Impressions of Smallpox in Bombay in 1958

"The majority of patients had fully developed smallpox in the suppurative stage, with confluent pustules covering the entire body. The head was usually covered by what appeared to be a single pustule; the nose and the lips were glued together. When the tightly filled vesicles burst, the pus soaked through the bedsheet, became smeared on the blanket and formed thick, yellowish scabs and crusts on the skin. When the pulse was taken tags of skin remained stuck to the fingers... When secondary haemorrhage appeared, the affected area of skin formed a single black mass.

"All the gravely ill patients were also tortured by mucosal symptoms. The tongue was more or less swollen and misshapen and hindered breathing through the mouth. The voice was hoarse and faltering. Swallowing was so painful that the patients refused all nourishment and, in spite of agonizing thirst, often also refused all fluids. We saw patients with deep invasion of the respiratory passages... Wails and groans filled the rooms. The patients were conscious to their last breath.

"Some... just lay there, dull and unresponsive. They no longer shook off the flies which sat on purulent eyelids, on the openings of mouth and nose, and in swarms on the inflamed areas of the skin. But they were still alive, and with touching gestures they lifted their hands and begged for help." (Translated from Herrlich, 1958.)

naturally immune, may be indistinguishable at the bedside, as in the laboratory, from 'variola minor'. Furthermore, it is affirmed that the sole method of determining with certainty the primary factor responsible for modification in the individual patient is continued observation of the character of the disease in other patients infected by him or from a source in common with him; and, similarly, that variola major is to be distinguished from variola minor only by epidemiological study of the course of the outbreak; for the clue is to be sought in the fact that, when the infective agent is of a persistently degraded virulence (variola minor), modification of attack is invariable, because it is independent of the patient's immunity."

Following Rao, a WHO Scientific Group on Smallpox Eradication (1968) defined modified-type smallpox in much the same way as had Ricketts:

"In this clinical type, which occurs mostly in vaccinated patients, the modification relates to the character and development of the focal eruption; crusting is complete within 10 days. The pre-eruptive illness may be severe and is not necessarily of short duration, but secondary fever during the evolution of the eruption is usually absent. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniformity characteristic of the more typical smallpox eruption. The lesions are often few in number, but even when they are numerous they show some pleomorphism and evolve rapidly."

A WHO Expert Committee on Smallpox Eradication (1972) qualified this description by relating modified-type smallpox specifically to smallpox in vaccinated persons.

When preparing this book, we debated this aspect of the definition at some length and eventually agreed to adhere to the older convention—namely, that the term "modified type" connoted smallpox that was accelerated in its clinical course, compared with the expected evolution of ordinary-type variola major, rather than smallpox whose course was modified by vaccination. By far the commonest reason for an accelerated course in variola major was vaccination some years earlier (Plate 1.19), although Mack et al. (1970), who did not categorize any cases as modified-type smallpox, noted that in their series the rapidity of maturation was not associated with either vaccination status or lesion density. In Rao's series, 25% of the cases in vaccinated subjects were classed as modified type, but only 2% of those occurring in unvaccinated subjects were so categorized. No fatal cases occurred in modified-type smallpox. Plate 1.20 illustrates the way in which even confluent lesions could progress much more rapidly than usual. However, modified-type smallpox was usually manifested by fewer lesions as well as by an accelerated clinical course.

VARIOLA SINE ERUPTIONE

Febrile illness sometimes occurred among vaccinated contacts of cases of smallpox, with

