

The Clinical Features of Smallpox PART III

BY

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This article is based partly on experience of the disease gained during the recent epidemic of smallpox in the Abercorn district of Zambia.

The progress of the disease, of which for many years the most clinical observations have been available, is now mirrored by a clear understanding of the underlying pathological processes.

The following extract is taken from an article by Downie (1959): "The site of entry of the virus is believed to be in the upper respiratory tract, and during the incubation period it probably multiplies in the lymphoid and other inter-

nal tissues. At first, or before the onset of the illness, there is viraemia, and from the circulation the virus localises in the skin, the mucous membranes and other tissues where lesions are shortly to appear. Soon after the focal skin eruption appears the patient's condition improves, the temperature drops and neutralising antibodies become detectable in the serum. By then the virus has multiplied within the epithelial cells in the focal lesions of the skin, and scrapings made at this time show enormous numbers of elementary bodies with appropriately stained smears. Virus within cells is protected from the action of antibody so that destruction of cells goes on with consequent inflammatory changes. The secondary rise in temperature associated with the stage of pustulation is probably due to the absorption of the toxic products of widespread cell necrosis.

"At first a few cells in the middle layer of the epidermis become enlarged and vacuoles appear in the cytoplasm, which stains poorly. The nucleus condenses and later disappears. As the process spreads to neighbouring cells the cell membranes rupture and a vesicle is formed. The vesicle tends to be loculated, with septa formed by the remains of incompletely destroyed cells. Pustules form when polymorphonuclear leucocytes enter the vesicle from the dermis and the septa which previously crossed the vesicle disappear. In the healing stage fluid is absorbed from the pustule and the contents dry up. Epithelial cells from the sides of the cavity encroach upon it and proceed to grow under the residual mass of the exudate so that finally a crust is left of degenerated epithelial cells, leucocytes and debris. The crusts separate in the third week of the illness."

To summarise, it appears from this description that the primary or prodromal phase of the illness is in fact a phase of secondary viraemia, and that the secondary or pustular phase is in fact a phase of localisation of the virus in the skin and its subsequent extrusion. Downie is evidently of the opinion that both pustulation and the secondary rise in temperature are due solely to the virus and are not related to bacterial infection of the pustular lesions.

A large number of the patients admitted to Abercorn hospital showed characteristic uncomplicated viral illness, the disease ending with a fall in the secondary temperature and the desiccation of the dried pustules. However, particularly when the patients sought admission to hospital at a later stage, there were a number of cases in which the secondary stage of the

disease was followed by features due to secondary bacterial infection. In some cases the secondary pyrexia was prolonged beyond the normal span, evidently due to bacterial invasion; in other cases focal lesions such as abscesses appeared at the conclusion of the second stage. It was the general rule that these focal complications did not make their appearance during the second stage, but after its conclusion, and sometimes these focal lesions, particularly in the case of osteomyelitis variolosa, were present many weeks after the conclusion of the second stage.

That the appearance of septic complications occurs at a late stage in the disease is noted by several authors. Marsden (1948) wrote: "It is recognised that boils and furunculosis may be troublesome features of the convalescence of many smallpox patients"; and Bras (1952), "Clinical observations in Djarkarta showed that arthritis may occur as a sequela in smallpox patients."

Dixon (1962) wrote: "I suggest it would be more accurate to describe three febrile stages, primary fever of the initial stage, secondary fever developing from the fourth day onwards, and tertiary fever due to the superadded sepsis.

"Although the development of sepsis and tertiary fever is closely related to the extent of the eruption in the benign case, it is also commoner where there is poor hygiene of the patient, particularly under tropical conditions."

In order to describe sequentially the various features of the disease, it is logical, therefore, to divide it into three stages:

- (1) First or prodromal stage.
- (2) Second or pustular stage.
- (3) Third stage, or stage of late complications.

It should be re-emphasised that the third stage by no means occurs in all cases.

