide variation in case fatality between different areas and communities.

Measles in Asia.—Information on the severity of measles in Asia is in general lacking. Information available from India was summarized by Taneja and Ghai.[12] They consider it to be severe, and the attitude of the public towards the disease, combined with some indifference on the part of the medical profession, makes it difficult for the health authorities to collect authentic data on incidence, morbidity, and mortality. Ghosh and Dhatt[13] drew attention to the severity of measles in Madras, suggesting that measles there was a more serious disease than diphtheria.

Central and South America.—Moraes[14] has reported on the decline in mortality from measles in Brazil over the last 50 years. While this has been considerable, the mortality in São Paulo is still approximately 30 times as high as it is in European countries.

Ristori and his colleagues[15] have described the severity of measles in Chile, showing that in the last decade it has increased in relative importance as a cause of death; in 1962 it was responsible for 2·3% of all deaths. They found an overall case fatality of 6·5% for the year 1960, and considered that measles was the most severe infectious disease of children in Chile.

Australasia, New Guinea, and Micronesia.—Some information about measles is available from territories in this part of the world, which are of interest in this connexion because of their isolation. Here measles may strike in a community that has

never previously experienced the disease.[16] With respect to measles, they have been the last unexposed populations in the world.

Measles in Previously Unexposed Communities

Both in tropical and temperate countries some severe measles epidemics in which a fifth or more of the population died have been recorded. These arose in communities, previously isolated, in which none of the members had been exposed to measles. Few or no such communities of any size still exist, and the repetition of such epidemics is now impossible. Hirsch[17] and Brincker[18] described such epidemics in Estonia, Hudson's Bay, Cape Colony, Tasmania, and Fiji. Dobyns[19] gives a detailed account of a series of epidemics of measles in the Andean Spanish colonies in South America from 1531. He records mortalities higher than 50%. Then as now, smallpox and measles were sometimes confused.

These were subsistence farming communities without previous exposure to measles, and whole families would simultaneously become infected. If every adult member was simultaneously taken ill, there would be no one to bring water, collect food from the farm, and undertake the long and tedious process of pounding, soaking, and cooking essential for the preparation of each and every meal. Starvation would follow in the wake of the disease, and the *Lancet*[20] recorded of the Fijian epidemic "... the great mortality has been in large measure due to the fact that the sick were exposed to the most unfavourable conditions. Unprotected from exposure, untended and untreated chiefly because of their unhappy prejudices, every complication of the disease must have been invited. ..."

Natural Immunity

In Europe and America a proportion of children apparently do not contract measles. Wilson[21] suggests that as many as 15% of children in Britain without a previous history of measles escape attack when they are exposed to close contact with a case. In East Africa, Stansfield, Warley, and Kintu[22] found antibodies in a quarter of children aged 1 year who had not had a history of clinical measles.

A satisfactory explanation for these findings has not been available until a recent study in New York by Krugman.[23] He showed that the HI antibody level in the majority of children declined to a titre below 1:8 by the age of 1 year. In a few infants, however, the antibody level suddenly rose during the period 6 months to 1 year. These children presumably experienced a subclinical infection in the period of decline in maternal antibody, chancing to be in contact with the disease at this particular time. These subclinical infections can occur in this age group only in a population where the disease is endemic, and this may well explain the absence of all natural immunity in previously unexposed populations. Christiensen and his colleagues[24] found that 99·9% of such a population in Greenland developed the disease.

Seasonal and Age Incidence

In the equatorial countries of Uganda, Kenya, and Tanzania, the peak month for measles is April. In Zambia, Rhodesia, and Malawi, the peak months are November, December, and January. Data from other sources in Rhodesia suggested a peak in November.[25] In general, the further a country is from the equator the greater the difference between the maximum and minimum monthly incidence appears to be.

The seasonal incidence of measles epidemics has been related by some workers to temperature and humidity. De Jong and Winkler[26] examined the survival of the measles virus at different humidity levels and found maximum survival at levels likely to occur in the wet season. In West Africa measles occurs throughout the year, but most epidemics develop in the hot dry months from December to February. At this time of year farm activities are reduced, and the people hold festivals attended by the young children on their mothers' backs, thereby offering opportunities for the spread of droplet infections. Epidemics decline with the onset of the rains and the dispersion of the families to their farms.

The age incidence of measles in temperate and tropical countries may be compared on the basis of the median age of notification. Some figures collected during a survey are given in the Table. Figures from Asia were small in number, but suggest a trend similar to that found in other developing regions. Infection early in childhood is believed to arise in communities where children are carried about on the mothers' backs and where the "extended" or "joint" family systems offer more opportunities for droplet infections.

