The Eruptive Stage

Chapter 3 concludes with an integrated picture of the pathogenesis of smallpox, which was a generalized viral infection with no recognizable primary lesion but with a viraemia whose onset was manifested clinically by the pre-eruptive fever, followed a few days later by the development of a focal eruption on the mucous membranes and skin. Following the example of Ricketts (1908), our description of the clinical features of smallpox is in large part based on illustrations, using a series of colour photographs taken for WHO during the smallpox eradication programme in Pakistan. The subject was a 9-month-old unvaccinated male infant in whom the onset of fever was recorded 1 day before the rash first appeared. He suffered from the commonest form of smallpox—discrete ordinary-type—and recovered without complications. Daily photographs were taken, until recovery was complete, of the entire subject and of face, trunk, arms and legs. Only a limited selection of these can be reproduced here, but they serve to illustrate the nature, evolution and distribution of the rash of smallpox. The temporal succession will be described in terms of the day of rash.

Order of appearance of the focal lesions

The lesions on the mucous membranes (the enanthem—Plate 1.3C) were the first to appear, and they were visible on the tongue and palate, as minute red spots, about 24 hours before the appearance of rash on the skin. Lesions also occurred at this time lower down in the respiratory tract, and some patients, who complained of sore throats during this stage, had an enanthem on the pharynx. Only a limited selection of these can be reproduced here, but they serve to illustrate the nature, evolution and distribution of the rash of smallpox. The temporal succession will be described in terms of the day of rash.

Evolution and distribution of the enanthem

The enanthem evolved rapidly, because of the absence of a horny layer in the stratified epithelium of the pharynx. The minute macules became papular and vesicular and then broke down before the 3rd day (Plate 1.3C), liberating large quantities of virus into the saliva. By the 10th day they had almost healed. The visible parts of the oropharynx most likely to show lesions were the hard palate, the tip and edges of the tongue and the pillars of the fauces. Different patients showed remarkable variations in the extent of the enanthem; in cases of equal severity the lesions were sometimes few or absent, or the mouth and throat might have been covered by a confluent enanthem that extended to the larynx and trachea. Although not as spectacular as the rash, the pharyngeal lesions were of great importance epidemiologically, as they constituted the major source from which virus was transmitted to other persons (see Chapter 4).

Evolution of the skin lesions

By the 2nd day of rash the macules were raised and usually described as “papules”. Reference to the histopathology indicates that this term was really a misnomer; they were raised above the skin surface because of the effusion of fluid into the tissue spaces and were in fact early vesicles (Plates 1.5 and 1.6).
By the 4th or 5th day they were obviously vesicular, containing at first an opalescent fluid, which became opaque and turbid in another 24–48 hours (Plates 1.7–1.9).

By the 7th day all the skin lesions were pustules (Plate 1.10) and between then and the 10th day they matured and reached their maximum size (Plates 1.11 and 1.12). By about the 11th day resolution started and the lesions flattened (Plate 1.13). The fluid was slowly absorbed, and by the end of the 2nd week the central portion hardened and finally a scab or crust formed, which later separated, leaving a depigmented area (Plate 1.14).

The palms of the hands and the soles of the feet, because of the very thick stratum corneum, were characterized by the persistence of lesions long after these had scabbed elsewhere. On the soles of the feet especially they had a very characteristic appearance (Plate 1.16). The thick cuticle lay over them and they did not protrude from its level surface, through which the disc-like scabs could be clearly seen. These lesions were called "seeds" and were often artificially removed with a needle in attempts to hasten discharge from the hospital, where patients were usually held until the last scab had separated.

The evolution of the rash can best be appreciated by scanning the series of colour plates provided, which show the lesions daily from the 1st until the 9th day (Plates 1.4–1.12), and then on the 13th (Plate 1.13) and 20th days (Plate 1.14).

**Characteristics of the individual lesions**

Variolous skin lesions, which usually had only a barely perceptible erythematous areola around them, were traditionally held to have three distinctive characteristics: loculation of the cavity of the vesicle, its umbilication, and the solidity and hardness of the lesion.

