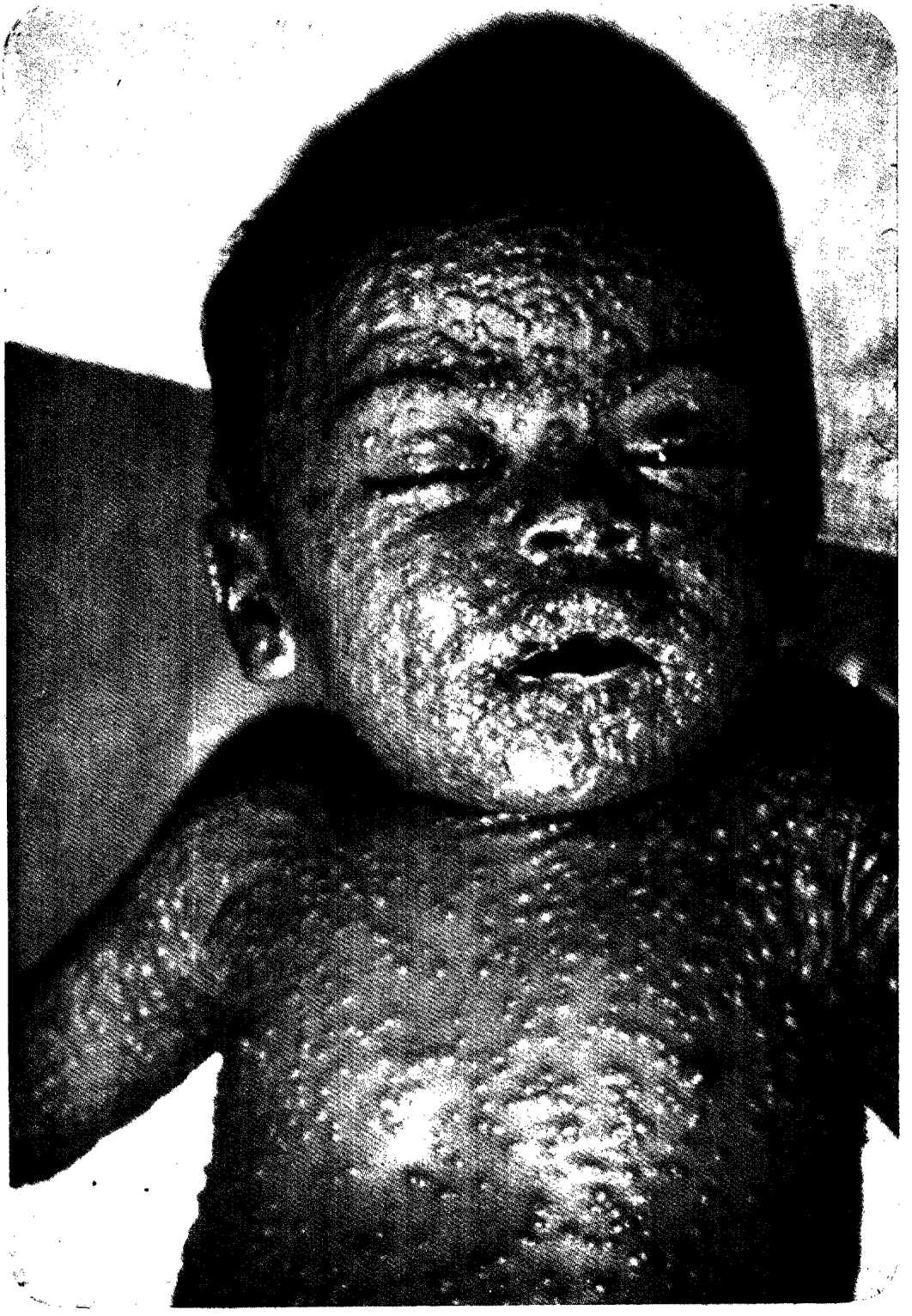
SMALLPOX

Smallpox in an unvaccinated child



SMALLPOX

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To My Mother

Mrs. A. RAJYALAKSHMI UMAMAHESWARA RAO

FOREWORD

Since independence, many of our Scientists have been engaging themselves in a continuous study in one or other facets of medical sciences, and are making worthwhile contributions in those fields. In view of this trend, the Indian Academy of Medical Sciences felt that it would be desirable to request such scientists to prepare monographs in the subjects of their choice. In making such a recommendation, the Academy had in view the possibility, that in the near future, higher education in the Universities, including Medical Sciences, could be imparted in regional languages in which case, the need for suitable text-books would be keenly felt. It is recognised that preparation of text-books is not an easy task. It is obvious that any text-books which are prepared in India must be based on Indian experience, with emphasis on Indian problems. It is in this context that scientific monographs can perform some useful functions. They will form the source material for both under-graduate and post-graduate teaching, and facilitate the preparation of text-books if and when such attempts are made. It is against this background that the value of the present monograph on "Smallpox" by Dr. Ramachandra Rao has to be judged.

Dr. Rao has had unique experience in dealing with the problem of smallpox over several years. As the head of the Infectious Diseases Hospital in Madras, he has had enviable opportunities for observing the behaviour of smallpox through many decades. Though Jennerian prophylaxis was introduced in India in 1802, and practised since then, in varying degrees of success in different parts of the country, the clinical picture of the disease had not altered materially. Of particular significance is the author's observation, that since the introduction of the smallpox eradication programme a few years ago, there is evidence, that the clinical picture of the disease is apparently changing and "now nearly ten percent of cases have become problem and borderline cases". The author had been responsible for the treatment of over 30,000 cases of smallpox admitted to his care in the hospital. The monograph is based, however, as the author has

pointed out, on a critical study of about 7,000 cases of smallpox admitted to the hospital since 1961.

As a result of this experience, the author has now evolved a clinical classification of cases which serves not only to differentiate one type of smallpox from another, but also provides criteria for forecasting of prognosis. It is important to note "that the pattern of transmission of the disease amongst the contacts in an infected household depends on the clinical type of the primary case."

Infectious Diseases Hospital in Madras has been, in recent years, one of the few centres in India which is engaged in the study of smallpox in all its essential aspects. The centre has a well equipped smallpox virus laboratory and it has attracted scientists from United States of America and United Kingdom. Apart from clinical studies, Virological and Epidemiological studies have been undertaken in this centre with interesting results. Notable amongst these, are the studies on blood coagulation factors in Haemorrhagic smallpox, disease enhancing property of cortisone in experimental variola in monkeys, and the study of viability of variola virus in infected room and infected linen. These studies are of great interest to epidemiologists, and immunologists and there is a great scope for further studies on these lines.

This is the first institution, where therapeutic and prophylactic trials with newer compounds have been undertaken by Dr. Rao and his colleagues in smallpox. Sound diagnostic procedures have been worked out and Dr. Rao's observations and suggestions on treatment of cases of smallpox would prove of particular interest to clinicians.

Madras city has been a highly endemic area for smallpox, reporting thousands of cases annually. Smallpox Eradication programme was introduced in the year 1963 under the direction of Dr. Rao. During the last two years, the incidence of the disease has come down so dramatically as to suggest that the disease is almost controlled. Section III of this monograph deals with this programme as executed in Madras city. The experiences outlined in this section should prove very useful to those engaged in similar work elsewhere.

I am confident, that the monograph would be found useful, not only by clinicians, epidemiologists and public health workers in India, but also by those working in other lands, where there is always the threat of the introduction of the disease by air, sea and land routes.

C. G. PANDIT
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Honorary Consultant, Post-Graduate Institute of
Medical Education and Research, Chandigarh.

PREFACE

An esteemed medical friend of mine asked me, when I showed him the typed script of this book, "For whom is this intended? Is this a text book on smallpox for under-graduates and post-graduates in Medicine? Or is it intended for Epidemiologists and Medical Officers of Health?" My answer was simple. It is intended for "any and every one, who is interested in smallpox and who is willing to read it". The value of a book does not depend only on the intentions of the author but more on the interest of the readers.

This is neither a text book on smallpox nor a treatise on the disease. It is just a monograph on smallpox, though it may not deal with every aspect of the disease with an exhaustive bibliography. It is just a book on "smallpox as I have seen it", narrating mostly my experiences with the disease. I do not claim anything more than that.

I have been in close association with this disease for nearly 30 years and during this period, I have seen, diagnosed and treated about 30,000 cases of smallpox. For 16 out of these 30 years, I have been attached to Infectious Diseases Hospital in various capacities, and the remaining 14 years I have been a Medical Officer of Health in charge of control of the disease, as well.

In spite of the vast clinical experience I had, the idea of writing a book on smallpox never struck me. This idea has been put into my mind for the first time, by my learned and revered friend Dr. C. G. Pandit, Emeritus Scientist and former Director, Indian Council of Medical Research and Dr. J. B. Srivatsav, the present Director General of Health Services, Government of India, on one evening in November 1965, at an informal dinner. They felt, that there is none now, with so much of clinical experience on smallpox as I have, and that I should write a book on the disease "AS I HAVE SEEN IT". The result of that post-dinner chat is this book.

As I said, this is not an exhaustive treatise on the disease, and was never intended to be. The whole book deals with the disease as is seen in India and especially relates to my experiences with the

disease in Madras city. Wherever references were made of the work of other authors, as far as possible, they were acknowledged. If any omissions have been made by oversight, I may be excused because such omissions, if any, were unintentional.

Mainly, the subject was dealt with, under three sections. Section one deals with the 'clinical aspects' of the disease. While discussing the various clinical classifications, stress has been laid on the particular classification, which has been in use in Infectious Diseases Hospital, Madras for several years. I am sure, the readers would appreciate the significance and the usefulness of this classification. The clinical course of each variety was described in great detail, profusely illustrated with photographs, depicting the various clinical varieties and their characteristics. All these photographs have been taken of the patients of the Madras Hospital, either by me or my friends from abroad, who have come here for training, and who have kindly sent me copies of these photographs, especially the coloured plates. Under chapters on 'Complications' and 'Differential Diagnosis', mostly such of those conditions that we have come across in our experience only have been described. Besides the chapter on 'Treatment', a special chapter on 'Chemotherapy and Chemoprophylaxis' has been included, because, ours has been the first institution that has tried for the first time antiviral drugs in smallpox.

Section two deals with Epidemiological and Immunological aspects of the disease. This section should be of great interest to Epidemiologists and Medical Officers of Health because it deals with not only the various aspects of the transmission of the disease but also the results of some of the special studies made by us on the various factors influencing pattern of transmission in infected families and community. There is a special chapter on 'Subclinical infection' in smallpox which I expect, should be thought-provoking since it deals with some new ideas. There is another chapter 'Pregnancy and smallpox' which should be of great interest to Epidemiologists, Immunologists as well as Obstetricians. This chapter is based on my experience with smallpox in nearly 400 pregnant women. In the chapter on 'Immunity' while briefly mentioning the various theories about the possible mechanism of immunity, the different types of immunity have been discussed with emphasis on vaccination and immunity against smallpox.

Section three deals with control of smallpox with special reference to smallpox eradication programme in urban areas. Madras city, a hyper-endemic area for smallpox, has been made completely smallpox-free by a successful, well organised eradication programme. The various aspects, both technical as well as operational, of the strategy of smallpox eradication programme have been discussed in great detail

in this section and I am sure, this would be of interest to smallpox eradication programme officers in other urban areas. In the end, a note of warning has been sounded, that we may have to be on alert still for some more years, even after the so called "elimination of clinical infection of smallpox from the world". Emphasis also has been laid on the need for further research on various aspects of the disease about which we know very little, if we want to achieve our objective of global eradication of smallpox.

Since this book deals with different aspects of the disease, though not in an exhaustive way, based on the vast clinical and public health experience, I hope it would be useful to all categories of medical and public health workers, besides under-graduates and post-graduates in Medicine. The book is mainly written to share my experiences with my medical colleagues and not with an intention of teaching anyone. With all humility, I place this book in the hands of the readers, with a request to offer their frank and critical opinion. It is for the readers to express whether they have learnt anything from this book after reading. Even if a few are benefited to the slightest extent, I feel my aim in writing this book will have been achieved.

April 1972 A. R. RAO

ACKNOWLEDGEMENTS

To the two great scientists Dr. C. G. Pandit, Emeritus Scientist, and former Director, Indian Council of Medical Research and Dr. J. B. Srivatsav, Director General of Health Services, Government of India, I am extremely grateful for the inspiration, encouragement and guidance, they have given me, in writing this monograph and I sincerely pay my humble respects to them.

I take this opportunity to express my deep sense of gratitude to Professor C. Henry Kempe, Head of the Department of Paediatrics, University of Colorado Medical Centre, Denver, Colorado, USA., and Professor A. W. Downie, formerly Head of the Department of Bacteriology, University of Liverpool, Liverpool, United Kingdom, but for whose initiative and drive, I would not have ventured to take up the various studies on smallpox.

The interest I developed in this disease, has been solely due to my long service for nearly 30 years in the Corporation of Madras in various capacities, as Resident Medical Officer, and Medical Superintendent, Infectious Diseases Hospital and Assistant Medical Officer of Health and Chief Medical Officer of Health for the city of Madras. I owe, therefore, all my knowledge about the disease to this institution I am serving, and I am very much indebted to the successive Health Officers, and Commissioners of the Corporation of Madras under whom I had the privilege to work. Special thanks are due to Mr. J. A. Ambasankar, IAS, former Commissioner, Corporation of Madras and the present Secretary, Health and Family Planning, Government of Tamilnadu, but for whose encouragement and great interest that has been shown in my venture, this monograph would not have been completed in such a short time. I owe a special debt of gratitude to Mr. K. J. M. Shetty, IAS, Mr. Ahluwalia, IAS, and Mr. F. J. Vaz, IAS, the former Commissioners and Mr. J. V. S. Rao, B.A., B.L., the present Commissioner but for whose dynamic enthusiasm and very keen interest in research, I would not have been able to continue my work on various aspects of smallpox with the same vigour, despite the fact that I had to work against several odds.

I acknowledge with thanks the kind interest, successive Worshipful

Mayors and Honourable members of the city Corporation have taken in me and my work and for having permitted me to publish this monograph.

I am also greatly indebted to Dr. D. A. Henderson, Chief, Smallpox Eradication, WHO, Headquarters, Geneva, who has been keenly following my studies on smallpox, who has been instrumental for my getting the financial aid from WHO for my research projects and who has kindly gone through the whole book in its manuscript stage and given me very valuable suggestions in preparing its final draft.

I have been assisted by my able assistants Dr. I. Prahlad, Superintendent, Dr. A. Lakshmi, Resident Medical Officer, and all other Medical and Nursing Staff of Infectious Diseases Hospital in maintaining the clinical records of smallpox cases, which have helped me immensely in writing chapters on clinical smallpox and I thank them all for their assistance.

But for the liberal financial assistance that has been granted by Indian Council of Medical Research and World Health Organization, I could not have conducted any investigations on the various aspects of smallpox and I take this opportunity to thank successive Directors General of Indian Council of Medical Research, and Director General, World Health Organization, for having given me the required assistance to conduct the studies.

The Indian Council of Medical Research Unit consisting of Mrs. S. Sukumar, Research Officer, and her assistants Miss S. Kamalakshi, Mr. T. V. Paramasivam, Mrs. Shantha Ramakrishan, Mr. A. R. Parasuraman, who are the main participants in all the research projects undertaken by me, have devoted all their time and energy in conducting the investigations and they deserve to be congratulated. The results of various studies of mine mentioned in this monograph are only the outcome of their interest in the work and to them I am greatly indebted.

In a book like this, photographs play a great role. Though most of them were taken by me, yet a few, especially the coloured ones, were taken by my friends from abroad who came to my institution for training in diagnosis and treatment of smallpox. I am extremely thankful to them for having kindly sent me those photographs and permitted me to include them in the monograph. I thank Messrs. Pandyan Studios, Madras who rendered me a very great assistance in taking all these photographs.

Writing a monograph of this size is not an easy matter. Before it came to the final stage, it has gone through several drafts. For patiently typing every draft, and for spending days and nights on correcting these drafts, I am greatly indebted to my friend, Mr. Kotees-

waran and my wife Mrs. A. Lalitha Rao, who have been great sources of encouragement throughout the preparation of this monograph.

I will be failing in my duty if I do not thank all my friends and colleagues who have helped me in several ways in bringing out this book.

Finally I thank the publishers Messrs Kothari Book Depot, Bombay who have kindly accepted to undertake the publication of this monograph and brought it out so nicely.

April 1972 A. R. Rao

COLOURED PLATES

Frontispiece — Smallpox in an Unvaccinated Child

1. Early haemorrhagic Type of Smallpox in a pregnant woman — 4th Day of disease
2. Flat Variety of Smallpox in an Unvaccinated Child — 8th Day of disease
3. Ashen grey coloration of lesions before death in a Flat variety of Smallpox
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CLINICAL

1

Introduction

It has long been recognised that smallpox, one of the most ancient communicable diseases, is caused by a virus. Though the disease may present in many forms in different individuals, there are only two recognised variants of variola virus, viz. 'variola major' and 'variola minor'. Recently a third intermediate variant, called 'variola tanzania' or 'variola intermedius' has been isolated by workers in Liverpool. These variants appear to be antigenically identical in most respects. Each confers immunity against the other. There is no evidence that one may be transformed into another by natural or artificial means.

In Madras, and probably in India as a whole, only variola major is prevalent. Although few attempts have been made to isolate other variants, case fatality rates and epidemiological studies of smallpox outbreaks strongly suggest, that other forms are either rare or even absent. In this monograph therefore, wherever the word 'smallpox' and 'variola' are used, they mean variola major.

Though the disease has been prevalent in India for centuries, there has been no remarkable change in its clinical picture. This may perhaps be due to the fact that there is an annual addition to the population of about 4 percent of new susceptibles by way of births, and a waning of immunity in the vaccinated for want of an effective continuing vaccination programme. With the population, especially in the cities, growing rapidly every year, and with cities attracting large number of people from rural areas, the herd immunity of the population in the cities is continuously diluted to a very great extent, with the result that the disease is not only persisting indefinitely in an endemic form, but is also maintaining its classical pattern to a very great extent.

However, with the implementation of the national smallpox eradication programme, which has the aim of protecting every child as early after birth as possible, and vaccinating all others atleast once in 3 to 4 years, the spectrum of cases observed may be quite different. Not only should the number of cases decline, but the clinical

picture in general may show a change from the classical to modified, and typical to atypical forms. Already, we have been experiencing such a change. Ten years ago, there was usually no difficulty in diagnosing a case of smallpox. Now, nearly ten percent of the cases have become 'problem and borderline' cases which create doubts in the minds of the physicians, because of variations in the classical picture. In all such cases, one would desire confirmation from a laboratory. The need for special attention on the part of physicians is all the greater now, since one cannot afford to miss or misdiagnose even a single case of smallpox until the disease is completely eradicated once and for all from the whole world.

In this section, it is proposed to discuss the various clinical classifications of the disease, the characteristics of different types and their course, and to describe the common complications that are usually encountered. In addition, diagnosis, differential diagnosis and treatment will be discussed. Various studies that have been conducted with several chemotherapeutic and chemoprophylactic drugs will be reviewed. The clinical features of smallpox, presented in this section, are mainly based upon my personal experience in caring for about 30,000 cases of smallpox during the last 29 years. However, the actual data presented were taken from a special study of a series of about 7,000 cases admitted to the Infectious Diseases Hospital, Madras, since July 1961.

2

Clinical Classification

INTRODUCTION

The clinical course of the disease varies from case to case depending upon the clinical type of the disease and hence it is proposed to discuss the classification of the clinical types first, before describing the course of the disease in each of the individual types.

Several authors have described smallpox and its clinical features in various books, illustrated in such a way that a physician, with such pictures in his mind, should be confident of diagnosing a case. Although he may be able to do so in majority of instances, diagnosis is often not so easy as one would imagine. Smallpox can present itself in many varying clinical patterns, especially in endemic areas. Unless one is conversant with the different clinical forms, there is a likelihood of missing or misdiagnosing some of the cases.

Therefore, apart from the need for descriptive purposes, even for correct diagnosis, a good descriptive clinical classification is essential. For assessing the prognosis of a case, of course, such a classification is always necessary. Recent studies at Madras (Rao et al, 1968) also suggested the possibility that the pattern of transmission of disease among familial contacts of a smallpox case depends partly upon the clinical type of the primary case (source). The importance therefore of a proper clinical classification cannot be over-emphasised.

THE EXISTING CLASSIFICATIONS

Several text books even now follow the old classification of smallpox cases (Curshmann, 1875) dividing them into 'haemorrhagic' and 'non-haemorrhagic' forms with a subdivision of the former into 'purpura variolosa' and 'variola pustulosa haemorrhagica' types, and the latter into 'confluent', 'semiconfluent', 'discrete' and 'modified' types. This classification was based principally on the density of the rash. Extensive clinical experience has shown that this classification provides little help either for establishing a diagnosis or for assessing prognosis.

Dixon (1962) avoiding the old terminology, classified smallpox

into nine clinical types. He purposely avoided the use of the word 'haemorrhagic' but termed that clinical entity 'fulminating' instead. This, in my opinion, does not describe that entity satisfactorily, because not all the 'fulminating' cases are 'haemorrhagic'. Further, the 'haemorrhagic' are a separate entity and that descriptive word has definite significance.

He also recognised, like other clinicians, that the density of rash in the non-haemorrhagic types is not in itself of great prognostic significance. Rightly, he introduced into his classification, four types depending upon the nature and evolution of lesions viz. (types 2 to 5) the 'malignant confluent', 'malignant semiconfluent', the 'benign confluent' and the 'benign semiconfluent'. Unfortunately, however, he listed three additional types (6 to 8) based solely on the actual number of lesions on the skin and called them by rather ambiguous terms viz. 'discrete', 'mild' and 'abortive', which are subject to considerable subjective interpretation. Classification based upon the count of the actual number of lesions is impracticable and further it is most unreliable in assessing the prognosis.

AUTHOR'S CLASSIFICATION

So far, no satisfactory clinical classification which is simple and workable has been proposed. From the author's experience in caring for thousands of cases of smallpox, two basic conclusions have been reached:

1. that 'haemorrhagic' smallpox is an entity, clinically and epidemiologically different from 'non-haemorrhagic' smallpox, and that the occurrence of haemorrhages into the skin and/or mucous membranes have definite prognostic importance;
2. that the number of lesions or the density of rash in the 'non-haemorrhagic' types are of secondary importance in assessing the prognosis of a case, and it is the nature and the evolution of lesions which determine the prognosis, not the number alone.

With these two conclusions in mind, a classification scheme (*Fig.* 2/1) was developed by the author and has been in use in Madras since 1961. It cannot be said that this classification is perfect, but it appears to be the most simple and workable proposed to date.

Under this classification, there are four clinical varieties based on the nature and evolution of rash. They are the *Haemorrhagic* (Variety 1), the *Flat* (Variety 2), the *Ordinary* (Variety 3) and the *Modified* (Variety 4). These four varieties are further subdivided into 12 types for purposes of detailed clinical description. The Haemorrhagic variety is divided into *Early Haemorrhagic* (Type 1) and *Late Haemorrhagic* (Type 2) depending upon the timing of occurrence of haemor-

rhages into the mucous membranes and skin in relation to the rash. The Flat variety is subdivided into three types viz. *Flat Confluent* (Type 3), *Flat Semiconfluent* (Type 4) and *Flat Discrete* (Type 5) depending upon the density of rash. Similarly the Ordinary variety is further subdivided, depending upon the density of rash, into *Ordinary Confluent* (Tpye 6), *Ordinary Semiconfluent* (Type 7) and *Ordinary Discrete* (Type 8). Though the number of lesions are quite few in the majority of cases of the Modified variety, we have come across cases with very dense rash. Hence this variety is also subdivided into *Modified Confluent* (Type 9), *Modified Semiconfluent* (Type 10) and *Modified Discrete* (Type 11). In addition, one more type, though rare, is included under the Modified variety, and that is *Variola Sine Eruptione* (Type 12) which is a modified form of smallpox where smallpox can occur without rash. These 4 varieties and 12 types are arranged in the descending order of their severity. *Table* 2.1 presents these clinical varieties and types and their frequency distribution in vaccinated as well as unvaccinated cases, and also gives the case fatality rates in each. From this table, it is evident, that both the nature and evolution of the lesions and the density of rash have prognostic significance. Differences, however, are most marked according to the first variable e.g., the fatality rates are higher amongst the Flat discrete cases than amongst the Ordinary confluent cases and, similarly Ordinary discrete cases are more frequently fatal than Modified confluent cases. Greater emphasis is therefore laid on the nature and evolution of lesions than on their density.