Age of Measles in Developing Countries Compared with the United Kingdom

	Median Age in Months	No. of Cases Reported
Jordan	18·0	2,038
Ghana	24·7	5,059
W. Nigeria	16·5	6,759
E. Nigeria	21·5	3,799
Uganda, Kenya, Malawi	18·5	2,997
Zambia, Tanzania and Rhodesia	29·7	2,801
S. Africa	29·4	1,364
England and Wales (1966)	51·7	343,525

Clinical Picture of Severe Measles

Observations on measles that I made during a longitudinal study[10] of children in a West African village indicate the differences between the disease as seen there and as now seen in England. These observations have been extended by a number of workers participating in a postal survey.[2 3] In a proportion of the children the rash darkened in appearance, and the darkened areas later underwent a much greater degree of desquamation. Children with more severe skin lesions tended to develop sequelae to measles. The association between a darkened rash and the severity of the disease was recognized as long ago as A.D. 850 by the Arabian physician Rhazes,[27] who wrote: "The measles which are of a deep red and violet colour are a bad and fatal kind."

When there is a severe rash on the skin, equivalent changes are likely to occur on other epithelial surfaces; as a result, lesions of the conjunctival sac, the mouth, larynx, bronchus, and intestinal tract can all be expected (Fig. 1). Such lesions

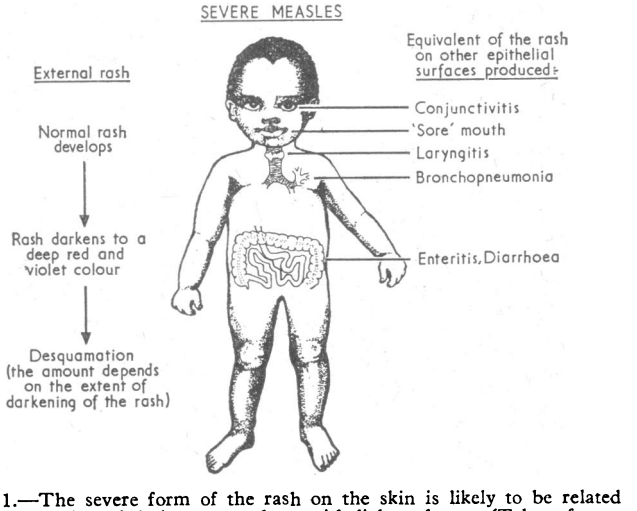

FIG. 1.—The severe form of the rash on the skin is likely to be related to the severity of lesions on other epithelial surfaces. (Taken from: *Modern Trends in Medical Virology*, edited by R. B. Heath and A. P. Waterson. London.)

are now uncommon in Europe, but were important in the past, and are frequently seen in areas where severe measles occurs. They will be briefly described below.

Mouth.—Mothers of small children with measles often draw attention to the soreness of the mouth. The soreness frequently interferes with sucking in the first two years of life, and at all ages limits food intake and predisposes to cancrum oris.[28]

Laryngitis.—Signs of laryngeal obstruction are relatively common in West Africa, as they were in the past in Europe and America Tracheostomy in measles carried a high mortality in West Africa, as once in England.

Bronchopneumonia.—Of 1,283 children admitted to the Ilesha hospital for measles over a three-year period ending in June 1961 604 had bronchopneumonia as a prominent clinical manifestation, and of these 169 (28%) died. In the past, bronchopneumonia associated with measles was severe and common in England: recent surveys have shown it to be infrequent.

Diarrhoea.—In West Africa the importance and danger of diarrhoea with measles was recognized by Daniell[5] over 100 years ago. In my experience its frequency and the severity of the disease are closely related. A quarter of the children admitted to the Ilesha hospital with severe measles had diarrhoea; half required parenteral fluid. The dehydration produced by the diarrhoea may be extreme and lead to a high mortality, as in the past in Europe. Thursfield[29] recorded that in England fatal diarrhoea usually occurred in the convalescent stages, while in the eruptive stages it was usually harmless.

Conjunctivitis.—Involvement of the conjunctival sac is common. It led to damage or destruction of one or both eyes in 31 (1·4%) of 2,164 inpatients in W. Africa.[2] In some areas eye lesions are particularly frequent, vitamin A deficiency being probably a contributory factor. In Rhodesia this combination is believed to be the main cause of blindness.

Otitis Media.—Involvement of the middle ear leading to a purulent discharge was present in 4·5% of children admitted to hospital.

Brain Involvement.—Encephalitis following measles has been described from West Africa by Arthur.[30] No records are available of its incidence, but there is ample evidence of involvement of the central nervous system. A history of convulsions was given by 33 (1·5%) child admissions, and 59 (2·5%) developed convulsions after admission. The mortality in these children was high.

