SMALLPOX

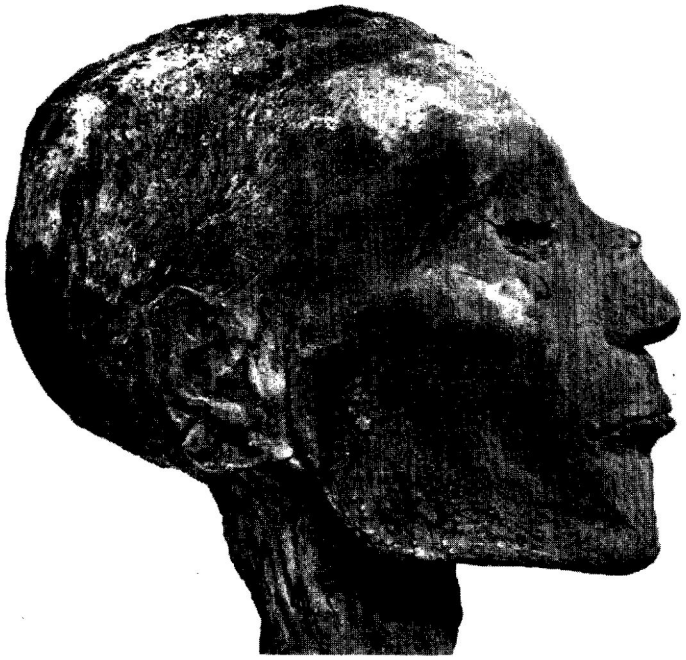


FIG. 1. Rameses V (*c.* 1100 B.C.)
Allowing for changes due to the process of mummification the lesions bear a considerable resemblance to smallpox. Rameses died from an acute illness at the age of forty.

SMALLPOX

by

C. W. DIXON
M.D.(Lond.), D.L.O.(Eng.), D.C.H.(Eng.), D.P.H.(Lond.)

Professor of Preventive and Social Medicine,
University of Otago, New Zealand
Formerly Reader in Epidemiology, University of Leeds
Sometime W.H.O. Consultant on Smallpox

With 284 Illustrations
including 74 in colour

J. & A. CHURCHILL LTD
104 Gloucester Place, London, W.1
1962

This book was set in 12-point Bembo type and printed by Spottiswoode, Ballantyne & Co. Ltd., Colchester, Essex, on Esparto White Art paper, 30 × 40, 100 lb., made by Clyde Paper Mills.

The blocks were made by John Filmer & Co. Ltd.

The coloured illustrations were printed in eight colours by John Waddington Ltd. from plates prepared by Vauvelle (Photo-litho) Ltd., Leeds.

The binding is by Webb, Son & Co. Ltd.

PRINTED IN GREAT BRITAIN

PREFACE

In this book I have endeavoured to present both the clinical and public health aspects of smallpox. To many this disease is a rarity and I have therefore included a large number of coloured and black-and-white illustrations so that the clinician may learn, or refresh his memory, when confronted with a doubtful case. All showing detail of rashes or of vaccination lesions are natural size.

In many countries with highly developed hospital services the first case is likely to be diagnosed in hospital, so some attention has been given to the problems of smallpox occurring in a general hospital as well as the organization of special accommodation for the isolation and treatment of the disease.

The medical officer of health needs an overall knowledge of the subject, but he is particularly concerned with control methods and vaccination policy and practice and I have devoted considerable space to the discussion of the basic principles in the epidemiology of smallpox and the lessons to be learnt from classic outbreaks of the disease. I have been frank in my comments on the situations presented as much can be learnt from the mistakes of others. My criticisms are not made in the spirit that I know all the answers—far from it. There is a little duplication of material in some chapters as I have kept in mind the separate needs of the clinician, the pathologist, the hospital administrator and the public health medical officer so that when smallpox occurs each will find information of most immediate value to him, without having to search from one section of the book to another, although I hope, when there is time, all will look at smallpox from a much wider view.

The history of smallpox, variolation and vaccination is not only interesting in itself and necessary to the proper understanding of practical smallpox control but it teaches much which is fundamental to our appreciation of the development of the public attitude towards inoculation procedures in general. Even when smallpox is finally eradicated I feel the story will provide a fund of knowledge useful in controlling other diseases.

I have possibly been unwise to put forward new views on some aspects of this subject and to suggest explanations based on clinical or epidemiological observations and not on laboratory investigations. These ideas, lacking scientific exactitude, are advanced in the hope of stimulating others to think, to investigate, and confirm or refute so that we may progress to a fuller understanding of this and, perhaps, similar diseases.

Part of this book was written while I was Reader in Epidemiology in the University of Leeds and I am grateful to Professor I. G. Davis for supporting me in my interest in this subject, and to the University Council who granted me leave of absence to accept an appointment with the World Health Organization as a consultant in smallpox.

In the list of references I have tried to acknowledge all my sources but if I have failed perhaps authors will bear with me and accept my apologies. "For in all these things I have been hindered neither by avarice nor by sloth, nor by fear, but only and always by time." (Leonardo da Vinci).

C. W. DIXON

ACKNOWLEDGEMENTS

I owe a special debt of gratitude to Dr. J. Pickford Marsden of Joyce Green, Dartford. We have met and discussed smallpox at intervals over the last fourteen years. He read the script of the clinical chapters and made many useful comments but this does not necessarily imply that he agrees with all my views.

Photography is very important in a book of this kind and many of the photographs are the work of Mr. W. Blackledge, A.I.B.P., A.R.P.S., F.R.S.A., Photographer to the University of Leeds. I would particularly like to acknowledge my deep appreciation of his assistance and in particular his willingness to come out to the smallpox hospital with me in the evenings, at week-ends and at other inconvenient times to take particularly valuable photographs. His uncanny steadiness of hand enabled us to take so many full-sized details of skin rashes, in desperately ill patients, where the depth focus was little more than an eighth of an inch. Apart from fifteen photographs which I took myself at Berkeley and Joyce Green, and those acknowledged below, the remainder are all Mr. Blackledge's work.

The photographs used for Figs. 30 and 31 were taken by Mr. R. M. Clemson of the Photographic Department of the University of Leeds, who visited Glasgow with me. Figs. 165, 169 to 174, 179, 180 are made from photographs taken for me by Mr. F. H. Knight, Senior Photographer of the Medical School, University of Otago.

Dr. M. L. Millard, son of Dr. C. Killick Millard, kindly gave me a large collection of smallpox photographs taken by his father. Many of these illustrate rare cases. The following illustrations are from this source: Figs. 16, 17, 39, 46, 63, 79, 80, 88, 89, 91, 92, 146 to 148, 153, 181, 182, 261.

I am also indebted to many friends who have allowed me to use their photographs and these are included in the following list of sources:

Dr. Abriol, Fig. 230; Dr. E. C. Allibone, Fig. 185; Dr. D. M. Blair, Figs. 83, 84; The Marquess of Bute, Fig. 202; Dr. A. F. Cameron, Figs. 8 to 10; Mr. Warren R. Dawson, Fig. 1; Dr. A. Douglas, Fig. 197; Professor A. W. Downie, Figs. 144, 145; Dr. T. H. Flewett, Fig. 164; Drs. R. A. Good and I. M. McLachlan, Fig. 140; Dr. C. J. Hackett, Figs. 38, 78, 154; Dr. P. Hansell, Figs. 151, 152, 184; Mr. E. H. Jesty, Fig. 209; Dr. S. E. Keidan, Figs. 188 to 190; Dr. B. Laurence, Figs. 191, 192, 194, 195; Dr. P. MacArthur, Figs. 162, 221 to 224; Professor A. S. McFarlane, Fig. 163; Dr. J. Pickford Marsden, Figs. 135, 139, 186, 187, 262 to 268; Dr. G. R. Painton, Figs. 123 to 131, 241, 270; Dr. C. D. Rosenwald, Figs. 155, 159 to 161; Mr. Thackrah, Figs. 114, 115; Professor C. E. Van Rooyen, Figs. 142, 143.

Miss D. McHugh, of the Medical School, University of Otago, copied the old illustrations for Figs. 221 to 224.

The attractive and clear diagrams are the work of H. Grayshon Lumby, Esq., M.S.I.A., N.D.D., Medical Illustrator to the Department of Preventive Medicine and Public Health, University of Leeds. I am indebted to him for a great deal of assistance. For many years we worked together experimenting with methods of graphic presentation and he designed about

half the diagrams whilst I was in England, but the remainder have been done since I came to New Zealand and have required much correspondence on my part and much skill in interpretation on Mr. Lumby's part. He also painted the originals for Figs. 5 and 27 and has given much advice on layout and typography. Mr. Lumby has also supervised the coloured illustrations with the colour lithographers, Vauvelle and Sons of Leeds. I would like to express my very sincere thanks to them for the original lithographs which they made and presented to me for use in my booklet on the "Diagnosis of Smallpox", and which were printed free through the generosity of Mr. N. Watson of John Waddington Ltd. Some of these are included in this book, as well as the lithographs of variola minor which Messrs. Vauvelle originally gave to me in 1953 and which have not previously been reproduced. I would also like to express my appreciation of the great pains they have taken to secure a lifelike appearance in the coloured illustrations, and to John Waddington Ltd. for such excellent colour printing.

I wish to thank Mr. H. D. Erlam, Librarian, University of Otago Medical School Library, for much useful advice on the compilation of the indexes and in other ways.

Over the years many secretaries have helped to shape the script: in particular Miss Eve Pigott, Miss Barbara Gill, Miss Christine Panes of the Department of Preventive Medicine and Public Health of the University of Leeds; Miss Veronica Hessian, Miss Margaret Laurie, and Miss Eileen Thomson of the Department of Preventive and Social Medicine, University of Otago. I am indeed grateful to them for their patience and industry.

Finally I wish to thank Mr. J. A. Rivers and others of the staff of Messrs. J. and A. Churchill Ltd. for their patience with the manuscript and their great help in solving many problems accentuated by my being across the other side of the world. I much appreciate Mr. Rivers' understanding of my desire for quality in the diagrams and illustrations, and in particular for allowing the colour illustrations to be produced by eight-colour lithography.

CONTENTS

CHAPTER 1 | *Introduction*

In a monograph it is usual to commence with the history of the disease, follow with the aetiology and pathology, and subsequently deal with the clinical and preventive aspects.

It hardly seems possible to understand the history and epidemiology of smallpox unless one fully appreciates the varied clinical manifestations. For this reason the clinical aspects of the disease are dealt with first, followed by pathology and immunology, so that the history, epidemiology, and methods of control can be examined more critically.

Smallpox is an acute virus infection, and, in spite of views sometimes expressed to the contrary, the virus appears to exist in only two distinct variants—that giving rise to variola major and that giving rise to variola minor. The laboratory differentiation and the possibility of different strains within these two forms is discussed later. Given a single case of smallpox it may be impossible to be certain which infection is present. When a number of cases occur and the epidemiological pattern is clear, variola major and variola minor appear to be two distinct variants which have never been known to change from one into the other. The title smallpox, therefore, includes both variola major and variola minor, and when this term is used it includes both variants. In the clinical diagnosis, in the epidemiology and control, it is necessary to distinguish one from the other, and the terms variola major and variola minor are then used. This gives a mixture of terms, but, apart from other reasons, smallpox is a very old English word and worth retaining. The term alastrim and local names such as amaas, Cuban itch, etc., as alternatives for variola minor, all tend to confuse the issue and imply that the disease is not a form of smallpox, and this may be dangerous.