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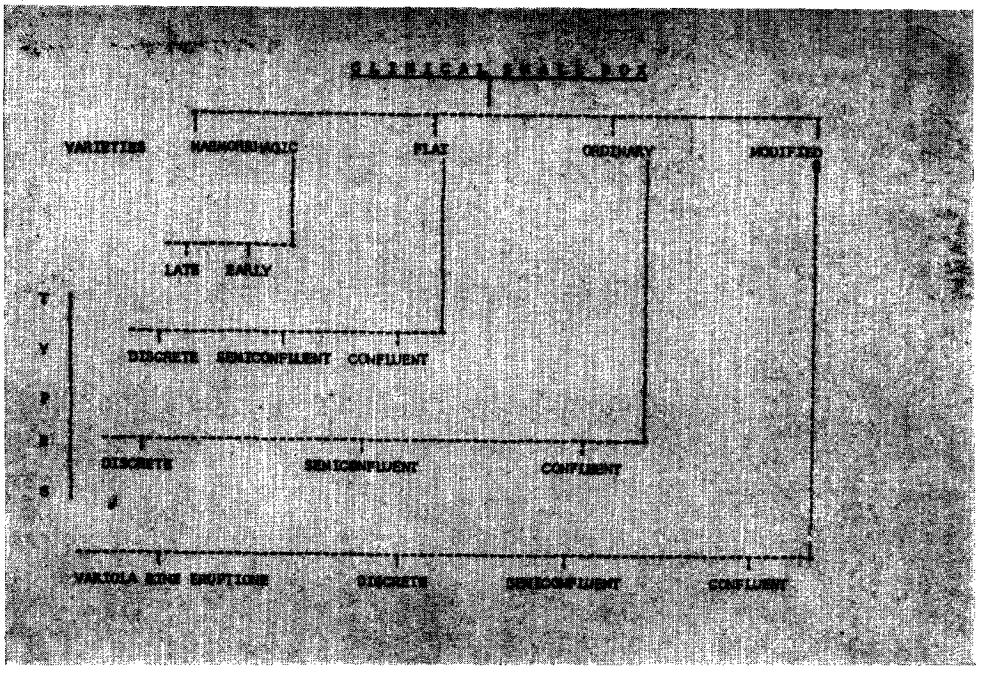
Table 2.1

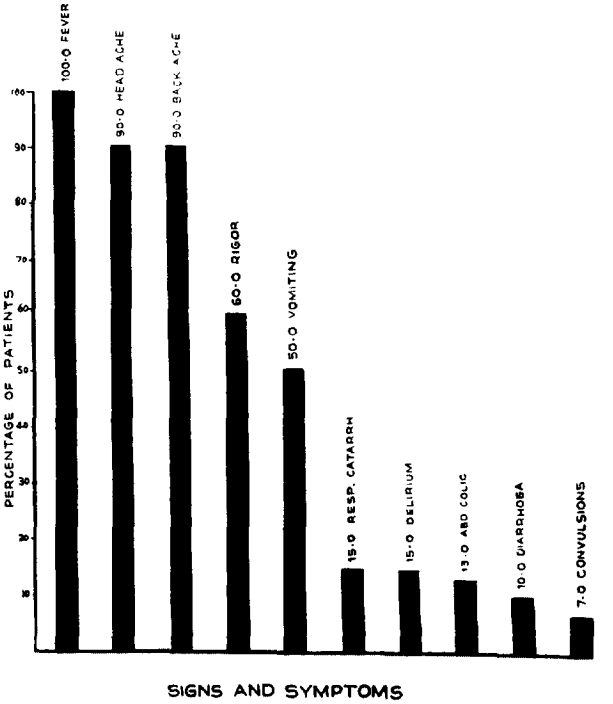
Distribution of Principal Clinical Varieties and Types of Smallpox with reference to the Vaccinal Status

Clinical Varieties	Vaccinated			Un-vaccinated			Clinical Types*	Vaccinated		Un-vaccinated	
	No. of Cases	Frequency*	CFR	No. of Cases	Frequency*	CFR		Frequency*	CFR	Frequency*	CFR
Haemor-rhagic	115	3.4	93.9	85	2.4	96.4	Early Haemorrhagic	1.4	100.0	0.7	100.0
							Late Haemorrhagic	2.0	89.8	1.7	96.8
Flat	45	1.3	66.7	236	6.7	96.5	Flat Confluent	0.6	85.7	4.2	100.0
							Flat Semiconfluent	0.3	60.0	1.2	95.3
							Flat Discrete	0.4	42.1	1.3	95.6
Ordinary	2377	70.0	3.2	3147	88.8	30.2	Ordinary Confluent	4.6	26.3	22.8	62.0
							Ordinary Semiconfluent	7.0	8.4	23.9	37.0
							Ordinary Discrete	58.4	0.7	42.1	9.3
Modified	861	25.3	Nil	76	2.1	Nil	Modified Confluent	0.1	Nil	0.00	Nil
							Modified Semiconfluent	0.5	Nil	0.05	Nil
							Modified Discrete	24.3	Nil	2.00	Nil
							Variola Sine Eruptione	0.4	Nil	0.05	Nil
Total	3398	100.0		3544	100.0			100.0		100.0	

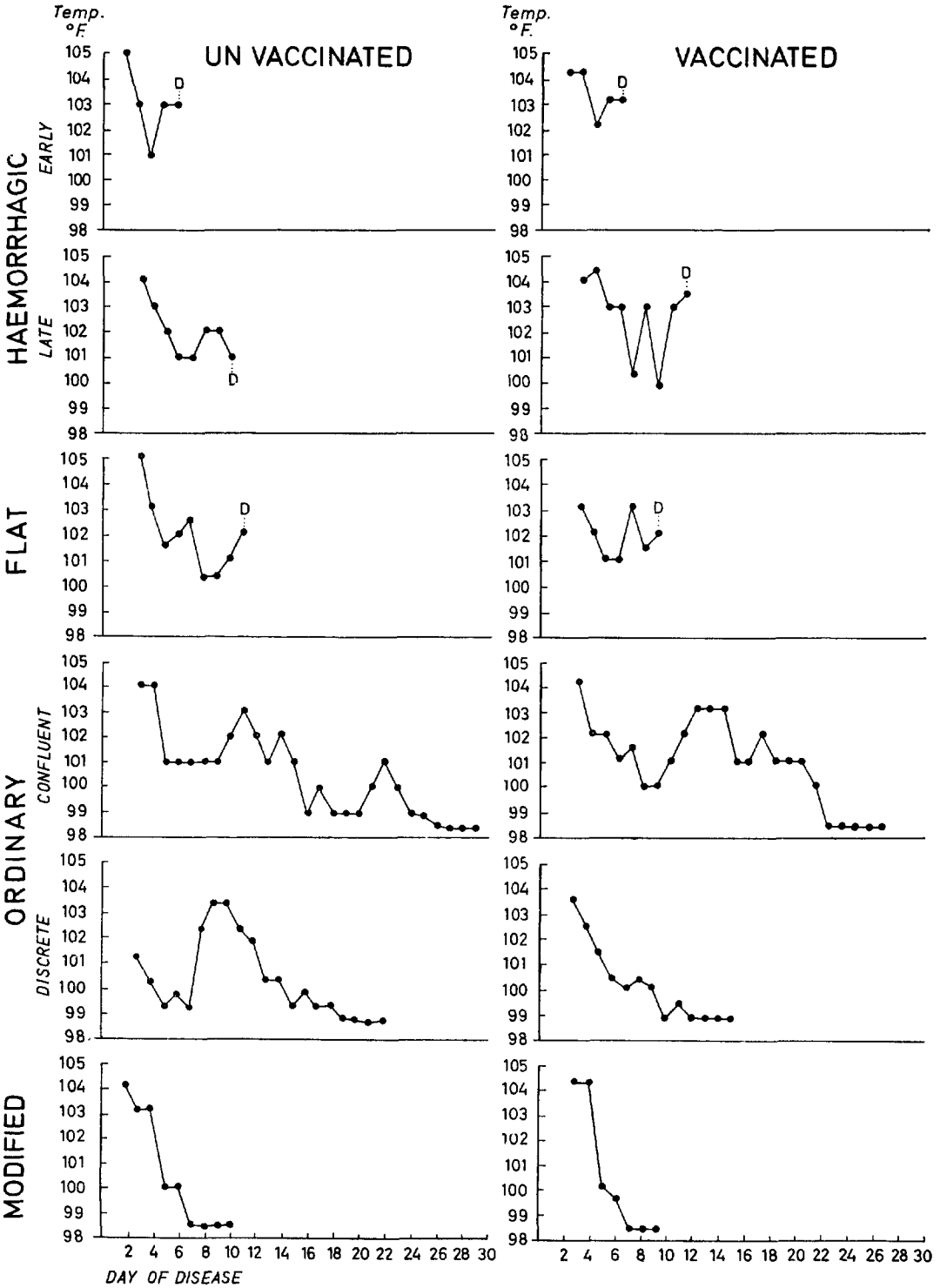
*Represents percentage of Total cases in that group
CFR = Case Fatality Rate



2/1. The Classification Scheme of Clinical Smallpox (Rao's)



3/1. Frequency of occurrence of signs and symptoms in the Pre-eruptive stage of Smallpox



3/2. Typical Temperature charts in different types of Smallpox cases

D = Dead

3

Clinical Course

INTRODUCTION

Each stage in the evolution of the disease in a case of smallpox has its own characteristics and individual variations. For proper diagnosis, as well as for the establishment of the prognosis of a case, careful consideration of the course of the disease in each stage and in each clinical type is essential. There is no definite demarcation between one stage and another. They may overlap, but for the sake of covenience, for better understanding of the disease process, and for descriptive purposes, the course of the disease can be described under three stages, viz. the incubation stage, the pre-eruptpive stage and the eruptive stage.

INCUBATION STAGE

It is conventional to consider that a person suffers from a disease only when he presents signs and symptoms of the disease. Signs and symptoms, after all, are only the visible evidence of reaction of two forces viz., the 'invader' and the 'host'. The distinction between the 'infected' and the 'diseased' is very subtle, and it depends mainly on our ability to diagnose the disease in the absence of signs and symptoms. But from the public health point of view, this may make quite a difference for obvious reasons. Whatever be the difficulties a clinician has in diagnosing a case, if a person, who is 'infected' but not 'diseased' according to the clinician, starts infecting others, he is a public health menace; and such a person is far more important to a Medical officer of Health and an Epidemiologist than even a frank case. One can never say that a person is not infected simply because he does not present signs and symptoms of the disease. Unless such exposed contacts are under active surveillance, they may develop the disease without the knowledge of the health authorities and cause an epidemic. Further, there is always a possibility that in some instances, signs of interaction between the 'host' and the 'parasite' may not be present in such a perceptible manner, as to enable one to diagnose the disease easily. Such inapparent,

subclinical and very mild cases may be responsible for the maintenance of continuity in the chain of infection in a community, and for keeping the disease persisting in an endemic form. It is also possible that such cases may raise the basic immunity to the disease in the population, by providing minute doses of infection which may stimulate an antibody response in the exposed. Hence an Epidemiologist and a Medical Officer of Health always have to consider a person who is 'exposed to infection' as a potential patient, till he is proved otherwise. For this purpose only, the stage of incubation is considered to be the first stage in the course of the disease, as this will help in proper understanding of the whole disease process.

The incubation period is the time interval between the day of infection and the day of presentation of the first clinical manifestation. To determine this precisely, two items of information are required, the day on which the virus entered the host and the day on which the first clinical manifestations were observed. To determine both exactly is difficult.

Although a case of smallpox may be infectious from the first day of the disease until the last scab separates, the susceptible contacts may get infected either on the first day of exposure, or after a prolonged period of contact, or never at all. It is therefore often difficult, if not impossible, to fix the actual day of entry of the virus into the host.

Similarly, there is often difficulty in fixing with certainty the day of presentation of the first clinical manifestation. Although several authors discuss the onset of the disease in terms of the onset of the rash, actually fever which is associated with viraemia, normally precedes the rash and thus technically, is the first clinical manifestation. Although both are subject to errors of memory, patients often do not notice the lesions on the skin for a time, particularly when they are very few in number. Even if noticed in the early stages, they may be mistaken for some other condition until the rash progresses. Additionally, people sometimes give a false history for fear, that legal action may be taken against them for not reporting to the Health authorities after noticing the rash.

In my experience, the day of onset of fever has been a more reliable finding. Patients tend to be more definite about its onset particularly since the fever of smallpox is invariably associated with some constitutional signs and symptoms, such as headache and backache. In the few instances, where fever from some other cause precedes the fever of smallpox, the date of onset of fever may be inaccurate. This often happens in patients who have had a successful primary vaccination after exposure. Fever following successful primary vaccina-

tion starts on or about the 6th day and thus the fever of smallpox may follow immediately the vaccination fever.

It is therefore difficult to arrive at the exact incubation period. However, since the day of onset of fever in the infecting case (source) and the day of onset of fever in the infected contact (host) can usually be ascertained almost correctly, a 'fever to fever' interval or 'exposure to fever' interval can sometimes be described. This interval usually ranges from 12-21 days, but in a few cases it may be prolonged even up to 24 days. In a study of the pattern of intra-familial transmission of smallpox made by the author of 1249 familial contacts exposed to 254 primary cases, (Rao et al, 1968b) 50 first generation (secondary) cases occurred. In these, the mean 'fever to fever' interval was 16.0 days. The range of 12-21 days included 82 percent of the cases. In 2 cases it was 24 days.

In determining the exact incubation period, only those patients who have been in contact with the infecting source for a short and limited period of time (one day or less) on one occasion, can be considered. From records of single and brief exposures in various epidemics, it has been determined that the incubation period of smallpox is fairly constant, ranging from 11-14 days, although in a few well documented cases it has been noted to be as short as 8-9 days and occasionally as long as 16-17 days (WHO, 1968).

Recently we came across a case of smallpox with history of a single brief exposure. A person 'R' was travelling in a train on 28 January, 1969 when a case of smallpox got into the same compartment at about 8 a.m. and sat by his side. He travelled with the patient for nearly 16 hours, in close contact, when he left the compartment and got into another, because of fear, that he might contract the disease. He visited several places in Northern India and while returning to Madras he developed fever on 8 February, 1969. He came to Madras the next day and developed a rash on 11 February and was admitted to the Infectious Diseases Hospital on 13 February. In this case the 'exposure to fever interval' was exactly 12 days. Very rarely do we get cases with such a specific history of single and brief exposure.

PRE-ERUPTIVE STAGE

Smallpox cases, without a history of fever and associated constitutional symptoms preceding the rash are very rare. Although this stage is often called 'prodromal', the term is somewhat misleading since a 'prodrome' is defined as 'an early premonitary symptom which is not infrequently of a different nature from symptoms of the true onset of the disease (GK—Prodromos—running

before)'. Since the clinical signs and symptoms of this stage are characteristic of the actual disease process itself, another term is to be preferred. Dixon (1962) called it the *'INITIAL'* stage, but this does not convey the importance and significance of this stage. The term 'pre-eruptive' appears to be more suitable, despite the fact that in rare instances certain eruptive fevers other than smallpox may give a similar history of signs and symptoms during this stage and, furthermore, in a particular type of smallpox 'variola sine eruptione', this stage is not followed by a rash. By and large, however, the term 'pre-eruptive' appears most suitable.

The duration of this stage is variable. Partly, it depends upon the ability of the clinician to detect the first lesion. After the viraemia occurs, virus is rapidly deposited in the skin and mucous membranes and, after 24 hours, the virus is rarely detectable in the blood, except in a few fatal cases. The development of the virus in the skin, to the point where lesions become visible, undoubtedly takes some time perhaps accounting for the fact that the rash is seen only 48-72 hours after the onset of fever. It is not uncommon to find this stage prolonged in haemorrhagic types to 4 to 6 days. In fact, sometimes, the rash is not visible before death. In these cases, the petechial macules are delayed in their evolution towards the more visible papules, and hence the difficulty in detecting the rash. Perhaps this is only an 'apparent' prolongation of the pre-eruptive stage.

The pre-eruptive stage, has some definite characteristics which are associated with all cases of smallpox irrespective of the clinical type. The constitutional signs and symptoms associated with this stage of the disease, which constitute the pre-eruptive symptom complex or syndrome in smallpox, are so important in diagnosis of the disease that they merit description. Except for some minor variations in the degree of severity of these signs and symptoms, depending upon the clinical type of the case, they are more or less constant in the history of every case of smallpox. Of course all the manifestations may not be present in every case. The frequency of occurrence of the constitutional signs and symptoms of this stage are diagramatically represented in *Figure* 3/1.

Fever

Fever, the most constant feature, is usually sudden in onset. The majority of the patients give a history of having gone to work in the morning, developed severe headache and fever in the afternoon and of being unable to continue to work. Because of this sudden characteristic onset, it is rather easier to fix the date of onset of the disease from the history of fever, than that of rash.

The temperature ranges from 100°F to 105°F. Fever by itself does not seem to incapacitate the person but the other associated symptoms do. This is of great importance in differential diagnosis. The height of fever does not correlate particularly well with the severity of the disease that follows.

Rigor

Some patients give a history of rigor, similar to that which occurs in malaria or filariasis. Most, however, complain of chills rather than of actual shivering. About 60 percent of adults and 20 percent of children complained of rigor in our series. The chills do not last long, and are usually associated with the first bout of fever only.

Convulsions

About 7 percent of the children under 5 years develop febrile convulsions. Though they are usually associated with hyperpyrexia, it is not uncommon to find convulsions even with comparatively low fever, especially in children, with ascaris infection. These convulsions are rarely associated with subsequent involvement of the central nervous system.

Headache

Next to fever, headache is the commonest symptom. Almost all complain of splitting headache. It is this, along with backache, that incapacitates the patient. It may be frontal in location but, not infrequently, it is generalised. Even young children complain of headache. In some cases the headache precedes the fever, and in a few others the headache itself is the principal complaint.

Backache

Like headache, backache is more or less a constant feature. About 90 percent complain of this symptom. It is more severe in cases which develop the early haemorrhagic type of smallpox. Pregnant women with this type of smallpox complain of excruciating back pain.

Delirium and hallucinations

About 15 percent of cases are reported to be delirious during this stage of the disease. It is mostly muttering in type, but violent delirium is not infrequent. Hallucinations also occur occasionally. In a few cases, the patient may be drowsy instead of being delirious. This clears as the rash develops, but in some cases it may progress to a semicomatose state with the development of encephalitis.

Gastro-intestinal symptoms

Vomiting occurs in 50 percent of adults and 40 percent of children, and diarrhoea in 10 percent of each. Though these symptoms are not generally so severe as to cause notable dehydration, I have experience of a few patients who were admitted as suspected cholera requiring immediate intravenous replacement of fluids.

Abdominal colic

About 13 percent of adults and 6 percent of children have abdominal discomfort or colic. It is mostly characterized as a vague discomfort round the umbilicus, rather than a colicky pain. It is very transient and its significance is not known. In non-endemic countries, a few cases have been mistaken for surgical emergencies, and have been operated upon. Similar abdominal discomfort is also noted with varicella.

Catarrhal Symptoms

Contrary to the usual impression, some patients present a mild upper respiratory catarrh, associated with sore throat and dry cough, on the second or third day of fever. In my series, about 15 percent of adults and 15 percent of children reported these symptoms. There may be also some difficulty in swallowing. This may be due to the appearance of early enanthem. These symptoms are rarely associated with running of the nose, sneezing, watering of the eyes etc., (cf. measles).

Rash

During this stage of the disease, different types of rash have been described. Some authors have even claimed, that this prodromal rash is one of the cardinal features in the diagnosis of smallpox. Because cases are mostly admitted to the hospital after the onset of focal rash, these prodromal rashes are rarely noted by us. The rash is reported to be confined mostly to the area between the loin and groin. It may be present in any form, scarlatinal, morbilliform, urticarial, petechial, papular etc. It seems to disappear with the onset of focal rash. Though rarely seen in our series, one or two fulminating cases of Early haemorrhagic smallpox showed petechial and purpuric spots on the lower half of the abdomen and in the groins, just before death on the third day of fever. The nature of these rashes is not known, though it is presumed that the rash is similar to the toxic rash found in cases of meningococcal meningitis etc., yet in cases, where these were observed by us, smears taken from the lesions showed elementary bodies of variola virus.

ERUPTIVE STAGE

Unlike pre-eruptive stage, the clinical course as well as the clinical features during the stage of eruption vary so greatly from person to person, that for proper understanding of the disease process, a detailed description for each clinical type is essential.

HAEMORRHAGIC VARIETY

These highly fatal cases are characterized by the occurrence of haemorrhages into the skin and/or mucous membranes at one stage or other in the course of the disease. Though several of the older authors have recognised this type as a separate entity, Dixon (1962) has stated "while haemorrhages are features of many types particularly fatal cases, they may also be present in quite mild and so have no unqualified prognostic significance". However, I feel that cases experiencing haemorrhages are different from others in several respects.

The pre-eruptive stage is usually prolonged to four to five days and the constitutional symptoms of this stage are more severe. Haemorrhages into the skin and/or mucous membranes may precede the appearance of rash on the skin in the Early haemorrhagic type, or follow the rash in the Late haemorrhagic type. In some cases, focal lesions on the skin may not be apparent even at death. Toxic symptoms may continue after the appearance of rash, if the patient survives to that stage.

Subconjunctival haemorrhages are most common. Bleeding from gums, epistaxis, haematemesis, haemoptysis, haematuria, as well as vaginal bleeding in women, may occur at any time. This variety is far more common in adults and women, especially the pregnant. Even successful vaccination does not seem to offer as much protection against this variety, as it does against the non-haemorrhagic. It is not uncommon to find pregnant women dying of Haemorrhagic smallpox inspite of being protected by primary vaccination in infancy, as well as by recent successful revaccination. The fact that Haemorrhagic smallpox is relatively more common in adults, especially pregnant women, indicates the possibility that this may depend upon some hormonal disturbances in the hosts which may make them more susceptible to severe varieties of the disease.

There is a feeling amongst some clinicians, that a particular strain of variola virus may cause this variety, but there is no evidence in support of this thesis because there has not been even a single instance in which a second haemorrhagic case has occurred amongst the contacts of a series of 385 cases of Haemorrhagic smallpox studied by the author. Conversely, there have been many instances in which non-haemorrhagic types occurred amongst the contacts. In a recent

study of 13 outbreaks of smallpox in Madras city (Rao 1968)a it has been found that there were two Haemorrhagic smallpox cases and two Modified smallpox cases which did not transmit infection at all to their contacts. On the other hand, two smallpox cases belonging to the Flat variety, produced Flat in two contacts, Ordinary in one contact, and Modified in one contact. Similarly five smallpox cases belonging to the Ordinary variety, produced Haemorrhagic smallpox in two contacts, Flat in one contact, and Ordinary in five contacts. These epidemiological findings tend to disprove the theory that different clinical varieties are produced by different strains of the virus. The occurrence of a particular clinical variety depends upon the factors pertaining to the host and not to the agent of infection.

There is another school of thought which believes that these cases are associated with a more virulent strain of variola virus. Sarkar (1967) has purported to show from his studies, that the virus isolated from Haemorrhagic smallpox cases differed in virulence from that recovered from non-haemorrhagic cases. It is noted that he has compared the virulence of virus isolates from the blood of Haemorrhagic smallpox with virus isolates from lesions of non-haemorrhagic cases. Conceivably this or other factors in the laboratory testing may have influenced the results. These observations need to be confirmed.

As noted above, in the course of the studies on the intrafamilial transmission of smallpox (Rao et al, 1968b), the author has shown that the haemorrhagic type of cases, as a source, do not transmit the disease more readily to the familial contacts; on the other hand, cases belonging to this type transmitted the disease least to their contacts when compared to other types. Though there are several other factors influencing the transmission pattern, it is reasonable to suppose that if the virus of Haemorrhagic smallpox is highly virulent, such cases should have transmitted the infection to a greater number of contacts. This is an indirect evidence suggesting that the occurrence of this variety is not due to differences in the virulence of the agent, but due to some factors pertaining to the host.

Blood coagulation studies carried out at Madras have shown, that the haemorrhagic types differ from the non-haemorrhagic, with regard to the haemostatic mechanism also. Roberts et al (1965), in a study of 93 patients at Madras suffering from various types of smallpox, summarized their findings as follows: "patients with severe and uniformly fatal, early haemorrhagic form of the disease, have demonstrated a severe thrombocytopaenia, and also a marked decrease in specific prothrombin, and prolongation of prothrombin complex, as evidenced by a very abnormal one stage prothrombin test. All early haemorrhagic patients studied to date, have also a marked prolongation of thrombin time suggesting the presence of circulating antithrombin.

Plate 1. Early haemorrhagic Type of Smallpox in a pregnant woman — 4th Day of disease

Both early and late haemorrhagic smallpox also have a marked abnormality of prothrombin indicating impaired plasma thromboplastin production. This finding could be explained by the thrombocytopenia that is present in all haemorrhagic cases".

Continuing this work, McKenzie et al (1965), in a study of 53 patients at Madras with haemorrhagic and non-haemorrhagic smallpox concluded that "the non-haemorrhagic smallpox patients revealed no coagulation abnormalities but some demonstrated thrombocytopenia. The early haemorrhagic patients reveal marked decrease of platelets, prothrombin and acceleratory globulin, and an increased circulating antithrombin. Individuals with late haemorrhagic smallpox showed significant thrombocytopenia and less severe deficiencies of the same coagulation factors. A few also had increased antithrombin".

These findings explain the bleeding tendencies, but not the cause of Haemorrhagic smallpox. To suggest that such defects were pre-existing before exposure is most unlikely, since none of these cases gave a history of previous haemorrhagic episodes. It is more reasonable to assume that these haemostatic defects were the result of the disease process itself, perhaps due to intense and continuous viraemia, which is present in these cases. Downie et al (1953), has found that, in all fatal cases, the virus can be isolated from the blood for a longer time, even till the day of death, whereas in the non-haemorrhagic and non-fatal cases, it could be isolated only for a day or so before the appearance of rash. This would indicate that in these persons, something permits the virus to circulate in the blood continuously, or allows the virus to continue to multiply in the reticuloendothelial system of various internal organs and to overflow into the circulation, or something interferes with the defence mechanism of the body, with the result that the virus multiplication continues unhampered. The haemorrhages may be only the result of damage to the capillary endothelium caused by the virus or its toxin (if present). Whatever be the reason, the clinical picture shows that in the majority of cases, death does not seem to occur as a result of severe blood loss but of severe viraemia and toxaemia.

EARLY HAEMORRHAGIC TYPE

This type is characterized by the occurrence of haemorrhages into the skin and/or mucous membranes before the appearance of rash on the skin. This, in general, corresponds to 'purpura variolosa' of Curshmann, and 'fulminating' of Dixon. In some instances, obvious focal lesions may not be visible even at death.

The pre-eruptive stage is usually prolonged to four to six days. The onset is sudden with chills. The temperature (*Fig. 3/2*) may rise

to 105°F to 106°F and is associated with severe splitting headache and excruciating pain in the back. No analgesic can relieve this pain. The clinical picture is typical. Patients are highly toxic, restless, anxious and pale. On the second day, the whole body has a generalized flush and erythema; petechae may be seen on the skin, and areas of echymosis also appear. Haemorrhages occur into the mucous membranes. Although subconjunctival haemorrhage is the most common (Plate 1) haemorrhages also occur elsewhere (*Fig. 3/3*). On the third day, the whole skin exhibits a finely textured matted surface and is velvety to the touch. In another 24 hours, the skin resembles dark purple velvet. This is most clearly seen in the fair skinned. Patients become restless, breathless, and complain of heaviness and pain in the chest. They appear to be aware of their impending death and are conscious to the end. Death occurs rather suddenly about the sixth day of fever. If the patient survives a day or two longer, the superficial layers of the skin become raised, fluid collects underneath, forming large blebs like the blisters of burns or scalds. The fluid within these is serous or sero-sanguinous. Being very superficial, even the slightest trauma is likely to rupture these blebs and the skin peels away leaving extensive raw areas. Though haemorrhages occur into the mucous membranes, death does not appear to be the result of excessive bleeding but appears to be due to toxaemia or viraemia. Surprisingly, none of the cases appear to develop cerebral haemorrhage. This type is invariably fatal.

The Early haemorrhagic type is more common in adults, 88 percent of all cases in our series being in persons beyond 14 years of age. Two-thirds of the cases were women, the pregnant being most susceptible. Of all smallpox cases in pregnant women, 16 percent were of this type, contrasted with only 0.9 percent of non-pregnant females and 0.8 percent of males of the fertile age group 15-44 years. Vaccination does not seem to offer much protection against a fatal outcome. Cases of this type occurred even among a few who had recently been successfully revaccinated.

LATE HAEMORRHAGIC TYPE

This type is characterized by the occurrence of haemorrhages into the skin and/or mucous membranes after the appearance of rash. The term 'variola pustulosa haemorrhagica' used by Curshmann is rather misleading, giving an impression that haemorrhages occur always into the lesions, and the haemorrhagic manifestations occur only during the pustular stage of the disease. Actually haemorrhages may or may not occur into the lesions and haemorrhagic manifestations may occur at any stage of the disease.

The pre-eruptive stage in this type also may be prolonged to three to four days. The temperature is usually elevated to 104°F to 105°F (*Fig. 3/2*) with severe constitutional symptoms which continue unabated even after the appearance of rash. The lesions, which start as macules, soon become papules and thereafter are very slow to mature. They may show haemorrhages into their bases giving them a 'flat' apperance. Bleeding may occur simultaneously into the various mucous membranes and skin, though the latter is less frequently observed than in Early haemorrhagic type. The frequency of the haemorrhagic manifestations in this type is shown in *Figure 3/4*. If the haemorrhagic lesions are 'flat', they do not evolve beyond the vesicular stage but flatten out and become black. In about 15 percent of cases, lesions may mature into vesicles and pustules and take an ordinary course. In these cases haemorrhages do not occur into the lesions but only into the mucous membranes.

Death occurs between the eighth and tenth day of fever. About 90 to 95 percent of cases are fatal. Late haemorrhagic cases with flat lesions, experience a higher fatality rate than those with ordinary lesions. Among those surviving, haemorrhages gradually resolve during prolonged convalescence. However in the few survivals with the flat type of lesions, scabs may form sooner resulting in a superficial scarring, whereas in cases with the ordinary type of lesions, the usual course is observed.

Like the Early haemorrhagic type, 80 percent of the cases occur in adults beyond 14 years of age. There is little difference between men and women in the frequency of occurrence, although pregnant women are slightly more susceptible to this type also. Of all pregnant women with smallpox, 6 percent experienced the Late haemorrhagic type, contrasted to 2 percent of non-pregnant females and 2.1 percent of males in the age group 15-44 years. Cases have been observed among persons who have been successfully vaccinated not only in infancy but also subsequently.

Whether Late haemorrhagic smallpox is a less severe form of what we have termed Early haemorrhagic smallpox, or a more severe form of non-haemorrhagic smallpox, has been a subject of controversy. Dixon classified these under 'malignant', and considered the haemorrhages to be a complication. However, several characteristics suggest that it is more closely related to the early haemorrhagic form, sharing with it similar characteristics in respect of distribution frequencies with reference to vaccinal status, age and sex, higher incidence in the pregnant and uniformly higher case fatality rates with the vaccinated as well as unvaccinated. Additionally, Roberts and McKenzie and their associates have clearly shown that the various blood coagulation defects

found in this type are similar to those found in the Early haemorrhagic, and not to those found in the non-haemorrhagic types.

FLAT VARIETY

The Flat variety is so called because the lesions flatten out and remain more or less flush with the skin at a time when vesicles normally form.

The pre-eruptive stage is about three to four days with the usual constitutional symptoms which are fairly severe, and which continue after the appearance of rash. There is a moderately extensive enanthem on the tongue and palate which may be confluent. A severe enanthem on the rectal mucous membrane and elsewhere may also develop.

The focal lesions are exceedingly slow to mature, and at the papulo-vesicular stage a small depression is seen in the lesions on the sixth day. By the seventh or eighth day they flatten out, and appear buried in the skin (Plate 2). The majority of lesions have haemorrhages into their bases and the central flattened portions appear black or dark purple. Usually the lesions have an erythematous areola around. They contain very little fluid, are not multilocular, and do not present umbilication. No further evolution of lesions occurs and frank pustules are rarely seen. In a few cases, however, some lesions, especially on the dorsum of the feet and hands, may become pustular, while on the body they remain as flat vesicles. Haemorrhages do not occur except into the lesions. Because of the superficial nature of the lesions even the slightest trauma may peel off the skin leaving extensive raw areas (*Fig. 3/5*). When confluent lesions occur on the palm and soles, the entire skin covering these areas may be peeled away, leaving raw surfaces.

