CHAPTER 1

THE CLINICAL FEATURES
OF SMALLPOX

Contents

INTRODUCTION

As this book went to press, endemic smallpox had been eradicated from Europe and North America for almost half a century and from the populous countries of China and India for some 25 and 10 years respectively. The majority of people—including the majority of physicians—now living have never seen a case of this once-dreaded disease. What was it like? For the physician, what were its clinical features and its complications? What factors influenced the prognosis? What diseases entered into its differential diagnosis? Nowhere is there a better answer to these questions than in the book written by Ricketts and illustrated by Byles over three-quarters of a century ago (Ricketts, 1908).

Since then, however, long series of carefully studied cases of both variola major (Rao, 1972) and variola minor (Marsden, 1936) have been documented, and laboratory investigation has become a powerful tool for confirmation of the diagnosis in puzzling cases. Further, during the global smallpox eradication programme a large number of WHO epidemiologists and their national counterparts had extensive experience of smallpox as it occurred in the field in urban and rural areas and among nomads, as distinct from the hospitals from which Ricketts's, Rao's and Marsden's material was drawn. However, only limited clinical studies were possible in rural situations, outside of hospitals. The most comprehensive clinical study of variola major in a non-hospital setting is a series of 539 cases seen in their houses in Pakistani Punjab in 1966–1967 (Mack et al., 1970). Where relevant, data from this study will be used to supplement the description of hospital-based cases described by Rao (1972). An attempt has been made to interpret the symptoms in the light of current understanding of the pathogenesis and immunology of orthopoxvirus infections, as outlined in Chapter 3.

The plan of the present chapter follows Ricketts in that the account of the clinical features of smallpox consists mainly of a description of the rash, based on photographs of patients, most of which were prepared during the global smallpox eradication programme. Because smallpox is now extinct, we have to take the unusual step, in the clinical description of a human disease, of referring to it in the past tense; this was previously the case only with diseases that apparently disappeared and could be identified only by contemporary descriptions, such as the "English sweat", or the "sweating sickness".

Plate 1.1. Thomas Frank Ricketts (1865-1918). Medical Superintendent of the Smallpox Hospitals and of the River Ambulance Service of the Metropolitan Asylums Board, London. His book on the clinical features of smallpox was based on the personal examination of many thousands of cases of variola major.

VARIETIES OF SMALLPOX

From the time it was first recognized as a distinct disease until about the end of the 19th century, smallpox was regarded as a uniformly severe disease, associated with a high case-fatality rate, in every part of the world. Mild cases and even mild outbreaks of smallpox were occasionally mentioned in the old literature, but they were the exception; nowhere did endemic mild smallpox occur. Smallpox was designated by many names in various languages, but no one saw a need to distinguish different varieties of smallpox, although the existence of different clinical types (see below) was recognized from the time of Thomas Sydenham (1624–1689) in Europe and much earlier in India and China.

The situation changed when Korté (1904) described a very mild smallpox-like disease, with a case-fatality rate of 1% or less in unvaccinated persons, that had occurred in South Africa for several years and was known locally as kaffir-pox, or "amaas", a word of uncertain origin, possibly a corruption of the Dutch word *masels* or *mazelen* (measles) (Dixon, 1962). Subsequently, Chapin (1913, 1926) recognized that a similar mild disease had been occurring in North America since about 1896, and had subsequently been exported from there to South America, Europe and Australia. There was controversy about the relationship of this disease to smallpox until the mid-1950s (Jong, 1956), but virological studies (see Chapter 2) showed that there was no doubt that "amaas" and "alastrim" (from the Portuguese *alastra*, something which "burns like tinder, scatters, spreads from place to place"), as it was called in South America, were indeed mild varieties of smallpox. Although many other names were used, this clinico-epidemiological variety of smallpox has come to be called "variola minor", a designation that led to the use of the term "variola major" for "classical" smallpox.

Recent studies of viral strains recovered from outbreaks of variola minor in various countries have shown that they fall into two groups distinguishable by biological properties, one consisting of strains derived from outbreaks in South America or traceable to an American source (which we shall call "alastrim" virus) and the other comprising most strains from Africa (see Chapter 2).