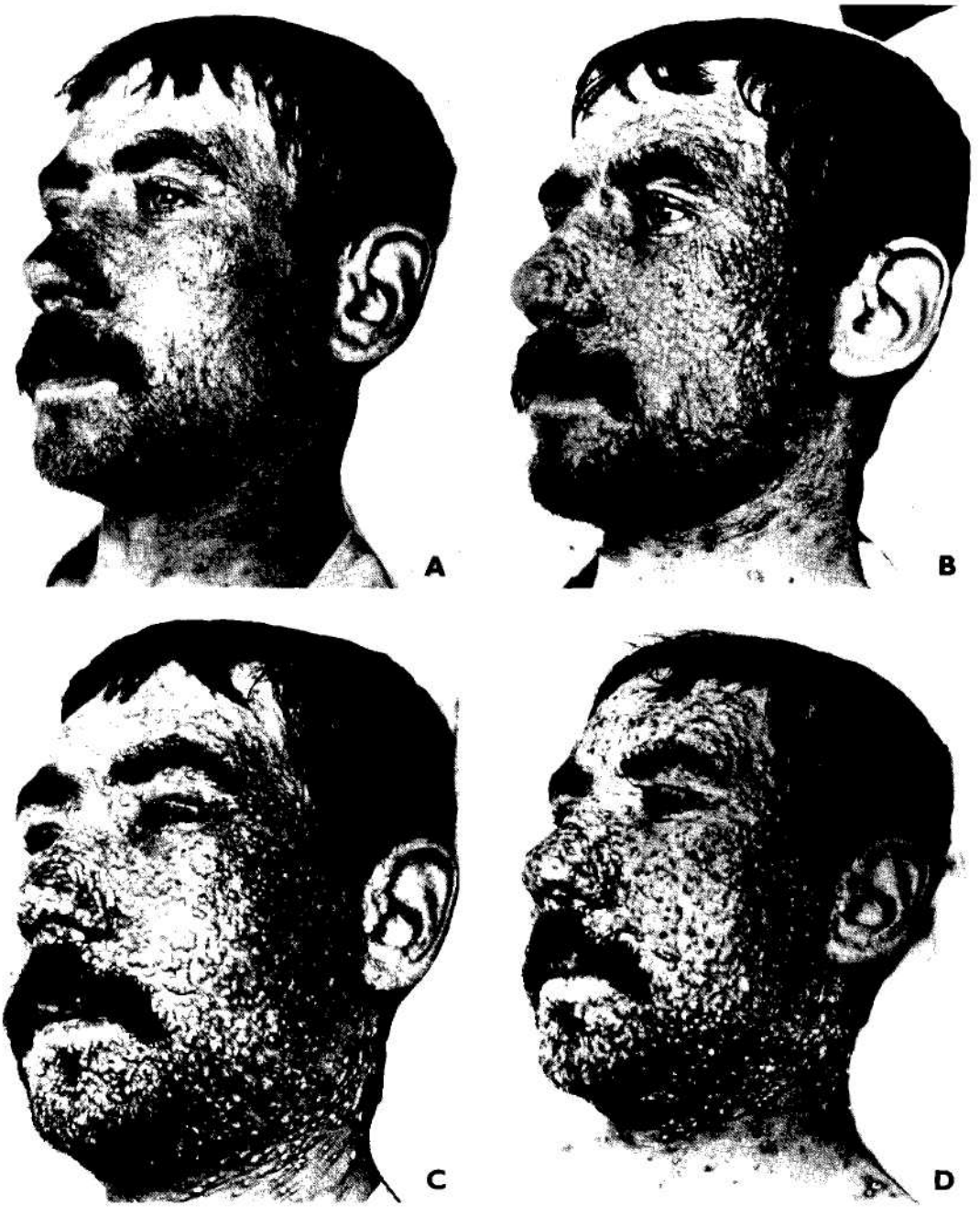

Plate 1.20. Confluent modified-type smallpox in a vaccinated adult male. **A**: In the papular stage but profuse. **B**: Early vesicles were confluent and suggested a severe attack, but although the face became swollen (**C**) the lesions did not increase in size and many became prematurely pus-capped. **D**: At a stage when the confluent rash of ordinary-type smallpox would have been approaching its maturity, the lesions had become encrusted and the swelling of the features had subsided. Individual lesions were small, with fleshy deep-seated bases. (From Ricketts, 1908.)

a sudden onset, a temperature of about 39 °C, headache and sometimes backache. Within 48 hours or often less the attack had subsided and the temperature was normal. Without laboratory tests it was impossible to determine whether these symptoms had been due to infection with variola virus, but the finding of high complement-fixing antibody in such patients (see Chapter 3), or a rise in antibody titres between the first and second bleeds, indicated that the fever had indeed been due to infection with variola virus; such cases have been called variola sine eruptione (Table 1.4).

Occasionally viral isolations have been made from oropharyngeal swabs or washings from such patients. Marennikova et al. (1963) mention one such case; virus was recovered

Table 1.4. Serological evidence for variola sine eruptione in contacts of cases of smallpox[a]

Patients' age and sex	History[b]			Antibodies in serum	
	Last vaccination	Contact with smallpox	Serum collection	Neutralization[c]	Complement fixation[d]
20 years (F)	D −1 year (primary)	D −12 days	D −4 days	77%	..
			D +8 days	98%	80
26 years (F)	D −4 years (primary)	D −25 days to D	D +7 days	..	80
33 years (F)	D −33 years (primary)	D −12 days	D +10 days	99%	5
			D +19 days	..	20
Adult, age unknown (M)	D −7 years (revaccinated)	D −12 days	D +10 days	98%	320
33 years (M)	D −4 years (revaccinated)	D −10 days	D +11 days	100%	30

[a] Based on Downie & McCarthy (1958).
[b] D = day of onset of fever; − = time before day D; + = time after day D.
[c] Neutralizing antibodies expressed as percentage reduction of variola virus pock count on the choriollantoic membrane; .. = data not recorded.
[d] Reciprocal of titre.

