MODERN PRACTICE
IN
INFECTIOUS FEVERS

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[*In two volumes*]

VOL. 2

PAUL B. HOEBER, INC
MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS
NEW YORK

[PUBLISHED IN 1951]

PRINTED IN GREAT BRITAIN BY
LOVE AND MALCOMSON, LTD., REDHILL, SURREY

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CHAPTER 1

MEASLES

WILLIAM GUNN

DEFINITION

MEASLES (morbilli) is an acute specific disease, exhibiting three stages: (1) initial or prodromal; (2) eruptive, corresponding to the acme of the attack and subdivided into enanthem, involving mucous membranes, and exanthem or cutaneous rash; and (3) decline with defervescence, subsidence of symptoms and disappearance of the rash, commonly followed by a characteristic brownish, mauve-tinted staining and by fine powdery desquamation. Catarrhal inflammations, constantly in the respiratory tract, less frequently, and usually limited to young children, in the gastro-intestinal tract, are so characteristic as to be clinical features rather than complications; extension to sinuses, including the ear, and to lung tissues is usually attributable to secondary infection of the virus-damaged mucosa. Measles is the commonest of the acute exanthems and few escape attack, latent or overt, in urban conditions of life.

HISTORICAL NOTE

The name morbilli is derived from the Italian word *morbillo* in contrast to the more deadly *il morbo* or plague.

Credit for distinguishing measles clearly from smallpox is due to the tenth-century Arabian physician, Rhazes. Nevertheless, confusion between these diseases persisted in the Middle Ages and it is clear that Sennert regarded measles as a mild variant of smallpox although distinct from scarlet fever of which he gave an exact description (Sennert, 1641). That it continued to be confused with other exanthems, including scarlet fever, which was often referred to as *morbilli confluentes*, is evident from Sydenham's classical description of the London epidemic of 1664–70. In 1758 Francis Home, professor of medicine at Edinburgh, attempted active immunization on the already familiar lines of variolization (*see* page 570); an area of the skin was scarified and blood taken at the height of the eruption was daubed on the surface with cotton-wool. This technique, in his hands, usually resulted in an attenuated attack after an incubation period of some 6 days, but the failure of subsequent workers to obtain similar results discredited his claims. An important advance was the announcement by Henry Koplik (1896) that the minute spots on the buccal mucosa, named after him, were peculiar to measles; it is clear from his description that these spots, as well as buccal stomatitis generally, were familiar to previous observers but that their diagnostic significance was not appreciated. Diagnosis in doubtful cases was assisted by the discovery of plasma and Türk cells in the blood (Türk, 1898). Subsequent advances are noted in the appropriate sections below.

AETIOLOGY

Geographical distribution

The disease is of world-wide distribution, affecting populations irrespective of climate and race, although less prevalent in tropical countries and amongst

Negroes. A favourable environment does not necessarily confer immunity from attack. Outbreaks in immunologically virgin soil are characteristically severe. These usually occur in remote islands, are introduced by ships, and commonly involve people living under primitive conditions. Outstanding examples are the outbreaks in the tropical Fiji Islands and semi-arctic Faroë Islands.

In large civilized countries the epidemic pattern remains fairly constant and extreme local fluctuations in incidence tend to be smoothed out in the total figures (Butler, 1947). On the other hand, in small compact population groups, as in Denmark, Holland and Switzerland, the whole country tends to be involved more or less simultaneously and violent fluctuations in incidence and severity occur from year to year. Almost everywhere, however, the disease has undergone in recent years a pronounced favourable change as regards severity, although not incidence, for which a number of factors, complex and intimately interdependent, must be considered; other virus diseases, such as smallpox and poliomyelitis, have not undergone a similar biological change.

Seasonal and environmental influences

In large centres of population epidemics tend to recur at intervals of two years, beginning in the early winter months and lasting some 6–9 months. The aggregation of susceptibles in schools, recreation centres, clinics, hospitals and doctors' waiting-rooms has in the past contributed materially to the biennial visitation.

In closed communities, such as nurseries and hospital wards, and to a less extent in semi-closed communities such as schools and barracks, attack in measles, as in chicken-pox, usually follows intimate exposure. Some 85–90 per cent of subjects contract the disease at some time, in populous areas in the first 5 years of life, due mainly to the frequency of effective exposure in such conditions. McKendrick (1940) suggested that epidemics are largely governed by the density of susceptibles; below a critical threshold the disease cannot establish itself as an epidemic process.