The term "varioloid" (Thomson, 1818) is still sometimes used to describe variola major in vaccinated persons as a "smallpox-like" disease. This use tends to suggest that it is a distinct disease, which is untrue, and may mask the fact that such a clinical condition occurring in a partly immune person is infectious and gives rise to any of the normal varieties of variola major in contacts. To add to the confusion, varioloid is also sometimes used to describe variola minor. It is a most undesirable term and should be abandoned.

Other terms have been handed down over the years, and although the meaning of many was probably clear fifty or seventy-five years ago when smallpox was common, they may lead to confusion in the minds of those whose experience of smallpox is limited. From the middle of the nineteenth century much smallpox in Europe and North America occurred in persons vaccinated some years previous to attack. In some outbreaks, over 90 per cent (Edwardes, 1902) of the cases were in vaccinated persons. A distinction was made between natural smallpox where variation in severity was determined by "nature" and modified smallpox where its severity was affected by art (vaccination). It became the fashion to talk of *natural* smallpox, which was often severe, and *modified* smallpox, which was frequently mild, and by implication to assume that mild smallpox could not be the natural disease. The term "natural" is only confusing and should not be used in this context.

Perhaps due to blind faith in vaccination the idea also grew up that because some mild cases showed "modification" or some departure from "normal" smallpox, all mild cases of variola major must be modified and that this modification must only be due to vaccination, variolation, or a previous attack. Relying largely on hospital experience, Killick Millard (1896) asserted that mild cases in the unvaccinated were so excessively rare that he hardly believed they existed and that frequently they were due to previous successful vaccination of which the patient was unaware. Cameron (1903) had much experience of smallpox, but wrote rather unconvincingly of this condition. Exceedingly mild smallpox in the unvaccinated had been observed by many of the older writers. De Haen (1775) described *variola sine variolis* and thought that this condition was not uncommon, but, of course, such cases rarely find their way into hospitals. Ricketts (1908) made his use of the words quite clear by saying, "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." In this book the unqualified term "modified" refers to clinical characteristics of the eruption and in no way implies post-vaccinial immunity.

Mild attacks occur both in individuals who have never been vaccinated and in individuals who have been successfully vaccinated, either many years before or during the incubation period in which it is impossible to decide whether the mildness is due to "man-made" immunity or to natural causes. It is always tempting to assume that a mild attack is the result of our own efforts when we have no proof that it is.

The term "haemorrhagic" has been used extensively in both the medical and lay press, usually to imply smallpox of considerable severity. Ricketts used the terms "haemorrhagic" and "toxic smallpox" indiscriminately, but he also pointed out that "haemorrhage from smallpox is not synonymous with haemorrhagic smallpox". It is to be noted that while haemorrhages are a feature of many types, particularly of the fatal cases, they may also be present in quite mild cases and have no unqualified prognostic significance. The writer is in complete agreement with Ricketts in being particularly averse to Curshmann's (1875) classification and his use of the two terms *variola haemorrhagica pustulosa* and *purpura variolosa*. Attempts to use these terms confused Bancroft (1906) in his clinical descriptions, and also Bras (1952*b*) in his attempt to classify cases and fit them to the pathological findings. In this book the term *purpura variolosa* is still used because it does describe a very clear-cut clinical entity, but it is only regarded as a word-picture of one form of "fulminating, type 1".

A term that has been used in a number of systems of classification is *variola vera*. It is this idea of true or typical smallpox so often forming the subject of illustrations in text-books of medicine that has fixed in the minds of practitioners a single picture of what smallpox should look like. The literature on smallpox abounds with statements that a case, particularly the first in an outbreak, was "atypical" as it did not fit the clinician's preconceived ideas on the subject. It must be emphasized that there is no such thing as atypical smallpox. The wide range of severity and variation in signs and symptoms is characteristic of the disease, and depends on the reaction of the host to the virus attack. It is therefore misleading to describe cases as typical or "classical" smallpox, sometimes calling it *variola vera*, and regard all other forms as unusual variations.

For the descriptions in this book smallpox is regarded as a disease with two main phases, the "initial", sometimes called the pre-eruptive stage, of sudden onset, followed by the "eruptive"

stage with the development of a focal (Ricketts, 1908) rash with many diagnostic and prognostic characteristics. In certain cases, both very severe and very mild, the main "pock" or "focal" eruption may be absent. The term "pre-eruptive stage" is convenient and often accurate, but other non-focal rashes may appear at this time so that it is more convenient to use the term "initial".

The focal lesion, which is later described in detail, commences as a macule, becomes a papule, then a vesicle which is filled with colourless fluid. Usually, the contents change so that the fluid has a milky or purulent appearance and is described as a pustule. Until quite recently this term was used in the sense that the lesion was an intracuticular collection of pus. Even Ricketts (1908) describes it as a "miniature boil". In some instances, especially in the tropics and where hygiene is deficient, lesions contain ordinary pus with white cells, cellular debris and secondary pyogenic bacteria. However, many lesions only contain cellular debris from the epidermis, a few leucocytes and no bacteria, although they look as if they contained pus. The term pustule is therefore used, as it has been for hundreds of years, to describe a stage in the development of the rash without implying that it has a pathological basis similar to a purulent lesion of the skin due to ordinary pathogenic bacteria.

Marson (1866), Ricketts (1908) and others have stated that the prognosis is greatly influenced by the extent of the eruption. These views have often been misinterpreted by those with little experience of smallpox to mean that extent of eruption and severity of attack are directly correlated. It has always been recognized that some moderate eruptions have a poor prognosis.

Like the word "haemorrhagic", "confluent" tends to be used loosely by the lay and medical press to describe any severe case. The term confluent is used when the individual lesions touch one another and coalesce, forming a network of lesions with small islands of unaffected skin. It is normally applied to the late vesicular or early pustular stage, although in very severe cases papular lesions may merit this description. When a few lesions touch one another, the term coherent has also been used. In many cases local increase in number of lesions with coalescence occurs over pressure points, but it seems unnecessary to use any special descriptive term. With a little experience, recognition of this local effect is easy. Descriptions and photographs of cases in the literature show that there is a tendency to use the term confluent far too freely, with the result that the reader obtains an exaggerated picture of the severity of cases and the possible effect of treatment. The term confluent should not be used without qualification, as the mere presence of confluence is not the most important prognostic sign. In this book the terms malignant confluent and benign confluent are used, the significance of which is described later. Confluence practically never occurs on the whole body, and this term is, in my opinion, best restricted to those cases which show general confluence of mature lesions on the face and forearms, the term semi-confluent being used where confluence occurs only on the face. This is the definition adopted by Ker (1939), whereas in Rickett's (1893) classification the term confluent includes all those cases where there is confluence on the face. In spite of increasing the number of terms, I feel the category semi-confluent is valuable, particularly in the malignant type where the moderate eruption on the trunk may lead the inexperienced physician to give an unwarranted good prognosis. The terms discrete, mild and abortive are used in relation to the number of lesions as set out in the table on pages 6 and 7.

Clinical methods used in the diagnosis of smallpox are similar to those used in other diseases, but it is as well to review the particular examinations needed.

One is taught to take a history before examining the patient, but there is considerable force

in Wanklyn's (1913*a*) argument that the history of the initial stage and of the vaccination state may produce sufficient bias to trap the inexperienced. If a definite eruption is present, that in itself should decide the diagnosis. On the other hand, when the rash is at a very early or very late stage inspection may be inconclusive and evidence from the history should be considered carefully. An accurate history should include details of the patient's movements within at least sixteen days before the onset of symptoms. It should be known whether the patient has been in any country or place where smallpox is present. Contact with cases of infectious disease should be noted, particularly if called chickenpox or measles, as this may be of significance whether the diagnosis is correct or not. The vaccination history should be obtained with date of primary vaccination and of any revaccinations, and as far as possible, a description of the kind of reaction obtained. This will have to be confirmed in the case of primary vaccination by examination for the presence of a scar. Revaccination may leave no identifiable scar but too much importance should not be attached to the patient's story or records. If first seen when the focal rash is present, the history of symptoms such as backache, headache, vomiting in the initial stages is very important. The type of onset should be determined, whether sudden or gradual, as this is of some diagnostic significance. With the appearance of the rash the continuance or intermission of symptoms should also be noted.

The usual methods are used for the examination of a rash. The entire skin should be examined, preferably with the patient completely stripped, in a good light, daylight if possible. Close inspection of the individual lesions is valuable, but the most important thing is to examine the body as a whole so as to observe the distribution. The stage of development of the various lesions should also be assessed, bearing in mind that many patients do not notice the earliest macules, particularly when they are scanty. The mouth and throat should also be examined. Examination of other systems gives no positive help in the diagnosis of smallpox. The prudent physician should note the presence of signs of other infections, for example pneumonia, but should bear in mind that this should not lead him to discount any evidence of smallpox, as the necessity for a double diagnosis occasionally arises.

Material may be taken from the patient for laboratory tests. A specimen of blood from a vein can be used for the culture of virus, the detection of soluble antigen or the complement fixation reaction. Scrapings may be taken from cutaneous lesions with a needle or scalpel and smeared on to glass slides and vesicle fluid or scabs collected. These may be used to detect virus by microscopy, by culture or for serological tests. Methods of collection and the significance of the results are discussed in Chapter 4.

CHAPTER 2 | *Classification of Cases*

A clinical classification is necessary to determine prognosis and is essential for the proper assessment of treatment, but it is also of much assistance in diagnosis which rests on the appreciation of the varied general and skin manifestations occurring in a definite time relationship to one another. It cannot be too strongly emphasized that in the "difficult" case of smallpox the skin lesions may closely resemble those occurring in other diseases, but the timing of their appearance in relation to the general symptoms determines whether the disease can or can not be smallpox.

The accompanying chart (Fig. 2) sets out the principal clinical characteristics of nine types of smallpox based on cases seen in Tripolitania (Dixon, 1948). Although originally worked out on the disease occurring in a predominantly Arab population, subsequent observations in Glasgow in 1950, Rochdale in 1952 and the West Riding in 1953, and by Murphy (1954), have confirmed that it applies equally well to the disease in a European population. Banks (1952) has advocated its use. Some writers assert that the variation in type from severe to mild is a gradual indefinite change; with this I cannot agree. There is an entirely different "pace" in the fulminating and malignant types, which sharply differentiates them from the benign. Many of the older writers recognized this, particularly Moore (1815). He even used the descriptions malignant and benign, although I adopted these in Tripolitania when unaware of this. The classification applies to both variola major and variola minor and in the vaccinated and in the unvaccinated. The case which has not fitted well into many of the previous classifications is the "discrete". As pointed out by Ricketts (1908) and others, although normally free from toxic symptoms in the eruptive stage, this type of case may occasionally show this feature and include small haemorrhages in the skin. The diagram in Fig. 5 shows the relationship of the types to one another and that the discrete may sometimes show some of the characteristics of both the malignant and the benign types.

It will be seen in Fig. 2 that a number of general and local features make up the character of each type. The term confluent is used with qualification, and the division between types 6, 7 and 8 is based on a numerical difference in the eruption. It should be noted that where vaccino-modification occurs, the differences in the type of lesion should be disregarded in making the classification, but such effects can be noted by using the term vaccino-modified as a supplementary description. The value of this procedure is not apparent until it is realized that vaccination, particularly when performed during the incubation period, may have no effect on the number of lesions but only on their maturation.