Contact Fever

"Variola major was introduced into Durban from India in 1943 and spread widely in South Africa. I was personally involved with one of the patients admitted to Baragwanath Hospital. The physician-in-charge phoned to say that a patient had developed a profuse rash which he felt was probably due to a virus infection. One look at the patient convinced me that she had virulent confluent smallpox. The patient coughed in my face as I was examining her. In spite of having been revaccinated many times, indeed each time I saw a patient with smallpox and again on this occasion and each time responding with an immune reaction, I developed a high fever 12 days later, beginning with chills, muscle pain, especially in the small of the back, and headache and photophobia. My throat became sore and intensely itchy and a white membrane formed on the tonsils and pharynx, presumably an outward sign of an immune reaction taking place at the virus–blood junction. Also of interest was a marked erythematous reaction which developed at the site of the inoculation of the vaccine, presumably an immunological reaction against the antigen deposited at the site in the skin. This reaction became apparent at the time of defervescence. At the same time two vesicles, one on my ankle and one on my wrist, appeared and went through the typical stages of vesicle, pustule and scab.

"My infection seems to have been a case of 'contact fever', a condition which had been recognized as occurring in fully vaccinated individuals many years ago. One of the sisters and the physician attending this patient developed a similar illness also, in spite of revaccination immediately the diagnosis was made." (J. H. S. Gear, personal communication, 1983.)

from pharyngeal swabs obtained on the 3rd day of illness from a patient who did not get a rash. Subsequently, Shelukhina et al. (1973) reported the isolation of variola virus from the throat swab of a recently vaccinated child who had been in close contact with a case of smallpox and who was feverish when the specimen was taken, but who did not develop a rash. Verlinde & Tongeren (1952) reported positive results in 2 out of 13 contacts of cases of variola major from whom pharyngeal washings were taken. One of them was a vaccinated woman from whom virus was recovered on the 14th day after contact, at a time when she had fever and constitutional symptoms. No rash developed. The other person apparently had a subclinical infection (see below).

Sometimes conjunctivitis was the only clinical manifestation of smallpox infection. Dekking et al. (1967) recovered variola virus from the tear fluid of 7 women, all thought to have had smallpox in infancy, who had signs of conjunctivitis after nursing children who died of smallpox. In a study directed at the possibility of conjunctival infection in smallpox contacts, Kempe et al. (1969) reported that conjunctivitis but no other illness developed in 21 out of 55 close family contacts of smallpox patients. Variola virus was recovered from the conjunctival exudate of 12 of them. Four of these 12 patients on whom serological tests were carried out showed antibody rises compatible with recent smallpox.

Medical attendants who had been vaccinated and revaccinated but had not often been exposed to smallpox cases sometimes suffered from what appeared to be an allergic pneumonitis ("smallpox-handler's lung"). Fever, constitutional symptoms and signs of pneumonia developed between 9 and 18 days after exposure to cases of smallpox, and X-rays showed diffuse mottling of the lungs (Howat & Arnott, 1944; Leroux et al., 1955; Evans & Foreman, 1963). None developed a rash, and attempts to recover variola virus from throat washings were unsuccessful.

SUBCLINICAL INFECTION WITH VARIOLA MAJOR VIRUS

There was no easy distinction between variola sine eruptione and subclinical infection, especially among persons living in circumstances in which malaria was endemic and feverish illnesses, from that or other causes, were so common as to be taken for granted.

Evidence from Viral Isolations

Only a few virological studies of smallpox contacts have been carried out (see above and Chapters 3 and 4). Variola virus was occasionally recovered from the throat swabs of such subjects, sometimes for several days in succession, but most of them had been vaccinated and never developed symptoms. Their infections would thus have to be classified as subclinical.

Evidence from Serological Studies

Serological diagnosis of past infection with variola virus depended on the fact that certain serological tests, such as the complement-fixation test, gave positive results (with high titres) for relatively short periods while others remained positive for a prolonged period, both after vaccination and after overt smallpox (Chapter 3).