Often the rash may not conform to the classical centrifugal type of distribution. Throughout the course of the disease the patient is toxic and febrile (*Fig. 3/2*). Respiratory complications set in by about the seventh or eighth day. The respiratory involvement may include viral pneumonitis and sometimes frank pneumonia. The unvaccinated, mostly children, develop an acute dilatation of the stomach about 24-48 hours before death. The usual day of death in this variety is between the eighth day and twelfth day. A day or two before death, the colour of the lesions also changes to an ashen grey (Plate 3), which along with acute dilatation of stomach, is indicative of a bad prognosis.

In cases with a confluent enathem on the tongue and palate, the mucous membrane sloughs and comes off like a sheet, leaving raw areas. Similarly in a few instances, the rectal mucous membrane also sloughs and comes off as a tubular cast, 12 to 18 inches long, im-

mediately before death. These cases pass blood and mucus in the early stages of the disease indicating extensive involvement of the rectal mucous membrane.

Among those who survive, scabbing may begin as early as the thirteenth to sixteenth day and be complete by about twenty-first day. The scabs are very thin and superficial *(Fig. 3/6)* and they separate rapidly leaving very superficial scars. The scabs are sometimes so minute, pin head in size, that it is very difficult to detect them. The colour of the scabs, before they dry, is purplish, unlike those of the Ordinary type which are dark brown. Perhaps this is due to the bleeding into the base of the lesions.

This variety is more common in children under 14 years. Nearly 72 percent of the Flat cases in our series were children. Of the total cases among children, 8 percent were of the Flat variety. There is a slightly greater incidence of this variety in pregnant women. Of all cases in the pregnant, 3.6 percent were of the Flat variety, contrasted with 2.4 percent among non-pregnant women and 0.9 percent among men in the age group 15-44 years.

No case of the Flat variety was seen in persons who had both primary vaccination as well as successful revaccination (cf. Haemorrhagic variety).

Depending upon the density of rash, this variety is subdivided into three types; confluent, semiconfluent and discrete.

FLAT CONFLUENT TYPE

The Flat confluent type has all the characteristics described above. The rash is confluent on the face, as well as on the extensor aspects of the extremities. The patient is febrile and toxic throughout the course of the disease, and invariably, has respiratory involvement (viral pneumonitis), which is not usually amenable to antibiotic therapy. In our series the case fatality rate was 100 percent in the unvaccinated, and about 86 percent in the vaccinated. Death usually occurs on or about the 10th day.

FLAT SEMICONFLUENT TYPE

The characteristics are the same as in Flat confluent. The rash is confluent on the face and discrete on the extremities. In our series, the fatality rates were about 95 percent in the unvaccinated and 60 percent in the vaccinated.

FLAT DISCRETE TYPE

Nearly 30 percent of Flat cases among the vaccinated and 20 per-

cent among the unvaccinated belong to this type. Lesions are fewer in number and they are discrete on all parts of the body, but the case fatality rate is equally bad among the unvaccinated, possibly lower among those previously vaccinated although the number of cases in this category is very few.

ORDINARY VARIETY

The term Ordinary variety is used to designate cases which conform to the usual description of smallpox cases. Patients experience about two to three days of pre-eruptive fever, with constitutional symptoms of varying severity. With the onset of the focal rash, there is a general abatement of symptoms, though they may not completely disappear, especially in the unvaccinated. The temperature tends to fall, but may not reach normal.

Order of appearance of lesions

The lesions on the mucous membranes (enanthem) are the first to appear and they are visible on the tongue and palate, as minute red spots, a few hours to 24 hours before the appearance of rash on the skin. Lesions may also occur lower down in the respiratory tract but are not visible. Some cases, who complain of sore throat during this stage, may be experiencing enanthem on the pharynx. However, not all cases do develop enanthem.

The rash usually appears on the third or fourth day, as angry looking fleabite-like macules on the face, especially on the forehead. In about 10 percent of the cases, history reveals that the rash was first seen not on the face but on the forearm or some other part of the body. Lesions then appear in quick succession on the proximal portions of the extremities, on the trunk, and lastly on the distal portions of the extremities. The lesions appear in such quick succession, that it is difficult to follow the timing of occurrence of lesions on the different parts of the body, and rarely does a patient notice this order of appearance and give such a history. Within a matter of 24 hours the whole rash appears and after that, normally no fresh lesions develop.

Evolution of lesions

The enanthem rapidly evolves. The minute macules, which appear on the second or third day, rapidly become papular and vesicular and break down before the sixth day of the disease, (Plate 4), liberating large quantities of virus in the discharges and saliva. By about the 12th to 14th day of the disease, they almost heal leaving a raw surface, but with no further liberation of virus (?).

Lesions on the skin, which appear as macules on the third or fourth day of fever, rapidly become papular by the fifth day. Although these are called papules they are really early vesicles and not hard papules as in papular syphilides. The skin over them can easily be split with an ordinary needle. By the seventh or eighth day they become vesicles containing an opalescent fluid, which becomes opaque and turbid in another 24 to 48 hours, and by tenth day of fever, all lesions are in the pustular stage. Though these are called pustules they contain tissue debris, as a result of the extensive tissue destruction, rather than frank pus. From the tenth to the thirteenth day, they mature and attain their maximum size. Usually on the fourteenth day resolution starts and the lesions have a tendency to flatten in the centre. The fluid then is slowly absorbed and, by about the eighteenth to twenty-first day, the central portion hardens and finally a scab or a crust is formed which later separates, leaving a deep, depigmented scar. The period of this evolution varies from case to case depending mostly upon the immunity of the patient. Evolution of the rash by various stages is shown in *Figures 3/7* to *3/11*.

Distribution of lesions

The rash of smallpox has a characteristic centrifugal distribution pattern *(Fig. 3/12)*. It would almost seem that the patient, during the stage of viraemia, had been fixed on a centrifuge with outstretched limbs and spun. The rash is more dense on the extremities than on the trunk; and, on the extremities, it is more dense on the distal parts than on the proximal. On the face, it is more on the upper half than on the lower half. There is no satisfactory scientific explanation for this type of distribution, though several theories have been put forward. However, in about 10 percent of our cases the distribution was not centrifugal.

On the extremities, the rash is more dense on the extensor (dorsal) aspect than on the flexor (volar) (*Fig. 3/13*). Similarly, it is more prominent on the convexities (prominences) than in the concavities (hollows) (*Fig. 3/14*). Even here, however, 10 percent of cases do not conform to this pattern. Relatively, the apex of the axilla is free compared to the folds. This is known as 'Ricketts' sign (*Fig. 3/15*). This is invariably positive, barring a few exceptions (*Fig. 3/16*).

On the trunk, the rash is more dense on the back (*Fig. 3/17*) than on the front. On the front, it is more dense on the chest than on the abdomen (*Fig. 3/18*). In our series this contrast was not present in about 20 percent of cases (*Fig. 3/19*). On the abdomen, the upper half is more involved than the lower half. This is known as Gaspirini's sign (*Fig. 3/20*). This sign was positive only in about half of our cases.

The palms and soles are involved in a majority of the cases. Even in mild cases, lesions can be seen on these areas *(Fig. 3/21)*. Of the two, the palms have been found to be more involved than the soles. The mere presence of rash on the palms is not diagnostic of smallpox, since such lesions sometimes occur among patients with varicella *(Fig. 3/22)*.

Individual characteristics of lesions

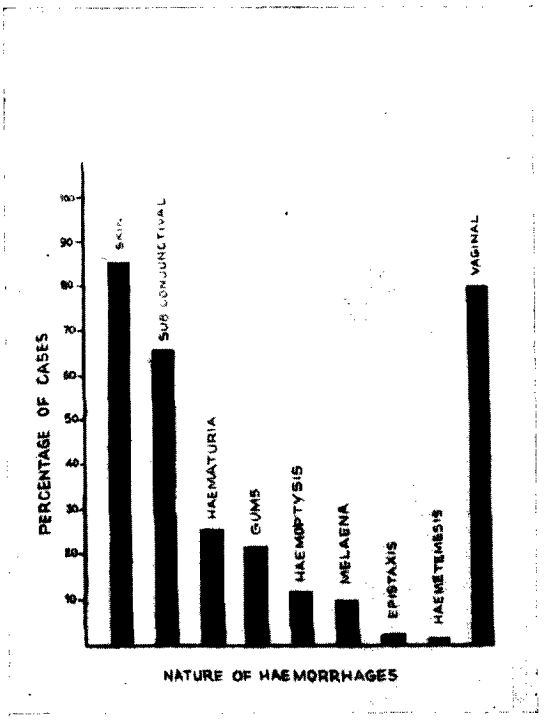
Lesions of smallpox are more deeply embedded 'IN' the skin than those of varicella. They are raised and project from the surface of the skin and feel shotty to the touch. They are circular in shape *(Fig. 3/23)* (cf. varicella) and are multilocular with fibrinous threads dividing the interior of the vesicles into several compartments (cf. varicella). Loss of fluid tension, and retraction of these threads, results in what is known as 'umbilication' *(Fig 3/24)* i.e., a dimpling at the apex of the lesion (cf. varicella). This umbilication is found in the vesicular and early pustular stages. When pustules mature and the fibrinous threads are destroyed, umbilication may also disappear.

The lesions usually have only a barely detectable erythematous areola around (cf. the flat type of smallpox and varicella). In a particular area, all the lesions will, more or less, be in the same stage of evolution, although of different sizes *(Fig. 3/25)* (cf. varicella). This is due to the fact that in smallpox, the rash does not occur in crops. However, upto the fifth day, because of the order of appearance of the rash, there may be papules on the face and macules on the legs, and similarly, after scabbing has started, lesions may be scabbing on the face, but may still be pustular on the legs.

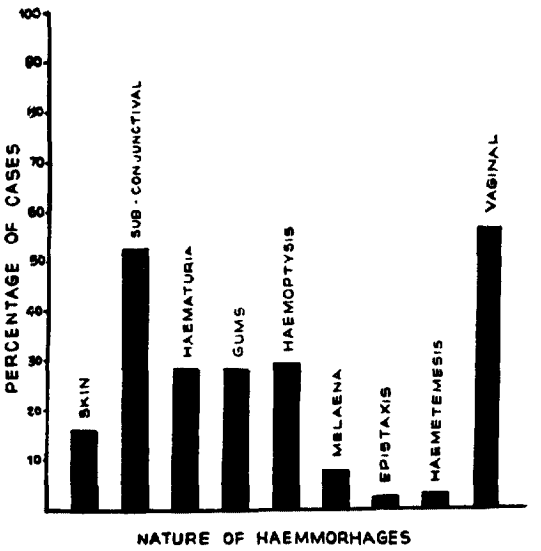
The fever, which shows a tendency to drop on the fourth or fifth day when the rash appears, again rises by the seventh or eighth day and continues to remain high throughout the vesicular and pustular stages, until scabs have formed over all lesions. Respiratory complications, especially in the unvaccinated, develop on or about eighth day, and they may be either bacterial or viral in origin. In fatal cases, death occurs between the twelfth and eighteenth day of fever. Among the survivals, scabs separate by the twentyfifth to thirtieth day. Scabs on the palms and soles usually have to be separated with a needle. The scars that are left on the body are initially depigmented and deep, and are more or less permanent.

In our series, 70 percent of cases among the vaccinated and nearly 88 percent among the unvaccinated were of the ordinary variety. There is no significant difference in the distribution frequency in relation to age and sex. The case fatality is about 3 percent in the vaccinated and about 30 percent in the unvaccinated.

Plate 4. Confluent enanthem on the tongue in an Ordinary Discrete Type



3/3. **Frequency of occurrence of haemorrhages in Early haemorrhagic type**



3/4. **Frequency of occurrence of haemorrhages in Late haemorrhagic type**

3/5. Extensive raw areas as a result of the pealing of the skin over the superficial lesions in a fatal case of Flat variety

3/6. Superficial scabs and scars in a case Flat variety

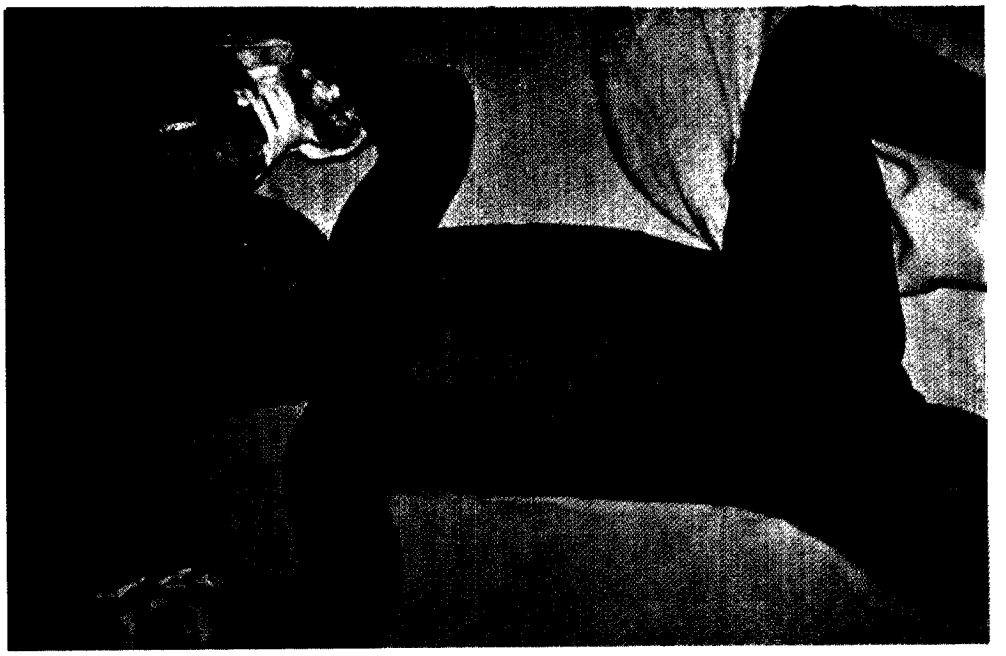
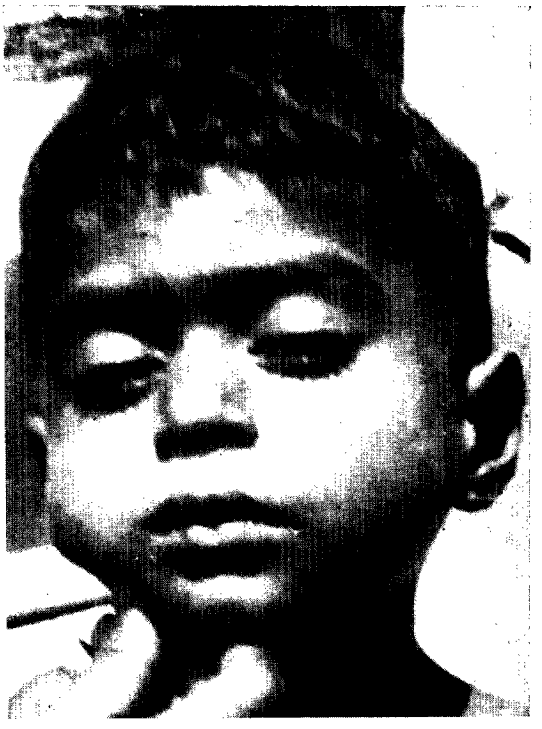


Plate 2. Flat Variety of Smallpox in an Unvaccinated Child -- 8th Day of disease



3/7. Evolution of lesions — 4th Day of disease — Maculo-papular rash in a case of Ordinary variety

3/8. Evolution of lesions — 5th Day of disease — Papular rash in a case of Ordinary variety

3/9. Evolution of lesions — 7th Day of disease — Vesicular rash in a case of Ordinary variety

3/10. Evolution of lesions — 9th Day of disease — Pustular rash in a case of Ordinary variety

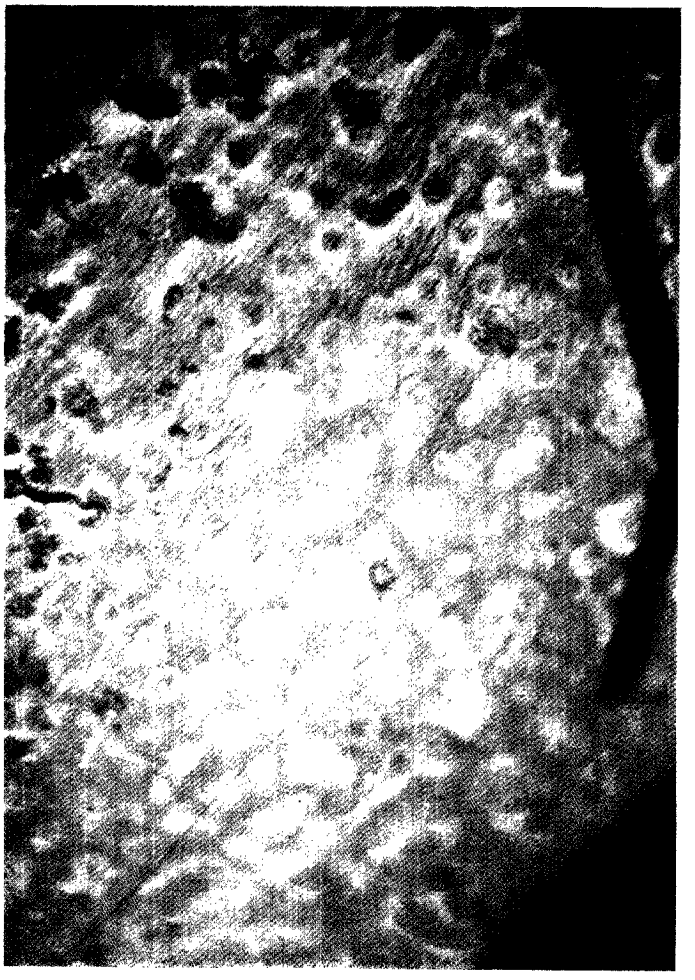
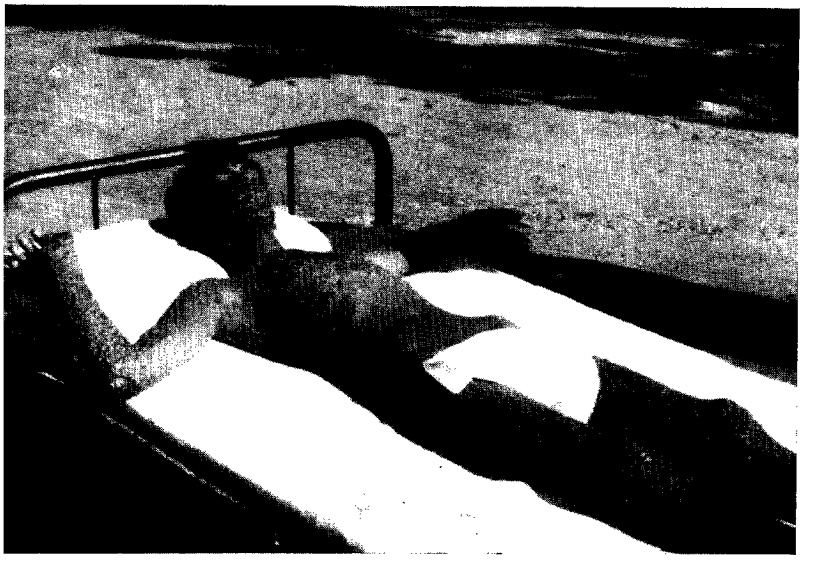
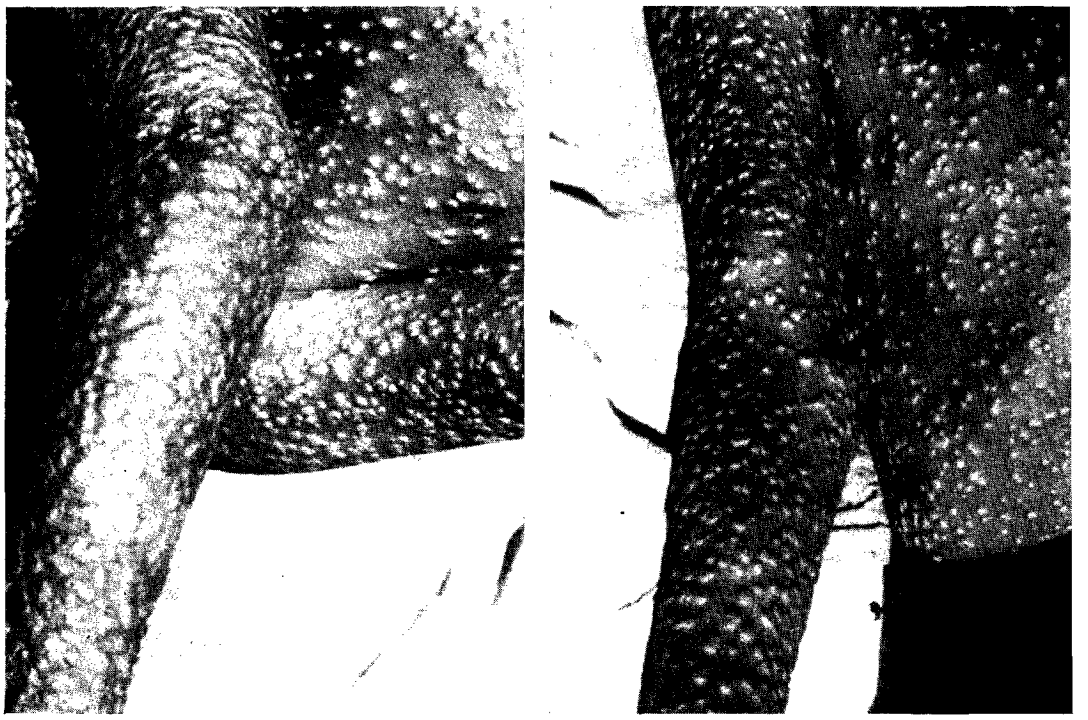


Plate 3. Ashen grey coloration of lesions before death in a Flat variety of Smallpox

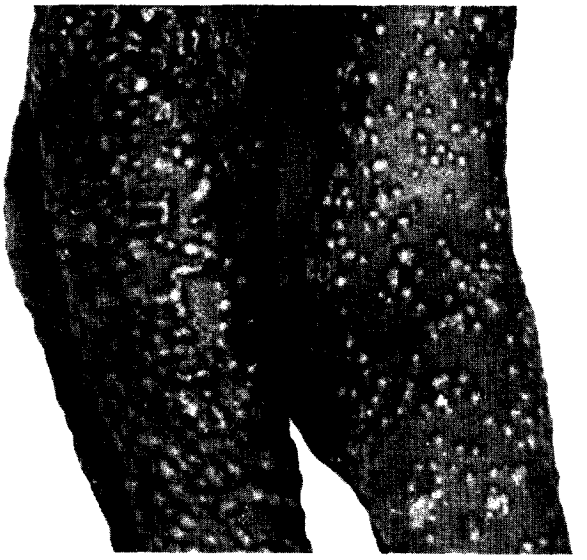
3/11. Evolution of lesions — 14th Day of disease — Mature pustules with tendency to scab in a case of Ordinary variety



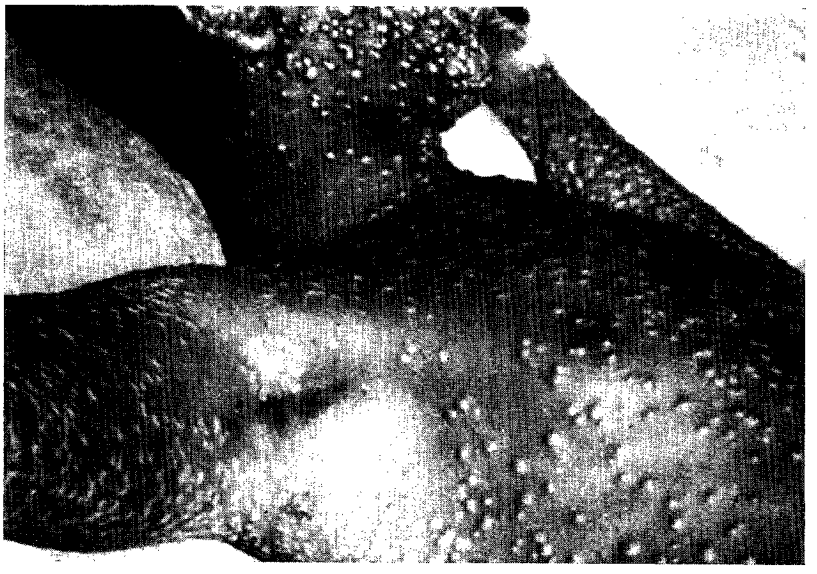
3/12. Distribution of lesions — Typical Centrifugal distribution



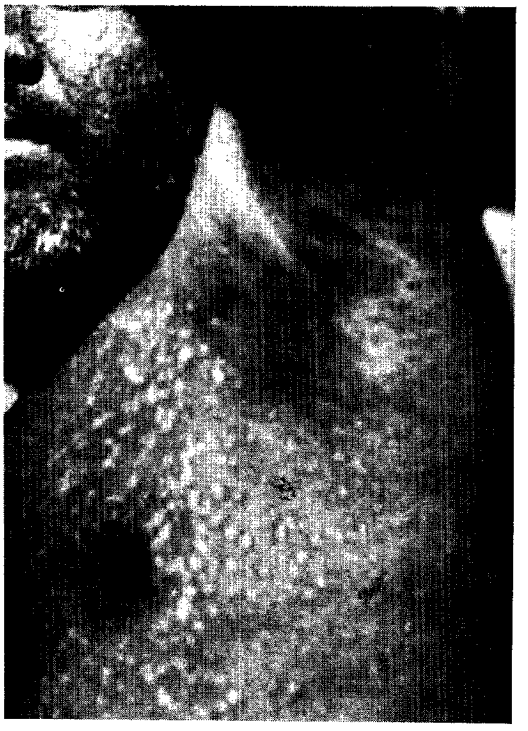
3/13. Distribution of lesions — More dense on Extensor surface than on Flexor



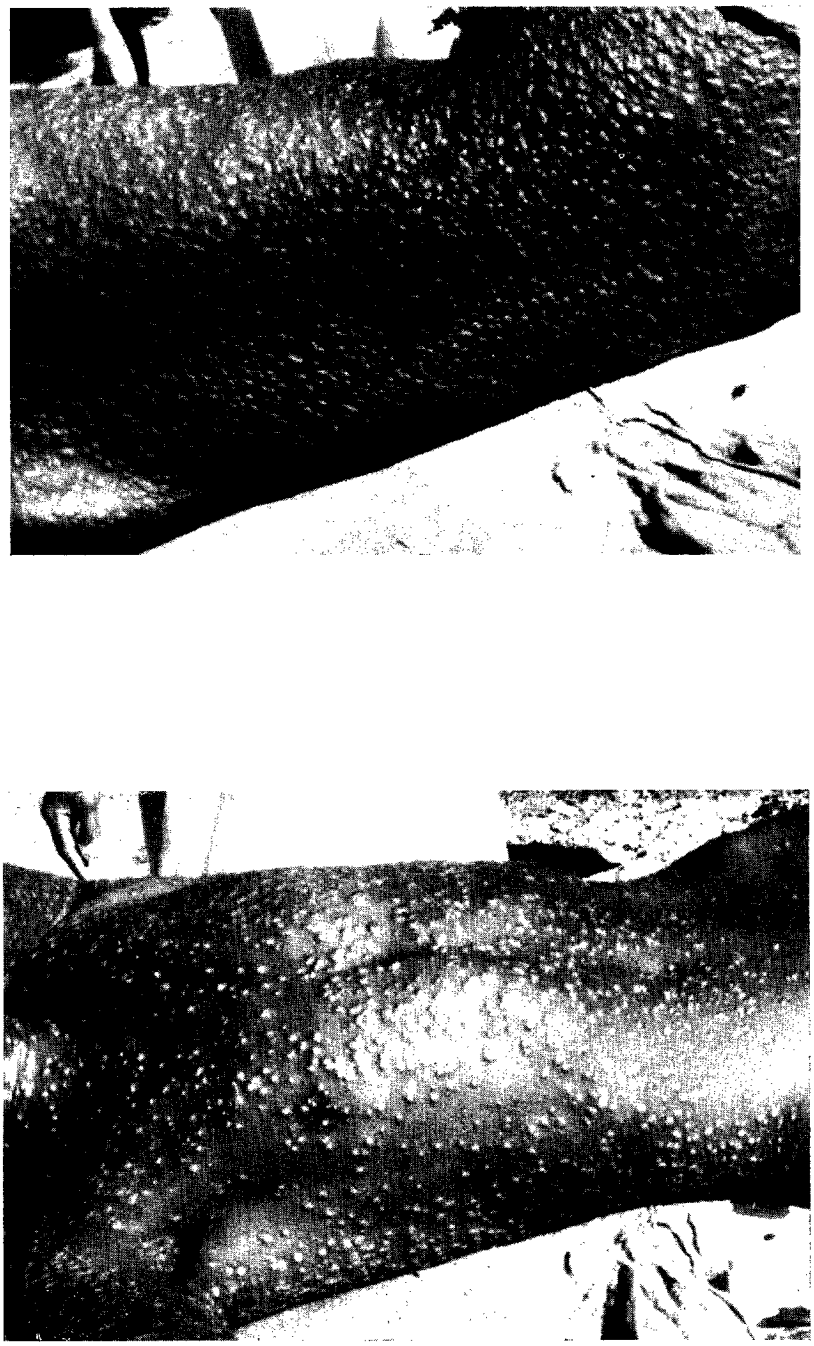
3/14. Distribution of lesions — More dense on Convex surface than in Concavities