TYPE 1—FULMINATING—(PURPURA VARIOLOSA)

In a small proportion of individuals smallpox infection runs a hyper-acute course. After an incubation period of about eleven to twelve days the patient is suddenly taken ill, with a feeling

FIG. 2. Principal clinical characteristics

Type	Name	Initial fever	Secondary fever	Laryngeal lesions	Mental symptoms
1	Fulminating (Purpura variolosa)	+ −	−	+ −	Anxiety +++
2	Malignant confluent	++	+++	++	++
3	Malignant semi-confluent	++	++	++	++
4	Benign confluent	+++	+	+ −	−
5	Benign semi-confluent	+++	+	−	−
6	Discrete	+++	+ −	−	+ −
7	Mild	+++	−	−	−
8	Abortive	+++	−	−	−
9	Variola sine eruptione	+++	−	−	−

of the nine types of smallpox

Haemorrhages	Rash	Pustulation (untreated)	Extent of focal eruption	Approx. mortality (%)
Early, esp. mucous membranes +++	Soft, velvety; often absent	Nil	—	100
Late in the skin and mucosa ++	Soft, velvety, hot and tender. Slow evolution, pseudo cropping	Nil	Confluent on face and arms	70
Late in the skin and mucosa ++	Soft, velvety, hot and tender. Slow evolution, pseudo cropping	Nil	Confluent on face only	25
—	Hard, pearly. Normal evolution, uniform on each anatomical part	Severe	Confluent on face and arms	20
—	The same as in type 4	Severe	Confluent on face only	10
Very occasionally in individual vesicles	Usually hard, pearly	Slight	No area confluent over 100 lesions	2
—	Hard, pearly. Some lesions abort	Slight	20–100 lesions	0
—	Pearly. Many macules and papules abort	Nil	Less than 20 lesions	0
—	No focal rash	Nil	Nil	0

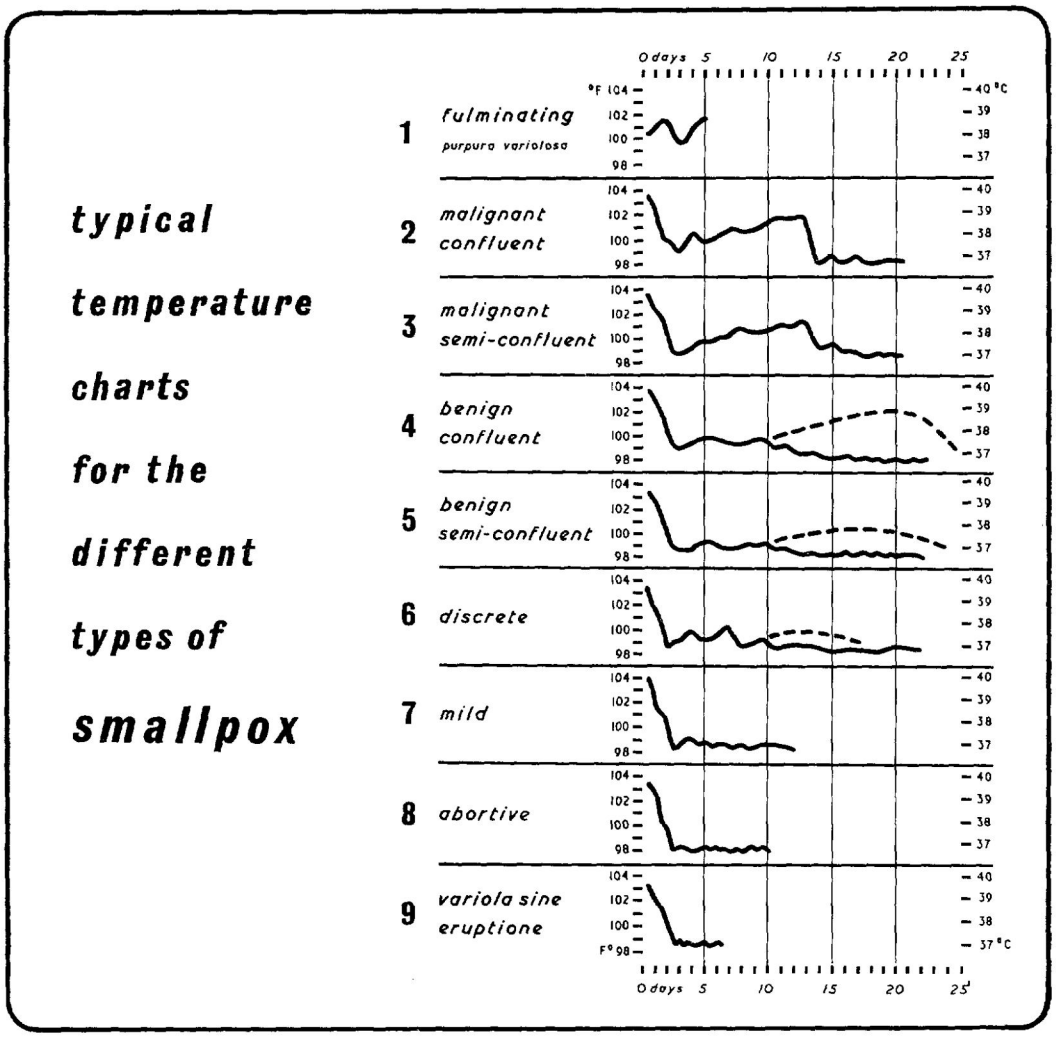


FIG. 3. Typical temperature charts for the different types for smallpox. Primary fever occurs during the first three to four days, secondary fever from the fourth to twelfth day in malignant types, from the fourth to tenth in the more severe benign types, in the latter merging with the tertiary fever to about the twentieth day or more if secondary sepsis intervenes. Types 7, 8 and 9 have no secondary fever.

of intense prostration accompanied by severe headache, and often backache. In spite of these symptoms the patient is very "wide awake" and peculiarly apprehensive. In some patients the infection is so overwhelming that death may occur within twenty-four to thirty-six hours with no outward manifestations at all. Consciousness is retained to the point of death, and the patient quietly expires. At post-mortem there may be a few haemorrhages in the submucosa, in the respiratory (Fig. 4) and alimentary tracts and in the heart muscle, the latter

FIG. 4. Fulminating, haemorrhage at the tip of the epiglottis, and in the left pyriform fossa.

To face p. 8

possibly contributing to death in some cases. The appearances are very indefinite, with no findings on which to base a certain diagnosis. The most likely one is some unknown acute infection or possibly an acute lymphatic leukaemia. The blood film shows a leukaemic picture with the white cells almost all lymphocytes and there may be many myeloblasts. This is "sledge-hammer" smallpox, and the diagnosis both clinical and at autopsy is impossible unless smallpox

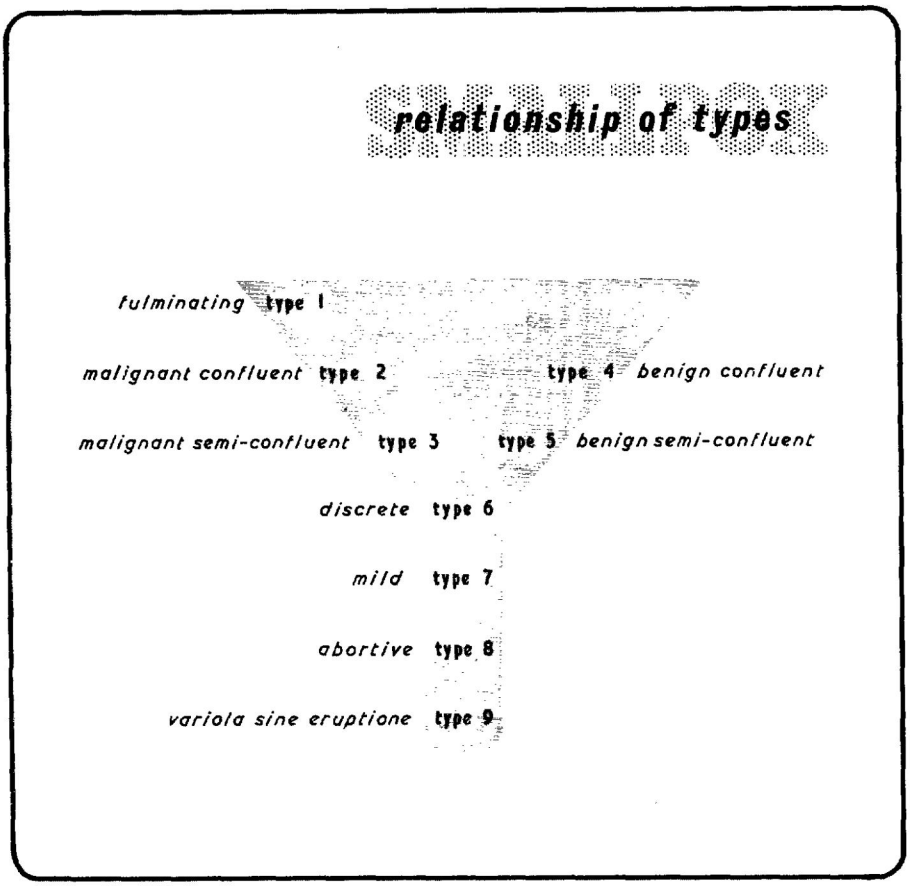


FIG. 5.

is thought of and unless laboratory facilities are available and used to grow the virus or detect soluble antigen in the blood during life, or after death. If the patient survives more than forty-eight hours there is often a slight but temporary improvement in the general condition, followed by the appearance of an erythema on the face and back of the hands, and a blotchy erythema on the arms and trunk, particularly the anterior abdominal wall and the upper part of the thighs (Figs. 6, 7, 9 and 10). The patient's general condition deteriorates, there is increasing prostration, but the temperature remains at about 101–102° F. (38·3–38·9° C.).