Heiner et al. (1971a) carried out a detailed study of subclinical infection in villages and individual houses in West Pakistan in 1968–1969, in which overt smallpox had occurred in 68.8% of the unvaccinated and 3.2% of the vaccinated household or compound contacts. Retrospective positive serological diagnoses probably included some cases of smallpox with very few lesions and variola sine eruptione (misdiagnosed or ignored) as well as truly subclinical infections, but the figures obtained give an indication of the frequency of unrecognized smallpox as it occurred in endemic regions.

Two groups of people were studied. "Healthy contacts" were individuals who had not contracted overt smallpox, but had been household or compound contacts of a recent case of smallpox, and had not been vaccinated within 9 months of the study. The principal control group (Group 1 of Table 1.5) consisted of similar subjects who lived in the same villages but had not been in such close contact with smallpox cases. Two subsidiary control groups were used to determine the persistence of antibodies after vaccination; members of one group (Group 2 of Table 1.5) had been vaccinated annually but not within 9 months

Table 1.5. Comparison of titres of complement-fixing and haemagglutinin-inhibiting antibodies among vaccinated close contacts of cases of variola major and vaccinated controls[a]

	Number of close contacts	Number of controls[b]		
		Group 1	Group 2	Group 3
	143	62	37	40
Complement fixation:				
Geometric mean	38.6	<10	<10	<10
% of sera ⩾1/40	54.5	6.5	8.1	10.0
Haemagglutination inhibition:				
Geometric mean	10.5	<4	4.2	5.8
% of sera ⩾1/16	49.0	11.3	13.5	22.5

[a] Based on Heiner et al. (1971a).
[b] Group 1: village contacts; Group 2: vaccinated annually; Group 3: vaccinated 5 years or more before study.

of the study, and members of the other group (Group 3 of Table 1.5) had last been vaccinated 5 years or more before the study. The highly significant differences between the close contacts and controls revealed by these tests were supported by similar results using other serological tests (neutralization, passive haemagglutination-inhibition and immunodiffusion). The frequency distribution of positive titres among the controls was unimodal, the majority being negative or having very low titres (Fig. 1.2). The titres of the contact group had a bimodal distribution, about half being negative or very low and the other half positive. This serological evidence indicates that subclinical infection that was accompanied by enough replication of virus to stimulate the production of complement-fixing and haemagglutinin-inhibiting antibodies occurred in many of the vaccinated close contacts of cases of variola major. Rao et al. (1970) came to a similar conclusion, using a gel-precipitation test with both variola and vaccinia antigens. There was also suggestive but inconclusive evidence that inapparent infection occurred among subjects who had recovered from smallpox years before, a result that has parallels in measles (Ueda et al., 1969).

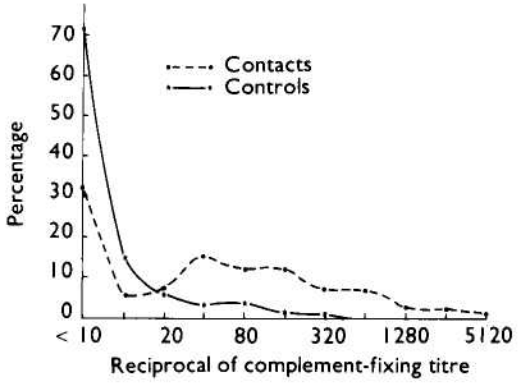

Fig. 1.2. Distribution of titres of complement-fixing antibodies to variola antigens in contacts and controls, as defined in text. (Data from Heiner et al., 1971a.)

FLAT-TYPE SMALLPOX

Flat-type smallpox was so called because the lesions remained more or less flush with the skin at the time when raised vesicles formed in ordinary-type smallpox (Plate 1.21). This manifestation of the disease was seldom encountered (6.7% of cases in unvaccinated subjects in Rao's series), and the majority of cases (72%) occurred in children. It was very rare in successfully vaccinated subjects. The prognosis was always grave and most cases were fatal (see Table 1.2).

The pre-eruptive stage lasted 3–4 days, with the usual constitutional symptoms, which were severe and continued after the appearance of the rash. The fever remained elevated throughout and the patient had severe toxaemic symptoms.