There are a number of different forms of smallpox with varying degrees of severity. The types of smallpox most frequently encountered in the Abercorn epidemic corresponded to Dixon's types 4, 5 and 6, namely, benign confluent, benign semi-confluent and benign discreet. These forms of the disease were also called variola vera, or non-haemorrhagic smallpox. Cases of Dixon's types 1, 2 and 3 with haemorrhagic features and the gradual appearance of the rash were not seen. The descriptions which will be given below therefore apply to variola vera or benign smallpox, call it what you will. A number of milder forms of the illness, especially

in vaccination modified cases, were seen. In general, however, there was a predominance of types 4, 5 and 6. A prodromal illness lasting about four days was followed by a drop in temperature and the appearance of the rash. The rash appeared quickly, so that if it was not possible to be certain of the diagnosis from the appearance of the lesions on the first day, the second day would always tell. The distribution of the lesions corresponded to the classical descriptions of smallpox. Cropping—that is to say, the simultaneous appearance on the skin of lesions at various stages of maturation—was absent, and this absence of cropping gave a significant lead in differentiating cases of smallpox from chickenpox. A detailed review of the clinical features of the various stages of the disease is given below.

The First Stage

The duration of the first stage may be taken from the time of the first appearance of fever and prodromal symptoms until the appearance of the rash.

According to Downie (1959), the first stage is a period of secondary viraemia following the incubation of the virus in the reticulo-endothelial system. The termination of the first stage is related to the appearance of circulating antibody, a fall in temperature and coincidentally the appearance of the skin lesions.

Marsden (1948) states that the duration of the primary fever was four days in 49.55 per cent. of his cases and between three and five days in 91.05 per cent. of his cases. In the Abercorn epidemic, of five patients admitted to hospital at the beginning of the prodromal phase, it was noted that the primary fever lasted four days in three cases, two days in one case and five days in one case. The height of the initial fever varied from 105.4° to 101.4° F. The fever was maximal at its onset, declining gradually thereafter.

As regards the symptoms of the prodromal phase, the impression given by other writers is of an influenza-like illness with few specific features.

A prodromal rash, often in the bathing trunks area, may be a feature of the first stage. Marsden (1948) found a prodromal rash in 0.32 per cent. of cases of variola minor, and Illingsworth (1944) in five out of 100 cases of variola major. Dixon (1948) wrote: "Prodromal rashes of the bathing drawers type were rarely seen, as many of the severely ill patients were admitted too late for this sign." In the Abercorn cases

the majority of patients were admitted at the beginning of the second stage; in these cases that were admitted in the prodromal phase a prodromal rash was not observed. It is doubtful in any case if a purely macular rash could be observed in the skin of an African patient (Fig. 1).



Fig. 1—The centrifugal distribution of the rash is well shown. The axilla is spared.

Backache is given a prominent place by most writers in the symptomatology of the prodromal phase. Hebra (1866) wrote: "The only distinctive character of smallpox at this stage of the disease is the presence of pains about the joints and over the sacrum and also, in some cases, at the spinal column." Backache seems to be a dominant feature in some descriptions of the prodromal phase. Smith (1948), Ker (1961) and Marsden (1948) found backache in 38.8 per cent. of cases of variola minor. Dixon (1948), however, wrote of the Tripolitania epidemic that backache was not a prominent symptom. In the Abercorn cases backache was not a feature. Possibly this is related to the fact that all the patients were children. Dixon (1962) suggests that backache as a symptom in the prodromal phase may be related to the use of these muscles by active people.

Vomiting is found frequently during the prodromal phase. Marsden (1948) noted vomiting in 34.16 per cent. of his cases of variola minor. Vomiting was found in two out of 19 cases in the small series of patients admitted to Abercorn hospital in the prodromal phase of the illness.

Other prodromal symptoms noted by other writers are abdominal pain, nausea, sore throat, myalgia and cough.

Out of 19 patients admitted to Abercorn hospital, cough was found in eight of them, no doubt related to the appearance of the exanthem on the lining of the respiratory tract, for, as

Downie (1959) points out, the exanthem matures earlier here than it does on the skin. Other prominent prodromal symptoms were sore eyes, diarrhoea, vomiting, headache, abdominal pain and loss of appetite.

The Second Stage

The second stage lasts from the appearance of the rash until the dehiscence of the pustules. Marsden (1948) noted that the rash appeared on the third and fourth days of the illness in 63 per cent. of his cases and goes on to state, "the average length of time occupied by a lesion at its different stages was two days as a papule, one day as a vesicle and three or at the most four days as a pustule." Bras (1952) wrote: "As regards the correlation between the duration of the eruption and the aspect of the lesion, the following may be said: (a) Papules can generally be seen in the first three days; (b) vesicles on the fourth or fifth days; (c) pustules generally after the fifth day. Crust formation starts on the face after eight or nine days and on the rest of the body four days later." No records were taken in the Abercorn cases of the days of the various stages in the maturation of the rash, but the second stage of the illness generally lasted about ten days, which is in rough accord with the observations of Bras and Marsden (Fig. 2).