Wanklyn's description (1903) is particularly apt. After three to four days the patient "has the general aspect of one who has passed through a long and exhausting struggle. His face has

lost its expression. The lines have partly disappeared. As it has been expressed, his face is mask-like and there is a want of tone in all the muscles. When he speaks, this condition becomes more apparent. He speaks with evident effort and his voice is low and monotonous. He is list-

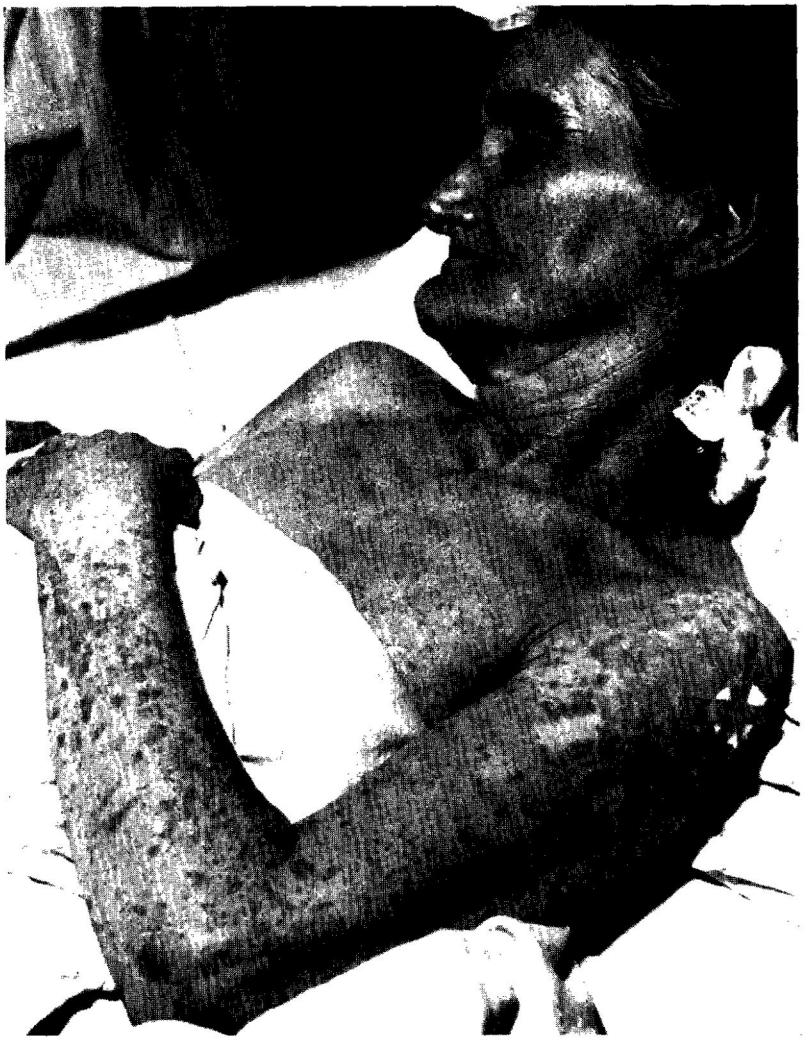


FIG. 6. Variola major, fulminating, third day. Dusky erythema of face and hands, patchy morbilliform eruption on arms. Note old vaccination scars on the arm, formed sixty years before.

less and indifferent to his surroundings, though his eyes may be clear and bright. The question as to the disease from which he suffers has little interest for him. The greater the physical development the more marked is this condition. The mental attitude is similar. There is loss of tension, showing itself in a lengthening of the reaction time and a defective control. When

a question is put the answer is appreciably delayed. A request to show his tongue or to put out his hand often requires to be repeated. Such movements are often retarded and tremulous or even jerky in their performance. It is evident that their completion gives relief. The patient staggers in his walk and tends to fall if not supported. Frequently he volunteers the statement that he feels much better and will soon be all right. Such is the typical condition. The more severe the attack the more striking is the picture. In the most fulminant case the aspect of the patient resembles that of one suffering from severe shock and loss of blood. His face is drawn and pallid. His respiration is sighing or even gasping. He tosses himself about continually and cries out at frequent intervals. His attention is fixed with difficulty and he complains only of agonizing pain, now in his chest, then in his back, his head or abdomen" (Fig. 8).

Examination of the mouth may reveal haemorrhages occurring under the mucous membrane and large blood-filled bullae which at first sight may be mistaken for true focal lesions. The

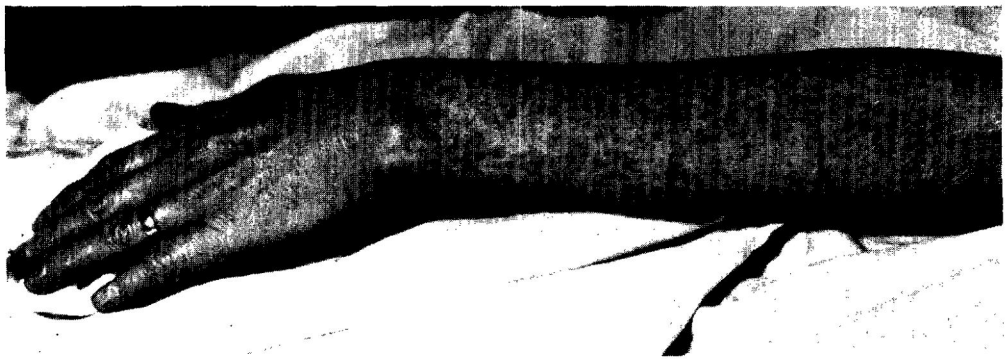


FIG. 7. Variola major, fulminating, dull erythema of hand and wrist, patchy erythema of forearm.

erythematous areas of the skin will reveal petechiae which during the next twenty-four hours rapidly enlarge forming ecchymoses of a peculiar bluish-purple colour (Fig. 19), particularly present on the abdomen and upper parts of the thighs; but just before death, which occurs within forty-eight hours of the onset of these haemorrhages, the whole body may be affected. When the haemorrhages occur only in the "bathing drawers" area (Fig. 10), a confident diagnosis of smallpox can be made; but when haemorrhages are more general, as is common, the picture has no completely characteristic features to distinguish it from other hyper-acute infections, although in smallpox there is a greater tendency towards symmetry. In infants the rash appears more frequently on the anterior abdominal wall and may be absent in the groins. With the appearance of haemorrhages in the mucous membrane or skin the patient's life may be terminated by massive haematemesis, intestinal or uterine haemorrhage. Death otherwise occurs very peacefully due to increasing toxaemia. The whole course of the disease lasts four or at the most five days, but is frequently less. Examination of the patient even on the fifth day may show no true focal lesions. In a number of these cases a diligent search of the body will reveal a very flattened type of vesicle (Figs. 11, 12 and 14), difficult to differentiate from the stripping of the epithelium which occurs over a haemorrhage. From the diagnostic point of view it cannot be overemphasized that the absence of any vesicular

eruption is the main feature of this condition and increases the difficulty in differentiating it from other acute haemorrhagic catastrophes.

The high white count in bacterial and the low count in early viral infections may help to distinguish between acute viral and acute bacterial, such as meningococcal, septicaemias, but

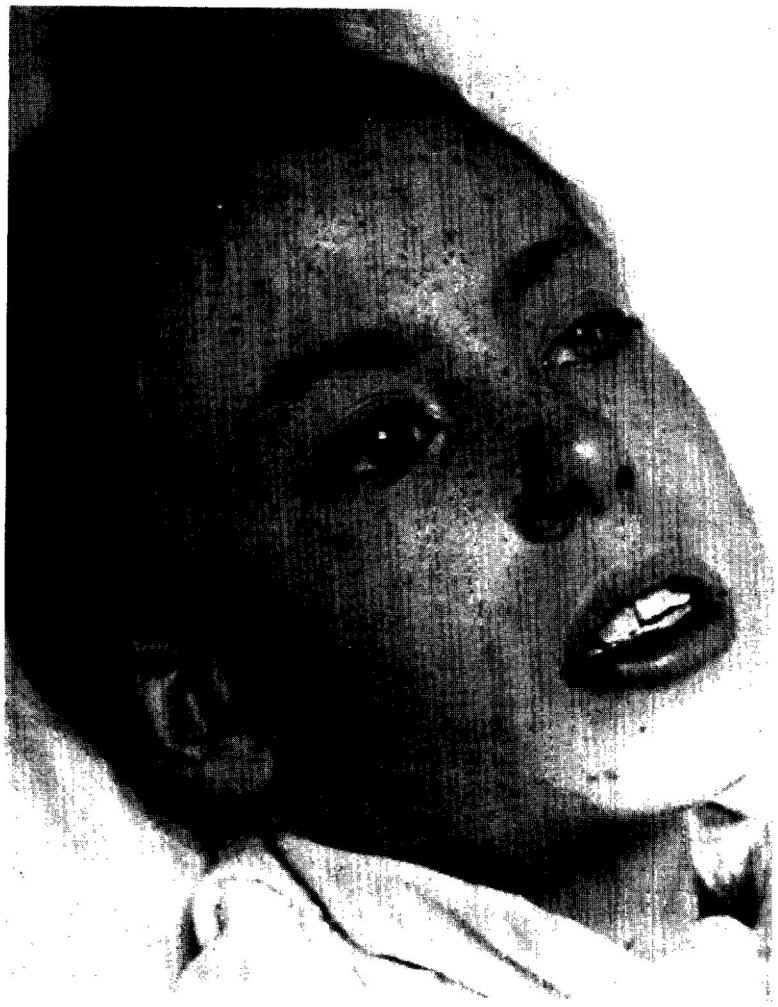


FIG. 8. Variola major, fulminating. The characteristic facial expression, loss of muscle tone, bright eyes.

too much reliance must not be placed on this, and if there is the slightest suspicion a blood culture during life or a specimen of heart blood taken after death should be sent to a laboratory for viral and bacterial examinations.

If laboratory facilities are not available do not hesitate to diagnose clinically and act accordingly.

FIG. 9. Variola major, fulminating. Erythematous and petechial eruption.

FIG. 10. Variola major, fulminating. Petechial eruption in the groin and some in the axilla.

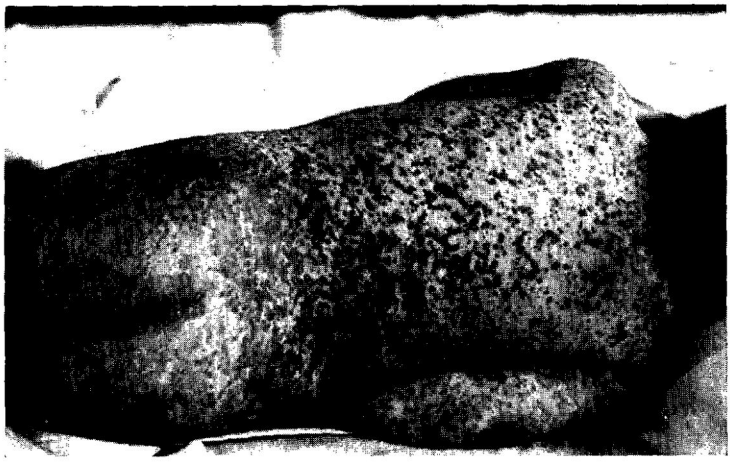


FIG. 11. Fulminating, fourth day. Although there are many haemorrhages, some very superficial vesicles are present.

FIG. 12. Fulminating smallpox, fourth day, death.

TYPE 2—MALIGNANT CONFLUENT

The onset is sudden, with a moderate temperature of 101—102° F. (38·3–38·9° C.). It should be noted that higher temperatures are common in the less severe types. Malaise, intense headache, and general aching of the muscles occur. Backache may be very severe, but is not such a constant symptom as one has been led to believe. In my experience it is less severe in Arab patients than in Europeans. Wilkinson (1942) and others noticed that this symptom was particularly severe in negroes. It seems probable that it is partly due to severity of attack

and partly due to occupation and the use of these muscles during the initial phase. Social customs may account for apparent variation with race.

When present, this peculiarly severe backache is a valuable pointer, but its absence is of no diagnostic importance.

Pain in the chest is sometimes complained of, but there are no respiratory symptoms, nor is the respiration rate raised appreciably at this stage. Vomiting is common and abdominal pain may be complained of which, by the second or third day, may be severe enough to make one suspect an acute abdominal condition. This is possibly due to mucosal or sub-mucosal haemorrhages as bleeding tends to occur in the mucous membranes before appearing in the skin. Laparotomies have been done, in error, on a number of smallpox cases of this type. Melaena may also be present, but is more profuse a little later in the disease. The patient is most anxious and has a peculiar mental alertness.