The effect of temperature and humidity on epidemics is variable. In Europe as a whole 92 per cent of the maximal incidence occurred from December to May in the years 1926–31, but in Spain, Portugal and Egypt it occurred in the hottest months. By contrast, epidemics have been worst, most widespread and severe, during the cold weather periods in Algeria, Turkey, Palestine and Iraq (League of Nations, 1932).

Epidemic periodicity

The regular biennial appearance of measles epidemics in large centres of population such as London was suddenly interrupted in 1939–40 by the war-time evacuation of a large proportion of the potential material (Martin, 1942), and the disease has not yet regained its former epidemic pattern; many factors, including the reduction in the size of families, may combine to prevent it ever doing so on the same scale in highly civilized countries.

Measles was made generally notifiable in England and Wales in 1940. Stocks (1949) estimated, however, that not more than 60 per cent of the cases of measles in 1944–47 are included in the official notifications; comparative estimates for other notifiable diseases are: whooping-cough, 20–25 per cent; pneumonia, 25–33 per cent; enteric fever, 80 per cent; respiratory tuberculosis, 90 per cent.

Analysing the notification figures, Butler (1947) demonstrated four epidemic waves, each of which conformed to a common pattern when the curves for the whole country are considered; on the other hand, there may be, and usually are, wide fluctuations not only in locality but in time, over the 2-year period roughly covered by each epidemic. Failure to exhaust susceptible material may prolong an epidemic unduly; sporadic cases may maintain a smouldering focus which may erupt into activity during the inter-epidemic period but lack sufficient impetus for spread. Accidental acquisition or loss of critical virulence as a result of biological mutation may influence epidemic potential as in other virus infections.

Age incidence

Measles is rare but by no means unknown in newborn and young infants (up to 6 months) of mothers who had had measles some time previously (Herrman, 1917); in the later months of infancy some degree of attenuation is the rule; by 9–12 months the child is fully susceptible, although attack is usually less severe than at 2–3 years or adolescence, indicating some residual resistance to the disease. The maximal age incidence in London is in the 2–3 years age-group; among the poorer strata rather more than 50 per cent contract the disease before entering school, but in the middle and upper classes the attack rate is highest at 5–10 years, sometimes even later. Butler (1912–13), analysing the histories of 14,000 persons, found that 8·4 per cent were attacked in the first 4 years and by 15 years 97·3 per cent had had clinical attack; Collins (1924) obtained evidence of attack in 90–95 per cent of American students.

Causal agent

Although Tunnicliff's green-producing coccus, Ferry's *Streptococcus morbilli*, and Caronia's Gram-negative diplococcus have all been claimed as the causal agent, a virus aetiology is now universally accepted.

Animal inoculation

Josias (1898) was the first to transmit the disease to animals, but Goldberger and Anderson (1911) first showed that the virus passes a Berkefeld N filter. In addition to the higher apes, rabbits and guinea-pigs can be infected and even fowls and mice but not rats.

Morphology

Elementary bodies, in size about 0·25 μ in diameter, rather larger than the Paschen bodies of smallpox and chicken-pox, were found by Coles (1937) in the nasal and faucial secretions, tears and blood.

Cultivation

The virus was cultivated from the blood by Plotz (1938) on chick embryo and Rake and Shaffer (1939) used serial passages to depress virulence sufficiently for safe use in the active immunization of non-immunes.

Physical properties

The virus can be preserved at 0°C. for several days, at −35°C. for 4 weeks and dried *in vacuo* from the frozen state for several months (Hurst and Cooke, 1941). It resists 10 per cent ether at room temperature for 30–40 minutes (Rake, Shaffer

and Jones, 1941) and survives for 3 months in 50 per cent glycerol (Taniguchi and his colleagues, 1935). Heating at 55°C. for 15 minutes kills the virus.