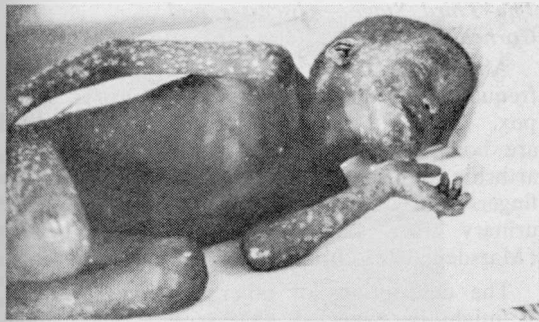


Fig. 2—The face is heavily involved, but the anterior triangle of the neck is spared.

The rash was generally established in its characteristic features in one or two days, although lesions on the face and arms were generally slightly ahead of those on the legs. Diagnostic points which were taken to be of importance, together with a history of prodromal illness, were the centrifugal distribution of the lesions, the presence of lesions on the palms of the hands and the soles of the feet, the absence of cropping, the large size of the lesions compared with chickenpox, and the presence of

umbilication. Apart from chickenpox, measles and herpes zoster were on occasion thought to be smallpox.

A detailed description of the distribution of the rash is given by Butterworth (1938): "I found the matured eruption distributed as follows: on the face, forehead, prominence of nose and cheek bones, occasionally on the ears and lips, at times on the scalp. On the neck the lines of the sternomastoid muscle were picked out, but the anterior and posterior triangles of the neck were avoided. On the arms the rash was more profuse on the forearms and hands than on the upper arm, and usually more on the extensor than on the flexor surfaces. The ante-cubital fossae were usually avoided and the axillae were free. The distribution of the rash on the legs corresponded with that on the arms. On the trunk the eruption was usually much less profuse than on the face" (Fig. 3).

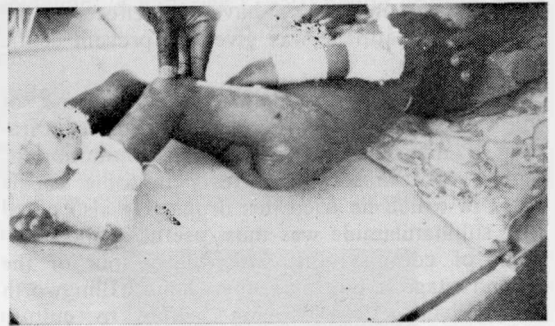


Fig. 3—Illustrating the areas of paler skin that are left behind after the dehiscence of the smallpox pustules. This patient also had multiple arthritis due to smallpox, as shown by the bandages.

A feature of the rash which is not emphasised in some descriptions is the presence of oedema, most noticeable in the face, but also present in the hands, feet and genitalia—indeed, in any place where the eruption was found. This oedema often caused the eyes to be closed, the fissure between the eyelids being filled with gleary matter, the lips to protrude and the nares to be so narrowed as to cause noisy breathing. In one case oedema of the prepuce caused temporary retention of urine. Hebra (1866) gives a good description of the oedema that is associated with the smallpox rash: "When the pustules are very numerous they of course lie close to one another, and this involves a swelling of the intermediate tracts of skin which are not themselves occupied by the eruption. These changes produce an extreme disfigurement, especially on

the face. The eyelids become closed by oedematous swelling, the nostrils are plugged up and the lips protrude outwards."

Another feature of the disease at this stage was the obvious illness of the patients. They did not cry or move about, but lay still, as it were at the mercy of the disease which had overtaken them.

After a pustule has dehisced it leaves behind a disc of coffee-coloured paler skin. These areas of paler skin become over a period of weeks darker than the surrounding skin. The well-known pockmarks on the face which, according to Bras (1952), are related to scarring of sebaceous glands, are a later development.

Second Stage—Effects of Treatment

All the patients who were admitted to Abercorn hospital received a broad spectrum antibiotic, penicillin, cough mixture and sulphacetamide eye drops. It was accepted that antibiotics were unlikely to have any effect on the virus; the treatment was given to prevent septic complications.