The general condition remains much the same for one or two days, but by the second or third day there may be some improvement and the temperature may fall a little, sometimes to normal. Some patients feel sufficiently well to get up and go out and may visit a doctor or hospital. The temperature rises again, but rarely above 102° F. (38·9° C.), although the patient is obviously far from well and the pulse rate has increased considerably. A dusky erythema appears on the face and a mixed petechial and macular eruption of rather irregular distribution appears on the upper chest, neck, back and upper arms (Figs. 21 and 22). Although present on the face, it is difficult to see clearly because of the general erythema. A few scattered macular lesions may be present on the lower arms and hands, but frequently there is no rash on the legs or feet. The rash is very pleomorphic in appearance and is not unlike rubella. At this stage the eruption principally affects the upper half of the body. On palpation it seems to have some substance, but the papules do not feel hard or "shotty", as is often described in the text-books. Examination of the mouth may show small areas of hyperaemia and small very early vesicles on the soft or hard palate or on the buccal mucous membrane, but their appearance is not constant and does not help very much in diagnosis.

The erythema on the face changes imperceptibly into a diffuse vesiculation. On the cheek and forehead it looks almost exactly like a very severe sunburn (Fig. 13). The appearance is not unlike a very fine-grained crêpe rubber set on a red base and seems to be due to a combination of very small nearly confluent lesions and a marked intracuticular oedema which leads to the scalded appearance of the skin at a later stage (Figs. 13 and 25). Epistaxis may occur; the lips are swollen and there may be slight bleeding from the corners of the mouth. By the fifth day the rash has not progressed very much, the papules remain soft, there may be some erythema of the backs of the hands, but many of the lesions on the chest, arm and back will have changed very little and may still consist of mixed maculo-papular and petechial elements. The appearance is so different from the usual description of "classical" smallpox where all the lesions on each anatomical part are at the same stage of development. On close inspection it may be possible to find one or two very flat thin-roofed vesicles, quite small, only about 4 or 5 mm. in diameter. The vesicles are so flattened as to be little more than a thin flake of epithelium over a flat papule separated by a very small amount of fluid. This lesion is more likely to be seen over a small haemorrhage, and, because of the appearance and apparent cropping, cases of this kind are often thought to be haemorrhagic chickenpox. This diagnosis is made as the patient's general condition remains fairly good although the apprehensive mental state remains. The prognosis is, however, very bad. During the next three days the

rash slowly continues to develop on the forearms and hands, on the upper legs, lower legs and feet, in that order. Although the general distribution follows a centrifugal pattern it is very much less pronounced than in the benign types of smallpox described later. The gradation of density of lesions on the limbs, increasing as one passes towards the periphery, is particularly slow to show, and at this stage the rash may appear as dense and sometimes more dense on the proximal parts.

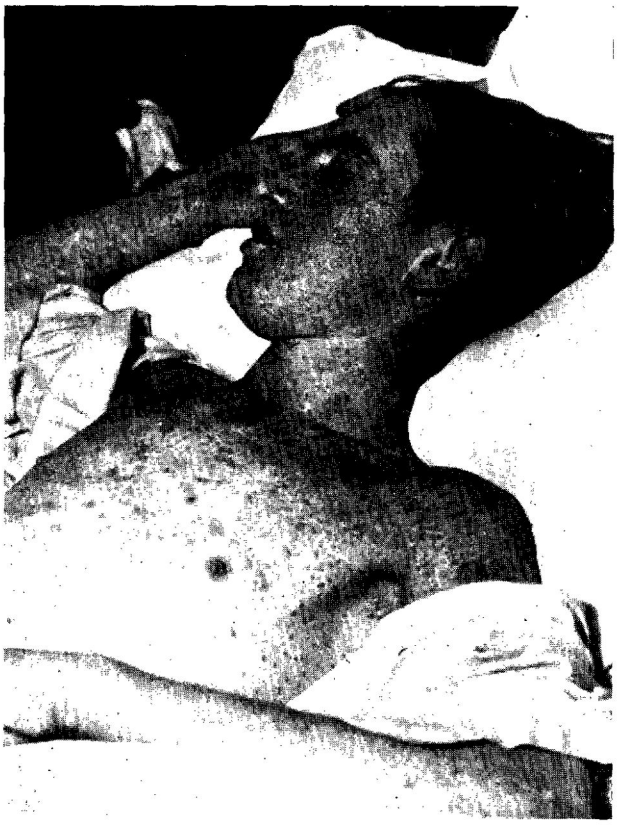


FIG. 13. Variola major, malignant confluent, seventh day, slow evolution, acute sunburn appearance of face, with tiny close-set vesicles, mixed lesions on the chest.

From about the seventh or eighth day of the disease there are complaints of increasing difficulty in swallowing, and pain on talking, due to extensive lesions in the mucous membranes (Fig. 26). The patient deteriorates slowly, being drowsy much of the day, but when roused will talk quite intelligently and unfortunately, only too frequently, realizes his ultimate fate. At night, however, he may be extremely restless, continually trying to get out of bed and requiring individual nursing attention. A condition closely resembling delirium tremens may occur and in the confused state much cunning may be shown in attempts to escape from the smallpox ward.

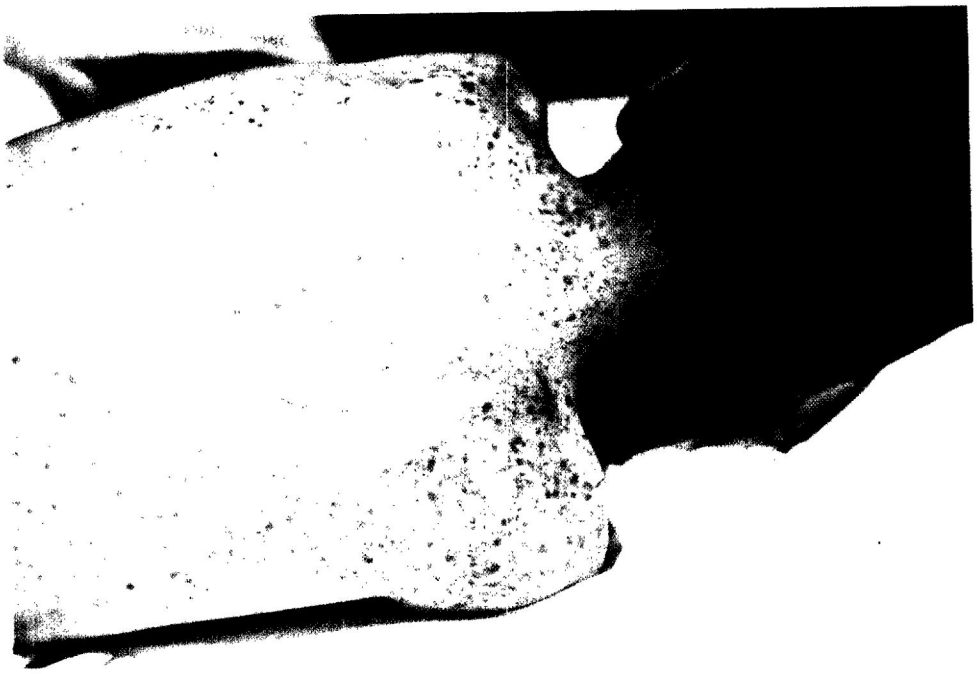


FIG. 14. Fulminating, mixed eruption on the back. On the neck are two *very* superficial flat vesicles

FIG. 15. Variola major, fulminating, fourth day, erythema of face, back of hands and wrists. Mixed morbilliform eruption elsewhere, with petechiae and ecchymoses. Haemorrhages from the angles of the mouth, anxious expression.

To face p. 16

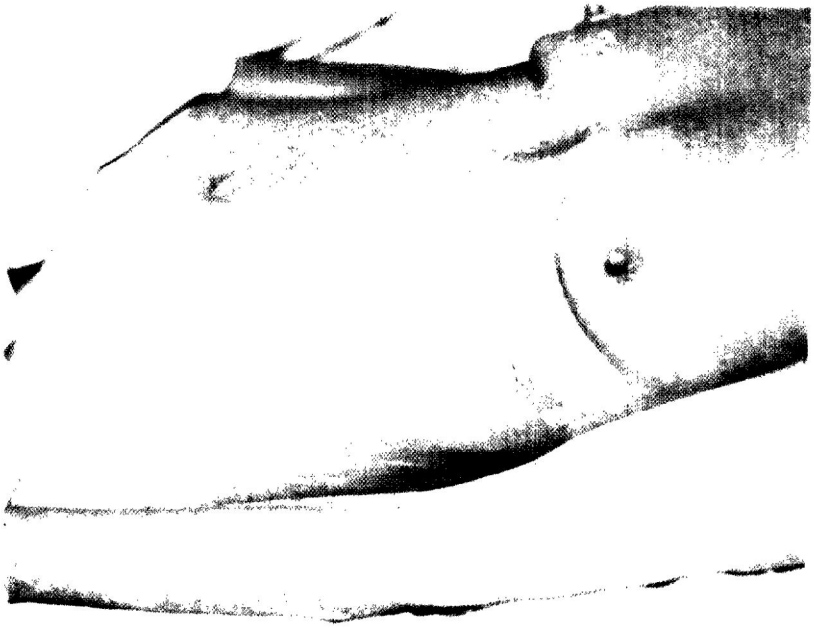
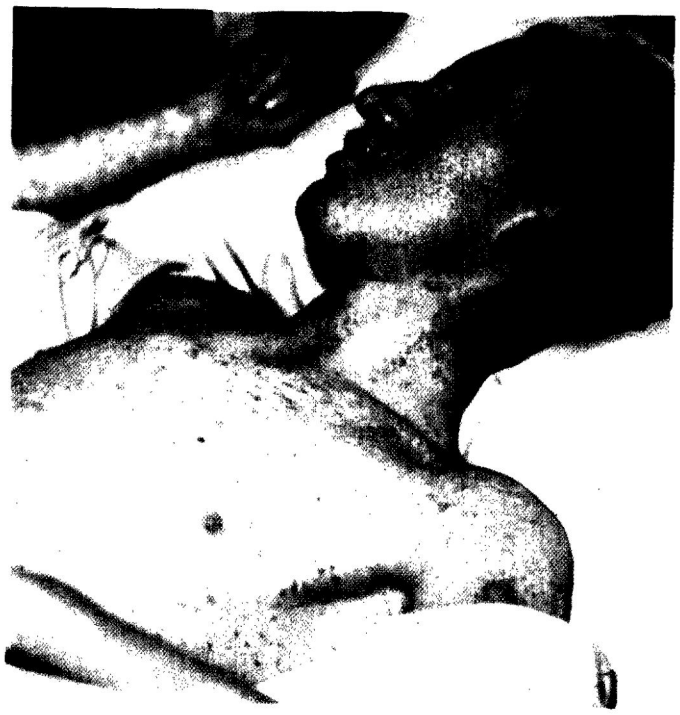


FIG. 16. Fulminating, Type 1, early diffuse erythema.

FIG. 17. Malignant confluent, Type 2, well marked "sunburnt" appearance of face and scanty, poorly developed rash on the chest.



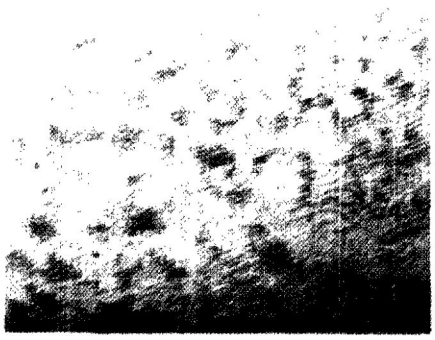


FIG. 18. Type 1, fulminating, early morbilliform eruption.