**Loculation.** The reasons for loculation are clear from a consideration of the histopathology (Plate 1.15); it used to be determined in cases of smallpox by piercing the vesicle and observing that the fluid contents could not be completely emptied through the wound. However, this was a rather inefficient clinical...
Histopathology of Skin Lesions

In order properly to appreciate the clinical features of the skin lesions it is necessary to consider their histopathology. This is described in detail in Chapter 3, but it is convenient to summarize the main features of the lesions here. Plate 1.15 represents a section of part of a skin lesion in which vesiculation was beginning. The lesion occupied the whole depth of the epidermis, the deeper layers of which provided the floor and the cuticle (stratum spinosum, keratohyalin layer and horny layer) the roof. At the centre the floor was thin and as the lesion grew the deeper layer of basal cells lysed and the dermis then formed the base of the vesicle. But ordinarily (except in the face, where the numerous sebaceous glands complicated the picture) the lesion was contained within the epidermis. As infected cells became necrotic and fluid accumulated, the tissue split, the columns of epidermal cells being forced apart irregularly, so that the fissures were usually perpendicular to the surface and the vesicle consisted of several separate compartments or locules. As cellular necrosis and polymorphonuclear cell infiltration proceeded the fluid became turbid and the lesions pustular, but their turbidity was due to the extensive tissue destruction by the virus and a leukocytic reaction to this; the pus was not associated with bacterial infection.

test, in that it was readily demonstrable in cases in which there was little doubt about the diagnosis but equivocal in cases in which doubt might arise because the vesicles were small or soft. It was rarely used for differential diagnosis by workers engaged in the global smallpox eradication campaign.

The “feel” of the lesion. The skin lesions of smallpox were usually described as “shotty”. Although as papules they projected little above the surface, they could be rolled between the thumb and forefinger and felt like hard round foreign bodies embedded in the epidermis.

Umbilication. This term refers to the central depression, of varying size, that was often seen in the distended vesicle. It is well illustrated in Plate 1.8. Umbilication often persisted into the pustular stage, but as the lesion progressed the fibrinous threads within it were destroyed and its surface usually became flattened because of absorption of fluid (Plates 1.11 and 1.12).

Distribution of the rash

The rash of smallpox had a characteristic “centrifugal” distribution pattern. This is apparent in the series of full-body photographs of the Pakistani infant (e.g., Plate 1.11), but is better shown in Plate 1.17. The rash was most dense on the face; more dense on the extremities than on the trunk; and, on the extremities, it was more dense on the distal parts than on the proximal, on the extensor than on the flexor surfaces and on the convexities than on the concavities. The apex of the axilla was relatively free of lesions compared with the folds; this was known as Ricketts’ sign. The palms of the hands and the soles of the feet were involved in a majority of cases (Plate 1.16).

On the face, the rash was more profuse on the upper than on the lower half, but in a small proportion of cases it was more uniformly distributed. On the trunk, it was usually denser on the back than on the front, and, on the front, it was more dense on the chest than on the abdomen. On the abdomen, the upper half usually exhibited a more profuse rash than the lower half.

Ricketts (1908) described at length the fine details of the distribution of the rash, which he regarded as a feature of great value in differential diagnosis. Such minute consideration was no longer necessary when laboratory confirmation of a tentative diagnosis became possible. Ricketts also provides several illustrations of the way in which irritation or friction could produce a local concentration of skin lesions. His suggestion that the “centrifugal” distribution of the rash was due to exposure of the face and forearms in habitually clothed persons was not supported by the universal observation of the same characteristic distribution in habitually scantily clothed patients made by workers in several countries during the global smallpox eradication programme.
Clinical Course

The appearance and evolution of the rash in ordinary-type smallpox have already been described and illustrated. In such cases, the fever, which had fallen somewhat on the 2nd or 3rd day after the onset of the disease, when the rash first appeared, usually rose again by the 7th or 8th day and continued to remain high throughout the vesicular and pustular stages, until scabs had formed over all the lesions (see Fig. 1.1).

If secondary pyogenic infection of the skin occurred, the fever usually remained elevated. Respiratory complications, which sometimes developed on about the 8th day of the disease, were either viral or bacterial in origin. In fatal cases, death occurred between the 10th and 16th days of the illness. Among survivors, scabs separated by the 22nd-27th days, but "seeds" in the palms and soles remained much longer unless artificially removed.