Other infections.—Sick children in developing countries seldom have a single infection. The coincidence of measles and whooping cough may be particularly dangerous. Measles may reactivate a primary tuberculous lesion, and in an epidemic involving children with active tuberculosis, 12 out of 67 children undergoing treatment in a S. African hospital died.[31] Though the combination of tuberculosis and measles is considered dangerous by most writers, Kendig and Hudgens[32] quoted evidence indicating that the severity of the tuberculosis was unaltered by measles. This evidence came, however, from countries where the state of nutrition of children was good.

Causation of Severe Measles

I believe that the nutritional state of the child before and during the attack of measles is the dominant factor in producing the severe form of the disease. Other causes for variation in severity must be considered.

Variation in virus virulence.—Different strains of measles virus have not yet been isolated, and a single strain is probably world-wide. A more virulent strain would be unlikely to remain confined to West Africa, with overnight transport to Europe.

Variation in host immunity.—In the U.S.A. the disease is similar in those of European and West African extraction, and has declined at a similar rate in the two populations living alongside each other. Measles in Glasgow in 1908 was responsible for a case fatality of 5·8% among children under 5.[33] In the five-year period up to 1966 it was responsible for a case fatality of only 0·13% of children in this age group.[34] This change in severity in 60 years suggests that hereditary factors are unimportant: the similarity of mortality between people of African and European extraction in the U.S.A. supports this view.

Variation in age specificity.—If the age specific mortality figures for measles in English children obtained by Babbott[35] are applied to West African children, among whom the disease is so frequent in infancy, the case fatality would be 0·6%, whereas it is probably 3–5%. This suggests that the younger age of infection is only of slight significance in the increased severity of the disease in West Africa.

Variation in the child's environment.—The child in a poor environment may be exposed to more cross-infection, which would increase the severity of the disease, but it would not explain the difference in the type of rash associated with the severe form of measles. A more probable explanation lies in the lack of some unspecified nutrient or nutrients which may cause a greater degree of perivascular extravasation, producing a darkening of the rash of the skin and exfoliation, with equivalent changes in the epithelium of other organs.

Measles and Malnutrition.—The interrelation between infection and nutrition is complex, and their combined impact on the child in developing countries is responsible for a high proportion of morbidity and mortality and has received increasing attention in recent years Two separate phenomena must be distinguished: measles making the nutrition of the child worse; and measles is more severe in the malnourished child.

Measles making the nutrition of the child worse.—In the Ilesha area, a simple weight chart[36] is used in the Under Fives' Clinic[37] to which 400 children come every day. The analysis of many thousands of these charts has shown that measles leads to loss of weight more than any other of the acute diseases in childhood. The children under close observation in the longitudinal study at the village of Imesi were weighed at every visit. Their loss of weight amounted to 10% of their previous weight in a quarter of the children, and 15% of the children took over three months to regain their previous weight.[10] There are many reasons for the loss. A sore mouth impairs the child's capacity to suck or its willingness to eat. Reduction in the amount of food ingested by the child is partly due to loss of appetite but is also due to traditional practices in the feeding of sick children. The weight loss which occurs in any disease with high fever, diarrhoea, and purulent lesions of the skin and elsewhere is, of course, also important.

Murphy,[38] working in Ghana, has been among those who have drawn attention to the frequency with which measles may precipitate kwashiorkor or marasmus. The same is true in Nigeria and East Africa, and has also been reported from the Sudan by Hassan.[39]

Evidence that Measles is More Severe in the Malnourished Child

The decline in mortality in measles in this century has antedated the introduction of antibiotics but came at a time when improved methods of child feeding were being widely adopted.

Drinkwater[40] described an epidemic in Sunderland in a period of industrial depression with a mortality of 8%. In half the children the rash was darker than in previous years. Chalmers,[33] in his detailed analysis of measles mortality in Glasgow, showed that mortality in children from families which could afford to live in a house with more than four rooms was only a sixth of that among children in families confined to one room.

In the survey of measles, a completed questionary from 600 doctors was analysed. This confirmed that measles is more severe in countries where malnutrition in childhood is common.[41] Among children admitted to hospital, the weights of children who died from measles was found to be very much below that of those who survived.[2] In Lagos, Rea[42] found the incidence of severe illness, including pneumonia and diarrhoea, was more frequent in the poorly fed slum-dwellers than in the better-fed section of the population. In India, Ghosh and Dhatt[13] found that of those with "complications" 84·5% showed poor nutrition, and only 14·5% were reasonably well nourished.

(The conclusion of the paper will be printed next week, together with a full list of references.)

TODAY'S TESTS

With the help of expert contributors we print in this section notes on tests in current use in clinical investigation.

Schilling Test of Vitamin B_{12} Absorption

Malabsorption of vitamin B_{12} may be due to gastric lesions which impair the secretion of intrinsic factor or to lesions of the small intestine which interfere with the absorption of the B_{12}/intrinsic factor complex. Tests of B_{12} absorption using radioactive B_{12} have their most useful application in the diagnosis of pernicious anaemia, but are also useful for demonstrating intestinal malabsorption of B_{12} even where there is no other evidence of intestinal malabsorption. In fact, absorption tests with radioactive B_{12} may provide the first evidence of impaired gastric or intestinal function.