Wilkinson (1942) claimed that the use of sulphanilamide caused an arrest of the maturation of the smallpox rash and a diminution or absence of the secondary fever in some of the cases in which he tried this drug. He also noted that sulphanilamide was most useful in the treatment of complications which arose out of the second stage. On the other hand, Illingworth and Oliver (1944), being unable to culture pathogens from the pustular lesions of smallpox patients, concluded that sulpha drugs were of no value in the treatment of the disease. Marsden and Coughlan (1951), Breen (1951) and Stolte and Sas (1951) all reported on the effects of antibiotics in smallpox. There was general agreement that antibiotics had no effect on the secondary fever or upon the maturation of the smallpox lesions. They were also in agreement with Wilkinson that antibiotics and sulphas were of value in preventing secondary infection. The situation is well summed up by Breen (1951): "The suppression of coccal proliferation is a welcome assistance to the defence, but it is rarely decisive. This is emphasised because it is sometimes loosely assumed that the secondary pyrexia is largely of septic origin, whereas in fact it is an essential feature of smallpox."

Comparing the Abercorn epidemic with other epidemics that have been reported, it is evident that the proportion of cases of secondary infection was higher than in some other epidemics. This is undoubtedly due to the fact that a pro-

portion of the villagers, either through difficulties of transport or through a distrust of hospitals, preferred their children to have smallpox at home, in the insanitary conditions of their mud-floored huts, and only brought them in when septic complications had supervened. In those cases which had been treated throughout in hospital, or as inpatients in a rural dispensary, with antibiotics and other adjuvant measures, the incidence of septic complications was low. In May, 1963, I examined 41 patients who had recovered from smallpox and who had been under the care of Mpulunga rural dispensary, which has inpatient facilities. Of these 41 patients, four had corneal opacities and only six had definite permanent facial scars; there were no other sequelae that could be found. On the other hand, in August, 1963, after the epidemic had spread to the more outlying villages, there were four patients in Abercorn hospital at the same time suffering from abscesses complicating smallpox. In the months that followed it was rare not to find a child in hospital suffering from either smallpox abscesses or from osteomyelitis variolosa.

The strong impression was received that antibiotics were of value in aborting the secondary septic complications (the third stage) of the disease.

The Third Stage—Abscesses and Corneal Opacities

Abscesses and corneal opacities are the most frequently found major complications of smallpox. Other complications which have been noted are boils, secondary septic dermatitis, whitlows, arthritis and related conditions, gangrene of the fingers and toes, otitis media, infections of the urinary tract, pneumonia and septic abortion (Marsden, 1948; Bras, 1952; Hebra *et al.*, 1866).

The descriptions of other epidemics indicate, as might be expected, that septic complications are more common among people who suffer from poverty and have a low standard of hygiene, such as people in Hong Kong, Arabia and Indonesia, than among people who have a better standard of hygiene.

Marsden (1948) found abscesses in 2.3 per cent. of patients with variola minor in England.

A good description of abscesses is given by Hebra (1866): "It generally sets in about the end of the third week. The patient first complains of pain in particular spots which are extremely tender and sensitive to the slightest pressure. A few days later they are found to be swollen and oedematous, and soon after, fluctua-

tion, which is sometimes indistinct, can be detected by the fingers. If an incision is made into one of these painful spots there escapes a large quantity of pus."

Although in one or two cases in Abercorn abscesses occurred while there were pustules still present, usually every pustule had dehisced when the abscesses first appeared. The abscesses did not appear to have any preference for particular sites, except that they only occurred where the rash had been and were not found on the abdomen. The abscesses were frequently multiple, sometimes being present simultaneously and sometimes appearing sequentially in different parts, an abscess in one part being followed by an abscess in another part. Often the children with abscesses also suffered from protein malnutrition. Sometimes a child would be found to have both abscesses and osteomyelitis.

Corneal opacities were noted by Marsden (1948) in 0.91 per cent. of cases of variola minor in England, by Sword (1961) in five out of 620 cases in Nyasaland, and by Corkill (1951) in five out of 218 cases in Jiddah. I found corneal opacities in four out of 41 patients in Mpulungu.

Corneal opacities make their appearance in the third stage of the disease—that is to say,

after the dehiscence of the pustules. Corneal opacities are usually in one eye only, but may be bilateral. Rarely panophthalmitis with destruction of the eyeball may occur.

The Third Stage—Osteomyelitis Variolosa

Lesions of the bones and joints following smallpox are reputedly rare and the literature upon them is scanty. In the Abercorn epidemic, however, osteomyelitis variolosa was not uncommon. Observers of the recent Nyasaland epidemic also noted that osteitis and arthritis were common in that epidemic.