The Rash

The enanthem on the tongue and palate was usually extensive and sometimes confluent. Occasionally a severe enanthem occurred on the rectal mucous membrane. The characteristic feature of flat-type smallpox was the nature of the skin lesions. Unlike the regular evolution seen in ordinary-type smallpox, the focal lesions in the skin matured very slowly, and at the papulovesicular stage, about 6 days after the onset of fever, a small depression was visible. By the 7th or 8th day the lesions were flat and appeared to be buried in the skin (Plate 1.21). Most lesions had haemorrhages

into their base, the central flattened portions appeared black or dark purple, and they were surrounded by an erythematous areola. The lesions differed from those of ordinary-type smallpox in that the vesicles contained very little fluid, they were not multilocular, and they did not show umbilication. In contrast to the "shotty" feel of the lesions in ordinary-type smallpox, they were soft and velvety to the touch. No further evolution of the lesions occurred and frank pustules were rarely seen, although occasionally a few lesions, especially on the dorsum of the feet and hands, became pustular, while elsewhere on the body they remained as flat vesicles. Because of their superficial nature, the skin over the lesions peeled off after slight trauma, sometimes leaving extensive raw areas. Often the skin lesions did not conform to the classical "centrifugal" distribution.

Clinical Course

Throughout the course of the disease the patient was toxic and febrile. Respiratory complications, including oedema of the lung and sometimes frank pneumonia, set in by the 7th or the 8th day after the onset of fever. Rao noted that unvaccinated children sometimes developed an acute dilatation of the stomach 24–48 hours before death, which usually occurred between the 8th and the 12th day. A day or two before death, the colour of the lesions changed to an ashen grey, which, along with acute dilatation of the stomach, was a bad prognostic sign. In cases with a confluent enanthem on the tongue and palate, the mucous membrane sloughed, leaving large raw areas. Some patients passed blood and mucus in the early stages of the disease, indicating the extensive involvement of the rectal mucous membrane, and in such cases, just before death, the rectal mucous membrane was sometimes sloughed off.

Among the few who survived, scabbing usually began on about the 13th–16th day after the onset of fever and was complete by about the 21st day. The scabs were thin and superficial and separated rapidly, leaving very superficial scars. Because of the bleeding into the base of the lesions, the scabs, before they dried, were purplish in colour.

Flat-type smallpox was probably due to the infection of particularly susceptible subjects with virulent strains of variola virus; it never occurred in variola minor. The appearance of the lesions suggested a deficient cellular immune response in these patients, but no relevant studies were ever reported.

HAEMORRHAGIC-TYPE SMALLPOX

General Features

Considering its comparative rarity (only 200 cases in Rao's series of 6942 hospitalized patients in Madras), a great deal has been written about haemorrhagic-type smallpox. No doubt this preoccupation was partly due to the rarity of the syndrome, its great severity and the difficult problem that it presented in differential diagnosis. This was particularly true in countries in which smallpox was no longer endemic; there were many instances in which outbreaks or their extension could be traced to an unrecognized importation of haemorrhagic-type smallpox (see, for example, Benn, 1963; Stojkovic et al., 1974).

Histopathological studies (Bras, 1952a) support the clinical distinction of two varieties of haemorrhagic-type smallpox—what Curschmann (1875) and Immermann (1895) called "purpura variolosa" and "variola pustulosa haemorrhagica." We shall follow Rao (1972) in calling them early and late haemorrhagic-type smallpox respectively. Early haemorrhagic-type smallpox was characterized by haemorrhages into the skin and/or mucous membranes early in the course of the illness. Subconjunctival haemorrhages were the most common, and bleeding from the gums, epistaxis, haematemesis, haemoptysis, haematuria, as well as vaginal bleeding in women, occurred at any time in the course of the illness.

In late haemorrhagic-type smallpox haemorrhages into the skin and mucous membranes often occurred, and usually also into the bases of the developing skin lesions. Some of these cases could equally well have been considered as cases of flat-type or confluent ordinary-type smallpox, associated with haemorrhages as a complication. However, all classifications contain an arbitrary element.

Haemorrhagic-type smallpox, of both subtypes, had two unusual epidemiological features: it occurred mostly in adults (Calcutta: Guha Mazumder et al., 1975; Madras: Rao, 1972) and in some extensive series (the Calcutta and Madras series) it was as common in vaccinated as in unvaccinated subjects (see