Infectivity and dissemination

Virus has been recovered from the upper respiratory tract in the pre-eruptive and early eruptive stages of the disease and has also been obtained from cutaneous lesions and from the blood. The catarrhal character of the disease provokes much coughing and sneezing with spread of both droplets and droplet nuclei over considerable distances, especially if strong air currents are present; ill-planned ventilation arrangements may therefore actually facilitate spread. Larger droplets tend to settle on clothing and horizontal surfaces, from which they readily rise as dust when dried, as shown by Hare and Mackenzie (1946) with *Bacillus prodigiosus*. The infectivity of measles in the prodromal and eruptive stages is about as high as that of chicken-pox, as all workers in children's hospitals know to their mortification.

PATHOLOGY

Blood picture

In the incubation period there is usually a neutrophil leucocytosis of moderate degree with a slight increase of eosinophils; at the onset of fever there is a transient leucopenia due to a reduction in the lymphocytes (up to one-third or one-half of the normal) until the first day or two after the appearance of the rash. In uncomplicated attacks lymphopenia is succeeded by lymphocytosis, returning to normal in the second or third week of the disease; Türk and plasma cells, which together may form up to 20 per cent of the total white cells, appear at some stage in most attacks, as in rubella, from which it is indistinguishable from the blood changes alone (Hynes, 1940). Pyogenic invasion may later complicate the picture by polymorph excess. There is a slight fall both in the number of red cells and in the haemoglobin content.

Morbid anatomy

The virus is widely disseminated throughout the body and can be recovered from most organs and tissues.

Mouth

The red areas on the mucosa correspond to the maculo-papules on the skin, and the grain of salt appearance (Koplik spots) is due to fatty and hyaline degeneration of the superficial cells. Varying degrees of subserous infiltration and of ulceration may be encountered, especially in the vicinity of the lips. Extensive deep ulceration (cancrum oris) is nowadays exceedingly rare.

Larynx and trachea

The larynx and trachea are swollen, congested and usually muco-purulent, but sometimes dry and glazed, especially after atropine therapy. In the sinuses and middle ear, mucus or pus is common in untreated cases.

Lungs

Naked-eye appearances include general congestion with patches of reddish or grey consolidation with broncho-pneumonic or lobular distribution; the red

patches are necrotic areas with blood in the alveoli and bronchioles, inflammatory reaction often being absent or minimal. Various amounts of hypostatic congestion and lobular collapse may mark the lower and posterior segments of the different lobes; contiguous areas may sink, just float or appear buoyant from emphysema.

Microscopically, two types of morbid changes may be present together but not equally in degree or duration. (i) The changes may be predominantly interstitial, closely resembling those of influenzal or other virus pneumonia; peribronchiolitis with inflammatory changes and sero-fibrinous exudate into and between the interstitial cells may cause great thickening, extending widely into the lung parenchyma and rendering it relatively airless. Giant cells of the non-specific fused respiratory epithelium type may be seen in large numbers in bronchi and bronchioles (Archer and Biggs, 1947). (ii) The changes may be predominantly in the walls of bronchioles and alveoli, produced either by extension of interstitial invasion but more usually from secondary infection descending from the upper respiratory tract. All the coats of the bronchioles are inflamed and infiltrated and covered with muco-purulent or frankly purulent exudate, depending on the particular bacteria present. Lobar consolidation may occur with a tendency to fibrinous or purulent pleural effusion in cases not receiving chemotherapy. Suppurations of surface and deep glands are not uncommon; a latent tuberculous focus may be stirred into activity, especially the primary complex in infants.

Gastro-intestinal tract

Inflammatory catarrh with desquamative changes extends the whole length of the digestive tract. Koplik spots may appear anywhere, including the vermiform appendix, which is often swollen and congested and may undergo suppurative or necrotic changes. Multinucleated giant cells may be found similar to those in the spleen, tonsils and lymph glands.

Central nervous system

In rare cases encephalo-myelitis occurs. Diffuse congestion and petechial haemorrhages may be seen widely scattered in the cerebral white matter, basal ganglia, mid-brain, pons and medulla. The most constant histological findings are congestion and oedema, haemorrhages and thromboses, with perivascular demyelination; perivascular mononuclear cuffing, common and severe in post-vaccinial forms, is less constant in measles encephalitis (Greenfield, 1928–29). Generally the nerve cells escape although slight degenerative changes have been described in some instances.