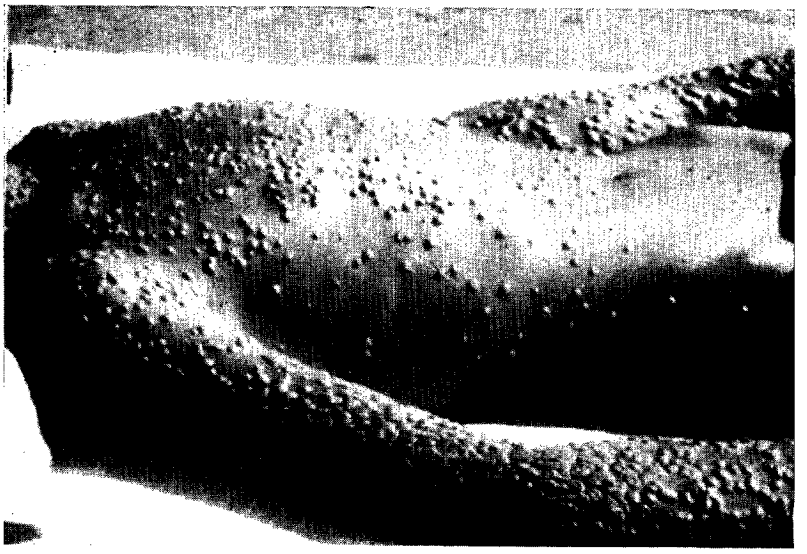
3/15. **Distribution of lesions — Positive Rickett's sign**



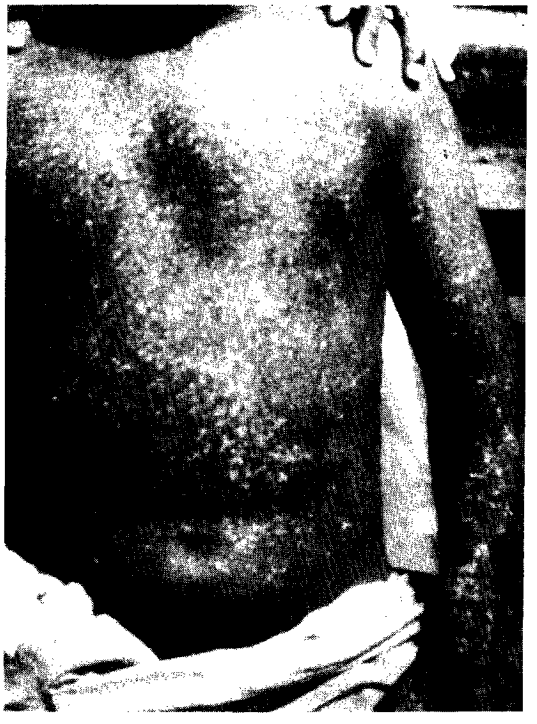
3/16. **Distribution of lesions — Atypical — Negative Rickett's sign**



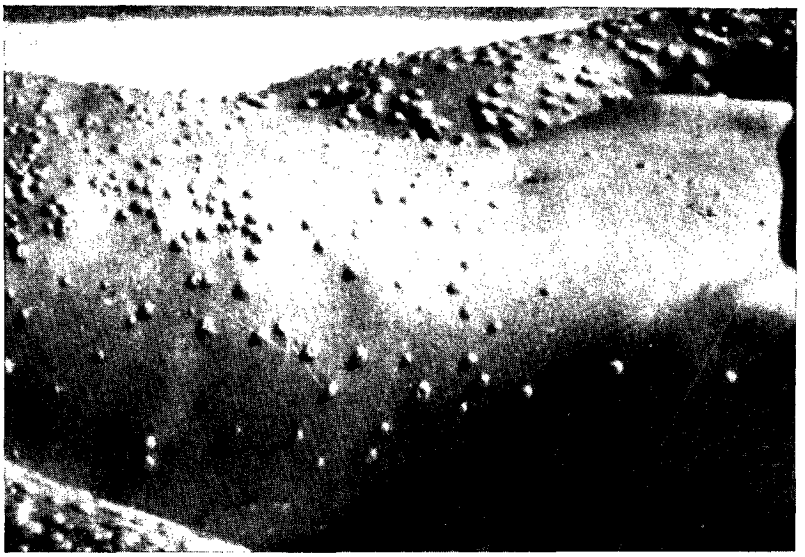
3/17. Distribution of lesions on the trunk — More dense on the back (above) than on the front (below)



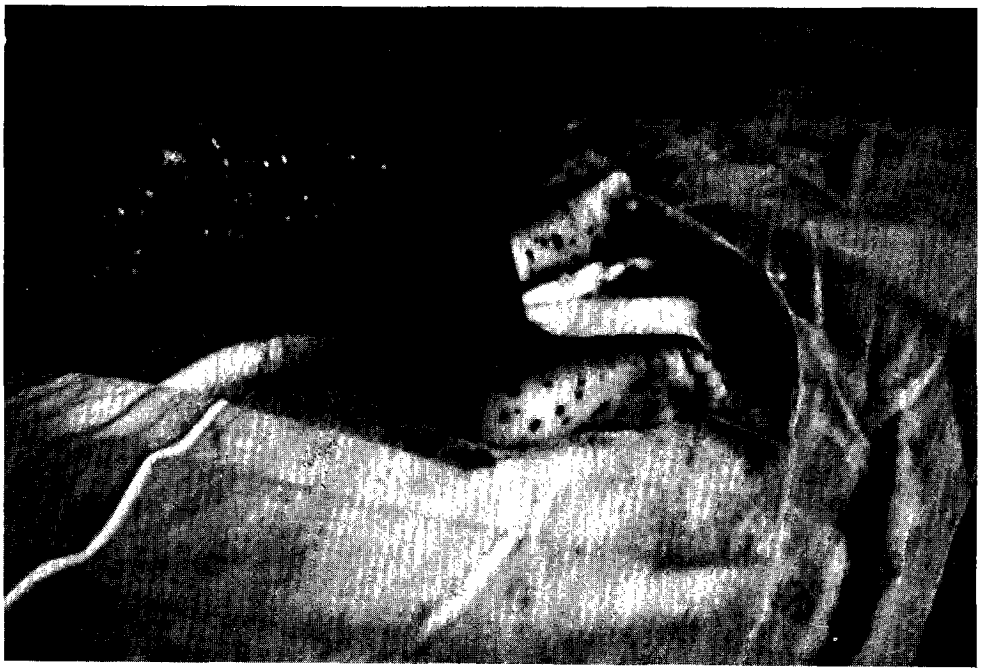
3/18. Distribution of lesions on the trunk — More dense on the chest than on the abdomen



3/19. Distribution of lesions on the trunk-Atypical — Equally dense on the chest and abdomen

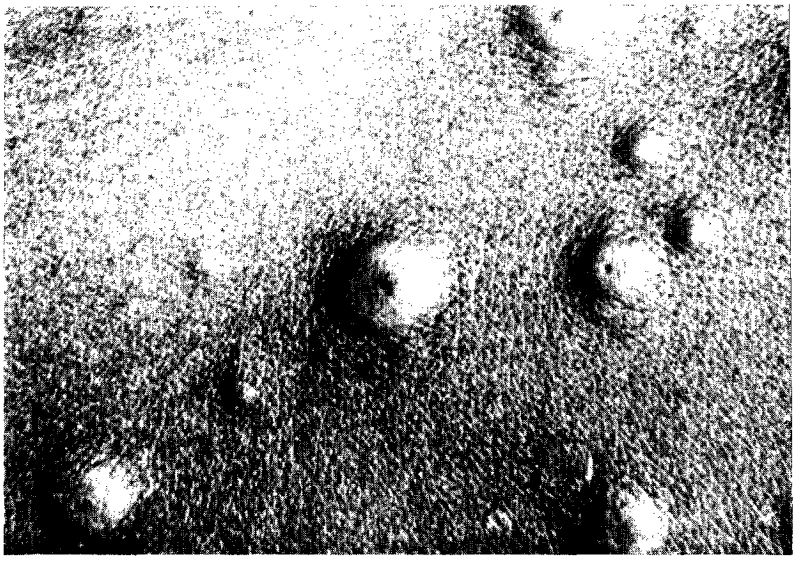


3/20. Distribution of lesions on the trunk — Positive Gaspirini's sign

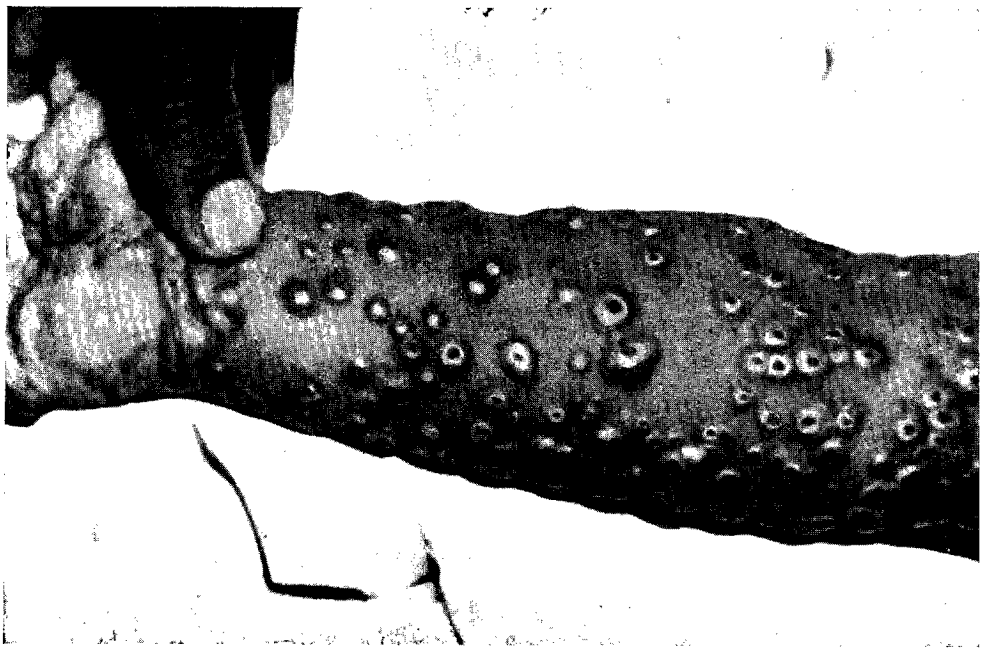


3/21. Scabs in soles of the feet

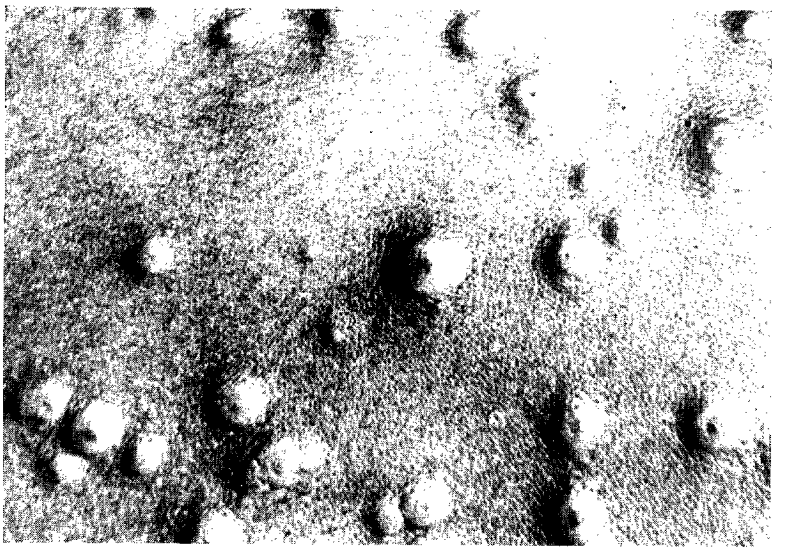
3/22. Lesions in the palm in a case of Chickenpox



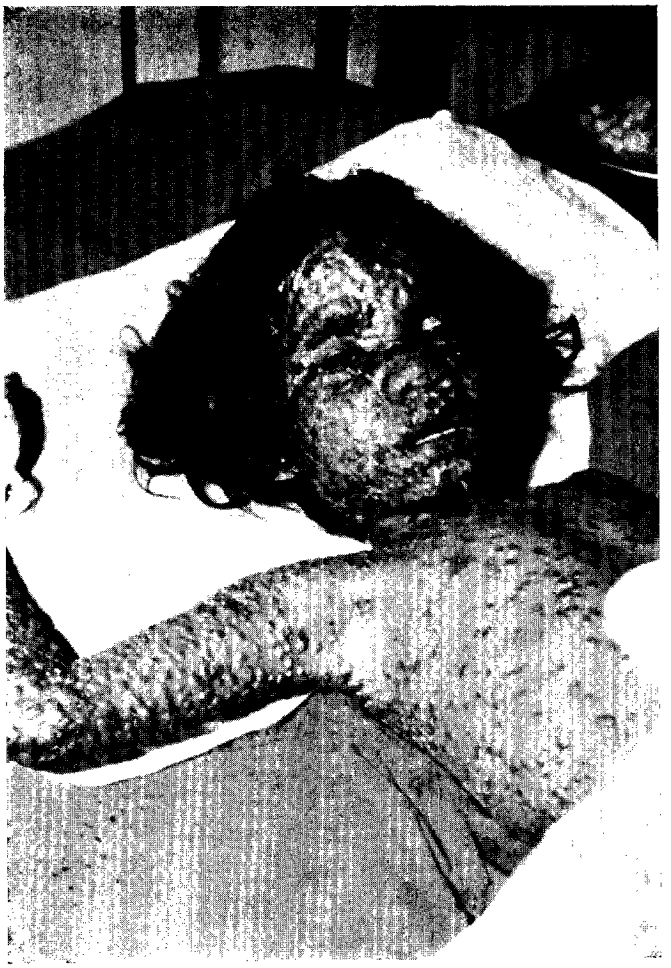
3/23. Characteristics of lesions — Deep, Circular and Umbilicated



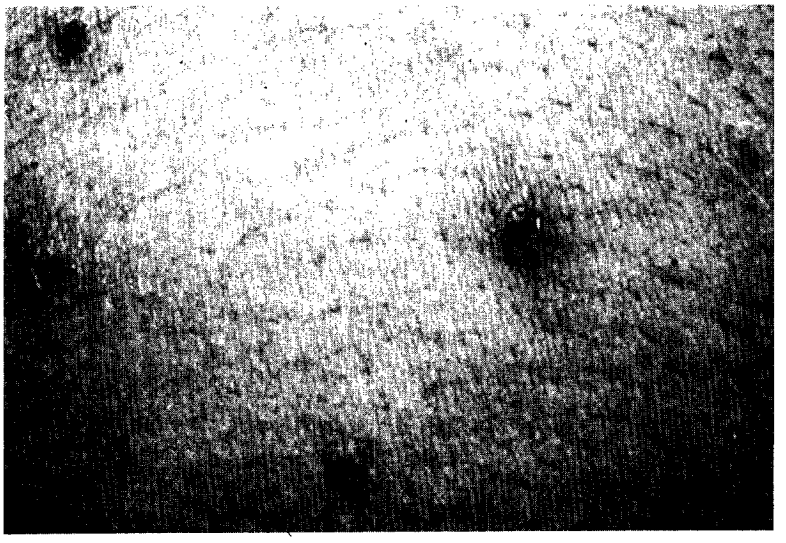
3/24. Typical umbilication in lesions of Smallpox



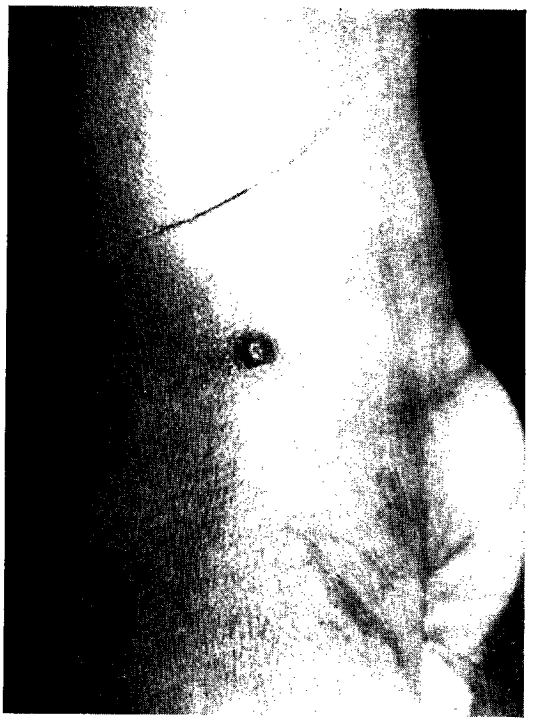
3/25. Characteristics of lesions — Absence of pleomorphism



3/26. Ordinary Semiconfluent case



3/27. Scabbed lesions in a case of Modified Smallpox — 7th Day of disease



3/28. One of the only 3 lesions in a Modified Smallpox — 7th Day of disease

3/29. Modified Semiconfluent case

Depending upon the density of rash this variety is further subdivided into three types; confluent, semiconfluent and discrete.

ORDINARY CONFLUENT TYPE

Lesions on the face as well as the extensor surfaces of extremities are confluent. The temperature which tends to fall on the fourth or fifth day, rises again after the seventh day *(Fig. 3/2)* and continues to be elevated until scabbing is complete. Sometimes, in the unvaccinated, the temperature remains elevated even after scabs have formed over all lesions. When this occurs, the prognosis is rather bad. This type is much more frequent among the unvaccinated than the vaccinated. The fatality rate in our series was 62 percent in the unvaccinated and about 26 percent in the vaccinated.

ORDINARY SEMICONFLUENT TYPE

The rash is confluent on the face but discrete on the body *(Fig. 3/26)*. A secondary fever may develop during the pustular stage, but it is less marked. The temperature subsides as soon as the scabbing starts. This type is also more frequent in the unvaccinated than in the vaccinated. The case fatality rate was about 37 percent in the unvaccinated and 8 percent in the vaccinated in our series.

ORDINARY DISCRETE TYPE

This is more common amongst the vaccinated. Nearly 60 percent of the total cases in the vaccinated were of this type compared to 40 percent among the unvaccinated. In this type, the lesions are fewer in number and discrete all over the body. There may or may not be a secondary fever during the pustular stage *(Fig. 3/2)*. In some cases, though the number of lesions is few, the course of the disease is the same as in the other two types of this variety.

The fatality rate in our series was about 9 percent in the unvaccinated but only 0.7 percent in the vaccinated.

MODIFIED VARIETY

The modified variety is so called, because in this, the characteristics and evolution of individual lesions, and the constitutional symptoms as well, are modified or in extreme cases of modification, all the signs and symptoms of the pre-eruptive stage are present without any rash following. Though the majority have comparatively few lesions, the number of lesions is less important than the rapidity and nature of their evolution.

These cases experience the usual pre-eruptive symptoms of two to

three days, with moderate to high fever, associated with mild constitutional symptoms of headache, backache etc. The temperature subsides to normal by about the fifth or sixth day *(Fig. 3/2)*. Enanthem in these cases is uncommon. The lesions, which appear as macules, rapidly become papular and vesicular and scab by the tenth day or before, without going through the pustular stage. Scabs may sometimes be noted as early as the seventh day *(Fig. 3/27)*. For purposes of classification, it has been decided empirically, that any case of smallpox, in which scabs are formed on all lesions on or before the tenth day of the disease, is termed Modified. The distribution of lesions may or may not conform to the classical pattern. The lesions also are modified. They are more superficial than normal, though usually not so superficial as in varicella, and may be pleomorphic. They may have an erythematous areola. They do not umbilicate. The scabs are more superficial, and separate usually before the fourteenth day, leaving very superficial scars which may not even be permanent. None of the cases is fatal.

Though there is a greater incidence of this type in the vaccinated, and hence the term 'vaccino-modified' is often used, yet it should be noted that modification does occur not infrequently even in the unvaccinated.

Illustrative of the problems in diagnosis of modified cases are the following examples:

A nurse was admitted with fever of five days' duration and with headache and body pains. Only three lesions were visible, one of them on the lip, one on the ear lobe and the third on the lateral aspect of the thumb *(Fig. 3/28)*. She had four primary vaccination scars and gave a history of revaccination every year. Her throat was very sore and congested, without any evident lesions. A throat swab was taken for culture which grew staphylococci. Smears from the lesions on the thumb revealed the presence of variola virus. The three lesions scabbed by the eighth day.

A woman aged 23 years was admitted to the Infectious Diseases Hospital with a history of fever, headache, backache and vomiting for three days and a papular rash of two days' duration. She had two primary vaccination scars and there was no history of revaccination. The rash was quite dense and confluent on the face though discrete on the extremities. The patient became afebrile after the sixth day. Smears from the lesions showed elementary bodies of variola. Scabs were present on all the lesions by the ninth day and they separated by the twelfth day *(Fig. 3/29)*.

A woman of 35 years, whose child had died of smallpox on the tenth day of disease, was admitted with her two other children for ob-

servation. All three were vaccinated after admission. She had two primary vaccination marks with no history of revaccination. On the second day following vaccination, this woman had a slight headache and a rise of temperature to 100°F. The vaccination site showed a raised papule which became a vesicle on the fourth day. A single papule was noticed on the upper lip on the third day after admission. The fever lasted only for a day and the single lesion on the lip became vesicular, and a scab formed on the eighth day. On culture, it was found to contain variola virus. A scab also formed on the vaccination lesion by the sixth day. The other two children developed an ordinary discrete type of smallpox.

These few instances illustrate the problems in diagnosis of this variety. Depending upon the density of rash, this variety is subdivided into four types; confluent, semiconfluent, discrete and variola sine eruptione.

MODIFIED CONFLUENT TYPE

Though rare, this type does occur occasionally. One such case was a man of 35 years with two primary vaccination scars, who was admitted with history of three days' fever, with severe headache and vomiting and a papular rash over the body of two days' duration. The rash was confluent. He was not toxic. The temperature subsided by the fifth day. Smears from the lesions showed elementary bodies and variola virus was isolated. Scabs formed over all lesions by the ninth day.

In our series only 0.1 percent of vaccinated cases belonged to this type and there were none in the unvaccinated.

MODIFIED SEMICONFLUENT TYPE

This type is a little more common than the Modified confluent. In our series, 0.5 percent of the vaccinated cases belonged to this type and it was rare in the unvaccinated. The rash is confluent on the face and discrete on the extremities.

MODIFIED DISCRETE TYPE

This is by far the most common of the modified types. In our series about 25 percent of the vaccinated and 2 percent of the unvaccinated belonged to this type. The rash is discrete in all areas. Although there may be only one or two lesions, the rash is definitely preceded by the typical pre-eruptive syndrome including fever, headache and backache etc.

VARIOLA SINE ERUPTIONE

This type is so called, because no rash occurs. Diagnosis is possible only by laboratory means. This usually occurs in well-vaccinated but rare in the unvaccinated too. The patients present the typical prodromal fever with the usual constitutional symptoms, but do not develop rash, though a few may complain of sore throat suggesting the presence of an enanthem.

Though it is generally agreed that immunity conferred by vaccination serves to modify the disease, yet persons who have not been vaccinated sometimes develop the Modified variety. Conversely of course, some persons, well protected by vaccination, develop severe types of the disease and die.

The severity of the attack is, probably in part, conditioned by host factors other than the vaccinal status, including the weight of infection and intensity of exposure etc.

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4

Complications

INTRODUCTION

It is well known that smallpox causes disfiguration, disability, deformity and death. About 20-25 percent of cases end fatally, and most of the survivors suffer from disfiguration which is a normal result of the disease process itself, and need not therefore be considered as a complication. Disfiguration is the result of healing of the lesions of smallpox. Permanent pitted scars are notably observed on the face. Such scarring is more prominent with the Ordinary types of the disease *(Fig. 4/1)*, than with others. Flat types often leave superficial scars in survivors. Modified types also produce superficial scars which may not even be permanent.

Persistence of scars depends upon the depth of the lesions, which is maximum with the Ordinary types. According to some, deep scarring is due to secondary bacterial infection of the lesions. There is no evidence in support of this. Certainly the pustular stage cannot be prevented with antibiotics. This is not surprising since the pustules, in fact, actually contain tissue debris resulting from the virus infection.

From a recent study on the persistence of scarring, made by us, it was found that, about 30 percent of the survivors of smallpox had no visible scars after 5 years. The study also suggests, that persistence of scarring depends upon the clinical variety of case, the vaccinal status, as well as sex and age of the patients. Smallpox scars seem to persist more in the unvaccinated than in the vaccinated, more in those cases of Ordinary variety than in the Modified, more in males than in females, and more in chidlren than in adults. However, since the number of cases is very few, the conclusions are necessarily tentative.

In the 1920's and 1930's, it was claimed that scarring could be prevented or minimized by immersing the patient in a potassium permanganate bath until a potassium permanganate crust was formed under which the rash evolved. Similarly, treatment with intravenous antimony was also advocated. Both procedures seem highly dubious, and there is still no known method by which disfiguration can be prevented or minimized.

COMPLICATIONS

Complications of smallpox may affect any system or organ, and with the exception of respiratory and gastrointestinal complications, they usually leave permanent damage either in the form of disability or deformity.

RESPIRATORY

Respiratory complications are common particularly in the severe types. Excepting the Modified, almost all the unvaccinated cases of other types in children, and a majority in adults, develop some sort of respiratory complications, ranging from simple bronchitis to pneumonitis or pneumonia, apparently of viral origin in most instances. Pulmonary oedema is fairly common in the Haemorrhagic and Flat varieties.

Secondary bacterial pneumonias are quite common in adults who have been previously vaccinated in childhood. In these cases, physical signs of consolidation are often present, and they respond fairly well to antibiotic therapy.

GASTROINTESTINAL

Gastrointestinal complications are less common. Vomiting and diarrhoea may be present during the pre-eruptive stage, as described During the course of the illness, about ten percent of cases, mostly unvaccinated children, have diarrhoea in the second week. Another complication which is common in the unvaccinated children is acute dilatation of the stomach which occurs on or about the 12th day of disease. Such cases usually end fatally.

Mucous colitis is frequently associated with the severe Flat types of smallpox with extensive involvement of the rectal mucous membrane. Patients pass bloodstained mucus in the stools and, in very severe fatal cases, it is not uncommon for the sloughed mucous membrane to come off as a tubular cast of varying lengths before death.

GENITO URINARY

In animals, the testes were found to be quite susceptible to the vaccinia-variola group of viruses. It is not known how frequently the testes in man are involved. Orchitis, as a complication, rarely occurs. There were only six recorded cases in our series giving a frequency of about 1 per 1000 cases. All these were in the vaccinated adults. Orchitis was unilateral and the complication occurred between the 10th and 15th day of the disease. Although none of these cases showed microfilaria in their blood, one cannot definitely exclude the diagnosis of filariasis in a city like Madras, where the disease is endemic. Only

one of these cases could be followed. This patient complained of frequent pain in the same testis after 4 years. There is no evidence that testicular function has been affected in persons who have had smallpox. No information is available regarding the involvement of the ovaries in women with smallpox.

Albuminuria is quite common in the acute phase of illness, but frank nephritis is very rare. There is no evidence of damage to the kidney, excepting in Haemorrhagic smallpox, in which haemorrhages may occur into the pelvis of the kidney producing haematuria.

NEUROLOGICAL

Encephalitis is common in smallpox, probably more common than in vaccinia, varicella or measles. In our series, strict criteria have been employed in diagnosis of encephalitis as follows: 'a semicomatose or comatose condition, altered sensorium, indifference to surroundings, increased tension of cerebrospinal fluid with a slight increase in the cells but without any abnormal biochemical changes'. We have recorded 13 cases of this type or approximately 1 per 500 cases of smallpox.