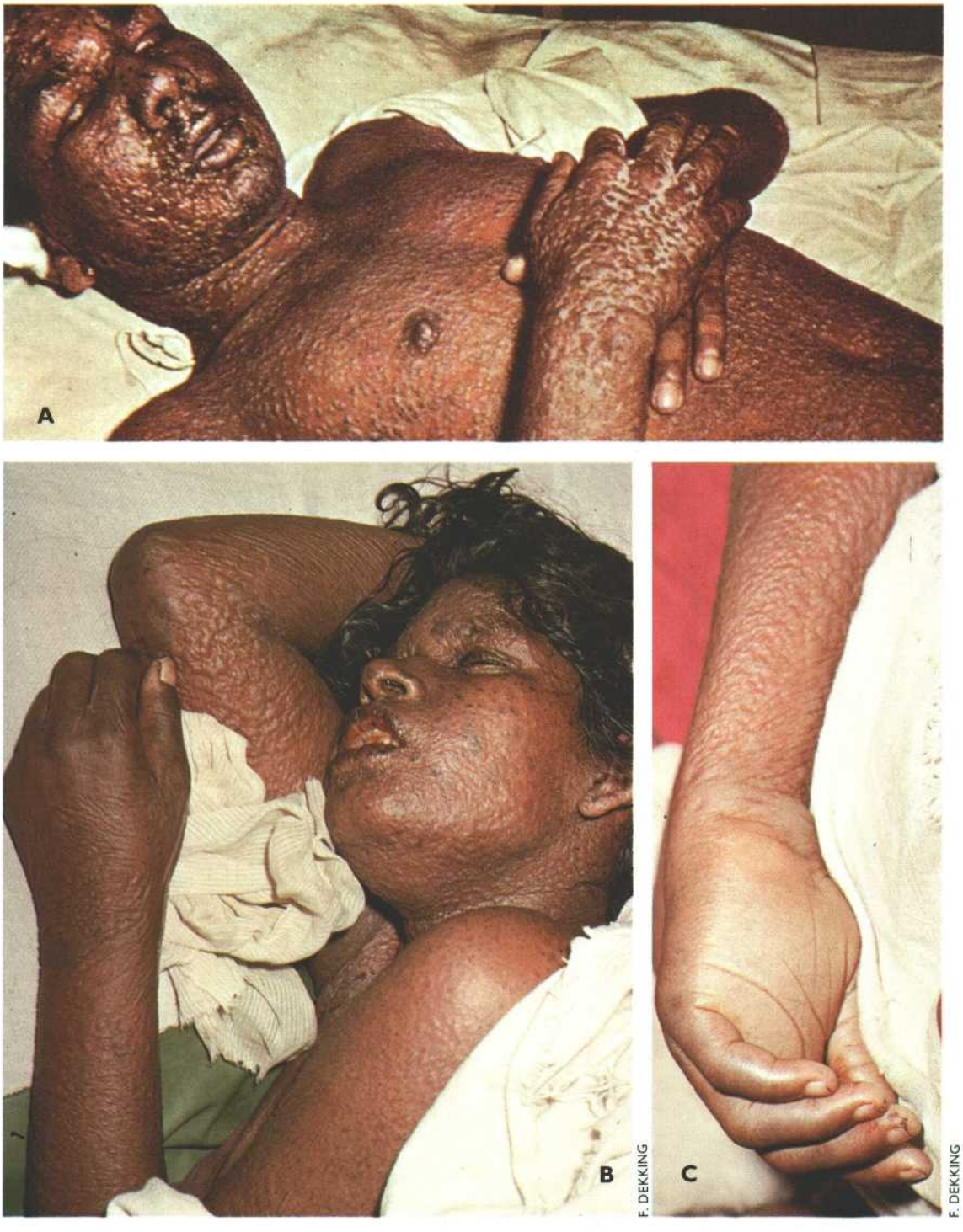

Plate 1.21. Flat-type smallpox. **A:** Adult Indian man. **B** and **C:** Unvaccinated young woman from Madras, India, on the 6th day of rash; she died 3 days later. Note severe toxaemia and extensive flat pustules in both cases. (**A** from Herrlich et al., 1967.)