Purulent meningitis, with or without cerebral or cerebellar abscesses and thromboses, are occasional sequelae of otitic, sinus or ophthalmic suppuration. The kidneys, liver and spleen are commonly marked by toxic changes varying from congestion and cloudy swelling to focal necrosis. Pericarditis, peritonitis and gangrene of the bowel from mesenteric thrombosis, or of the lower limb from popliteal embolism, are infrequent but dangerous accidents, usually terminating fatally.

Skin

According to Mallory and Medlar (1920) changes in the rash are of two kinds; exudation of serum causes swelling and vacuolation of the epithelial cells forming small vesicles below the keratinized layer; in addition individual cells or groups

of cells may undergo retrograde changes up to necrosis; these changes may also involve the hair sheaths and sebaceous glands.

The superficial layers of the corium show proliferation of endothelial leucocytes; the vascular endothelium in the areas covered by the rash is swollen with granular changes in the cytoplasm. The characteristic post-eruptive staining is due to capillary stasis; red blood corpuscles and broken-down pigments adhere to the damaged intimal lining. Various inclusion bodies, staining Gram-positively, have been described in the vascular endothelium and are variously attributed to aggregations of virus, phagocyted cocci and nuclear material; they have also been found in Koplik spots and monocytes of the blood.

CLINICAL COURSE

Incubation period

The commonest interval is 11 days; a range of 10–14 days comprises the large majority, with extreme limits of 7–21 days. Consideration should be given to the possibility of a missed case being responsible in respect of intervals longer than 18 days. Stillerman and Thalhimer (1944) found that, in the second year of life, the incubation period tended to be 15 days or longer, and suggested that the prolongation was attributable to residual maternal immunity.

Usually silent, the beginning of the incubation period may occasionally be marked by transient pyrexia and catarrhal features termed by Goodall (1925) the "illness of infection"; within a few hours of exposure, sneezing, conjunctivitis and in some cases a scanty, transient morbilliform rash may appear in a minority of contacts; attacks of average severity follow in the usual time, indicating the development of little or no immunity from the initial stimulus. Other workers, notably Erdheim (1926), and Abercrombie (1929), have confirmed these occurrences. The blood changes are too inconstant to warrant reliance for diagnostic purposes.

Invasive period

Measles may start abruptly with high fever, convulsions, vomiting and occasionally severe diarrhoea, but more typically the onset is on a more subdued note with malaise, anorexia, slight fever, sneezing and a short, irritating cough, often with a croupy element; soon heavy eyes with glistening suffusion and rhinitis appear and the temperature rapidly rises, ranging from 100°F. to 104°F.

Prodromal rashes

At this early stage prodromal rashes may appear; the incidence varies greatly, from 5 to 25 per cent of all cases, from one epidemic to another and at different stages of a particular epidemic, being most frequent at its height. The commonest form is scarlatiniform, usually patchy, but it may become confluent and be indistinguishable clinically from scarlet fever. Morbilliform rashes, faint and sparse, resembling the rash of rubella rather than of measles, and often localized to the upper trunk, are next in frequency; these may fade or merge into the ordinary eruption subsequently.

Urticarial maculo-papular eruptions, occasionally typical wheals, are often marked by some itching, but this is rarely of the intensity of serum disease.

Although occasionally of help in early diagnosis when the fact of exposure is known, these prodromal rashes usually mislead, as they appear and may disappear before the more characteristic mucous membrane changes are manifest.

Enanthem

The widespread distribution of the lesions causing conjunctivitis, rhinitis, tonsillitis, pharyngitis and laryngitis simultaneously or in sequence, has been somewhat overshadowed by the characteristic Koplik spots, which are pathognomonic of the disease. Brownlee (1920) drew attention to early subconjunctival oedema and Stimson (1928) to a "line" of congested mucosa crossing the lower lid at the margin of the tarsus, but their observations apply to a minority of generally severe cases. Koplik spots are more trustworthy but may be absent or at least undetectable in some 5–10 per cent of cases. They range from 3 or 4 minute red areas, pin-point to pin-head in size, with greyish centres, generally opposite the lower molar teeth, to several hundreds covering the whole buccal mucosa, including the lips; in severe cases the normal smooth appearance of the mucosa is everywhere lost and it looks granular, as if it were violently rubbed with sand-paper. The tongue becomes heavily furred with enlarged papillae, often resembling the scarlatinal white strawberry tongue; in a few days the fur is shed and again it may imitate the red strawberry tongue, albeit with a mauve tint (raspberry tongue); the broad, flabby tongue is often in marked contrast to the pointed tongue characteristic of scarlet fever. The interval between onset and rash averages 3 days, but may range from 1 day to 10 or 11 days (Selby, 1936).