Grades of Severity

As has been pointed out earlier, so many cases of variola major belonged to the ordinary type, covering a wide range of severity, that some subdivision that was related to prognosis was found useful. That commonly employed related to the extent of the rash, and the terms "confluent", "semiconfluent" and "discrete" were used by Rao (1972) and others. However, it is important to point out that such grades were part of a continuous spectrum; the numbers of pustules in individual cases could vary from a few to several thousand.

Confluent ordinary-type smallpox

This subtype encompassed cases in which the pustular skin lesions on the extensor surfaces of the extremities as well as those on the face were confluent (Plate 1.18). In such cases the temperature, which had fallen on the 4th or 5th day after the onset, rose again 2 days later and remained elevated until scabbing was complete. Sometimes the toxaemia did not abate and the temperature did not fall even after scabs had formed over all lesions; when this occurred the prognosis was poor. In Rao's series the case-fatality rate of confluent ordinary-type smallpox in unvaccinated subjects was 62%.

Semiconfluent ordinary-type smallpox

This was distinguished from confluent ordinary-type smallpox by an arbitrary criterion: the rash was confluent on the face but discrete on the body, including the forearms. A secondary fever often developed during the pustular stage, but the temperature and toxaemia were less marked than in the confluent subtype and the temperature subsided as soon as the scabbing had started. In Rao's series the case-fatality rate in unvaccinated subjects was 37%.

Discrete ordinary-type smallpox

This was the commonest clinical type in variola major (42% of cases in unvaccinated subjects and 58% of those in vaccinated subjects in Rao's series). Plates 1.11 and 1.17 illustrate such cases. The lesions were fewer in number and discrete (i.e., separated by normal skin) on the face and elsewhere. In some cases, although the lesions were less numerous, the course of the disease was the same as in the other two subtypes; sometimes there was no secondary fever during the pustular stage. The overall case-fatality rate was much lower than in confluent or semiconfluent ordinary-type smallpox—about 9% in unvaccinated subjects in Rao's series.

MODIFIED-TYPE SMALLPOX

In 1908 Ricketts wrote:

"By the use of the terms 'modified smallpox' and 'abortive lesions', no assumption is made as to the state of the patient with regard to vaccination. All that is implied is that he exhibits lesions which, in certain particulars, differ from the type most common among unvaccinated patients. The pustules, instead of developing into the large vesicles and pustules of natural smallpox, are transformed into lesions which are generally smaller and often of a different conformation, which do not form pustules of the usual size or wholly fail to suppurate, and which hasten through their course of evolution more quickly than is natural."

This was written before variola minor became endemic in Great Britain. In reviewing data on 13686 cases of variola minor, Marsden (1936) suggested that:

"... the end results of the action of any of the factors which produce modification are indistinguishable in the individual patient... for example, 'variola major' in a vaccinated subject, or in a
Plate 1.16. A: Lesions on the sole of the foot on the 14th day of rash. B and C: Palm of the hand and sole of the foot of a 2-year-old Zairean boy on the 21st day of rash. Elsewhere on the body the scabs had separated; on the palms and soles they remained as dark disc-like scabs ("seeds").
Plate 1.17. Distribution of the rash in smallpox. Dorsal and ventral views of a 3-year-old unvaccinated girl from Zaire, on the 5th day of rash. The case would be classified as mild discrete ordinary-type smallpox. The pustules were characteristically most numerous on the face, arms and legs and rather sparse on the trunk.
Plate 1.18. Confluent ordinary-type smallpox in an unvaccinated woman in her twenties, on the 9th day of the illness. Pustules were confluent on the face, forearms and legs but discrete on the trunk. (From Stojkovic et al., 1974.)
Plate 1.19. Modified-type smallpox. **A:** Vaccinated Japanese man aged 42 years, on the 10th day of the illness. Note the varying size of the lesions and their rapid evolution. **B:** Vaccinated Japanese woman aged 19 years. Very mild case. **C:** Adult female, Delhi, India. Note lack of toxaemia and diversity in size of lesions. (A and B from Uchida, 1955; C from Herrlich et al., 1967.)