About the fifth or sixth day of the disease when the rash is in the papular stage, the patient with encephalitis becomes drowsy. This drowsiness may deepen into either a semicomatose or comatose condition in the next four or five days. The patients are not usually delirious or boisterous, but incoherent muttering is not uncommon. They do not recognize people, do not answer questions and are not responsive to their surroundings. Generally there is no spasticity of the limbs, the neck is not rigid, Kernig's sign is usually absent, and there are no other signs of meningeal irritation. This condition may persist till about the 15th to 20th day of the disease, when slowly the sensorium clears followed by a prolonged convalescence. When the patients begin talking, there is a slurring of words (dysarthria) and, when they start walking, they have an ataxic gait. These are the only two residual effects noticed in our cases. The gait becomes normal in two to three months, but speech takes more than six months to become normal.

Eight of 13 encephalitis cases were among females, and 11 of the 13 cases were adults in the age group 15-44 years. The other two were in a girl of 12 and a woman of 63.

Nine of the 13 cases had marks of primary vaccination, and the remaining 4 gave a history of vaccination. All but one, experienced the Ordinary type of smallpox; the other was a Late haemorrhagic case, the only fatal case, who died late in the course of the disease. No virus was grown from the CSF taken from these cases. The etiology of encephalitis occurring in cases of smallpox is still obscure. It does not

seem to be either the result of viral or bacterial involvement of central nervous system. Perhaps, as in other cases of postinfective encephalitis, it has an underlying basis of hypersensitivity.

Peripheral neuritis is not uncommon during convalescence.

OSTEO-ARTICULAR

By far, the most uncommon complication in smallpox is the involvement of joints. We had 119 cases of arthritis in our series (1.7 percent of the total). More than 80 percent of these were in the unvaccinated: 80 percent of cases occurred in children under 10 years. Hence it is a complication of childhood and the unvaccinated.

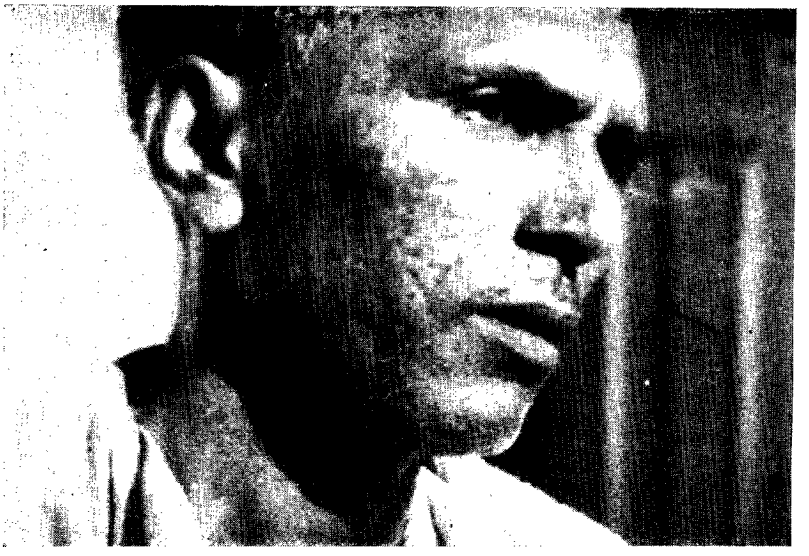
Of those experiencing this complication, 94 percent had the Ordinary variety 2 percent the Flat variety, and 4 percent the Modified. Like encephalitis, it was not associated with the more severe forms. In fact, 75 percent of those with the Ordinary variety had the Ordinary discrete type.

The joints involved included elbow (86 percent), shoulder (7 percent), knee (6 percent) and metacarpals (1 percent). Involvement of multiple joints occurred in 6 percent. In half the cases, the involvement was bilateral.

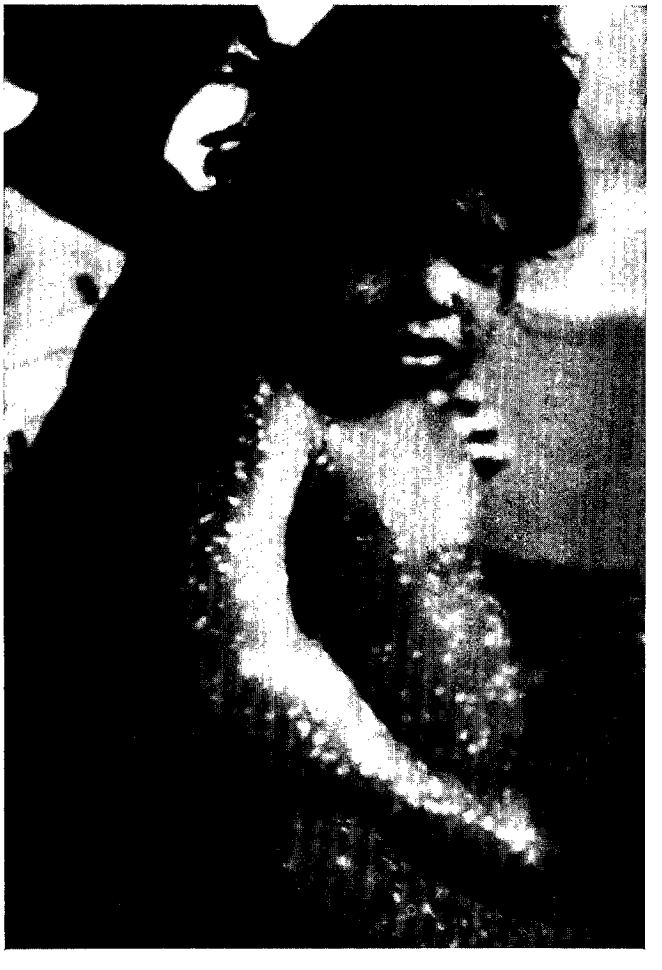
Follow up was possible in two-thirds of the cases; 9 percent had permanent disability and deformity.

This complication occurs late in the course of the disease, usually after the 15th day *(Fig. 4/2)*. The mean day of onset was the 18th day in our series, although it occurred as late as the 29th day. A child in whom the disease has run an apparently normal course, develops sudden rigor, with temperature rising to 103°F to 104°F for a day or two during the scabbing stage. The temperature returns to normal, but on the third day after fever, on careful examination, one can elicit tenderness on pressure on either side of the joint, and in another day or two, effusion occurs into the joint which becomes swollen. The skin over the joint is warm to touch, and stretched. Movements of the joint are limited. If the case is neglected, disorganization of the joint may occur leading to ankylosis.

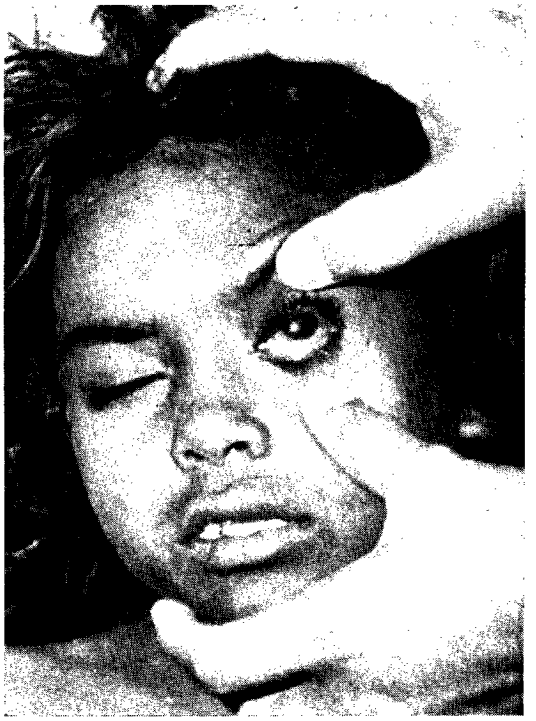
We made no attempts to aspirate the fluid for culture. However, treatment with antibiotics and cortisone appear to have minimized the permanent disability of this complication. The fact that it occurs late in the course of the disease, that it is mostly associated with milder types of smallpox and that it can be successfully treated with antibiotics and cortisone, suggests the possibility that this complication may not be of viral origin. Although it could be a bacterial arthritis, these cases do not have the severe constitutional symptoms usually associated with suppurative arthritis.



4/1. Permanent scars (Pitting) in Smallpox



4/2. Arthritis elbow — Complication of Smallpox



4/3. Corneal ulcer — Result of Smallpox

A special affinity for the elbow cannot be explained. Similar findings have been noted by Cockshott and McGregor (1959) and Chatterjee (1950), in their series of cases.

Frank cases of osteomyelitis have not been noted in our series. It is said that even in cases of the so called arthritis, it is the epiphyseal end of the bone that gets involved first, which results in involvement of the joint later.

OPHTHALMIC

Next to the joints, the eye is most often involved. In the past, smallpox was noted as one of the major causes of blindness. Perhaps, even now it is partly true. Nearly 1.7 percent (116) of the cases of smallpox in our series had some kind of complication or other, involving the eye.

Conjunctivitis

About 10 percent of those, with eye involvement, had conjunctivitis. 80 percent of them were in the vaccinated and 75 percent were females. Only 25 percent of the cases were children under 14. Excepting one, all were associated with the Ordinary discrete type of smallpox, the one exception experienced the Modified type.

In all these cases, conjunctivitis occurred during the course of the disease. In the majority, the eye swabs as well as tears were positive for variola virus. Whether the conjunctivitis was the result of systemic infection with localization, or local variola infection from the lesions on the palpebal margin, one cannot say. The fact that it occurs with the onset of rash suggests that it is a systemic infection with localization, like any other enanthem. The signs and symptoms were slightly different from those of acute catarrhal conjunctivitis. The eye becomes red and congested, with slight photophobia and swelling of the eyelids and a smarting sensation and excessive watering of the eye without any purulent discharge or sticking of the eyelids. Interestingly, this complication was familial in a few cases. In one instance, the husband and wife had the same eye affected and in another family, the mother and two daughters each had a unilateral infection of the same eye.

Conjunctivitis preceding the attack of smallpox is not uncommon and similarly viral conjunctivitis, as the only manifestation of smallpox also is not uncommon. This is discussed elewhere.

Keratitis

A generalized diffused haziness and loss of lustre of the cornea,

later becoming opaque, are the characteristic features of keratitis in smallpox. About 23 percent of the eye complications were keratitis. 80 percent of the cases were children under 14 years and 85 percent of the cases were in the unvaccinated. It is far more common in malnourished and is associated with the more severe types of smallpox. In a third of the cases involvement was bilateral.

Corneal Ulcer

Corneal ulcers occurred in one percent of all cases of smallpox and accounted for nearly 70 percent of eye complications. Unlike keratitis it was not infrequent in the vaccinated; only 60 percent were in the unvaccinated. Between the sexes, it was slightly more prevalent in females (62 percent). Again, two-thirds of cases were amongst the children under 14 years.

It was equally common in the severe and mild types. Three percent of the cases were among those with the Modified type and about 60 percent among those with the Ordinary discrete type.

In 10 percent of cases, the ulcers were bilateral. This complication, unlike keratitis, occurs a little later in the course of the disease. On or about the 10th day, a small area of redness is seen with a small white spot on the cornea, which rapidly spreads; if not treated, it becomes opaque resulting in staphyloma (*Fig.* 4/2). Whether it is viral or bacterial in etiology is unknown. To start with, the lesion is probably viral and when it ulcerates, it may get bacterially infected with resulting scar formation.

Of 53 cases followed, 32 had no residual defective vision, and of the remaining 21 cases, 4 had poor vision and 17 were blind in one eye or the other. Luckily, none were blind in both eyes.

Considering the 60 cases of keratitis and corneal ulcer, followed, 40 percent had loss of vision in one eye, and one in both the eyes.

MISCELLANEOUS

Ear

Ottitis media occasionally occurs during the course of the disease. It is quite possible that smallpox lesions occur on the tympanic membrane also. Temporary deafness also has been recorded during the course of the disease (Kapur 1970).

Parotitis

Inspite of the fact that many cases have confluent enanthem and that oral hygiene is difficult to maintain, few cases of parotitis occur.

In our series, only 1 in 1000 cases developed this complication. It may perhaps be due to the routine antibiotic therapy given to every severe case.

Bedsores

This is one of the inevitable complications of severe cases of smallpox, but fortunately rare. Efficient nursing and early hospitalization can certainly prevent this, in most of the cases.

Cutaneous complications

Secondary bacterial infection may occur in the broken down lesions. Multiple abscesses sometimes occur during convalescence.

Alopecia

Alopecia is not infrequent, following an attack of smallpox.

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5

Prognosis

The prognosis in a case of smallpox depends upon the clinical type of the disease and the vaccinal status of the patient. Vaccination does not confer life long immunity. Immunity naturally wanes, and hence the interval between the last successful vaccination and the exposure to infection is also important in determining the prognosis. Further, it has been noted that hormonal disturbances at the time of infection, particularly in the pregnant, also influence the severity of the disease and so the clinical outcome.

Among the clinical types, Haemorrhagic types are the most frequently fatal and Modified types, the least. *Table* 5.1 gives the details of the case fatality rates of the different types both in the vaccinated and the unvaccinated. In general, there are far greater chances of survival in the vaccinated in all types (*Fig.* 5/1) except the Early haemorrhagic in which, irrespective of vaccination status, all cases are fatal.

Amongst the non-haemorrhagic types, the overall case fatality rates in the vaccinated and in the unvaccinated are about 3 percent and 33 percent respectively. Cases of smallpox in persons who have had both primary as well as successful revaccination are very rarely fatal except in the Haemorrhagic types.

In those who have primary vaccination scars only, there is no correlation between the case fatality rate and the number of primary vaccination scars, if patients of all age groups are considered. But up to the age of 10 years, the prognosis seems to be more favourable in persons who have multiple vaccination scars (*Table* 5.2). There were no deaths amongst children of this age group who had more than 1 scar, except in the Haemorrhagic variety. Under the age of 5 years, all deaths in the vaccinated were amongst children who had only one vaccination scar. The case fatality rates are somewhat less in the 'successfully vaccinated for the first time after exposure' compared to the 'never vaccinated', although the numbers are small and the differences are not statistically significant. Even between the 'never

Table 5.1

Case Fatality in Smallpox by Clinical Varieties and Vaccinial Status

Vaccinal Status	CLINICAL VARIETIES								Total	
	Haemorrhagic		Flat		Ordinary		Modified			
	Cases	C.F.R.	Cases	C.F.R.	Cases	C.F.R.	Cases	C.F.R.	Cases	C.F.R.
Unvaccinated	22	100.0	120	99.1	1296	36.9	15	0.0	1453	42.7
Unsuccessfully Vaccinated	59	96.6	88	96.6	1425	27.2	16	0.0	1589	33.3
Primarily Vaccinated after exposure to smallpox	4	100.0	28	96.4	426	20.6	44	0.0	502	23.6
With primary vaccination scars only	111	94.0	45	66.7	2302	3.3	808	0.0	3266	6.5
With primary and revaccination scars	4	100.0	—	—	75	0.0	53	0.0	182	3.0

Table 5.2

Case Fatality in Smallpox amongst the Vaccinated in 0-9 years group by the number of Primary Vaccination Scars and Clinical Variety

Number of Scars of Primary Vaccination	CLINICAL VARIETIES								Total	
	Haemorrhagic		Flat		Ordinary		Modified			
	Cases	C.F.R.	Cases	C.F.R.	Cases	C.F.R.	Cases	C.F.R.	Cases	C.F.R.
One	3	100.0	4	100.0	79	16.4	22	0.0	108	18.5
Two	1	100.0	1	100.0	39	0.0	42	0.0	83	2.7
Three	—	—	—	—	14	0.0	8	0.0	22	0.0
Four	3	100.0	—	—	17	0.0	33	0.0	53	5.7
Total	7	100.0	5	100.0	149	8.7	105	0.0	266	1.2

vaccinated' and the 'unsuccessfully vaccinated' the latter group shows a slightly lower mortality (*Table* 5.1).

One would expect to find the lowest mortality rates in vaccinated children under the age of 5 years, due to more recent vaccination. The data from our studies (*Fig.* 5/2) however show that the lowest mortality rate is in the age group 10-14 years with maximum rates at the extremes of age. Why infant vaccination, which affords good protection against morbidity, fails to protect against mortality in 0-4 years old children is not known. However, it is noted again that all deaths in this age group among the vaccinated were in those who had only a single primary vaccination scar. Children over 4 years of age may have been vaccinated several times, though no scars are seen, which may also explain a lower mortality rate in the age group 5-9 years.

The prognosis is slightly worse among women in the age group 15-44 years than in men of the same age group, both in the unvaccinated as well as the vaccinated, and both in the Haemorrhagic as well as in the non-haemorrhagic varieties.

Pregnant women fare most poorly with smallpox. They are more susceptible to the severe types, and the prognosis is worse among them (*Table* 5.3). The case fatality rate is about three to four times more than that in the non-pregnant women and men of the same age group. It is about five to six times higher in the vaccinated and twice as high in the unvaccinated when compared with the non-pregnant and men.

It is true, that the haemorrhagic types are more common in the pregnant and that may be one of the reasons for the high fatality rate amongst them. However, as can be seen from the Table 5.3 even in non-haemorrhagic varieties, the pregnant had suffered a uniformly higher fatality rates when compared with the men and non-pregnant women of the same age group.

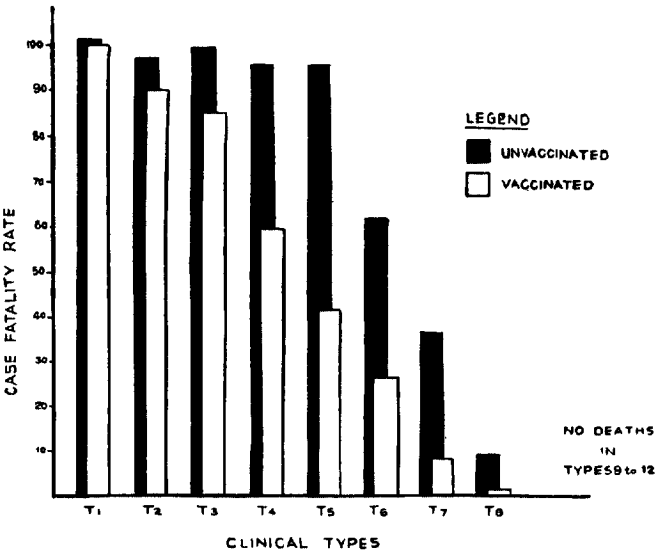
Thus, primary vaccination offers considerable protection from death due to smallpox, while primary vaccination with successful revaccination offers greater protection. Those with multiple primary vaccination scars seem to be better protected against a fatal outcome, at least upto the age of 10 years. Compared with the 'never vaccinated', even those who appear to have been unsuccessfully vaccinated as well as those successfully vaccinated after exposure have a somewhat better chance of survival. The exceptions to all these are the pregnant with smallpox and cases of haemorrhagic smallpox.

Table 5.3

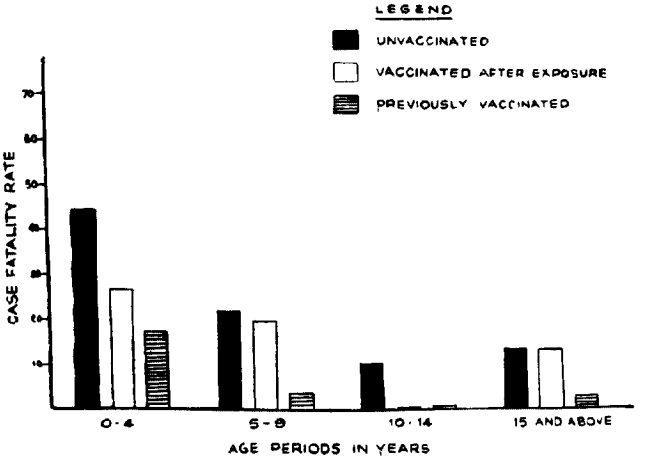
Case Fatality in Smallpox amongst the Pregnant, Men and Non-Pregnant Women

Clinical Varieties	Pregnant (377)			Non-Pregnant (1228)			Men (1720)		
	Vaccinated	Unvaccinated	Total	Vaccinated	Unvaccinated	Total	Vaccinated	Unvaccinated	Total
All Varieties	27.2	61.1	36.6	3.6	34.7	9.6	4.1	30.2	7.8
Non Haemorrhagic	8.7	46.3	14.5	1.9	31.4	7.5	1.9	25.2	5.2

( ) Number of cases of smallpox treated.



5/1. Prognosis in Smallpox — Case fatality with reference to Clinical type and Vaccinal status



5/2. Prognosis in Smallpox — Case fatality with reference to Age and Vaccinal status

Plate 5. Chickenpox — 5th Day of disease

6/1. A case of Pustular Syphilides

6/2. A case of Papular Syphilides

6

Differential Diagnosis

INTRODUCTION

If the diagnosis of smallpox is in doubt, it is better to consider the case as smallpox, rather than the reverse, as only one individual will be the sufferer, whereas if an actual case of smallpox is misdiagnosed, the health of the whole community may be endangered. Most of the recent epidemics in non-endemic areas in the West have been the result of such misdiagnosed first cases. A smallpox case after the rash appears may not present much difficulty in diagnosis, though at times, even for an experienced clinician, about 10 percent of the cases may give rise to uncertainty and require virological confirmation. In non-endemic areas, the cases which are imported from endemic areas are mostly adults who have been vaccinated during childhood and the clinical features, modified by vaccination, may not conform to the standard, classical textbook description. Only after the infection has spread to the indigenous unvaccinated, is the diagnosis of smallpox made. In endemic areas also, such instances of misdiagnosis are not uncommon.

Another problem in the endemic areas is that, particularly during epidemics, many persons with exanthemata are removed to hospital as suspected smallpox, and the clinician has to diagnose them quickly before they are confined to smallpox wards. Therefore, every clinician should know the various conditions that are likely to be confused with smallpox and how they can be differentiated.

In discussing the differential diagnosis, every case of fever followed by rash on the skin has to be considered. Obviously, it is not possible to describe all such conditions in this book. Some of the diseases which the author has seen and a few others, that are likely to be encountered, which may be confused for smallpox are described in this chapter.

During the pre-eruptive stage it is difficult to differentiate smallpox from other diseases such as influenza, measles, dengue-like-fevers, and rubella which may present a similar symptom complex to that of the pre-eruptive stage of smallpox. However, the toxicity, severe headache,

and backache with fever for three days, which are associated with smallpox, may help in differentiation.

Acute Leukaemia is sometimes mistaken for Haemorrhagic smallpox. The toxic, anxious, restless look of Early haemorrhagic smallpox associated with haemorrhages into the skin and/or mucous membrances can help in differentiation.

After the appearance of the rash on the skin, several diseases may simulate smallpox of which the most common are described here.

VIRAL DISEASES

VARICELLA

Chickenpox is the commonest disease that may be mistaken for smallpox. Usually there is no history of fever preceding the rash in chickenpox. If there is fever, it is almost simultaneous with the rash. The majority are afebrile during the appearance of the first two or three crops of lesions. A few cases will give a history of two to three days of fever preceding the rash, but careful examination will normally reveal that there are two or three crops of lesions on the back, to account for the so called pre-eruptive fever.

The actual rash is not centrifugal in its distribution, the lesions are superficial and appear to be 'ON' the skin, are more elipsoid in shape and unilocular, and do not present true umbilication. They contain more or less clear fluid, evolve rapidly, and develop in crops. The last feature results in typical 'pleomorphism' (Plate 11) i.e., in a given area, the lesions appear in different stages of evolution. It is quite common to find pustules, vesicles, papules and macules simultaneously. False umbilication may be present at times, the result of rupture of vesicles. When this occurs, the central portion of the vesicle is completely depressed, the patency of the vesicle is lost and it presents a puckered appearance. Lesions of chickenpox usually have a broad erythematous areola and this is sometimes seen even after the scab is formed.

Haemorrhagic chickenpox, which is very rare, may be confused with the Flat types of smallpox. Even in haemorrhagic chickenpox the lesions are more superficial and they retain their shape in spite of haemorrhages. The pre-eruptive constitutional symptoms of the Flat types of smallpox, which are very severe, are usually absent.

MEASLES

Rarely does a case of measles cause confusion. Though the pre-eruptive history of measles is similar to that of smallpox, the severe upper respiratory catarrh, congestion and watering of the eyes and

flushing of the face, characterise a case of measles and easily differentiate it from smallpox.

However, a rare case of haemorrhagic measles may be mistaken for Haemorrhagic smallpox. Differentiation may be difficult, but the prodromal catarrhal symptoms of measles help.

RUBELLA

Cases of rubella are characterized by a brief mild illness, followed by the development of a pale pinkish papular rash on the body which does not evolve beyond the papular stage. Some desquamation may follow. Tender enlarged suboccipital and post auricular lymph nodes are present.

GENERALIZED VACCINIA

Generalized vaccinia may be difficult to differentiate from smallpox, particularly when it occurs in exposed contacts. It is most common after primary vaccination. The lesions usually appear between the 7th and 14th day after successful vaccination. They look like smallpox lesions. The constitutional symptoms of the pre-eruptive stage are milder than those of smallpox and the lesions are usually discrete, larger in size and have a different distribution to those of smallpox. These cases, if they are admitted to Infectious Diseases Hospital, can be kept along with cases of smallpox. In endemic areas, it is better to isolate the cases of generalized vaccinia, since it is difficult to differentiate them from smallpox. Differentiation can be done by the appearance of characteristic pock lesions on chorio allantoic membrane on culture.

DENGUE AND DENGUE LIKE FEVERS

Dengue and similar arbo-virus diseases like Chikungunya are not infrequently associated with rash on the skin, which appears usually on the 3rd or 4th day of fever. The pre-eruptive constitutional symptoms are almost identical with those of smallpox, though joint pains are a predominant symptom in these diseases. The rash is usually macular, but occasionally is petechial or papular (Plate 12). There is no further evolution of the rash beyond the papular stage. During a recent epidemic of fever caused by Group A Chikungunya virus, a few of these cases were mistaken for smallpox (Ramachandra Rao, 1965).

RICKETTSIAL DISEASES

Among the rickettsial diseases, fever with rash may develop in typhus, a disease common enough in many areas to pose problem in diagnosis.

EPIDEMIC TYPHUS

Epidemic or louseborn typhus is characterized by the sudden onset of fever with rigor, which lasts about four days with severe constitutional symptoms, followed by a rash on the fifth day. The rash starts on the shoulders, then spreads to the axillae, chest and abdomen. It rarely appears on the face. The rash is usually maculo-papular and later fades, thus differentiating it readily from smallpox. The Weil-Felix reaction will be positive for OX 19 and negative for OXK antigens.

MITE TYPHUS

Mite typhus also produces a rash about the fifth day of fever. However, an eschar is usually apparent at the site of the bite by the vector. The rash is mostly maculo-papular and confined only to the trunk, although it may spread to extremities. Pustules do not occur.

TICK TYPHUS

The commonest variety of tick typhus with rash is Rocky Mountain spotted fever. Similar to the other varieties of typhus, the rash appears on the third or fourth day of fever and is morbilliform in appearance. It appears first on the wrists and spreads to the ankles and then rapidly extends over the whole body including the face, palms and soles. In a few cases, the rash is confluent with petechial haemorrhages into the lesions, which appear dark red in colour. The lesions may slough and become gangrenous.

BACTERIAL DISEASES
TYPHOID

Typhoid patients may exhibit increasing toxemia, a sustained or intermittent temperature of about 103°F for one week, and the appearance of maculo-papular rose spots about the end of the first week. These are mainly confined to the abdomen and flanks and fade on pressure. They disappear after three or four days. Rarely is this disease confused with smallpox.

SCARLET FEVER

The rash appears within 24 hours after the onset of fever, but may be delayed by three days or longer. The rash usually appears first on the chest and neck and then spreads rapidly over the body. The trunk is mostly affected. The face is flushed and circumoral palor is present. This rash is more like a diffuse erythema and may last a few hours to 48 hours followed by desquamation. The fever is usually

associated with enlarged tonsils with follicular tonsillitis and patches of exudate. The scarlatinal rash that may occur as the prodromal rash in smallpox may at times be confused with scarlet fever rash.

SPIROCHAETAL DISEASES

SYPHILIS

The papular syphilides, even more than chickenpox, are the commonest condition that is mistaken for smallpox. Several cases of secondary syphilis have been transferred to the Infectious Diseases Hospital as smallpox. The author himself has misdiagnosed cases on two occasions.

One case, a woman of 25 years, with successful vaccination marks of infancy, was transferred to the Infectious Diseases Hospital with a history of fever, headache and backache for three days and a rash of two days duration. The rash was papular and the distribution was centrifugal. The case was admitted as smallpox to the smallpox wards. On observing the case for another three days, it was found that there was no further evolution of the lesions beyond the papular stage and no scabbing occurred. The blood was strongly positive by the VDRL test and the case was transferred to the venereal department of a General Hospital and was treated successfully.