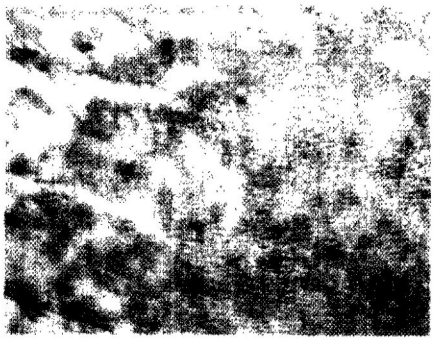


FIG. 19. Type 1, fulminating, early erythema.

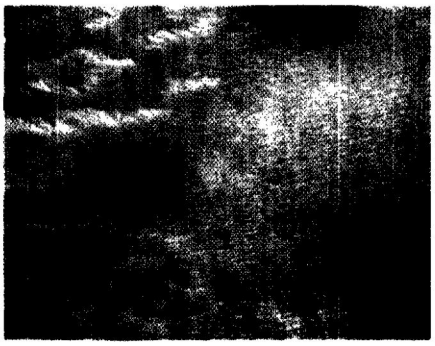


FIG. 20. Type 1, fulminating, deep haemorrhages, ink spot type.

FIG. 21. Type 2, early morbilliform eruption, fourth day.

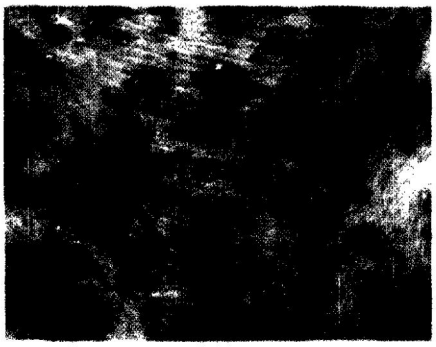


FIG. 22. Type 2, mixed elements, very slow evolution, poor superficial vesicles, eighth day.

FIG. 23. Type 2, slow, poor vesiculation, tenth day.

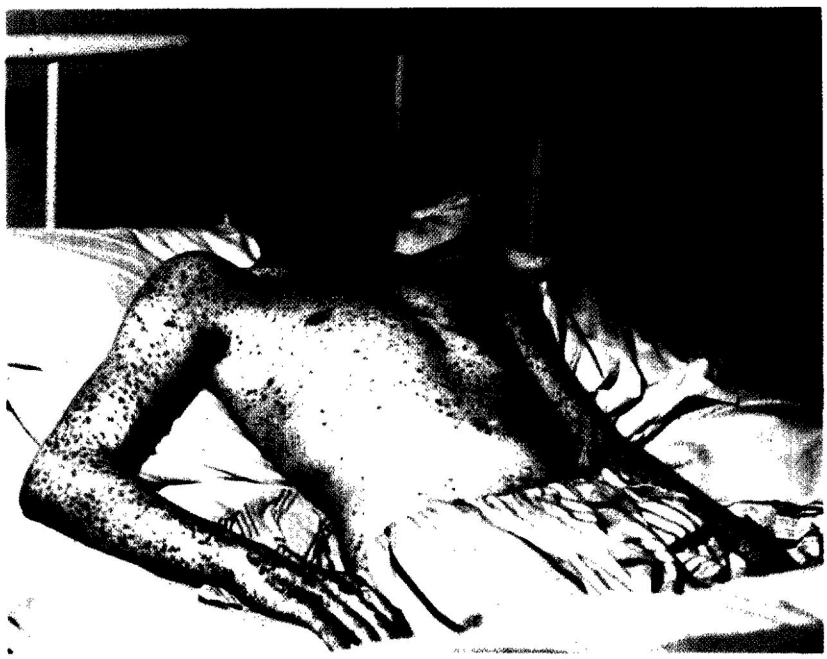


FIG. 24. Malignant confluent Type 2, early rash, mixed elements, slow evolution, sixth day.

FIG. 25. Malignant confluent Type 2, scalded appearance of face, rash limited to upper trunk, eleventh day.

FIG. 26. Variola major, extensive almost confluent vesiculation of mucous membrane of hard palate, sixth day.

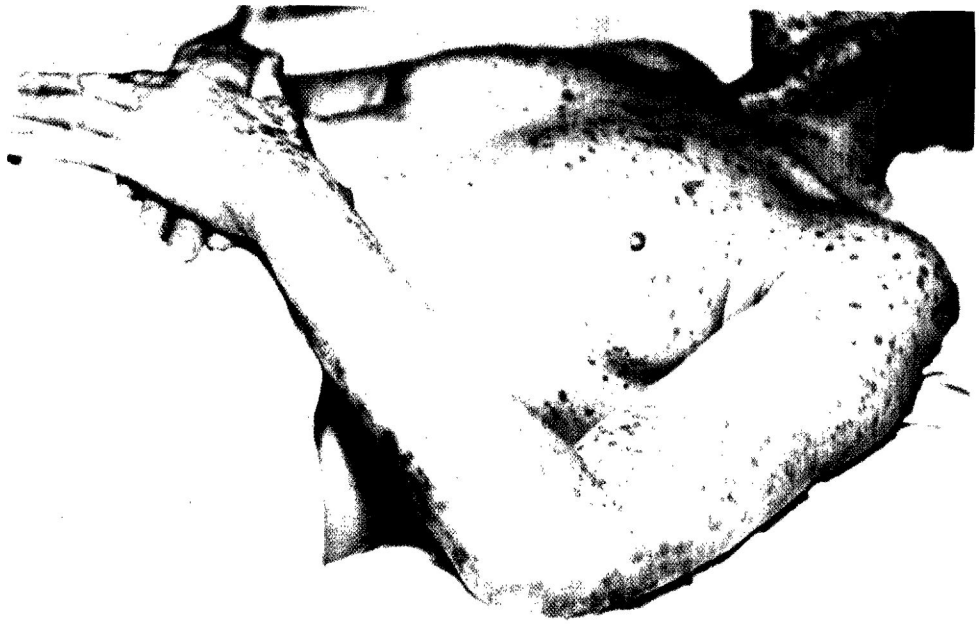


FIG. 27. Malignant semi-confluent.

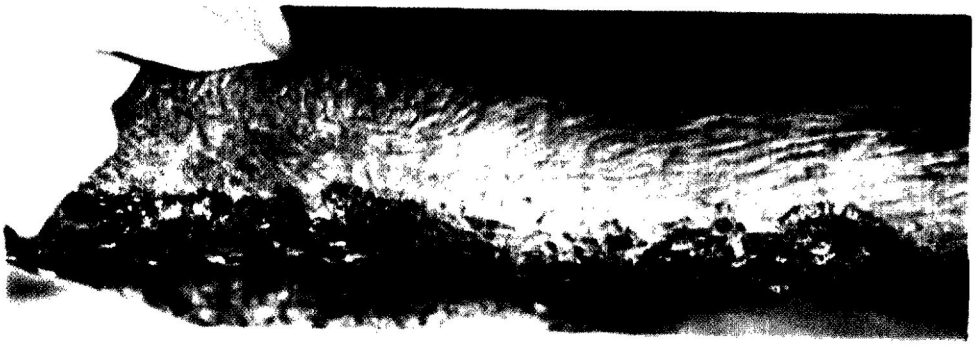


FIG. 28. Malignant confluent, exfoliation.

FIG. 29. Malignant confluent, exfoliation.

FIG. 30. Malignant confluent, tenth day, morbilliform and haemorrhagic elements. Great delay in evolution of vesicular elements.

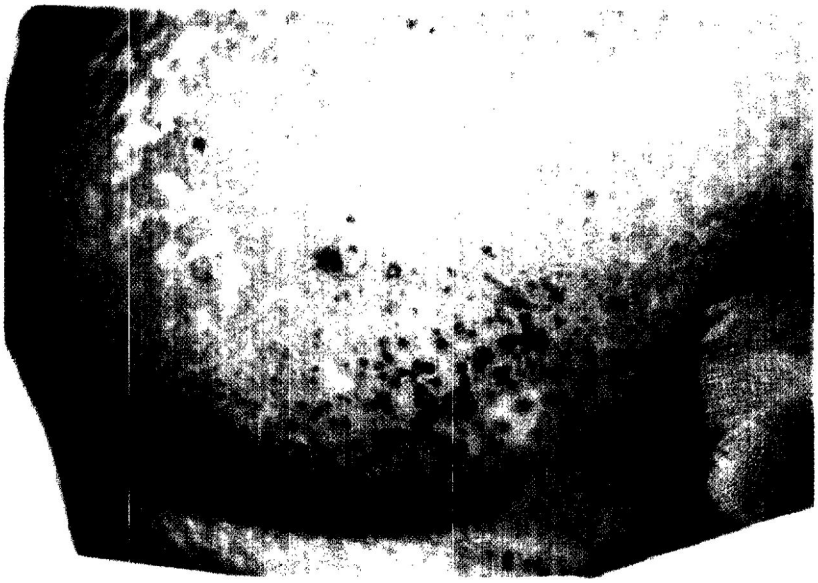


FIG. 31. Malignant eruption, fourteenth day, vesicles drying without pustulation, leaving copper-coloured superficial scars.

FIG. 32. Malignant. Flat soft vesicles, some with adherent roofs, simulating haemorrhage, ninth to tenth day.

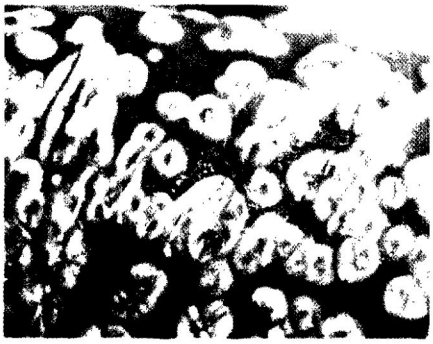


FIG. 33. Malignant, fluid absorption, "lobster" intervening skin, tenth to twelfth day.

FIG. 34. Malignant confluent, vesicles, bullae, tenth to twelfth day.

FIG. 35. Malignant, massive exfoliation, twelfth to thirteenth day.

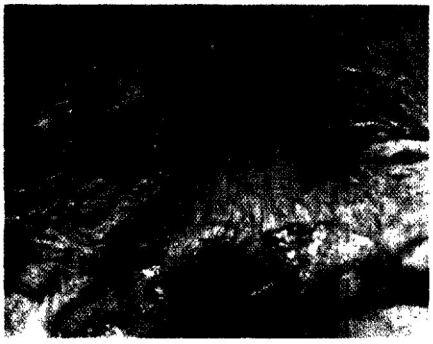


FIG. 36. Malignant, massive exfoliation, vesicle structure absent, twelfth to thirteenth day.

FIG. 37. Benign (in contrast). The birth of a macule on a typical site of solitary lesions.