Advance

The eruption rapidly advances from above downwards but not in a strictly regular fashion; the hands and feet are last affected and often escape completely. Areas stimulated by friction, inflammation or rubefacients such as camphorated oil or ultra-violet light may show the rash earlier and in a fashion more marked than in contiguous areas.

Exanthem

The measles rash is too well known to require a minute description here, but variations in the rash are so wide that it may imitate at some stage scarlet fever or rubella so closely as occasionally to mislead the experienced observer. It starts behind the ears, at the junction of the face and scalp, and around the nostrils almost simultaneously, and already a few lesions appear around the clavicle before it is well advanced on the face. During this period of high infectivity and considerable misery, rapid, sometimes grunting respirations, due to tracheal and bronchial congestion, may suggest the onset of broncho-pneumonia; occasionally suffocative bronchiolitis may be so severe, with deep cyanosis, that the patient may die before the onset of the rash, or just as it is appearing with a mottled, cyanotic hue. Enlargement of lymph glands is widespread but not so constant as in rubella, at least not in the sub-occipital and posterior cervical regions. Involvement of mesenteric glands, especially the ileo-caecal group, may raise the question of appendicitis. The individual lesions, maculo-papular from the first, often remain discrete, especially in young children, but rarely remain round; oval and pleomorphic shapes are commoner, due in part to irregular spread, in part to fusion of adjacent lesions; the crescentic or blotchy pattern is

characteristic, together with the bloated face and suffused, discharging eyes. In colour the rash varies from pale pink to lobster or brick red, usually with a mauve or brownish hue as it gets older. The lesions fade on pressure but after a day or so fading is only partial or absent, due to the development of staining.

The rash is heralded by an increase of temperature or return of fever after the remission or intermission which is common on the second or third day from the onset, but already the patient may feel better, as the distressing symptoms due to the enanthem are usually by now somewhat alleviated. Constitutional symptoms, such as insomnia, digestive upset, sweating and oliguria are transient features unless some complication supervenes.

Stage of decline

Defervescence is usually by rapid lysis in uncomplicated attacks and subsequent recovery is prompt and uneventful. The rash fades in the order of appearance and nearly always is marked by varying degrees of brown or mauve, dirty-looking pigmentation, commonly referred to as post-measles staining. In some cases the areas affected by the rash acquire a deep purple hue, resisting pressure, occasionally indistinguishable from petechial and purpuric extravasation; some corpuscles do escape the capillary confines but intimal staining by dead cells and their pigments is chiefly responsible. In the majority of cases there is slight desquamation, especially on the face and trunk, branny or flaky in character but rarely pin-hole or in shreds, or prominent on the extremities as in scarlet fever; occasionally it is both extensive and pronounced.

Clinical types

The ordinary attack is as described above.

Mild measles.—Mild measles occurs in children under 12 months old and sometimes up to 2 years old; catarrhal features are minimal, pyrexia is slight or absent and the first feature noted may be the rash, commonly attributed to food allergy or teething; this group embraces some of the 5–10 per cent of exposed subjects who are said not to contract measles. Exactly the same clinical picture is obtainable with timely use of immune serum. This form used to be designated *morbilli sine catarrho.*

Toxic or suffocative measles.—In young, ill-nourished, rachitic children, whose lungs had already been damaged by previous disease, especially by whooping-cough, this form used to be common and occasionally killed before the rash appeared; cyanosis and dyspnoea from spasm and congestion, pulmonary oedema or cardio-respiratory failure are the chief features. A variety has been named ataxo-adynamic measles, characterized by hyperpyrexia and extreme prostration (Rolleston, 1929).

Haemorrhagic (*"black"*) *measles.*—Haemorrhages into the skin and from the alimentary and respiratory tracts and kidneys are the distinguishing features; doubtless most of the cases formerly so named were instances of haemorrhagic smallpox, fulminating meningococcal septicaemia or concomitant measles and some blood diathesis now more precisely characterized. A few cases have been described within recent years (Baker, 1941; Lineham, 1942).