Another case, a woman of 35 years, with a similar history was admitted as smallpox on the sixth day of the disease, with a fairly severe papular rash. The case missed the attention of the author for nearly 4 days, and on the 10th day, when he found the rash still papular, the case was diagnosed as secondary syphilis, and was transferred to the Venereal Department where she was treated with antisyphilitic drugs. The rash almost disappeared in a day or two. About the 10th day after transfer from the Infectious Diseases Hospital, the patient came back with an attack of fever and rash. This time she had smallpox. Presumably she got the infection in the smallpox wards of the Infectious Diseases Hospital during her stay of four days.

In another instance, a boy of 18 years was admitted with a vesiculo pustular rash of about 20 days duration (*Fig.* 6/1) with a typical centrifugal distribution. The onset of illness had been preceded by fever. On examination, he was found to have some hard shining papules as well as vesicles. The duration of the rash was definitely against smallpox. He denied all history of exposure but on examination he had a healed primary chancre. He was transferred to the General Hospital as secondary syphilis.

Cases of secondary syphilis may sometimes give an eruptive history typical of smallpox and the rash may mimic smallpox. However, the papules of syphilis are hard papules (*Fig.* 6/2) unlike those of smallpox

which are really early vesicles. A simple test which we call the 'needle test' is to pass a needle through the papule. The papule of syphilis cannot be split. The indurated feel of the papule, its shining appearance, its readiness to scale, its dull red colour and absence of further evolution are characteristic of the rash of secondary syphilis. Observation for two or three days will usually clinch the diagnosis, since these papules do not evolve further.

DERMATOLOGICAL CONDITIONS

In several dermatological conditions such as lichen planus, erythema multiforme and Stevens-Johnson syndrome, erythema nodosa, etc. one finds a rash, but in these cases, the illness does not have the characteristic pre-eruptive history, nor is the disease so acute as smallpox.

DRUG, FOOD AND ALERGIC RASHES

Rashes resulting from allergic manifestations are quite common and not infrequently cause confusion with smallpox, but the type of rash, itching sensation, and associated other allergic manifestations will usually clarify the diagnosis. A problem arises when both an allergic rash and smallpox coexist, as happened in one instance.

A man of about 45 years had experienced fever for three days for which he was given some white tablets and an injection by a local doctor. On the fourth day he developed some rash and the next day the whole body was covered with a rash accompanied by severe itching. Day by day, it became worse and fluid started oozing out from the lesions. On the 14th day of the rash he was brought on a stretcher to the Infectious Diseases Hospital with an exfoliative type of dermatitis. Immediately he was diagnosed as a case of 'allergic rash' and was given antihistaminics. On a detailed examination of his palms and soles, there were a few deep scabs. Scabs were dug out, when the patient was recovering and they were found to contain variola virus. After the drug rash had completely disappeared small healed scars of smallpox could be seen on the body. It is not unlikely, that patients, who are experiencing smallpox may be treated, during the pre-eruptive stage with drugs, to which they are sensitive. The drug rash may completely mask the smallpox rash. A careful record of the history of the onset, and a thorough examination of the case, will generally help to clarify the diagnosis.

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7

Diagnosis

Majority of cases of smallpox can be diagnosed clinically, though in recent times there has been an increase in the number of cases in which confirmation of the diagnosis by a laboratory is found necessary. Complete dependence on the laboratory findings also is not advisable. An example of a situation of this sort is illustrated by the following case.

A case of suspected Haemorrhagic smallpox was admitted one evening to the Infectious Diseases Hospital, having been transferred from a lying-in-hospital. She was admitted to the smallpox ward. On the following morning, the patient was seen by me on my rounds. She was sitting comfortably in bed, she did not appear toxic, nor did she have the usual anxious look. There were extensive subconjunctival haemorrhages in both eyes, and bleeding from the gums, as well as petechial and maculo-papular lesions on the body, with a few areas of echymosis. She was bleeding per vagina also. Except for the haemorrhages, her clinical condition did not suggest Haemorrhagic smallpox at all. Smears from the papular lesions were examined for elementary bodies and cultured. They were negative for elementary bodies. The patient was treated with the usual haemostatics. After two days, since there was no deterioration in her condition, and it was almost definite that she was not a case of smallpox, she was transferred to a general hospital as a case of idiopathic thrombocytopenic purpura. Two days later, a report from the virus laboratory was received, stating that variola virus was grown on culture. I did not believe it and went personally to see the pock lesions on chorio-allantois. There were only 6 doubtful lesions. I suspected that they were non-specific and gave instructions that they should be passaged. On passage, no variola virus was grown. If smallpox virus had been present, the membrane should have been heavily infected. Obviously the case was not smallpox. Always clinical findings must be carefully weighed in reaching the diagnosis. A definitive diagnosis should never be made on the laboratory report alone. If a proper history is elicited, and a careful and thorough examination is made, there is no reason why the clinical diagnosis should not be correct in the overwhelming majority of cases.

In the developing countries, the history in some cases is unreliable, and absolute dependence on it alone is risky. However, there are three aspects of the history which should be sought for in every case, viz., a history of exposure to smallpox, susceptibility to smallpox and onset of the present illness.

In obtaining the history, the questioning should be indirect, polite and tactful. At no time, should the patient or his relatives be made to feel that some drastic legal action may be taken against them for not notifying the case more promptly. They must be encouraged to talk freely about the illness. It is sometimes useful to avoid the word 'smallpox' itself in questioning.

HISTORY REGARDING EXPOSURE TO SMALLPOX

One should attempt to learn first whether any one in the family or household has suffered from a similar disease or whether any one in the locality, whom the patient visited or whether any one in the school or work spot, where the patient was attending during the two to three weeks prior to the attack, has experienced an illness of this type.

If the source of infection is not revealed by this questioning, it should be determined whether or not the patient has travelled during the last two to three weeks preceding the onset. Detailed information regarding his movements, either in the area or away, should be elicited, including places to which he has been, with the dates, whether anyone else was with him, and whether he came in contact with any person with an illness characterised by rash during the period. If the source is still not apparent, it should be determined whether anyone with such a disease has visited the family during the preceding two to three weeks. Information should also be elicited whether there was any death either in the family or locality due to any eruptive fever during a three week period preceding the date of attack or whether the patient has attended funeral of any person who died of eruptive fever.

These questions will often elicit information regarding the source of infection. Sometimes, however, one may be misled. Though rare, it is not uncommon to find two infections in the same family, chickenpox as well as smallpox. There have been quite a number of such instances in our experience. Recently, we have seen a family of nomad wanderers consisting of a man, his wife, three children and his mother-in-law. One of the daughters was an old case of smallpox and had evidence of pitting. The man was experiencing chickenpox and his wife, smallpox. All the others were admitted to the hospital as 'contacts' but none of them got either of the infections.

HISTORY REGARDING SUSCEPTIBILITY

One should determine whether the patient has experienced a previous attack of smallpox, as evidenced by scars. The incidence of second attacks of smallpox in our series is about 1 in 1000, and they occur only 15-20 years after the first attack.

One should verify the vaccinal status by examining for marks of vaccination. A history of vaccination is of no importance unless it is substantiated by vaccination scars.

History should be elicited reagarding any special conditions (Chapter 15) which might make the persons susceptible to the disease inspite of a good vaccinal status, particularly whether the patient has been suffering from diseases of reticulo-endothelial system, whether the patient has seen on long term therapy with steroids or any other immuno-suppressive drugs or has been receiving deep X-ray or radium therapy. If so, the details of treatment should be elicited. It should also be determined whether or not the patient, if a woman, is pregnant and if so the period of gestation. From these data one would have some idea of the susceptibility of the patient to smallpox.

HISTORY OF ONSET OF PRESENT ILLNESS

History as to the type of onset, the associated constitutional symptoms and their duration, the date of onset and the order of appearance of rash should be elicited. The characteristic pre-eruptive syndrome of smallpox was discussed previously.

CLINICAL EXAMINATION

The clinical examination should be thorough. It should be done by exposing the body of the patient to the maximum extent and examination should be done in good natural light. A definite diagnosis should never be made following examination under artificial light only.

First, one should determine whether the patient has a rash, if so the stage of the rash, and whether this stage is consistent with the history of duration of fever provided by the patient; for example, if a patient has only a papular rash with a history of fever of six days' duration, he is more likely to be a case of smallpox than chickenpox. On the other hand if there are scabs, pustules and vesicles and the interval since the onset is only six days, it is definitely not smallpox. If one always considers carefully the stage of rash observed, and determines whether or not this is consistent with the history, rarely will the diagnosis be missed.

Careful examination has to be done to determine the depth of the

lesions, their distribution, and other characteristics. The important diagnostic triad for smallpox are:

1. A definite pre-eruptive symptom complex or syndrome of fever with constitutional symptoms followed by rash.
2. Deep set lesions in the skin.
3. The absence of pleomorphism at a particular time on any particular area of the skin.

Other characteristics also help to confirm the diagnosis.

Even after eliciting the history and a thorough clinical examination, still if there is doubt about the diagnosis, the case should be considered as smallpox and the Medical officer of Health be informed. Materials (see below) for laboratory examination should be collected and sent to the nearest laboratory, if available. The patient should be vaccinated with known potent vaccine. Observation of the case for two days, will usually clinch the diagnosis, as the characteristic evolution of lesions of smallpox will help. If there is a major reaction following vaccination, this is usually against the diagnosis of smallpox, because rarely, does vaccination of a smallpox case after the appearance of rash, produce major reaction.

LABORATORY DIAGNOSIS

The efficacy of laboratory diagnosis mostly depends upon the nature of collection of specimens, the quantity collected, the method and quickness of their transport to the laboratory. However, diagnosis of a case based on the report of laboratory alone is sometimes dangerous. Clinical and epidemiological findings are much more useful at times where the hospital has no laboratory of its own.

Collection of material:

Readers are requested to refer to the standard text books for details regarding methods of collection and laboratory investigations in diagnosis of smallpox. In this connection it may be stated that WHO publication, on the subject (WHO 1969) may be extremely useful to all Medical officers of Health as well as Medical officers in charge of Infectious Diseases Hospitals. However, some guidelines are mentioned here for ready reference. When a case is seen in the early maculo-papular or papular stage, smears taken on glass slides, of the scrapings of the base of lesions, would be helpful for demonstration of elementary bodies as well as for culture. If a case is seen in vesicular and vesiculo-pustular stage, the best material will be, fluid from the lesions collected in a capillary tube. It will be useful for culture as well as demonstration of antigen by precipitation in gel (PIG). Of the

different methods of collection of specimens, it has been found that cotton swabs and cotton threads soaked in vesicular fluid retain the virus viable for the longest time (Rao et al, 1971). If the case is seen in the convalescent stage, scabs or crusts have to be collected and sent. Besides other specimens, if the patient is seen in the early stages of the disease, a sample of blood taken on admission and another taken during recovery would be ideal for serological diagnosis. In cases of Haemorrhagic smallpox, blood, either citrated or whole, may be collected and sent for culture for variola. But isolation of virus from the blood despatched from distant places is usually difficult because of the time lag.

Simple investigations that can be done in hospitals, which are not equipped with a regular laboratory, are described below.

IDENTIFICATION OF ELEMENTARY BODIES IN STAINED SMEARS

Microscopic examination for the presence of elementary bodies in smears of scrapings taken from early papulo-vesicular lesions of smallpox is a simple method for provisional diagnosis. Indentification of elementary bodies by an experienced person is very helpful in majority of the cases. However, a negative finding is of no importance. There are several staining methods but Gutstein's is simple and quick. The following is the procedure:

Clean the surface of the lesion gently with cotton wool soaked in alcohol, and allow to dry. With a sterile needle or scalpel, split a few lesions, dab the fluid with sterile cotton wool, and scrape the base of the lesions with the needle and spread the material on 4 to 6 clean glass slides. Allow the smears to air-dry.

Fix the air-dried smears, in either acetone-free methanol or ethyl alcohol, for about half an hour. To prevent evaporation, it is better to keep the slides covered with alcohol in a closed petri dish. Wash the alcohol off the slides with water, and place the slides again in a fresh petri dish. Mix equal volumes of freshly prepared aqueous solutions of 1% methyl violet and 2% sodium bicarbonate in a test tube. Filter the mixture on to the slides in the petri dish through a filter paper. Keep the petri dish covered at room temperature or in an incubator at 37°C for 20 to 30 minutes. Take the slides at the end of the time, rinse with distilled water and air dry. Examine the smears under an oil immersion lens.

With this method of staining, elementary bodies of variola are seen in large numbers as sheets of uniformly stained light purple, or violet or pink spherical bodies about 1/4 to 1/5 the size of staphy-

lococci. Staphylococci and streptococci stained by this method are dark blue and can be readily distinguished. Sometimes tissue debris may look like elementary bodies, but the debris is dark blue in colour, and not uniformly stained. However, elementary bodies of variola, cannot be differentiated from those of vaccinia and cowpox.

DETECTION OF ANTIGEN AND ANTIBODY BY 'PRECIPITATION IN GEL' TEST

If a case is seen late in the vesiculo-pustular stage, when it is rather difficult to identify elementary bodies in stained smears, the fluid, can be taken from about six to eight vesicles for detection of antigen by the 'precipitation in gel' technique (WHO 1969). The precipitation lines sometimes appear as early as six hours and so this test is of great help to the clinicians. This can also be employed to detect antigen in the sera of Early haemorrhagic smallpox cases, where diagnosis is otherwise difficult in the pre-eruptive stage. All other methods require not less than 48-72 hours to provide information and require an experienced virologist as well as an equipped laboratory. Although the virus has to be grown for final confirmation of the diagnosis, clinical findings confirmed by the presence of elementary bodies in stained smears and a positive 'precipitation in gel' test are usually quite sufficient.

Sometimes, clinicians are faced with the problem of diagnosis in a person who presents himself with scabs or scars of a recent attack. If there are scabs, these could be collected for viral culture. But if the patient has no scabs at all, or if there are no laboratory facilities for culture of virus, diagnosis becomes a problem. Presence of a high level of CF, HI and neutralising antibodies in the sera may be suggestive of a positive diagnosis of smallpox. But in a previously and recently vaccinated person, it may not be possible to diagnose the case as smallpox, by the titre of these antibodies alone, unless the titres are very high or there has been at least a four-fold rise in the titres in paired samples of sera taken one in the acute stage and the other during convalescence. Further even for these studies, there should be a well equipped laboratory. Recent studies (Rao et al, 1970) have shown that the 'precipitation in gel' test would appear to be of great use, both for diagnosis in acute stage by detection of antigen in the lesions, as well as in convalescent stage retrospectively by detection of precipitating antibodies against variola antigen in the sera. However, one has to be guarded in interpretation of the results of this test, especially in detection antibody.

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8

Treatment

INTRODUCTION

In the absence of any specific antiviral drug, the treatment of smallpox is mostly symptomatic and is directed to alleviate the suffering of patients and to prevent secondary bacterial complications. Basically, it consists of the use of palliative drugs and antibiotics, good nursing care and an adequate nutritious diet.

DRUGS

No specific drug has so far been found to be effective against smallpox. Several have been tried (see chemotherapy) but none have yet proved to be of any value. The milder cases of smallpox normally do not require any drugs except sedatives.

Cases of the Early haemorrhagic type are invariably fatal. Nothing has so far been discovered that can save them. The patients themselves are aware of their impending death and therefore it is necessary to keep them quiet by using hypnotics. Antibiotics are of no use. To replace blood loss, whole blood, dried plasma and fresh blood have been tried but with no effect.. Human fibrinogen has also been administered to correct the blood clotting defects, but again with no success. All types of haemostatics and styptic drugs have been tried and found to be of no use.

In Late haemorrhagic cases, about 8 to 10 percent may survive. Vitamins C, K and P, (Styptobion) adrenochrome monosemicarbazone (styptochrome) and tissue extracts (Claudine and Coagulum Ciba) have been tried but in the absence of any controlled studies, their efficacy cannot be assessed.

Since cases belonging to types 2 to 7 normally survive beyond seven days, it is possible that secondary infection of local lesions or septicemia may occur and to prevent it, antibiotics can be used. In the Infectious Diseases Hospital, Madras, crystalline penicilin in a dose of 0.5 million units, is administered intramuscularly every six hours for about four to six days. Intramuscular chloromycetin suc-

cinate in a dose of 0.5 — 1.0 G. twice a day is then substituted and administered until a total of about 10-12 G have been given. No special claims are made for this regimen. No controlled studies have been made and it is quite possible, that the mortality rate and the incidence of complications may not have been influenced by their use. This is further suggested by the fact that smallpox mortality rates are little different now than what they were in the pre-antibiotic days. Downie (1959), has stated "in our older studies on smallpox, the importance of bacterial infections as a cause of death was emphasised, and the morbid anatomy was complicated by evidence of superadded infection with streptococci and other organisms. Recent observations indicate that although bacterial infection and particularly broncho pneumonia may contribute to a fatal issue, it is not an essential feature of pathology, nor is it responsible for the high mortality in variola major. Although antibiotic treatment was used in the outbreaks in Britain during 1949 to 1953 there were 32 deaths amongst 115 cases (mortality rate 28 percent). Blood cultures made before death in fulminating cases frequently fail to reveal bacteria and cultures of unbroken pustules are usually sterile". This is also our experience.

Itching is a frequently associated symptom and especially children scratch the lesions leading to secondary bacterial infection. Trimeprazine tartrate (Vellergan) has been used successfully to reduce the itching. It has a helpful sedative effect also.

External application of drugs does not alter the course of the disease or the evolution of lesions. Potassium permanganate baths have been used by older physicians, but in a tropical climate the patients find them most uncomfortable, and they prefer only an oily application to relieve the sense of skin tension, which most of the confluent cases experience. In the Madras Infectious Diseases Hospital, eucalyptus oil and cocoanut oil in a proportion of 1:7 is applied freely to the body twice daily after the seventh or eighth day of disease. Although of no medicinal value, the patients are far more comfortable. Eucalyptus oil also minimizes the offensive odour that emanates from the Confluent smallpox cases.

NURSING

Good nursing is of far more importance than any other form of treatment. It is difficult to nurse a case of smallpox. The patient himself often feels that he is a nuisance to himself, as well as to others. He is uncomfortable physically and mentally. Kind words pleasing bedside manners, assurance and moral support, go a long way in helping a smallpox patient to recover.

Special attention has to be paid to oral hygiene, care of the eyes and prevention of bedsores. Cases with severe enanthem in the mouth

are prone to develop parotitis. Frequent cleaning of the mouth with antiseptics will minimize this complication.

Sticky sputum may trouble patients and they may not be able to expectorate. Frequent cleaning of the throat is essential, and in cases, where the respiratory tract is severely involved, suction apparatus may have to be employed to clear the passages. All discharges are highly infectious and attendants must be very careful in their handling and disposal.

Daily bathing of the eyes with normal saline or boric lotion and the application of antiseptic eye drops is helpful in the majority of cases. No drugs can prevent viral involvement of the eyes, but secondary infection of these lesions can be prevented by using an antibiotic ointment. Chloromycetin "applicap" in single dose dispensers are very useful. Early detection of lesions in the eye and treatment may help to prevent extensive and permanent damage.

In patients with severe rash, it is difficult to prevent bedsores, since the patients cannot move so easily. Further, due to constant lying on the back, the lesions break down due to pressure, leaving raw ulcers. The bed linen then gets stuck to these ulcerating lesions, which become secondarily infected. Application of oil to the body helps to prevent this difficulty to some extent, but a more convenient method in tropical countries is to spread a full sized banana (plantain) leaf on the bed, smear a little oil on it, and keep the patient on it and cover the patient. The patient feels much more comfortable and cool, and the adherence of bed linen to the lesions can be avoided. The leaf has to be changed, of course, at least once a day if not more frequently.

Glycerine enemas may be administered whenever required. In some cases, there is retention of urine due to lesions occurring on the urethral mucous membrane and also at the external meatus. As far as possible, catheterization should be avoided and patients encouraged to pass urine. When necessary, catheterization should be done with the utmost aseptic precautions, to prevent infection of lesions which are broken down.

Hyperpyrexia should be controlled by appropriate hydrotherapy and antipyretics.

The scabs of smallpox patients are potentially infectious and their proper disposal is of paramount importance to avoid transmission of infection. The best method is incineration. It is difficult to ensure proper collection of all the scabs. Scabs on the palms and soles have to be carefully removed after they are completely dry, with the help of a needle, curved scissors or scalpel. A little softening with oil before removal may help. Removal of these scabs requires experience and

skill, since in inexperienced hands, removal may leave bleeding ulcers which may become secondarily infected, when an antiseptic dressing should be used.

Visitors must be properly regulated. Prohibition of visitors is not advocated at least in endemic countries like India. If this precaution is enforced, cases may be hidden at home, and notification will be still poorer. Experience has shown that with a few elementary precautions, there is no additional risk of spread of infection in the community. All visitors should be checked at the entrance to the hospital itself, to determine whether they have been recently sucessfully vaccinated. Only protected persons should be admitted. Pregnant women, irrespective of their vaccinal status, should not be allowed to enter the smallpox wards because of the high mortality, should they contract the disease during pregnancy. Visitors should never be allowed to handle the patients, their clothes or the bed. They should be prevented from sitting on the floor lest they carry home some infective dust on their clothes. These elementary precautions appear to be quite sufficient at least for endemic areas.

Changing of bed linen and the patient's linen is associated with release of virus into the air. Hence the nurses should handle the linen carefully and with minimum of agitation. The soiled linen, after change, should immediately be immersed in a disinfectant lotion to prevent the release of virus.

Since most of the virus released from the patient, as well as from his linen, settles on the floor in the form of infective dust, dry sweeping of the floor should never be done. The floor should be cleansed only by washing or wet swabbing, so as to prevent the dust from rising and contaminating the atmosphere.

DIET

There is no need for restriction of diet. During the acute stage, it is likely that the patient may become dehydrated partially due to loss of fluid into the lesions. Patients should be encouraged to take plenty of fluids like barley water, milk, fruit juice etc. If necessary, intravenous fluids may be administered. Solid foods like bread, biscuits, etc., can be given if the patients can swallow them without discomfort. During convalescence, patients feel unusually hungry and they must be given an adequate and nutritious diet to minimise the period of convalescence.

TREATMENT OF COMPLICATIONS

RESPIRATORY

Respiratory complications, whether viral or bacterial, can be treat-

ed only with antibiotics. Any of the broad spectrum antibiotics in heavy doses may help.

NEUROLOGICAL

Encephalitis cases do not require special drugs. Recovery is spontaneous in the majority, although special nursing is required. Feeding has to be done through a feeding tube. Retention of urine is common and catheterization may be required. These patients also have a tendency to develop bedsores. The nurse should turn the patient frequently to prevent pressure sores. Though some physicians claim that these cases can be treated successfully with corticosteroids, yet it is doubtful whether they are really needed at all. Further there may be a risk in using steroids at this stage of the disease.

OSTEO-ARTICULAR

Early detection of this complication is most important for successful management of the case. Since this complication occurs late in the course of the disease, when the patients have recovered, these cases can safely be treated with corticosteroids. The routine treatment in the Madras Hospital was immobilization of the joint and administration of phenylbutazone with cortisone (delta butazalidin), one tablet three or four times daily, together with a broad spectrum antibiotic for a period of seven to ten days. In young children the dose is correspondingly less. Cases detected early, and treated thus, have rarely developed disorganization of the joint.

OPHTHALMIC

Cases of conjunctivitis are treated by bathing the eyes with either normal saline or boric lotion and the application of Chloromycetin applicaps. In cases of corneal ulcer, the same treatment is employed. Atropine drops are also instilled in the eye. In keratitis, in addition, heavy doses of vitamin A are given intramuscular to help healing. Local applications of cortisone to the eye, in any form are scrupulously avoided.

BEDSORES

Sloughing sores are dressed with eusol solution and when granulation tissue is formed, they are covered with an acriflavin-shark liver oil dressings.

CORTICOSTEROIDS IN THE TREATMENT OF SMALLPOX

The use of corticosteroids in the treatment of smallpox is a subject of controversy. Several clinicians believe, that they help in the treat-

ment of severe Confluent cases. However, no controlled studies have been done in support of these claims. On the other hand, many clinicians have found that cortisone has clearly been harmful in treatment of some viral infections. The local application of cortisone in corneal herpes has been found to prolong the acute phase of corneal infection and delay the onset of healing. Similarly, in varicella "cortisone should be avoided as its usage seems to favour the development of severe complications and haemorrhages" (Rhodes and Rooyan, 1962). In our view, corticosteroids are likely to interfere with the normal defence mechanisms if they are administered in the early stages. In monkeys with experimental smallpox cortisone has been shown to enhance the disease resulting in the Haemorrhagic variety and death (Rao et al, 1968). Even in the treatment of corneal ulcer, cortisone ointment with locally acting antibiotics is likely to endanger the eye. None of the antibiotics have any action against the virus, and the ulcer is likely to spread more rapidly under cortisone. Since an initial experience in which cortisone was used in a few cases and the small corneal lesions spread rapidly, resulting in ulceration of the entire cornea in two days, the use of cortisone has been abandoned in our hospital.

In cases of arthritis, a very late complication, corticosteroids may be used with no untoward effect.

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9

Chemotherapy And Chemoprophylaxis

During the last decade, considerable work has been done in the field of viral chemotherapy and chemoprophylaxis. Thousands of drugs have been screened for antiviral activity, but few have withstood *in vitro* tests. Innumerable problems must be solved before a drug can be placed in the hands of a clinician for even limited clinical trials. Such trials must be undertaken by competent persons and should be strictly controlled, and double blind.

Though smallpox has been eradicated from several countries yet in these days of jet travel, as long as it is prevalent somewhere in the world there is always a possibility and risk of importation of infection from endemic areas like India, Pakistan etc., into these countries which are free from the disease. This danger poses very important problem in the non-endemic countries. The imported cases might produce very severe though not widespread, localized epidemics. Perhaps there is adequate machinery to control the spread of infection but in several instances, the first cases have often been missed resulting in a number of unprotected people being exposed to infection without their knowledge. Since the basic immunity in those countries is very low, the type of disease is also likely to be severe, resulting in high mortality. Secondly, such an unusual occurrence as an outbreak of smallpox will produce a great scare in the population resulting in people rushing for vaccination, inspite of the fact that it is almost improbable, if not impossible, that all of them will contract smallpox. This unnecessary scare not only creates problems of an administrative nature, but also in such an unprotected population complications due to vaccination will be numerous. Thirdly, chances of prevention of smallpox by even a successful vaccination in persons who have already been exposed, are rather remote. The same is the case in endemic areas, where cases are detected very late in the course of the disease, when vaccination of contacts at that stage of exposure may not be of much use. Hence antiviral drugs, if available, would be helpful for administration to contacts of patients, who come to recognition late in the course of the disease.

In recent years, hyperimmune gamma globulin (Kempe et al, 1961) has been proved to be of some value as a prophylactic agent among contacts exposed to smallpox. This drug, however, is difficult to produce and is available only on a limited scale.

Also on the therapeutic side, there is no specific drug to treat cases of smallpox, since none of the antibiotics which are useful in bacterial infections have been found to be in any way effective either in reducing the mortality or even modifying the course of the disease. Hence there is a great need for antiviral drugs to treat cases of smallpox.

The important compounds found so far, to possess some antiviral activity against smallpox virus, belong to the groups of thiosemicarbazones, pyrimidine derivatives, and sulphones.

The antiviral activity of thiosemicarbazone was first reported by Hamre et al (1950), but little work has been done with it until recently. Various derivatives of the thiosemicarbazones have been screened for their antiviral activity by Thompson et al (1953), Bauer and Sadler (1960 a & b), Shefield (1962). It was found that this group of compounds inhibits multiplication of rabbit pox virus in tissue culture cells at concentrations that are not toxic for the cells. Easterbrook (1962) showed that these compounds affected the last stage of the pox virus growth cycle, but Appleyard et al (1965), found that these drugs do not seem in any way to prevent the synthesis of viral DNA. Polikoff et al (1965), have claimed that the antiviral activity of isatin beta thiosemicarbazone is due solely to its virustatic activity. Squires and McFadzean (1966), suggest "it would appear, that in mice injected with neurovaccinia and treated with certain thiosemicarbazones, some interfering substance is probably produced and plays an important part in protection observed; this may be different from interferon". Of these compounds, Bauer (1955), has especially studied the 'isatin beta thiosemicarbazone' which was found to confer complete protection against death and the development of symptoms in mice infected intracerebrally with as much as 100,000 Ld 50 of neurovaccinia virus. The studies suggested that this drug might be a possible chemoprophylactic and chemotherapeutic agent for smallpox. Less toxic derivatives were sought by altering the structure of the parent compound. Several were obtained including N-methyl-isatin beta thiosemicarbazone, known as Marboran (Burrows Welcome). Simultaneously work has been done with other derivatives including 4 bromo-3-methyl-isothiazole-5-carbaxaldehyde thiosemicarbazone or M & B 7714 (May and Baker).