During the first half of the 20th century all outbreaks of smallpox in Asia and most of those in Africa were due to variola major (with case-fatality rates of 20% or more in the unvaccinated). Variola minor (with case-fatality rates of 1% or less) was endemic in some countries of Europe and of North and South America and, together with variola major, in many parts of Africa. With the more careful study that began after global eradication had been proclaimed as a goal of WHO in

1959, it was recognized that some outbreaks of smallpox in western, central and eastern Africa and in Indonesia were associated with a lower case-fatality rate than classical variola major, in the range of 5–15% instead of over 20%. Some of these lower figures resulted from aggregating all reported cases in places where both varieties of smallpox were endemic (see Chapter 8), but there were other places where this was not the explanation. The clinical picture of smallpox with a case-fatality rate of 5–15% was indistinguishable from that of variola major, both haemorrhagic and flat types of the disease occurring with about the same frequency as in classical smallpox. Preliminary tests suggested that certain laboratory characteristics of some of the strains recovered from these outbreaks were intermediate between those of variola major and variola minor (see Chapter 4), but later studies failed to support the differentiation of a separate "intermedius" virus. In this book all outbreaks of smallpox will be categorized as either variola major, with case-fatality rates of 5–25% and occasionally more, or variola minor, with case-fatality rates of about 1% or less.

WHO, 1971

Plate 1.2. A. Ramachandra Rao (b. 1917). Formerly Superintendent of the Infectious Diseases Hospital, Madras, India. His book on smallpox was based on the personal study of nearly 7000 hospitalized cases of variola major. He also made important contributions to the understanding of the epidemiology of smallpox in India (see Chapter 15).

THE CLASSIFICATION OF CLINICAL TYPES OF VARIOLA MAJOR

It has long been recognized that several clinical types of variola major could be distinguished which differed in prognosis, differential diagnosis and transmissibility. The old subdivision according to the density of the focal eruption was shown by Dixon (1962) and Rao (1967) to have less prognostic value than a classification based on the nature and evolution of the rash. For this reason a WHO Scientific Group on Smallpox Eradication (1968) adopted the classification proposed by Rao and fully described in his book on smallpox (Rao, 1972). A WHO Expert Committee on Smallpox Eradication (1972) reaffirmed its acceptance of this classification (Table 1.1), according to which the commonest clinical type (ordinary-type smallpox) is subdivided in relation to the density of the rash, since this had prognostic significance. The great majority of cases of variola major seen in hospitals among both unvaccinated and vaccinated persons—88.8% and 70% respectively in Rao's series of 6942 cases

Table 1.1. A classification of clinical types of variola major[a]

Ordinary type	Raised pustular skin lesions. Three subtypes: confluent—confluent rash on face and forearms; semiconfluent—confluent rash on face, discrete elsewhere; discrete—areas of normal skin between pustules, even on face.
Modified type	Like ordinary type but with an accelerated course.
Variola sine eruptione	Fever without rash caused by variola virus; serological confirmation required.
Flat type	Pustules remained flat; usually confluent or semiconfluent. Usually fatal.
Haemorrhagic type	Widespread haemorrhages in skin and mucous membranes. Two subtypes: early, with purpuric rash; always fatal; late, with haemorrhages into base of pustules; usually fatal.

[a] Based on Rao (1972).

Table 1.2. The frequency and case-fatality rates of different clinical types of variola major, according to vaccination status (presence of a scar) in hospitalized patients in Madras[a]

Clinical type	Unvaccinated subjects			Vaccinated subjects		
	Number of cases	Percentage of total	Case-fatality rate (%)	Number of cases	Percentage of total	Case-fatality rate (%)
Ordinary type:	3 147	88.8	30.2	2 377	70.0	3.2
Confluent	808	22.8	62.0	156	4.6	26.3
Semiconfluent	847	23.9	37.0	237	7.0	8.4
Discrete	1 492	42.1	9.3	1 984	58.4	0.7
Modified type	76	2.1	0	861	25.3	0
Flat type	236	6.7	96.5	45	1.3	66.7
Haemorrhagic type:	85	2.4	96.4	115	3.4	93.9
Early	25	0.7	100.0	47	1.4	100.0
Late	60	1.7	96.8	68	2.0	89.8
Total	3 544	—	35.5	3 398	—	6.3

[a] Based on Rao (1972).