Only by about the tenth day of the disease will many of the lesions on the trunk and arms have become vesicular, but they will be soft, flattened and velvety, hot and tender to the touch (Figs. 32 and 33). On confluent areas there may be large bullae containing clear fluid, but it is absorbed fairly rapidly leaving bluish-white dead sodden epithelium like a scald (Figs. 29 and 35). Haemorrhages may occur into the vesicles but more frequently in the normal skin between the lesions. Due to the general dehydration of the patient, fluid is absorbed from the lesions,

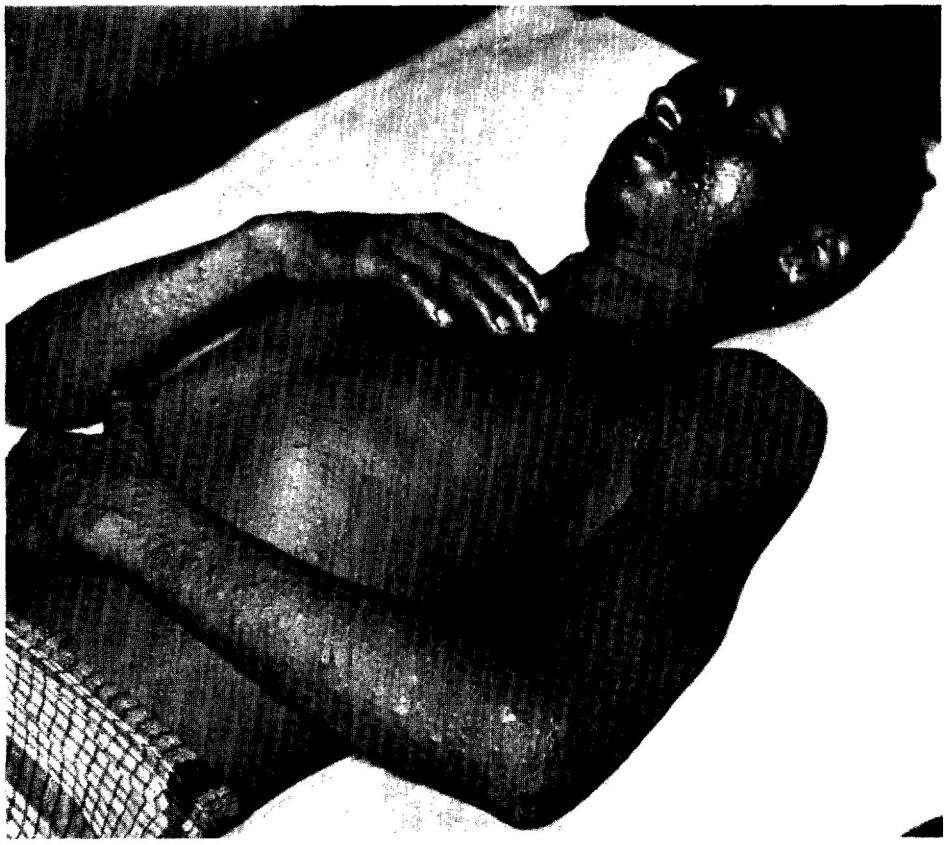


FIG. 38. Variola major, early malignant rash about the eighth day of disease.

particularly on the trunk and arms, and the flaccid roof of the vesicle adheres to the exposed dermis of the base producing a brown-coloured centre (Fig. 32) not unlike that produced by haemorrhage into a vesicle. Skin punctures made for therapy or for diagnosis continue to bleed for many hours. Uterine haemorrhages are common and may be severe; in pregnant women abortion or premature labour is almost certain to occur. Severe haemoptysis or haematemesis is common and the patient may die at this stage. The blood picture explains this part of the clinical condition. There is a complete absence of platelets, a lymphocytosis and a neutropenia. Although lesions along the palpebral margins are quite common, the rest of the

orbital skin remains surprisingly free from the rash (Fig. 40). Lesions may occur on the palpebral conjunctiva and give rise to a serous or sero-purulent conjunctivitis. Keratitis, referred to in Chapter 5, is common from about the eleventh day onwards and corneal ulceration with subsequent blindness may occur in the few cases of this type of smallpox who recover.

A peculiar sickly smell gradually develops—the foetor of smallpox. This cannot be adequately described although it is quite characteristic. It renders the discharge-sodden bed linen most offensive.

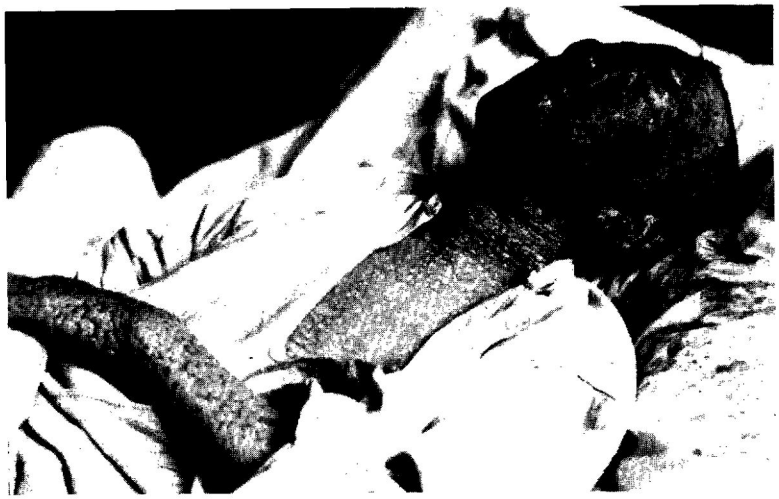


FIG. 39. Malignant confluent, so-called "black" smallpox. Death at about the twelfth day of the disease.

The relentless deterioration in the general condition continues. It is increasingly difficult to get the patient to drink, and even milky fluids seem to cause pain, due to the burning sensation in the throat on attempting to swallow. Great loss of weight, as much as 30–40 lb. (13–18 kg.) occurs during the twelve or thirteen days of illness. There is complete loss of muscle tone, and a cadaveric typhus-like appearance so transforms the patient that he would hardly be recognized by his relatives. By the thirteenth day of the disease a soft vesicular rash covers much of the body. The rash by now has a fairly definite centrifugal distribution, although it may cover such a large part of the body that recognition of this feature is difficult. It does, however, still tend to be less dense on parts of the body protected from pressure, such as the groin, the axilla and the orbit. By now many lesions have become confluent with large areas of epidermis peeling off like a scald (Figs. 28, 29, 35 and 36). Almost any part can be affected, but the back of the trunk and other areas where pressure occurs, such as the elbows, are likely to suffer most. Slight rubbing of the bedclothes or movement of the arm by the nurse or doctor may cause a large piece of dead epidermis to become detached. Although the patient may die from about the eighth day onwards, many live until the fourteenth or fifteenth day of the disease and die just as this stripping of the epithelium has become widespread. These areas are quite painful and contribute considerably to the frightful appearance and misery of the patient. The patient quietly expires, due to general toxaemia, or there may be some haemorrhagic catastrophe to

complete the picture. Although a fatty liver has frequently been recognized by pathologists at post-mortem and an enlarged liver may sometimes be palpable during life, this sign is not of any prognostic value compared with the appearance of the skin.

Even without any antibiotic treatment this type of rash never develops a "pustular" stage, although on some sites such as the pinna, palms of the hands, or soles of the feet the fluid looks cloudy, no real pus forms, even on the large desquamated areas. With so much of the dermis exposed, secondary infection can undoubtedly occur but there is little evidence of it. In the past when haemalytic streptococci were of considerable virulence and when smallpox patients

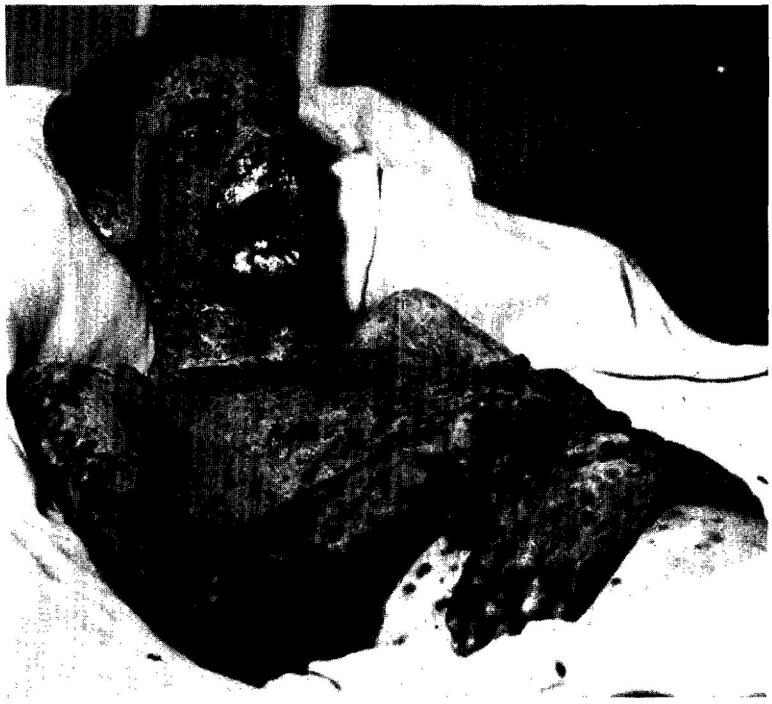


FIG. 40. Variola major, malignant confluent, eighteenth day, mortification. Patient has survived the stage of profound toxaemia between the tenth and fourteenth day, but tissue destruction is so severe that the body is unable to recover. Patient died two days later.

were nursed in large wards, terminal septicaemia must have been common and accounted for the isolation of streptococci from most cases *post mortem*. This gave rise to the frequently expressed view that haemolytic streptococcal infection plays a considerable part in causing death from smallpox. In experiments (1948) with penicillin in the treatment of this type of case, I demonstrated that the course and outcome is not due to superadded streptococcal infection, but to the essentially tissue destructive form of the disease. The few patients who recover from this form of attack are, however, in a most vulnerable state and susceptible to secondary infection with streptococci or staphylococci. The mortality would appear to be about 70–80

per cent, but the course of events today does not appear to be very different from the description of the illness and death of Queen Mary in 1694 (Chapter 10).

Occasionally, malignant confluent smallpox will proceed to the fourteenth and fifteenth day when, with the patient *in extremis*, a crisis will occur, the temperature will drop and the patient take a dramatic change for the better, a crisis similar to that observed in typhus. Presumably some immunological reaction takes place, but serological investigations have not yet been done. The patient commences to take fluids and the dehydration is reversed. The lesions, rather copper-coloured, desquamate, but this is fine and flaky and not a true "scab". The classical "punched-out" pitted scar does not occur even on the face, but instead there is a fine tissue-paper scar, continuous over quite large areas, rather like that after a scald.

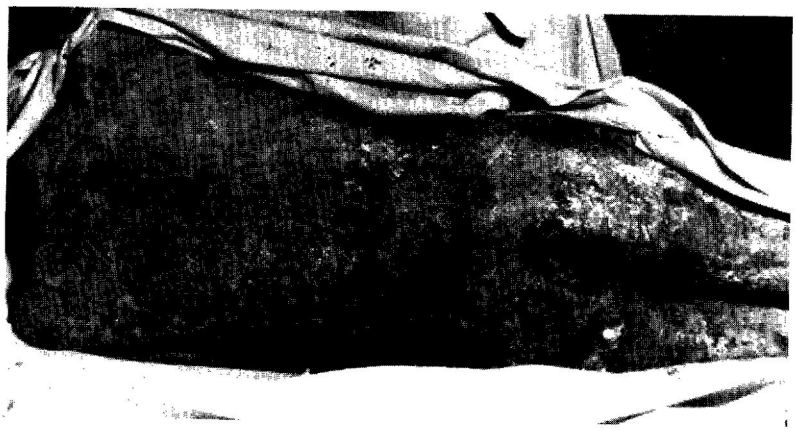


FIG. 41. Variola major, malignant confluent, eighteenth day, mortification.