Various studies suggest that antimetabolites, particularly pyrimidine analogues may be useful. Amongst these the halogenated pyrimidines especially, 5 Iodo 2 deoxy uridine (IUdR) has been found to inhibit the biosynthesis of DNA and in addition to be incorporated

as IUdR 5 phosphate into DNA in place of thymidine 5 phosphate. This opened a new field in the application of these halogenated derivatives in treatment of DNA viral infections. Kauffman (1965) has reported that IUdR is effective in herpes simplex keratitis, both in rabbits and human beings. Similarly, occular lesions with vaccinia have also been treated and the results have been uniformly encouraging.

In clinical trials, Calabresi (1965) has found that IUdR was more effective than other related agents, in suppressing vaccination 'takes' among patients who were vaccinated during chemotherapy. However, he found no suppression of the immune response. He has also treated successfully a patient with progressive vaccinia. The drug appears to be effective in topical application but it is too toxic when administered parenterally. These compounds are being studied further.

Collaborative studies at Yale University and at the Institute of Organic Chemistry and Biochemistry at Prague, have revealed that an antimetabolite, 6 Azuridine or Azuracil riboside exerts a profoundly toxic effect on certain types of neoplastic cells in man, with little toxic effect on normal cells. This drug inhibits the biosynthesis of functional pyrimidine at the level of conversion of orolidylic acid into uridylic acid. Rada and co-workers (1960) found that this drug exhibits an inhibitory effect on the growth of vaccinia virus and the results of a few clinical trials have suggested that the drug may be useful either in the prophylaxis or therapy of smallpox.

Another group of drugs found to be potential antiviral agents, are sulphones. The urea derivative of the diphenyl sulphone (CG 662 Chemie-Grunenthal, Germany) has been found to be an effective antiviral agent in the experimental animals which suggests its possible use in the Chemoprophylaxis and chemotherapy of smallpox.

Amongst the drugs found suitable for clinical trials in man, the following have been evaluated by the author at Madras.

1. 4 bromo-3-methyl - isothiosole-5-carbaxaldehyde - thiosemicarbazone (M & B 7714).
2. N-methyl isatin beta thiosemicarbazone (BW 33T57)-Marboran
3. The urea derivative of diphenyl sulphone (CG 662).
4. 6 Azuridine.
5. 5 iodo-2-deoxy uridine. (IUdR)

Clinical studies were made on 1300 cases of smallpox with M & B 7714 (Rao et al, 1965) (Ramachandra Rao et al, 1966a) on 423 cases with Marboran and 684 cases with CG 662 (Rao et al, 1969a) to find out their therapeutic effect in treatment of smallpox. None of the three drugs have exerted any beneficial effect either in reducing the mortality or altering the course of the disease. On the other hand,

M & B 7714 as well as Marboran have produced nausea and vomiting in a few cases. Hence none of these have a place in chemotherapy in smallpox.

The other two drugs, 6 Azuridine and 5 IUdR (5 iodo-2-deoxy uridine) are still under trial. Both drugs have to be administered by the intravenous route which is rather difficult in the severe cases of smallpox.

Although none of these agents can replace vaccination as a prophylactic, as soon as the first reports were made regarding trials with one of the drugs, Marboran (Bauer et al, 1963), many press reports in India stated that 'at last a drug has come to replace the much dreaded vaccination'. This was most unfortunate, for vaccination alone can prevent smallpox. The antiviral agents can only suppress or prevent the development of the disease, in an already infected person, in whom vaccination may or may not be of value.

We (Ramachandra Rao et al, 1966b) have studied the chemoprophylactic effect of the drug M & B 7714 in exposed contacts (familial) of smallpox and found that in the drug treated group there were 40 cases of smallpox with 7 deaths among 196 unvaccinated contacts as against 60 cases with 12 deaths out of 201 unvaccinated contacts treated with a placebo. The difference in the incidence of smallpox was significant at the 5 percent level, but there was no significant difference in case fatality rates. It was concluded that "because of the toxic effects of the drug and relatively small reduction of the case incidence achieved, M & B 7714 is not recommended in the routine prophylaxis of smallpox although its use might be indicated in special circumstances".

Bauer et al (1963) have reported a marked prophylactic effect of Marboran in prevention of disease among contacts exposed to smallpox. However, studies made by the author (Rao et al, 1969b) did not confirm the findings of Bauer. Similarly the CG 662 also was not found to have any chemoprophylactic effect in contacts exposed to smallpox.

However, these few trials that have been done in prophylaxis seem to be more encouraging, than therapeutic trials. Further studies are required before any of the drugs can be recommended for routine field use.

Recently two indigenous drugs have been studied for their antiviral activity, one at the Haffkine Institute, Bombay, and the other in our laboratory at Madras.

Dutta et al (1968), have isolated three essential principles from seeds of Banakadali (Ensete superbum) which have been found to inhibit the growth of vaccinia and variola on the chorio-allanotic mem-

brane of chick embryo. In mice infected with variola this drug seemed to have prevented the disease and significantly cured the disease even when the drug was given in late stages of infection. Thus the authors opined that these drugs "hold the possibility of being useful in treatment of smallpox". The drug is administered orally. The seeds in the form of a crude powder were used in the treatment of 110 cases of smallpox in our hospital with a placebo in 98 cases, but there was no difference either in the case fatality rates or on the course of the disease. It should however, be admitted the dosage administered was very small. Perhaps the active principles isolated now may have some therapeutic or prophylactic effect in human smallpox. Trials are under way.

Another indigenous drug that has been found to have antiviral activity in our laboratory (Rao et al, 1969c) is the aqueous extract of tender leaves of the Neem tree (*Melia azadericta*). A 10 percent aqueous extract of these tender leaves is not toxic either to the chick embryo tissue culture or to the chorio-allantoic membrane of chick embryo. This extract inhibited the growth of vaccinia virus both in tissue culture and on chorio-allantoic membrane and variola virus on chorio-allantoic membrane. Further, five minutes contact with the virus seems to be sufficient to destroy the virus. Studies are being made to isolate different extracts of these leaves subject them to further trials for their antiviral activity in experimental animals in our laboratory. Work also is being done to see how far antiviral activity of this indigenous plant can be given a practical application in disinfection of infected fomites, besides its use in chemoprophylaxis and chemotherapy.

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SECTION – 2

EPIDEMIOLOGY AND IMMUNOLOGY

10

Introduction

Our knowledge of smallpox is very limited and there is enough scope for study of this disease in its various aspects. It is rather improper to think that there is less need for such studies now, simply because a programme for global eradication of smallpox has been launched. Of course we have a potent tool to control, and perhaps even to eliminate, this disease from the world. Yet to presume that vaccination and vaccination alone is the answer to this vast problem and forget all other aspects, is dangerous. Further, as the incidence of the disease decreases, we may meet with several situations, where a greater knowledge of the disease and its transmission in a community will become more and more essential. Apart from this, these studies will be of great assistance immediately, in organizing the various control measures and the strategy of the eradication programme itself.

Although there is only a single agent of infection, the variola virus, the response of the human host to the infecting agent varies greatly from person to person. On exposure to infection, not all the persons so exposed, do get the disease, and even among those who develop the disease, the manifestations, the severity, the clinical outcome and perhaps even the immune response, vary to a very great extent.

For transmission of disease, there should be an agent of infection (infecting organism), a source of infection which is capable of infecting a host who should not only be susceptible to the reception of the agent of infection but also to its multiplication in his body, and more than these, the environment in which the source and the host meet should be congenial and favourable. Only then, will there be successful transmission of disease.

Thus the causation of disease in an individual and the spread of the disease in a community, seem to be the result of a complex pattern of several determining factors, which may pertain to the infecting organism, the source of infection, the host and the environment. A study of the transmission pattern of the disease and of the various 'disease determinants' is the study of epidemiology of smallpox. This section is devoted to consideration of these aspects of the disease.

11

The Agent Of Infection

The causative organism or the agent of infection in smallpox is a filtrable virus falling under the group 'pox virus' and is termed 'pox virus variolae'. Antigenically similar to this virus, are the viruses 'pox virus bovis'—(Cow pox) and 'pox virus officinale' (Vaccinia). Pox viruses which affect animals and birds have also some common antigenic components with pox virus variolae. The two variants of variola virus viz., the one that produces variola major and the other that produces variola minor (Alastrim) are almost antigenically identical and they induce cross immunity. The third variant, 'variola intermedius' isolated recently from cases of smallpox in Tanzania seems to lie in its characters, between variola major and variola minor but it is more like the latter in several aspects.

MORPHOLOGY

Variola, one of the large viruses, was first demonstrated microscopically as small spherical bodies by Bruist in 1887 in the material from pustules. These bodies were again described by Paschen in 1906 and since then, they have been known as 'Paschen-Bruist bodies', 'Paschen bodies' or 'Elementary bodies'. Demonstration of these bodies, in stained smears of material taken from lesions, is considered fairly diagnostic. They are small about the size 300 x 250 millimicrons (one-fourth of the size of staphylococci) and almost spherical in shape. With suitable staining techniques, they can be demonstrated in large numbers in smears taken from lesions, especially during the early stages of the disease. Under the electron microscope, these bodies are reported to appear brick shaped, almost indistinguishable from those of vaccinia.

HOST RANGE

The monkey appears to be the only animal, besides human beings, which may develop clinical smallpox similar to that in man, both in nature as well as in the laboratory. Monkeys can be infected by different routes. Application of virus on the scarified skin, intradermal inoculation, intranasal instillation, intravenous administration, inhala-

tion of virus aerosol in a cloud chamber, etc., are all followed by generalized rash, which is quite similar to smallpox in man in its distribution, evolution etc. However, the disease in monkeys is almost non-fatal (Westwood et al, 1966), except in the pregnant, where it is fatal (Rao et al, 1968). Rabbits and calves are not easily susceptible. Intracerebral inoculation of mice may be helpful only for experimental purposes since this is not followed by any generalized rash.

CULTIVATION OF VIRUS

Variola virus can easily be grown on the chorio-allantoic membrane of a 10 to 12 day old developing chick embryo. It produces, after inoculation, small dome-shaped greyish white, pock like lesions on the membrane, after 48 to 72 hours of incubation at 35°C to 37°C, (variola virus may not grow at temperatures above 37°C). These lesions can be distinguished from those of vaccinia, which produce less convex and bigger lesions and have a tendency to central necrosis and haemorrhage. Usually the embryo survives unless the dose of inoculum is heavy.

Variola virus can be grown on tissue cultures also. Several cell lines are used, the common ones being monkey kidney, Hela, Hep 2, human embryonic skin etc. Maximum cytopathic changes are seen rather late, beyond 72 hours. The infection, however, can be detected early, by haemadsorption technique using sensitive fowl red cells.

ANTIGENIC STRUCTURE

There appears to be only one antigenic type, variola major and variola minor being almost similar antigenically. The antigenic structure of variola virus is rather complex and has not been well studied. However, it seems to comprise of V antigens which are bound to the elementary bodies, and soluble LS antigen. Besides, there is haemaglutinin which is also soluble. All these play a part in the several antigen-antibody reactions which are employed in serological diagnosis. It is not possible to differentiate variola major, variola minor and vaccinia by these serological tests since these three share common V, LS and haemaglutinating antigens. It is claimed that variola and vaccinia virus share a common protein antigen which is responsible for resistance to infection. Though not proved, it is suggested that variola virus also has a virulence and invasiveness antigen, which is supposed to have been lost or modified, when variola virus is transformed into vaccinia virus by repeated passage in animals in the laboratory, which perhaps may explain the difference in their responses, in the human host, of these two antigenically similar viruses. So far as is known, there is no definite evidence to indicate that there is variation in the

virulence amongst various strains of variola virus isolated from cases of different clinical types.

RESISTENCE TO PHYSICAL AND CHEMICAL AGENTS

Variola virus is one of the most stable viruses. It resists drying and freezing. In the moist state, it is stable for several months at —20°C. In a dry form, it is stable even for years, when kept at 0°C. Virus can be isolated from scabs, kept at room temperature, even after several months and if kept at below 0°C for several years. The less the relative humidity, the greater is the viability at room temperature. Results on studies on the viability of virus in fomites is discussed elsewhere (Chapter 12).

The virus is reported to be quite sensitive to ultra-violet and gamma rays. Exposure to sun in tropical countries for a few minutes to 3 hours was found to destroy the virus in the free state.

The virus is relatively resistant to ordinary coal-tar disinfectants in the usual dilutions. Contact with 1:40 dilution of lysol or carbolic acid or white fluid for 12 hours, perhaps, would be required to destroy the virus. Oxidizing agents like 10 percent potassium permanganate solution has been reported to be virucidal on prolonged contact. Formaldehyde is employed for disinfection work. Chlorine compounds and chloromines are reported to be better virucidal agents. Recent studies in our laboratory (Rao et al, 1969) have shown, that aqueous extract of tender leaves of Neem tree (Melia Azadericta) destroys the virus very quickly in a matter of minutes. Work is being done to see how far this property could be utilized for disinfection of infected clothes and infected surfaces.

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12

Sources Of Infection And Their Infectivity

A case of smallpox is the most important and the commonest source of infection for smallpox outbreaks. In endemic countries like India, detection of the source has been always very difficult. In epidemiological investigations of smallpox outbreaks, the investigator should never rest content, until and unless the human source has been traced out. However, there have been a few instances, where despite the possible best efforts on the part of the investigator, no human source could be found, with the result it was presumed that some inanimate sources have played a vital role in the transmission of the disease. Though rare in tropical conditions, the possibility of inanimate sources as possible causes of smallpox outbreaks cannot be altogether ruled out. Similarly there may be some non-human animate sources also, and our knowledge about these is still very meagre. Broadly speaking, the sources of smallpox infection, therefore, can be human, non-human animate, and inanimate.

Human Sources and their infectivity

Case: This is the commonest source for the spread of infection. Whether it is a notified case or a death due to smallpox at home, it is a source till the day of last contact, i.e., the day of isolation or the day of death of the case.

Mis-diagnosed case: Misdiagnosis of the first cases in smallpox outbreaks has become quite a common feature in non-endemic countries nowadays. Almost all the recent smallpox outbreaks in Western countries were the result of such wrong diagnosis. It is reported that in majority of these, it was the third or fourth generation case, that was diagnosed correctly as smallpox. To quote a few; the Bradford epidemic of 1962 started from a case of smallpox imported from Pakistan, misdiagnosed as Malaria, and in a more recent epidemic of variola minor in Birmingham in 1966, only after about 25 cases have occurred, a correct diagnosis was reported to have been made. Such misdiagnosed cases may remain at home without isolation or, even if they are admitted into

hospitals, they are not segregated from other cases, with the result they are likely to spread the infection in the community. In this country also, it is not uncommon for physicians to misdiagnose cases of smallpox as chickenpox or some dermatological condition. During epidemics of chickenpox, several such misdiagnosed cases of smallpox are likely to remain at home. This may be one of the reasons why smallpox outbreaks usually follow outbreaks of chickenpox, although these two viruses have absolutely nothing in common.

Hidden case: Hiding cases from local health authorities is almost a normal feature in endemic areas. The public health staff cannot easily detect them even during their routine house inspection, because such cases are kept in locked rooms, lumber rooms, in attics, behind heaps of rubbish or fruit (Ramachandra Rao et al, 1966) etc. From a study of 362 consecutive cases during the year 1965-66 at Madras, the author found that only 255 were voluntarily removed to the hospital, 86 were detected by the public health staff, and 21 were deaths detected at the burial grounds at the time of disposal of the dead. Thus, nearly 6 percent of the total cases were undetected while they were alive. Even in a city like Madras, where smallpox notification is reported to be quite fair, only 70 percent of the total cases were notified voluntarily. The same is the case in other cities too. There may be several factors responsible for this state of affairs: firstly, people may not be aware that they have to notify all cases of smallpox to the health authorities and remove them to the Infectious Diseases Hospital, secondly, people may have superstitious beliefs that smallpox patients should not be treated with drugs, injections etc.; thirdly, it may be that Infectious Diseases Hospitals, in general, are not properly maintained and so have a bad reputation, fourthly, those institutions may be situated so far away from the centre of the city, that people may have to spend daily large sums of money to visit their patients; fifthly, if such patients die in the hospital, the dead bodies are not handed over to the relatives, thereby offending the sentiments of the people; and lastly, people in general may be indifferent to the public health laws and to the health of the community. All these and more may be responsible for not notifying and isolating all cases of smallpox at Infectious Diseases Hospitals, with the result, that these sources play a great role in the spread and persistence of infection in a community.

Mild and atypical case: It is the experience of clinicians, who have seen a large number of cases of smallpox, that in every epidemic, there is a sizeable number of mild and atypical cases of smallpox with very few lesions and such cases are likely to be missed both by the patients as well as clinicians. These cases may be as infective as others.

Subclinical (inapparent) case: Recent studies (Rao et al, 1970) (Heiner et al, 1971) have shown that subclinical (inapparent) infections do occur with smallpox also especially amongst the familial contacts (Chapter 14). A few of these persons with subclinical infection have also been found to void the variola virus through nasopharynx and hence they may have to be considered as potential sources of infection. But to what extent these persons actually play any role in transmission of disease is not known.

Carrier: Carrier state in smallpox has not been so far described. It has been shown from experimental studies in animals, that smallpox virus multiplies in the mucous membrane of the lower respiratory tract during the first three to four days after infection. It is possible therefore, that during this time, virus may be voided in the nasopharyngeal discharges and droplets, due to shedding of the superficial layers of the mucous membrane and such incubating persons may act as sources of infection. They may therefore come under the definition of carrier and can be termed as 'incubation carriers'. There have been a few instances, where variola virus has been reported to have been isolated from the throat washings of such incubating contacts. (Chakrabarthy, 1971).

While we were studying the serological response of contacts of smallpox cases, we have also isolated variola virus from throat washings of a few of the close contacts of smallpox cases, who neither developed clinical disease, nor subclinical infection later (Chapter 14). These findings suggest the possibility of the presence of 'contact' carriers. However, the actual role these 'incubation' and 'contact' carriers play in the transmission of disease is not known still.

Similarly, medical and paramedical personnel who constantly attend on smallpox patients, are found to be quite immune to the disease, perhaps because of the constant exposure to disease and continuous inhalation of minute doses of virus. It is possible that in these hyperimmune persons, when closely exposed to severe cases of smallpox, the virus may enter their nasopharynx, and if they have no local cellular immunity, it may multiply in the cells of the mucous membrane of the respiratory tract without developing viraemia. Due to constant denudation of mucous membrane of the respiratory tract in such individuals, virus may be voided in which case, they without suffering from disease, may be transferring the infection. This possibility has to be further studied. If such a state exists, perhaps, they can be classified as 'healthy' (immune) carriers.

All these types of carriers (?) 'incubation', 'contact' and 'healthy' can be potential sources of infection. However, there is not much evidence to prove that they exist and if so, they can spread the disease in a community.

Infectivity of human source. It should be clearly understood that although all cases of smallpox are potentially infectious throughout the entire course of the disease until the last scab separates off, yet they may not be infective (i.e., they may not have the capacity to infect others) during the entire period. Similarly, several materials like nasopharyngeal droplets, discharges, sputum, tears, urine, foeces, scabs etc., are all 'infectious' because they contain the virus. Yet it is doubftul, whether all these really play much role in the transmission of infection. Practical experience therefore indicates that 'to be infective' (i.e., capacity to infect) is different from 'being infectious' (i.e., containing viable virus).

It has been found from our studies (Rao et al, 1968a) on intrafamilial transmission, that the maximum number of first generation cases amongst the familial contacts got infected from the primary case (source) during the first seven days of the disease (*Fig.* 12/1) especially between fourth and seventh day. No contact in that study got infected after the 13th day of disease of the primary case. This may not mean that cases of smallpox are not infective in the later stages, but it only indicates that, from the point of view of transmission, especially intrafamilial, the maximum number of susceptible familial contacts get infected from the primary case in the family, during the first seven to ten days of the disease, which appears to be the most infective period.

There is some virological evidence in support of this epidemiological observation. In experiments conducted at the Infectious Diseases Hospital, Madras, we (Downie et al, 1961) were able to isolate the virus from throat washings of patients suffering from smallpox from the third to the thirteenth day of disease (calculated from day of onset of fever and not rash) with maximum isolates during the sixth to ninth day. It was also found (Downie et al, 1965) that the circumoral skin swabs of patients and swabs taken from pillow covers used by the patients, yielded large amount of virus even from the fifth day. These studies indicate that the respiratory virus of variola is voided quite early in the course of the disease, and maximum transmission of disease in an infected family occurs therefore through this virus.

Although virus in smallpox scabs is viable for several months or even years yet it is not free and it is therefore doubtful whether even a susceptible person can get smallpox by putting a scab into his nose. To what extent, and for how long these scabs are infective and what role they play in the transmission of smallpox is a subject of controversy. Priestly (1894) thought that the scabbing stage of smallpox was not infectious. McVail (1905) found even the indiscriminate removal and disposal of scabs in the hospital did not spread the infec-

tion to other patients. Our experience also confirms the above findings, namely that despite the fact patients throw away scabs indiscriminately, there have been no instances of cross infection. These facts may not conclusively prove that the scabbing stage is not infective, yet there is sufficient evidence to suggest that scabs, though infectious, may not be infective, unless they are converted into infective dust, and hence may not play much role in transmission of disease.

Another important aspect requiring study, is to see whether there is any difference in virulence or invasiveness between the virus isolated from scabs and virus isolated from blood, or throat washings. At present there are no reliable methods for testing the virulence of variola virus isolated from different sources. Dixon (1962) has suggested that "the virus extruded through the skin perhaps, modified by its passage, is in some way different from the virus from respiratory tract". I am inclined to agree with him but it requires further confirmation.

Inspite of the fact that a case of smallpox transmits infection to others to a maximum extent during the first week of the disease, yet all cases may not be equally infective. The infectivity seems to vary from case to case depending upon several factors, such as, the degree of severity of enanthem the patient has in his upper respiratory tract and buccal mucous membrance, the vaccinal status, and even the clinical type of the case. These will be further discussed in subsequent chapters. Theoretically speaking, mild and atypical cases should be as infective as others, yet clinical and epidemiological evidence show that they are not so.

A question of great public health importance is whether or not a person incubating smallpox is infective. Dixon (1962) did not find any spread of infection by allowing contacts of smallpox cases to move freely with others in the epidemic of Tripoli. But that does not prove anything, since one does not know how many such exposed contacts were actually incubating, and what was the immunity status of the population in which they were allowed to move, and how closely they moved. When the virus is actively multiplying in the lower respiratory tract during the first 3 or 4 days of incubation, there is every possibility of discharge of the virus in the nasopharyngeal droplets (Chakrabarthy 1971) and secretions.

In *Figure* 12/1 the day of infection of 83 smallpox cases amongst the familial contacts of 254 primary cases, is plotted against the day of infection of the primary case, assuming 12 days as the incubation period both for the primary case as well as contact smallpox cases. Of these 83 contact smallpox cases, 31 were infected before the day of onset of the disease of the primary case and 52 after. If one assumes

that a smallpox case is infective only after the appearance of clinical manifestations, then 52 are the true first and second generation cases of smallpox, having got infected from the primary case. The remaining 31 cases that were infected before the day of onset of the disease of the primary case, should be considered as 'co-primary' cases, assuming that these 31 cases, as well as the primary cases, have been infected from a common extra familial source.

But from the figure, it is seen that nearly half of these 31 co-primary cases were infected within the first 96 hours of infection of the primary case. Whether this increased occurrence of infection in the contacts during this period has been the result of infection from the primary case, or from extrafamilial common sources, cannot be definitely stated. However, this only indicates a possibility that a smallpox case could be infective during the first 96 hours after infection. There is some experimental evidence to show that in monkeys, when infected with variola virus through the nasopharynx (Hahan and Wilson, 1960), virus could be isolated from the respiratory tract during the incubation period especially during the early stages. Hence there is a possibility that similar voidence of virus may occur in human beings also. This is of great epidemiological importance requiring further study.

NON-HUMAN ANIMATE SOURCES AND THEIR INFECTIVITY

Animal: The monkey is the only animal that can be infected naturally as well as experimentally with smallpox virus. There have been a few reports in the literature of occurrence of smallpox epidemics in humans associated with an epizootic of smallpox in the local monkey population. There was another report of an Ourangoutang in a Zoo (Gispen 1949) developing smallpox having presumably got infected from a human case of smallpox. Barring these isolated instances there has been no evidence of smallpox occurring naturally in monkeys. However, there is some evidence from the work done by different authors to show that monkeys infected with variola virus are infective during the acute stage of the disease. Healthy monkeys contracted smallpox on close exposure to monkeys with smallpox (Westwood et al, 1966). In our experiments with variola in monkeys (Rao et al, 1968b), when infected by the intradermal route, about 20 percent of them developed enanthem on the mucous membrane of the nose, mouth and lips. All these yielded virus on culture during the acute phase of the disease. Studies recently made in Pakistan by Mack and his colleagues (1970) have shown that natural transmission of smallpox may occur to monkeys from human smallpox cases on close exposure. However, the authors concluded saying that the "implications are

more likely to be of ecological curiosity than those of potential disease reservoirs". It is possible therefore, though remote, that monkeys under special circumstances, and in certain types of communities, who have these animals as pets, can get infected from human beings, and also transmit infection to human beings. Similarly, certain other animals like dogs, cats and squirrels are found to eat smallpox scabs but it is not known what happens to the virus in the gut of these animals, whether it is destroyed, altered, or excreted as such.

Bird: Birds like crows and sparrows also swallow scabs, but the fate of the virus in these birds also is not known. If virus is not completely destroyed in their gut, they may act as potential sources of infection and play a very great role as transporters of infection from place to place.

Insect: Common house flies (Musca domestica) which hover round the patients suffering from smallpox have been found to be contaminated with virus on their wings and legs and so mechanically may carry the virus. However, it is most unlikely that these act as sources of infection. Dixon (1962) described one case, infected through flies, in the Tripoli epidemic, but there was no proof except his guess as to its possibility.

Vaccinia virus was reported to multiply in bed bugs (Epstein et al, 1936), however, there is no evidence to show that bugs can be infected with variola virus. Theoretically speaking a bug and a mosquito can get infected naturally only when they feed on the blood of a smallpox case during the viraemia stage, and even if such infected bugs and mosquitoes act as sources, they can only inoculate the virus into the skin of a human host producing 'variola inoculata'. The fact that 'variola inoculata' is very rare, rules out the possibility of these insects being sources or vectors for transmission of smallpox.

INANIMATE SOURCES AND THEIR INFECTIVITY

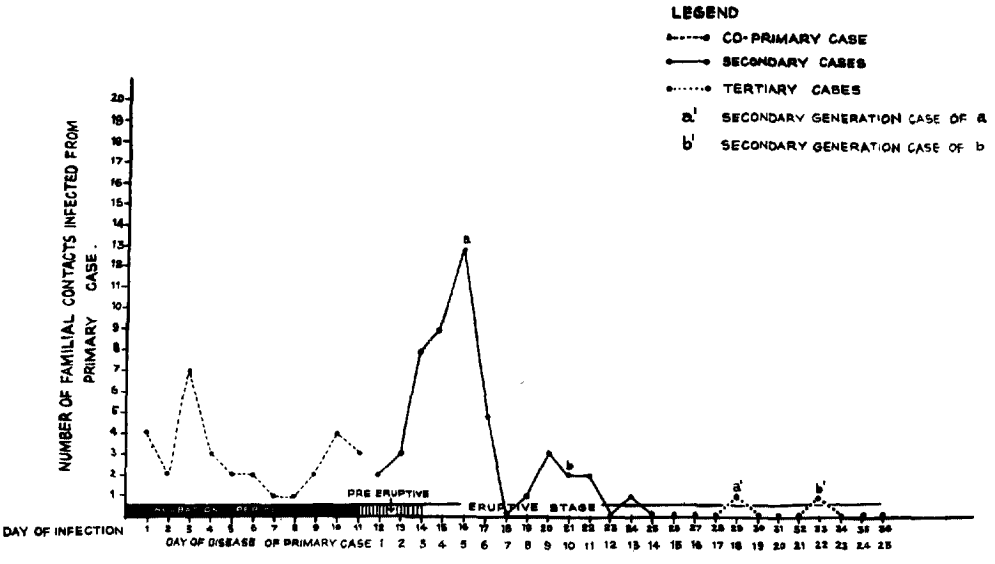
As described already a person suffering from smallpox voids variola virus throughout the course of the disease through one portal of exit or other. The virus is viable for a considerable time outside the host, and hence there is every possibility of the room occupied by the patient, as well as the fomites handled, getting contaminated with variola virus. All these, therefore, may have to be considered as potential sources for transmission of disease, even in the absence of a patient.