Measurement of B_{12} Absorption

This is essentially a two-stage procedure. The test is first carried out by giving the patient a small oral dose of radioactive B_{12}. If the patient fails to absorb this normally, the test is repeated with the addition of intrinsic factor.

The absorption of vitamin B_{12} can be assessed by one of the following methods:

(1) Urinary excretion method (Schilling test).
(2) Faecal excretion method.
(3) Hepatic uptake method.
(4) Whole-body radioactivity method.
(5) Plasma radioactivity method.

In clinical medicine the urinary excretion method of Schilling[1] is undoubtedly the most widely used test for assessing B_{12} absorption. However, it should be pointed out that the measurement of B_{12} absorption with whole-body counters is almost certainly the best method, and will probably replace the other tests as more hospitals are able to afford the relatively expensive equipment.

Principle of the Schilling Test.—The patient is given an oral test dose of radioactive B_{12} and at the same time an injection of non-radioactive B_{12} to ensure maximum urinary excretion of the absorbed radioactive vitamin over the next 24 hours. The test is thus rapid and simple to carry out, and any error in urine collection will not n sk defective B_{12} absorption. However, the large injection of non-radioactive vitamin B_{12} may be a disadvantage in the initial stages of the investigation of a patient with megaloblastic anaemia. As in all tests which depend on urinary excretion, the results may be unreliable in patients with renal disease. A repeat test can be carried out three days after the original test, provided a second injection of non-radioactive vitamin B_{12} is given to the patient 24 hours after the first test to flush out any radioactive vitamin B_{12} that can still be mobilized.[2]

Test Dose of Radioactive B_{12}.—Doses of between 0·5 and 2·0 μg. of radioactive B_{12} have been used for routine diagnostic tests. Cobalt-57 and cobalt-58 are suitable labels for B_{12} when measuring urinary radioactivity by scintillation counting. The introduction of single-dose capsules of radioactive B_{12} (1 μg. B_{12}/0·5 μCi)* has facilitated the procedure of the Schilling test.

Intrinsic Factor.—Ideally, normal human gastric juice should be used as a source of intrinsic factor, but in practice it is usually more convenient to use commercially available vitamin-B_{12}-free hog intrinsic factor concentrate (H.I.F.C.). The dose of H.I.F.C. should be large enough to produce maximal possible absorption from the particular dose of vitamin B_{12} used, and this is the dose usually recommended by the manufacturer. A measured dose of the bulk batch of intrinsic factor is either dissolved in water just before administration to the patient or is put up in gelatin capsules.

Clinical Procedure

The patient fasts overnight and empties bladder before test.

DAY 1—8 a.m. Patient takes test dose of radioactive B_{12} by mouth. Then give intramuscular injection of 1,000 μg. non-radioactive B_{12}. Patient may have a light breakfast after two hours.

COLLECT ALL URINE PASSED FOR 24 HOURS

DAY 2—8 a.m. Second injection of 1,000 μg. of non-radioactive B_{12}. The purpose of this injection is to "flush out" any residual radioactivity that can be mobilized and thus prepare the patient for a repeat test with intrinsic factor should this be necessary.†

DAY 3—Rest day—no injections or urine collections.

IF THE RESULT OF THE FIRST TEST IS ABNORMAL, THE TEST SHOULD BE REPEATED WITH INTRINSIC FACTOR

Patient fasts overnight to start second test.

DAY 4—8 a.m. Patient takes test dose of radioactive B_{12}+ intrinsic factor by mouth. Then give injection of 1,000 μg. non-radioactive B_{12} as above. Patient may have light breakfast after two hours.

COLLECT ALL URINE FOR 24 HOURS AS ABOVE

A modification of Schilling's original method combines the two stages of the test into a single diagnostic procedure.[3 4] Two differently labelled forms of B_{12} are given to the patient simultaneously, one free (e.g. ^{58}Co-B_{12}) and the other (^{57}Co-B_{12}) bound to normal gastric juice. The two isotopes can be counted separately in a mixture because of their widely different scintillation spectra. The double-isotope test has potential advantages over the standard test, but so far it has had only limited clinical application because of the need for individual laboratories to prepare the gastric-juice-bound isotope of B_{12}.

Counting Procedure.—The procedure for measuring the amount of radioactivity in urine has been described in detail by Mollin and Waters[5] and will not be elaborated here.

* Available from the Radiochemical Centre, Amersham, Bucks.

† Urine is usually not collected during the second 24-hour period. However, results of the 48-hour test are statistically more significant than the standard 24-hour test, and are therefore valuable for comparative studies.[3]