Occasionally the patient does not die at about the twelfth to fifteenth day, but lingers on in a state so aptly described by the older writers as "mortification" (Figs. 40 and 41), and has the appearance of being mummified whilst still being alive; the skin of the face is fixed in a grotesque mask with the mouth permanently open, not unlike a ventriloquist's dummy. In spite of the really dreadful appearance the patient remains quite rational; hearing is acute, although vision may be impaired by keratitis. He remains alive for four or five days, but as in the severe burn, is just as unable to recover by reversing the destructive process in the skin, although by this time the smallpox virus has almost certainly ceased to have any effect on the tissues.

TYPE 3—MALIGNANT SEMI-CONFLUENT

A number of cases develop a type of smallpox malignant in character and otherwise identical with malignant confluent, except that the extent of the rash is less and satisfies our definition of semi-confluence. The prognosis is definitely more favourable, the mortality being of the order of 25 per cent rather than 70–80 per cent, and in this respect is in keeping with the view so often expressed that the extent of eruption determines mortality. It is important to differentiate this type from the malignant confluent, not only because of the patient's better chance of recovery,

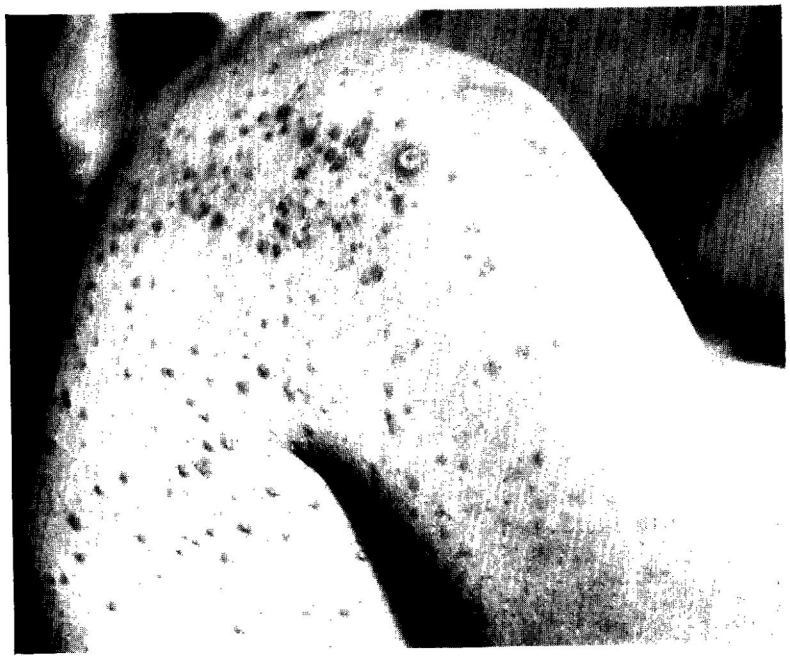


FIG. 42. Variola major, malignant semi-confluent, Type 3, rash at the sixth day. Note the lesions on the site of vaccination attempted late in the incubation period, (?) vaccinia, (?) variola.

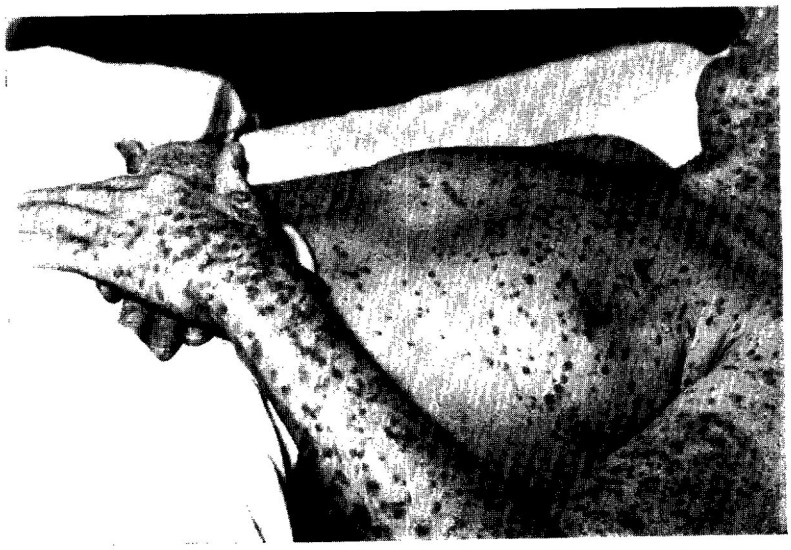


FIG. 43. Variola major, malignant semi-confluent, eighth day. Although the eruption is not extensive the patient died.

but because this is the type of case which, although severely ill and with quite severe haemorrhages from the mucous membranes or the skin, may recover, apparently as the result of therapy. The recovery, however, is unconnected with treatment, being in keeping with the normal prognosis of this type of case.

The attack commences in the same way as type 2 with a sudden moderate rise in temperature, 101–102° F. (38·3–38·9° C.). The initial phase is the same as in type 2, but the remission of temperature and symptoms at the commencement of the eruptive stage is more marked, and may make it more difficult to classify the case until about the sixth day of the disease.

The elements of the rash show variation in size and rate of development, and because it is less dense the resemblance to "cropping" so characteristic of chickenpox is more obvious. However, the evolution is slow and the rash hot and tender. A diffuse erythematous base of a lobster-red colour may not appear until the tenth or eleventh day of the disease (Fig. 33), and deterioration in the general condition is less rapid. The most characteristic feature is the delay in the appearance of vesiculation, particularly on the limbs, shown in Figs. 42 and 43. Because the lesions are less concentrated, haemorrhages in the intervening skin may be more obvious than in type 2. Due to the absence of confluence on the limbs and trunk large areas of desquamation are less likely to occur. If death does not supervene between the twelfth and fifteenth day from toxaemia or haemorrhage, the lesions dry up at the vesicular stage without the formation of pustules. The absorption of fluid from the vesicles, without pus formation, is very similar to that seen in some of the benign types which have been treated with antibiotics, but the lesions themselves are more superficial and when separation has occurred the exposed dermis is copper-coloured (Fig. 31). Scarring is of the thin tissue-paper kind without sharp-edged pocks. Although the patient may well escape with his life, there is a risk of keratitis and corneal ulceration from about the twelfth day onwards. Loss of weight is considerable and convalescence may be protracted.

TYPE 4—BENIGN CONFLUENT

After the usual incubation period of twelve days the onset is sudden, with headache, vomiting, backache and general malaise. The initial temperature is likely to be higher than in the malignant types, usually 103–104° F. (39·4–40·0° C.) and occasionally as high as 105° F. (40·6° C.), but at the end of forty-eight hours the patient feels a little better and the temperature has dropped appreciably. By the third day the patient feels much better, the temperature may be practically normal and he may leave his bed. He does not usually feel well enough to work, but may do so for personal or economic reasons. At the same time the macular rash appears; the first few spots are very delicate (Figs. 49, 66 and 74), occurring on the face, particularly the forehead, malar region, bridge of the nose, along the sterno-mastoid muscles and over the trachea. There may be one or two on the chest, forearms, and particularly on the back, but frequently none are present on the abdomen or the legs. These early lesions show a great tendency to occur on particular sites so brilliantly described by Ricketts, and present a feature of smallpox of much diagnostic value. Within twenty-four hours many more macules join these original "herald spots", the rash becoming more profuse on the face and on the scalp, particularly if the hair is absent or thin. Papules rapidly replace the macules, and, in particular, the herald spots will feel deep and shotty even at this stage. This is due to vacuolation of the epidermis and the formation of fluid under pressure in what appears to be a papule but what is really an early vesicle. Patients sometimes complain of a pricking sensation in the skin. The

FIG. 44. Benign (in contrast) Type 6, discrete, early vesiculation, sixth day.

FIG. 45. Malignant confluent Type 2, eighth day.

To face p. 22

forearms will show macules and early papules especially over the "sites of election", over the head of the radius and ulna, across the wrist joints, along the extensor tendons and the head of the metacarpals and phalanges (Figs. 37 and 83). At this stage the lesions on the palms of the hands may or may not feel "shotty". The legs and feet are likely to show only one or two herald spots, whilst the back will show lesions more advanced than most on the arms, but less advanced than those on the face. The order of development of the rash is face and scalp, back, arms, chest, hands, legs and feet. This orderly progression of lesions is very characteristic and occurs in the majority of benign cases of this type, although in some instances of benign confluent, semi-confluent and discrete the eruption is uniform over the whole body and passes through each stage simultaneously (Fig. 46).

The most important feature of this type of rash is its adherence to a "centrifugal" distribution (Ricketts, 1908). If one examines each anatomical part separately, such as the face, arm, leg or trunk, there is seen a gradual change in the density of the lesions, the maximum being at the

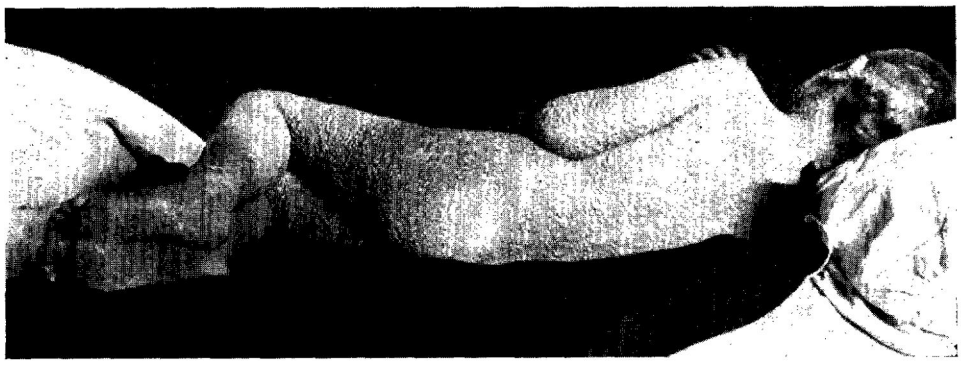


FIG. 46. Benign confluent, very uniform distribution. Even here some variation can be seen.

periphery, the minimum at the centre. For example, the upper face has more lesions than the lower face; the hand is more densely covered than the forearm; the forearm greater than the upper arm; the chest more than the abdomen. The back of the trunk is more affected than the front, and the extensor aspect of the arm more than the flexor.

The density will also be affected by other anatomical features. There will be increased density over bony prominences, points of pressure, or of mild irritation, and the converse; decreased density in areas subject to protection either because of anatomical configuration or from clothing. It should be noted, however, that even when the subject is habitually naked the rash is still centrifugal (Fig. 84). A knowledge of the occupation, peculiarities of clothing, social habits or early treatment of the patient will often explain an otherwise peculiar distribution. Unaccustomed activity on the feet will sometimes lead to a very early and extensive rash on this site. Tight corsets, or pressure on a fat abdomen whilst at work, may cause a dense rash on the abdomen compared with other parts. Severe trauma usually gives rise to no local increase in density, but trivial and invisible irritation is quite likely to. In Fig. 105 a group of lesions on the arm has occurred as a result of applying surgical spirit and rubbing the skin prior to venipuncture during the initial phase. It is important to recognize that smallpox lesions may appear