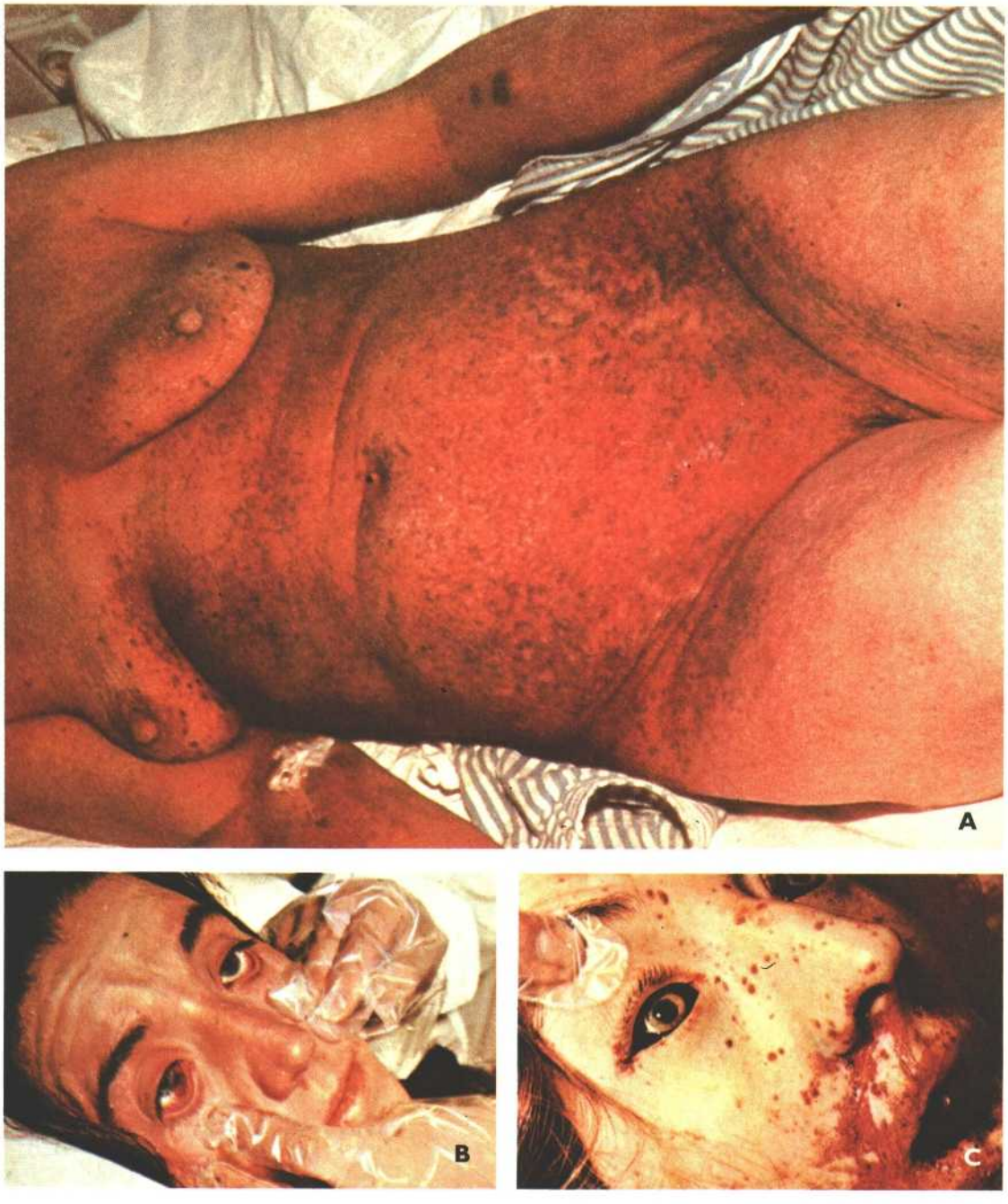

Plate 1.22. Early haemorrhagic-type smallpox. **A:** In an unvaccinated 60-year-old woman, who died on the 4th day of illness. Besides the rash illustrated she bled from many other sites, with subconjunctival haemorrhages, a bloody enanthem, epistaxis, haematuria, blood in the faeces and metrorrhagia. **B:** Subconjunctival haemorrhage. **C:** Fully developed haemorrhagic diathesis and death. (**A** from Stojkovic et al., 1974: **B** and **C** from Herrlich et al., 1967.)