(Table 1.2)—were ordinary-type smallpox (and other reported series confirm this); the case-fatality rates in unvaccinated cases with confluent, semiconfluent and discrete rashes were 62%, 37% and 9.3% respectively. Although its use was suggested by Rao, such a subclassification is hardly justified for modified-type or flat-type cases, but it is useful to consider early and late haemorrhagic-type cases separately, since they were probably the results of different pathophysiological processes.

A special comment is required on the designation of cases as vaccinated by both Rao (1972) and other investigators. Until freeze-dried vaccine became available and regular assessment was made of the results of vaccination, many vaccinations, especially in tropical countries, were performed with vaccine of less than the required potency (see Chapter 11). The categorization of a subject as "vaccinated" was made on the basis of the presence of what was regarded as a vaccination scar. The presence of such a scar was, however, not certain evidence of successful vaccination. The rotary lancet, used for vaccination on the Indian subcontinent, was attended by considerable trauma, and sometimes bacterial infection alone could produce scarring. On the other hand, vaccination by the jet injector sometimes resulted in a very small scar which might be overlooked on the skin of subjects bearing many scars of traumatic origin. In spite of these shortcomings, the vaccination scar provided a more easily determined and reliable index of an individual's immune status *vis-à-vis* smallpox than was possible with other infectious diseases.

ORDINARY-TYPE SMALLPOX

The Incubation Period

The incubation period is the interval between the implantation of infectious virus and the onset of the first symptoms, which in smallpox were fever and constitutional disturbances. Determination of the length of the incubation period is discussed in detail in Chapter 4; in exceptional instances the duration, from the time of infection until the onset of fever, was as short as 7 days or as long as 19 days, but in the great majority of cases the period extended over 10–14 days, usually 12 days.

Symptoms of the Pre-eruptive Stage

The incubation period in smallpox was a period of intense activity in terms of viral replication and spread within the body and the development of the immune response (see Chapter 3), of which there was at that time no clinical evidence. It ended when the patient became feverish and ill (Fig. 1.1). The onset of fever and malaise was sudden, the temperature usually rising to between 38.5 °C and 40.5 °C. Other symptoms varied in frequency (Table 1.3). Patients suffering from variola major usually complained of a splitting headache, sometimes frontal but usually generalized, and many complained of severe backache (Rao, 1972). A small proportion of children had convulsions and some adults were delirious at this stage. Vomiting occurred in about half of all patients, and
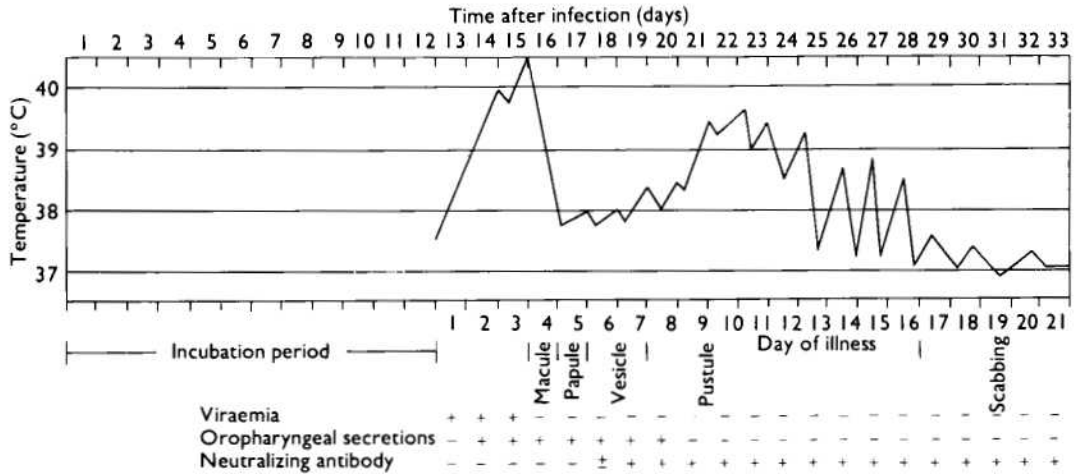
Fig. 1.1. The clinical course of moderately severe ordinary-type smallpox in an unvaccinated subject: the temperature chart, the development of rash, the presence of virus in the blood and oropharyngeal secretions and the time of appearance of neutralizing antibody in the serum. (Data from various sources.)

diarrhoea in about 10%. Some suffered abdominal colic, which could lead to a diagnosis of appendicitis. The patient was usually ill, with an appearance of general toxaemia. By the 2nd or 3rd day (rarely the 4th) the temperature had fallen and the patient felt somewhat better; at this time the macular rash appeared.