Marsden (1948) found no cases of osteomyelitis variolosa in his large series of patients in England with variola minor. Corkill (1951) found bilateral elbow joint arthritis in two out of 218 cases of smallpox in Jiddah. Wilkinson (1942) noted that some cases occurred in the Hong Kong epidemic he describes. Bras (1952) mentioned a score of cases in the Djarkarta epidemic. Chatterjee (1950) found arthritis confined to the elbow joints in 10 out of 2,341 cases.

Both Chatterjee (1950) and Brown and Brown (1923) noted that osteomyelitis variolosa seemed only to occur in children. Possibly the fact that this condition seems to have been more common in Abercorn and Nyasaland is accounted for by



Fig. 4—Arthritis in smallpox. Note the deformity of the ankle joint.



Fig. 5—Smallpox osteomyelitis. Gross changes in upper end of tibia.

the fact that the majority of cases in these epidemics were children.

It appears that there are two different conditions of the bones and the joints which occur as a sequel of the second stage of smallpox. The first is an embolic osteomyelitis such as might occur in any illness complicated by bacterial infection. This condition, which might be called true osteomyelitis variolosa, is not common and only one case was seen. The second condition, greatly more common, is a condition of certain joints in the early stages of which osteomyelitis is not a feature and which might more properly be called smallpox osteoarthropathy.

(a) *True Osteomyelitis Variolosa*

Only one case of true osteomyelitis variolosa was seen. The osteomyelitis occurred in the os calcis.

(b) *Smallpox Osteoarthropathy*

This is a condition of the joints occurring in the third stage. It appears at first to be non-infective, but is characteristically prone to suppuration at a later stage.

Brown and Brown (1923) considered that smallpox osteoarthropathy was due solely to the smallpox virus and was not related to bacterial infection. This opinion is in part supported by



Fig. 6—A.P. osteomyelitis. Note the changes at the lower end of the tibia.

Chatterjee (1950), who was unable to culture pathogens from the joint effusions of some of his patients.

If smallpox osteoarthropathy were due solely to the smallpox virus it would be more logical, surely, to expect to find it in the first or prodromal stage, when there is viraemia, and before antibodies have been elaborated. As it is, smallpox osteoarthropathy is only found in the third stage, along with the other "septic" complications of smallpox.

It is accepted by the writer that smallpox osteoarthropathy may be non-infective in the early stage, but so great was the incidence of suppuration that it does not seem possible to fractionate the condition into suppurative and non-suppurative elements.

It is suggested that the condition may be analogous to rheumatic endocarditis and bacterial endocarditis. The former condition is non-bacterial, but renders the diseased valves particularly liable to subsequent bacterial infection. Possibly smallpox osteoarthropathy is similar.

Smallpox osteoarthropathy is an affection of the joints and the bones contiguous to the joints



Fig. 7—In this photograph of the left forearm changes in both the elbow and wrist joints can be seen. The wrist is particularly badly affected, with erosion of the bone ends and subperiosteal pus formation.

which may be of various grades of intensity, ranging from a slight effusion in the joint cavity without neighbouring bone involvement to a condition in which the adjacent bone undergoes widespread destruction.

The distribution of the joint lesions is characteristic. The elbows, knees, wrists and ankles are involved. There is generally symmetry, both elbows and both wrists, for example, being involved. Smallpox osteoarthropathy was not found in the hip or shoulder joints, nor in the small joints of the hands and feet. The intervertebral joints were not affected.

On examination, the joints were seen to be swollen, but without the presence of contractures. The knees had a drum-stick appearance, but were not flexed. The wrists had a puffy deformity reminiscent of Colles fracture. Similarly, the ankles had an appearance somewhat reminiscent of Potts fracture. The elbows were generally held in the midflexion position. Although the joints were swollen they were not usually tense with fluid, and on some occasions aspiration of these joints produced no fluid, while on others a quantity of pus was withdrawn. The joints were not hot to the touch, and on light touch there was no tenderness, although movement of the joints always elicited pain. Sometimes sinuses were present between the joint cavities and the skin. Movement of the joints, when bone destruction had occurred, elicited crepitus.

As far as the X-ray appearances are concerned, some cases of joint swelling showed no X-ray changes at all. The earliest changes seemed to be a nibbling and erosion of the adjacent bone similar to the X-ray appearance of gout. More advanced cases showed widespread destruction of the joint surfaces, subperiosteal collections of pus, sequestrum formation and pathological fractures. It was notable that in the elbows the radius and ulna were more involved than the humerus: in the wrists, the radius and ulna more than the small bones, and in the ankles, the tibia and fibula more than the talus.

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