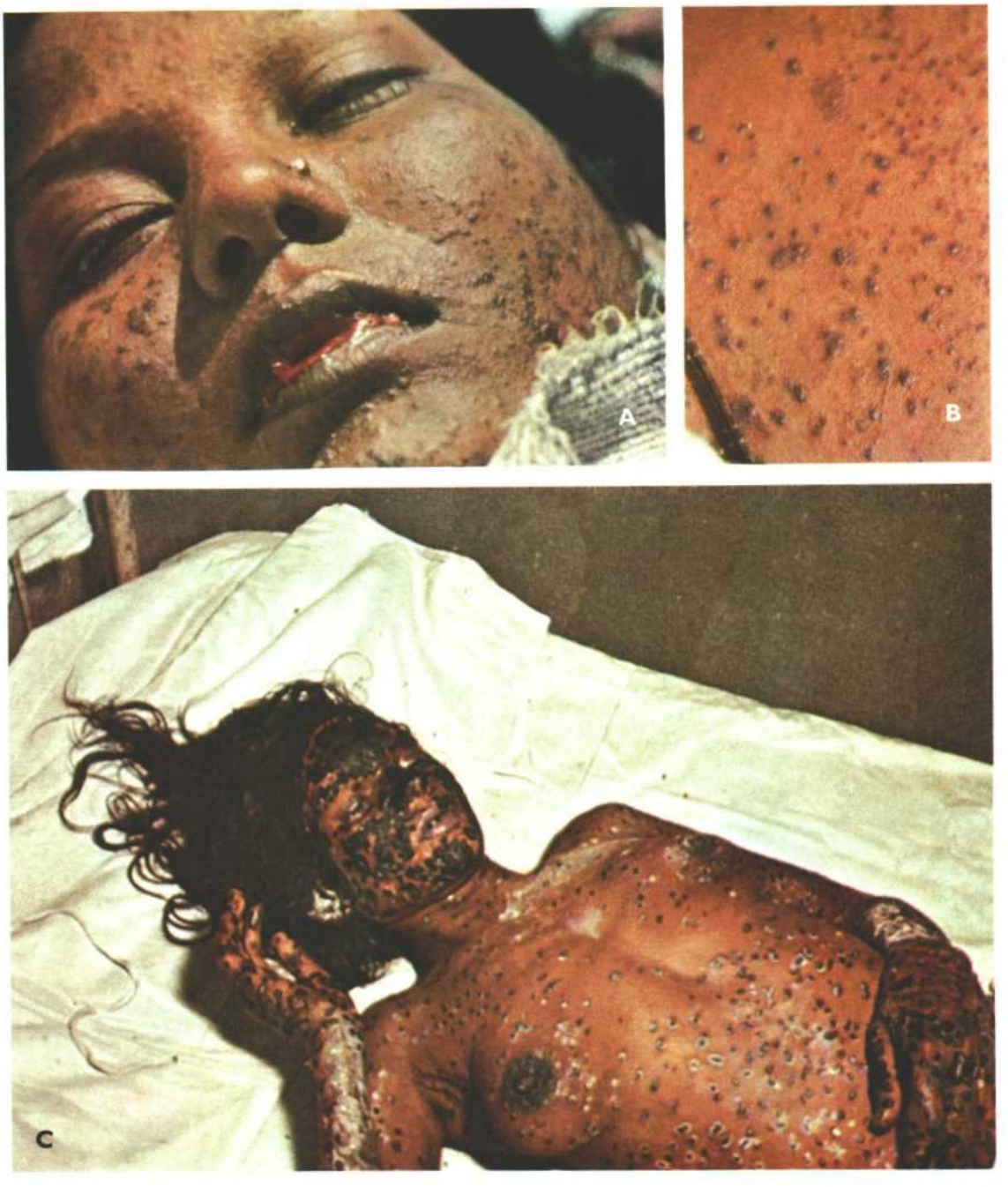

Plate 1.23. Contrast between early and late haemorrhagic-type smallpox. **A** and **B:** Early haemorrhagic-type smallpox in a pregnant 18-year-old woman, showing severe toxaemia, petechial exanthem and bleeding from body openings; 1 hour before death. **C:** Late haemorrhagic-type smallpox in young woman, showing bleeding in base of pustules and development of a general haemorrhagic diathesis late in the disease. (From Herrlich et al., 1967.)

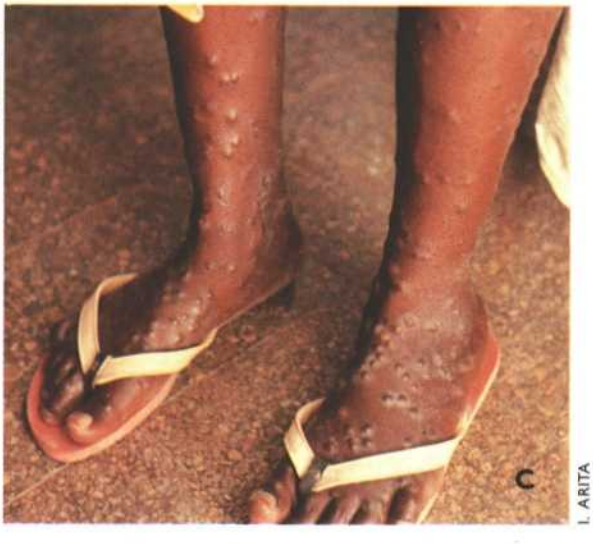

Plate I.24. Variola minor in a 30-year-old unvaccinated Somali woman, 12 days after the onset of rash. The patient was not very sick and was ambulant throughout the disease. The lesions on the face were sparse (**A**) and evolved more rapidly than those on the arms and legs (**B** and **C**).

I. ARITA