In older writings (e.g., Ricketts, 1908) there was often reference to the occurrence of an erythematous rash during the pre-eruptive phase (prodromal rash), best seen in fair-skinned subjects (Plate 1.3A and B). Some authors (Dixon, 1962; Rao, 1972) have cast doubt on its occurrence in unvaccinated subjects, but all agree that a fleeting "allergic" rash sometimes occurred in vaccinated individuals, most readily visible around the vaccination scar (see Plate 1.3), in the axillae, behind the knees and in the inguinal region. The erythematous rash common in the early stages of haemorrhagic-type smallpox had to be distinguished from the prodromal rash of ordinary-type or modified-type smallpox.

Table 1.3. Frequency of symptoms (percentages of cases) in the pre-eruptive stage in variola major and variola minor

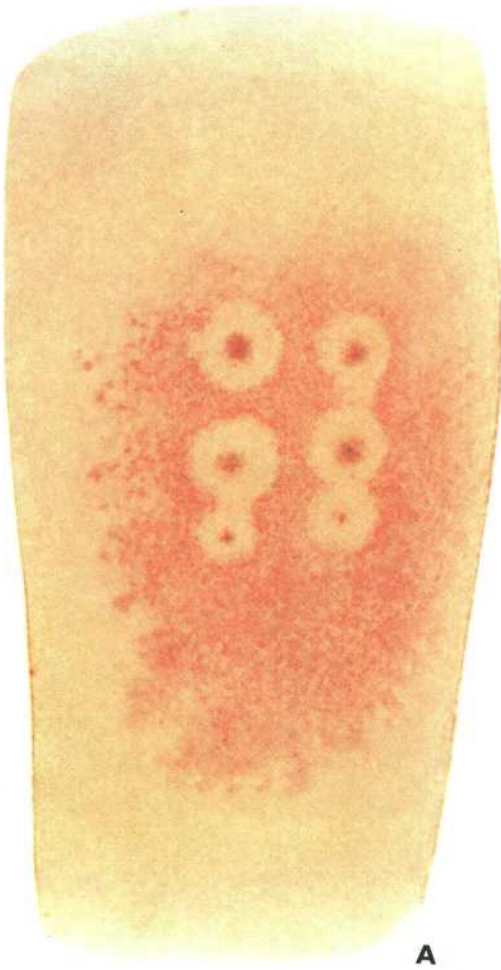| Symptom	Variola major[a]	Variola minor[a]	
	6942 cases (Rao, 1972)	12 847 cases (Marsden, 1936)	859 cases (Noble et al., 1970)
Fever	100.0	..	98.2
Headache	90.0	75.0	79.4
Malaise	..	..	66.7
Chills	60.0	34.0	62.4
Anorexia	..	..	60.6
Backache	90.0	38.8	44.2
Pharyngitis	15.0	20.6	38.2
Nausea	..	11.0	37.0
Vomiting	50.0	34.2	30.3
Diarrhoea	10.0	..	3.6
Delirium	15.0	..	..
Abdominal colic	13.0	..	..
Convulsions	7.0	..	..

[a] .. = data not recorded.

Plate 1.3. **A** and **B:** Prodromal rashes. These were best seen in fair-skinned persons (for example, Caucasians and Japanese) and were more common in those previously vaccinated. **A:** Erythematous prodromal rash on the upper arm, near the sites of vaccination performed 8 days earlier but sparing the skin immediately adjacent to the vaccination lesions. **B:** Measles-like prodromal rash on the lateral side of the trunk on the 4th day of illness. **C:** The enanthem. Lesions occurred throughout the oropharynx and in the nasal cavity, as well as on the tongue. The lesions on the palate were usually smaller than those on the posterior pharyngeal wall and tonsil. (From Uchida, 1955.)