Infected room. Instances have been reported, especially in non-endemic areas, where the infected room was incriminated as a source for isolated outbreaks of disease. Dixon (1962) described how a nurse contracted the disease in the Tripoli epidemic "after cleansing the room and removing the bedding, following a very perfunctory dis-

infection three days earlier". He also quoted an outbreak of smallpox at Hendon in 1923 where "two persons who subsequently occupied the same hotel room as first case, developed smallpox". In both cases either the infected room or even the infected linen, or both, might have been the sources of infection.

If a patient has stayed long enough in a room, the atmosphere in the room is likely to be loaded with virus voided by the patient through nasopharyngeal droplets and other discharges. These droplets may lose their moisture envelope, and float in the atmosphere in the room as droplet nucleii for some time and settle down as infective dust on the floor. In such rooms if the floor is swept dry, the air in the room may get heavily charged with the virus infected dust. However, we (Meiklejohn et al, 1961) failed to detect any virus either in acute or convalescent smallpox wards at the Infectious Diseases Hospital, Madras. Only in one isolated instance out of 38 sampling runs, were the authors able to detect the virus. Of course, it was thought later, that there was something wrong with the technique employed, but this was checked not only before, but also again after the field studies. With experimental aerosols, the techniques were found to be quite good in detecting vaccinia virus. The authors concluded "it is possible that virus excreted in saliva or scabs is not efficiently detected by these methods. It is also likely, that very considerable air movements through the open type of wards of the Infectious Diseases Hospital, Madras, produced rapid dilution of the excreted virus".

Continuing this work, Downie and others (1965) showed, that even with better techniques and with liquid impinger, virus could not be detected in large quantities in air, even at short distances from the patient. They stated "that the frequent failure to find virus in the air samples collected in the impinger was surprising. Even air sampled with impinger held even near the mouth of the patient, who had obvious mouth lesions and who talked, coughed during the period of collection were negative". But at the same time, in many of these instances, they found that settling plates, circumoral skin swabs and pillow cover swabs were positive and yielded plenty of virus. The liquid impinger used has been shown to be effective in recovery of vaccinia virus only in 1 micron aerosols in a cloud chamber. The authors therefore concluded "that our results indicate that very little virus is discharged from the mouth of the patient in droplet nucleii of the order of this size when he is breathing, talking and coughing". This work throws some light on the size of the infected droplets that come out of the mouth and nose of the patient. The fact that settling plates are invariably positive, even where impingers have failed to detect the virus, is a clear indication that virus is definitely voided through the nose and mouth, but not in such small sized particles as



12/1. Infective Period of Smallpox

can be caught by the impinger. It appears therefore, from these data, that the air in the room is not infected by droplets direct from the patient, since they settle down quickly either on the floor or clothes of the patient or bed linen. However, the results of these studies do not rule out the possibility of the air in the room getting infected later with infective dust, either from the floor or from infected linen.

A room occupied by a smallpox case can therefore be a source of infection, even in the absence of the patient, if it is kept closed without any disinfection or disturbance whatsover, after the removal of the case. Studies have been made by the author to find out how long these rooms can remain infectious. Preliminary data (Rao et al, 1971b) show that virus can be isolated from the floor of the infected room for a maximum period of four to six weeks. On the walls opposite to the face of the patient, virus could be isolated for 48 hours only if there was no wall paper, and for seven days if there was wall paper. However, when monkeys were kept in the same closed room and were exposed to infective dust for 24 hours, with the fan switched on to raise the dust, they did not develop the disease.

Practical experience, air sampling studies made with different types of impingers both in acute and convalescent wards, and monkey experiments therefore suggest, that though infected rooms are potential sources of infection, and infective virus can be isolated from floors of those rooms for nearly a month or even more, yet they may not play much role in the transmission of infection in the absence of a patient. This, perhaps, may be due to the fact, that there may not be enough virus load, to infect.

As soon as a case is removed or dead, if all the linen is carefully collected and soaked in disinfectant lotion to prevent the release of the virus, and the room is not swept dry, but only washed immediately and thoroughly or wet swabbed either with plain water or disinfectant, and the room is kept open for 48 hours to 72 hours, the chances of such a room by itself becoming a source of infection are negligible. By following such a procedure, we did not have even a single case of cross infection amongst the patients suffering from other diseases, who had been accommodated in wards, previously occupied by smallpox patients. It is quite possible that tropical heat, fresh and free droughts in well ventilated wards, also might have played a great role in reducing the virus load in the atmosphere of infected rooms of the hospital.

Common inanimate sources of infection

There are several materials and objects which have been incriminated as sources of infectoin in a few smallpox outbreaks in the

past. Dixon (1962) has described such outbreaks, where inanimate sources like infected clothing and bedding, cotton, lacemaking materials, toys, coins, letters etc., have been reported to be responsible.

In addition, currency notes, goose feathers, rags, stationery etc. also have have been mentioned as sources of transmission of smallpox in some outbreaks. In majority of these outbreaks, there is no direct evidence to trace the infection to these sources. As in the case of human sources most of these inanimate objects may be infectious by harbouring the live virus, but may not have the capacity to infect human beings. In a few of these outbreaks described above, there were even obvious possibilities of infection occurring from direct contact with a smallpox patient, but they were overlooked and the remote possibility of contracting infection from the infective inanimate objects were considered and described. Though smallpox patients are known to be highly infective in the early stages of the disease, yet one should not forget, that they can infect, under certain circumstances, even in the late stages also. Hence before incriminating any inanimate object as a probable source, all the possibilities of transmission from human sources have to be thought of, carefully considered and then eliminated. Hence in discussing the role of inanimate objects in transmission of smallpox, one should find out firstly, whether inanimate objects used by smallpox patients can get infected with variola virus, secondly, if they get infected, how long they retain that infection, thirdly, whether such infected inanimate objects are capable of transmitting the disease, and lastly to what extent such infected inanimate objects play a role in transmission of smallpox in a community.

Laboratory evidence and results of various studies

Studies made at Madras by Downie and his associates clearly indicate that bed clothes and clothing used by smallpox patients get easily infected even from day 3 of the disease. Such clothing, naturally, has to be considered as a potential source of infection. A limited study, though not exhaustive and systematic, has been conducted in our laboratory (Rao et al, 1971b) to find out the viability of variola virus in the infected clothing. Summary of the results of this study is shown below.

A standard procedure was followed in all except in No. 8, in collection of infected clothes. The patient is admitted into a separate cubicle ward. From the day of admission, both the bed sheet and pillow cover were kept unchanged. The surface of these clothes exposed to the patient is clearly marked with a marking pencil. On 6th day of admission, the patient is transferred from this experimental room to the smallpox ward. The infected clothes are collected and

Summary of the Results of Studies of Viability of Variola Virus in Infected Clothes

Manner of Preservation	Case Nos.	Vaccination Status	Clinical variety	Period of the year	Day of Exposure when the clothing yielded last +ve on culture	Day of Exposure when the clothing yielded first —ve culture (without being +ve again)
Bundled and kept in	1	Unvaccinated	Flat	Jan-March	37	76
ventilated	2	Vaccinated	Ordinary	Jan-March	33	62
Masonry shed	3	Unvaccinated	Ordinary	Jan-March	36	58
Spread as it	4	Unvaccinated	Ordinary	July-Sept	12	46
is on the bed	5	Vaccinated	Modified	February	7	9
Bundled and kept in the room	6	Unvaccinated	Ordinary	Feb-March	20	54
In Wooden Box	7	Unvaccinated	Ordinary	Jan-April	66	78
	8		Ordinary	Jan-March	56	73

preserved in a manner described in each individual case. In No. 8, which was an outstation case, as soon as we came to know about the occurrence of the case, a telegram was sent to the Health Officer concerned to see that the clothing used by the patient till then is not changed until our epidemiological unit collects it. The dhoti used by the patient was collected on 21st day of the disease. Though we do not know how long actually the patient has been wearing this dhoti, yet in all probability, as per the usual custom in villages under such circumstances, he would not have changed it since the onset of rash.

To collect specimens for culture from the infected clothes, the infected surface is exposed, a cotton swab wetted with normal saline is taken and about 20 strokes are made with that on the infected surface to and fro and inoculated into 2.0 ml of normal saline with Penicillin and Streptomycin (P & S). The cotton swab is thoroughly agitated, squeezed and then discarded. On a few occasions a 1″ square piece of cloth from the infected surface is cut and soaked in 2.0 ml of normal saline with P & S, thoroughly agitated, squeezed and discarded. 0.1 ml of such treated inoculum is used for culture on CAM as per standard techniques.

As stated, on 6th day of admission the patient is transferred and so, that was the last day of exposure and contact for the clothing with the patient. The infected clothes of Nos. 1, 2 and 3 separately were folded, bundled with the exposed surfaces 'In', and were kept on a raised platform in a well ventilated masonry shed provided with a cement asbestos roofing.

The infected clothes of Nos. 5 and 6 were kept, as they were, spread on the bed itself without any disturbance. The clothes of No. 4 were folded, bundled and kept in one corner of the experimental room itself. The clothes of Nos. 7 and 8 were folded and kept in closed airtight wooden boxes. The boxes were kept in a cool but non-airconditioned room.

No definite conclusions can be drawn from these results, since the number of specimens collected are very few, and no systematic procedure of sampling was done at regular specific intervals. However, this may give some idea of the viability of the virus on such fomites under different conditions of preservation.

After cessation of exposure, the load of the virus in the clothing appeared to be invariably low. Except in Nos. 4 and 7 where the pock lesions on CAM were semiconfluent and confluent, in all others the lesions were discrete and few in numbers.

The viability of the virus appears to vary to a little extent depending upon the manner of preservation. The results are not quite

comparable since in several instances, there were long intervals during which samples for culture were not collected. However, when stored in cool dark places (as in a box) the virus was viable for a period of 66 days; when kept bundled in a well ventilated shed, it was viable upto 37 days; when kept on the bed undisturbed with the infected surface exposed to indirect light etc., virus could be isolated upto 12th day only; and when the clothes were bundled up and kept in the same room, it could be isolated upto 20th day. Though the method of study was imperfect, yet in general, it can be stated that variola virus is likely to remain viable on infected clothes for a maximum period of 30-40 days if kept bundled up in a well-ventilated room and for 60-70 days if kept in dark, cool and ill-ventilated room. It appears, exposure of the infected surface even to indirect sunlight destroys the virus quickly.

Of the 8 patients from whom the infected clothing was collected and studied, 2 were among the vaccinated and 6 in the unvaccinated. The virus load appears to be comparatively less in the clothes of the vaccinated patients. Even on the bed sheets used by them there was not much virus, for the matter of that there was almost no virus at all in clothes used by No. 5 after cessation of exposure.

Case No. 2 belongs to the Flat variety and 5 to Modified, others to the Ordinary variety of smallpox. The Modified almost had no virus at all on the infected clothing after exposure to the patient ceased. Between the others, there seems to be no difference having a bearing on the clinical variety of the case.

Clothes of all cases were preserved through January to March except in the case of No. 4 which was July to September. In this case (unvaccinated) the clothes were positive on 12th day of exposure and negative on 46th day. In the absence of information as to when the clothing has become negative for virus before 46th day and after 12th day, it is not possible to state whether seasons of the year influence the duration of the viability of the virus in the infected clothes.

Cotton. Mac Callum and Mac Donald as quoted by Dixon (1962) have carried out studies on the survival of variola virus in scabs preserved in raw cotton at 30°C at different percentages of relative humidity. They could recover the virus from the scabs even upto 185 days at a relative humidity of 58 percent and for less number of days in the presence of higher humidities. Virus in the scabs was also found to be viable even upto and after 530 days when stored at room temperature at 55 percent relative humidity, in indirect sunlight. The results of these studies only indicate the viability of virus in scabs under such conditions of storage. The results do not state

whether cotton surrounding the scabs got infected by any virus released from the scabs under such storage conditions. This is very important because, while handling cotton, the scabs cannot be inhaled as such. Scabs by themselves, are known to be infectious for several years, but unless free virus is released from them as infective dust, they are not, I am sure, capable of infecting any one. On the other hand, if the cotton is infected with nasopharyngeal droplets of smallpox patients in the early stages of the disease, it would be different. It would be interesting, in such cases, to study the viability of virus in such cotton.

Recently, investigations have been made by us in our laboratory to find out whether scabs stored in cotton, can release the virus and infect the surrounding cotton. For this purpose, for want of better material, we have taken the usual packed absorbent cotton rolls (used for dressing in hospitals). Ten cm square pads of cotton (about 2 cm thick) were cut. Between two such pads, smallpox scabs weighing 0.2 gm (about 20 in number) were kept in an area of 2 cm^2. Two identical pads were taken and the area where the scabs were kept was previously wetted with 1.0 ml of distilled water to keep it humid. These two sets of pads are kept in the verandah exposed to indirect sunlight (at no time they were in the sun). On 11th day of such storage, the scabs are separately taken out and cultured. Cotton around the area, where scabs were kept, to a depth of 0.5 cm was carefully collected, soaked in 2.0 ml of normal saline with P and S, agitated, squeezed and discarded. 0.1 ml of that fluid was used for culture on CAM. The cotton was negative in both. It is evident from this experiment that no virus is released within 10 days from scabs to infect the cotton surrounding, either in a moist or dry state. It is not known whether cotton could get infected on longer contact. However it is doubtful, whether raw cotton, even if it is infected with smallpox scabs, can be a source of infection for the outbreaks described by Dixon. For the matter of that Dixon himself has stated that the fact that several towns with major cotton industries have been free from smallpox outbreaks at a time when these so called cotton-borne outbreaks occurred, is itself an evidence against the thinking that cotton was the source of infection.

Other miscellaneous inanimate objects

No laboratory studies seemed to have been made about the possibility of coins, toys, stationery etc., getting infected from the patients and if they get infected, about the viability of the virus on such objects. We too had no occasion to make studies on such naturally infected materials. However, we happened to investigate (Rao et al,

1971 a) in some other connection, the viability of variola virus on filter paper, cotton threads (taken from a piece of lint) when artificially infected either with egg passaged variola emulsion or vesicular fluid of smallpox patients. On filter paper, the virus was viable for more than 144 hours and on cotton thread for nearly 216 hours at room temperature. We were able to isolate virus from samples of vesicular fluid from smallpox cases collected on cotton swabs even on day 7. Therefore, it is theoretically possible, for cotton, filter paper, blotting paper, cotton threads to get infected if these are handled by a patient with his fingers having broken down lesions and such infected objects may retain the virus perhaps for a period of 10 days if not more. But we do not know the viability of virus on coins, non-absorbing paper like stationery etc.

As regards coins, again a small study has been conducted by us. 0.02 ml of egg passaged variola virus emulsion (titre 10^6) was placed on a large number of nickel one Naye Paise coins. These coins were kept in petridish and it was kept in the verandah in indirect sunlight (at no time it was in sun). Every day one such coin is taken and to each smear on the coin 0.18 ml of normal saline with P & S is added, virus is emulsified and 0.2 ml (10^1) of this emulsion is further diluted to give a dilution of 10^2. 0.1 ml of this is inoculated on to CAM. The results showed that there was very little virus on the coins at 72 hours and no virus at all at 96 hours.

Effect of direct sunlight on infected inanimate objects

Sun is a well known disinfectant in control of communicable diseases. On exposure to sun, which of the three, the heat, the light or the U. V. rays of the sunlight are responsible for the destruction of infecting organism is not known. Perhaps all the three may play a role in tropical countries.

Naturally infected clothes of smallpox patients, were found to become virus free 2-3 hours of exposure to direct sun at Madras. Virus in smears of vesicular fluid on glass slides, was destroyed within an hour and vesicular fluid in capillary tubes was virus free in 2 hours on exposure to direct sunlight. A piece of cloth 1″ square soaked in 1.0 ml of egg passaged virus emulsion on exposure to sun (August) between 11 A.M. and 3 P.M. for 4 hours was virus free (the virus might have been destroyed even earlier. We have not investigated.). Nickel one Naye Paise coins with a thick drop of 0.02 ml of egg passaged variola virus, were virus free on exposure to sun for 30 minutes.

If these inanimate objects which have been heaviiy loaded with variola virus artificially could be made virus free in a matter of half an hour to 3 hours of exposure to direct sun, I am sure any fomites

including blankets, can easily be made virus free within 2-3 hours by exposing them to direct sunlight. The results of various studies made by us also indicate that even indirect sunlight can destroy the virus on these inanimate objects in a matter of a few days. Hence infected clothing and other fomites if kept exposed in a well ventilated room will be relatively free from virus in a short time. It looks as though, storage of these, unexposed, in a dark and cool ill-ventilated room keeps the virus viable for longer duration.

The infectivity and the role of these inanimate objects in the transmission of smallpox

We have enough evidence therefore that inanimate objects used by smallpox patients get infected, though it is rather difficult to understand how coins, stationery, currency etc. can get infected. The only possibility besides handling with fingers with broken down lesions, is either that they may get infected from nasopharyngeal droplets of the patients like the clothes, or with fingers contaminated with virus due to licking. Both are very remote possibilities.

Having agreed that these inanimate objects get infected, the question is whether they are capable of transmitting the disease. To our knowledge, smallpox is still an inhalation disease. Whatever be the source, the virus has to enter through the nose by inhalation. To get infected from these sources, therefore, the virus has to be released into the atmosphere around the susceptible host from these inanimate objects. As regards the clothes, it can happen by dusting the clothes. If there is a heavy load of released virus in the air, the person, if he is susceptible to smallpox, in the act of dusting, can inhale the virus and get infected. Same is the case with cotton, provided, it is infected with free virus and not scabs. As regards other objects, the release of free virus is impossible. The only possibility is that the person may put his fingers contaminated with the virus into his nose. This is too far fetched a possibility.

Though there are several possibilities of inanimate objects getting infected, practically they do not seem to play much role in transmission of smallpox for the following reasons:—

1. The virus load in the infected materials is very little.
2. Though virus could be isolated in clothes even upto 70 days when kept in a dark and cool place, the virus load is considerably lowered within a few days.
3. Slightest exposure to sun destroys the virus quickly and even exposure to indirect sunlight reduces the virus load rapidly in a matter of a few hours to days.

4. Release of virus from these objects in sufficient concentration to infect a person is almost impossible, though theoretically this is possible.
5. Smallpox is a disease that can be contracted only on close, continuous and heavy exposure.

However, occasionally, a few cases may occur resulting from inhalation of virus from heavily infected clothing. As regards other objects, even that remote possibility seems to be absent. Hence, it is felt that inanimate objects (fomites) do not seem to play much important role in transmission of smallpox at least in tropical countries.

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13

Transmission Of Infection

For the successful transmission of infection, the agent of infection should leave the source through a portal of exit, be transferred to and transplanted in a new host, and multiply somewhere in his body. In smallpox, there are many portals of exit and several routes of transfer.

PORTALS OF EXIT

Depending upon the nature of the infectious material, the agent of infection may leave the human source by different routes or even simultaneously through more than one route.

Respiratory Tract. The commonest portal of exit is through the respiratory tract. Lesions in the upper respiratory tract and nasal mucous membranes break down very early in the course of the disease and the nasopharyngeal discharges, droplets, sputum, contain much virus. Downie et al (1961) have found that the throat washings of a few cases yielded virus as early as the third day of fever. Most of the transmission of infection occurs from virus voided through this route.

Gastro-intestinal Tract. Lesions occur very frequently on the tongue, lips, palate and buccal mucous membrane, especially in severe cases of smallpox. These break down very early and infect the saliva. During the acts of coughing and sneezing much virus is voided. Circumoral skin swabs are positive even on fifth or sixth day, showing thereby that saliva is highly infectious as early as that.

Involvement of the rectal mucous membrane results in the excretion of virus in the foeces.

Genito Urinary Tract: Virus has been isolated from urine (Downie et al, 1965). The source of the virus in the urine is perhaps from lesions on the urethral mucous membrane and the external meatus.

Skin. Skin is a very important portal of exit. Broken down lesions exude plenty of virus. Scabs separate from the body and contain virus viable for years. Perhaps the maximum amount of virus leaves the patient through this route.

Placenta: The placenta is not a barrier for virus but the fact that very few infants born of mothers during an attack of smallpox get infected *in utero* shows that there is some mechanism that may also perhaps depend on the virus load in the blood of the mother during the viraemia stage, apart from some other factors.

Eye: In smallpox cases with conjunctivitis, virus is excreted in tears. In a few cases, eye swabs were positive for variola virus even without conjunctivitis. In rare instances, eye swabs were positive for virus in close contacts who had not even suffered from the disease.

TRANSFER OF AGENT OF INFECTION

Although variola virus may leave the source through different portals of exit, for transmission of disease in a community, the infective agent has to be transferred to a susceptible host and this transfer can be effected by several routes.

Contact: By contact, it does not always mean, contact by skin to skin, or mucous membrane to mucous membrane. Close proximity within a short distance, say three or four feet, is also a contact, where the infection can be transferred by projection of infective particles on to the new host during the acts of coughing and sneezing without any intermediary media. As has been stated already, this requires a very close association between the patient and the new host, because at a distance of even 12 inches, most of the droplets containing the virus are found to settle down on the bed due to the weight of the droplets. However, it is not impossible even under such circumstances for contacts to get infected directly especially in this country, where the patients lie on a very low cot or more frequently on the floor itself, sleeping very near the contacts or sometimes even sharing the same bed. This is a very common experience in Madras. Hence quite close contact is possible and perhaps infection is mostly transferred this way.

In addition to this, percutaneous transfer or infected material also may occur, resulting in 'variola inoculata', where the virus is actually implanted on the broken skin or mucous membrane when local variolation may occur which later may be followed by a generalised rash. Though rare, it has been seen to occur, notably in mothers nursing smallpox cases, and in hospital staff.

Air: Smallpox is generally considered to be an airborne disease. However, from available evidence, air does not seem to play much role in the transfer of infection especially over long distances.

Failure to isolate virus from the air, even though sampled close

to the patients, clearly indicates that air does not seem to get directly infected by the patient through the nasopharyngeal droplets or droplet nucleii. If at all air gets loaded with virus, it can happen only by contamination with the infective dust from the floor or by dusting infected linen. Whether or not the air so infected can carry the infection over long distances, has been a controversial subject for decades. In the 19th century it was believed that prevailing winds carried the virus, up to a distance of a mile, and there was some circumstantial evidence in support of such views. Even now, several Medical Officers of Health hold that view. There have been recorded instances both in support of, as well as against, this.

Basically there are three aspects to this question to be considered. Firstly, does the air in a smallpox ward of a hospital get loaded with enough virus to infect persons; secondly, if it does, can it carry the virus over long distances far away from the smallpox ward; and lastly, does the air which carries the virus to such a distance, contain enough virus to infect susceptible persons and produce the disease? These are very difficult questions to answer, since no work has been done systematically and scientifically on these lines. In the absence of such, one may have to answer only on circumstantial evidence. The results of the studies of Meiklejohn and Downie (already described) and later by us, indicate that the air in the infected room is not loaded with virus from patients. Even the raising of dust from the floor did not lead to the detection of virus in the air of the open wards. Monkeys exposed for 24 hours to dust in a closed room which was used by a smallpox case for 5 days did not develop the disease. Such being the case, it is doubtful whether air can get charged with a sufficiently heavy load of virus to infect people at a long distance. This appears to be a rather remote possibility.

In support of this, I would like to mention three observations from our experience. *Figure* 13/1 shows the disposition of the wards of the Infectious Diseases Hospital, Madras. Wards 1, 2 and 3 were almost always occupied by smallpox cases every year and throughout the year. Wards 9 to 11 were always occupied by cases of measles, chickenpox and other diseases.

The patients in wards 9 to 11 usually rested and spent their afternoons in the connecting corridors between wards 2 and 3 and the open space between wards 3, 9 and 11. During the period of ten years from 1959-1968 about 17,000 cases of smallpox and about 1,30,000 cases of other diseases including chickenpox, measles, cholera, choleraic diarrhoeas, mumps etc., were treated, but even so, only 7 persons suffering from diseases other than smallpox, who presumab-

ly got infected in the hospital, were admitted again for smallpox within two to three weeks after their discharge. The fact that there is barely 20 feet distance between smallpox wards and other wards, and despite the fact, non-smallpox cases actually use the corridors leading to smallpox wards for resting, the instances of cross infection were so few that it only indicates that neither air in smallpox wards is loaded with enough virus nor can it carry infection over a distance of a few feet.

Secondly, around the hospital, there are hundreds of huts, abutting the compound wall. In no epidemic, it was found that there was any greater incidence of smallpox amongst these slum dwellers near the hospital when compared to other areas in the city. Of course, it can be argued, that their constant and close proximity near the hospital, might have made them partially immune. But during the eradication campaign, the vaccination success rate was in no way different here from other places to suggest that they had greater basic immunity. Further, these were the persons who have been evading vaccination all these years before starting of National Smallpox Eradication Programme.

Thirdly, there are some data regarding the actual transmission rates, in the familial contacts as well as extra familial contacts in infected houses. (*Table* 13.1) 115 out of 254 infected families studied were living in household complexes sharing with other families.

Table 13.1

Smallpox Transmission Rates amongst Intrafamilial and Extrafamilial Household Contacts of Smallpox Cases

	Intra-familial	Extra-familial
Number of families exposed	115	433
Number of families experiencing secondary cases	13(11.3)	4(0.9)
Number of contacts	581	1841
Number developed smallpox	15(2.6)	6(0.3)
Number of vaccinated contacts	549	1758
Number developed smallpox	4(0.7)	4(0.2)
Number of unvaccinated contacts	32	83
Number developed smallpox	11(34.4)	2(2.4)

( ) Percentage.

These 115 houses had altogether 548 families. The average number of persons living per house was 25.8. The average size of the infected families was 6.0, and that of the other families exposed was 5.2. Most of these houses have only one common entrance, and majority, a common closet and a bath, The usual pattern of construction (*Fig.* 13/2) is that there is a central open courtyard around which, there are rooms with or without connecting corridor. This corridor connects all the entrances into the rooms. The corridor and open courtyard are mostly used for sleeping in the nights. Clothes are washed either in the bath room, or at the tap or a well, if one is available. Under such conditions of living, on comparison of transmission rates, the extrafamilial transmission rates are far significantly lower than the intrafamilial transmission rates. If air were to be heavily laden with virus, and were to carry infection over long distances, in this kind of housing set up, the extrafamilial transmission should not be in any way much different from intrafamilial transmission rates. On the other hand, from the data we find that even amongst the unvaccinated extrafamilial contacts, the transmission is 16 times less than that in the familial contacts, but in the vaccinated extrafamilial contacts, it is only three times less. This again shows even in such overcrowded houses, unless persons go near the infected family and patient (as in the case of adult vaccinated contacts) infection cannot be contracted, and air borne infection even over such short distances in such overcrowded houses appear to be insignificant and negligible. Thus, we find at least in endemic areas like Madras, air borne type of transmission of smallpox does not seem to exist in any significant manner.

However, air may play some role in transfer of infection especially when the infectious material is in form of dry infective dust, but only over short distances. Perhaps the familial contacts may get infected by inhalation of infective dust especially during the nights when the room is over-crowded, and when the atmosphere in the room gets heavily loaded with virus voided from the patient.

Fomite: This has been discussed at great length. The infected linen seems to play some role in transfer of infection not only from the source to the new host in the near vicinity, but also over long distances. It is also possible, that the infected linen may be responsible for further transmission of infection over a long distance of time, without any intermediary continuity in the chain of infection in human beings.

Water and food: There are some who are inclined to feel that smallpox infection may also be transferred through infected food and drinks. The possibility may be always there but so far there is no evidence to indicate this mode of transmission.

Extra human agencies: As discussed already, there is no evidence to show that extra human agencies play much role in transfer of infection. However, this method of transmission cannot be ruled out completely.

Blood. Although the cord blood may carry the virus from the mother to the foetus in utero through the placenta, the transfer of infection to the foetus in utero, seems to depend upon several other factors.

PORTALS OF ENTRY

Nasopharynx: Unlike the other diseases, the portal of entry for infection in cases of smallpox, does not seem to depend on the nature of the infective material. From the evidence available, smallpox is still only an 'inhalation disease'. The infective material whether it be nasopharyngeal droplets, discharges, tears, urine or foeces or scabs, has to be only inhaled as infective dust to get infected. It is almost certain now that the virus initially multiplies in the alveoli of the lungs. Nasopharynx therefore is the commonest portal of entry for the virus.

Skin: Variolation or variola inoculation may occur naturally, or sometimes even accidentally by implantation of virus on the broken skin, which may result in a localised lesion in hyper immune individual or in generalised variola in susceptible persons. Both these conditions, though rare, do occur. Three cases of variola inoculata were recorded in our series. In one, a nursing mother got a typical localisation on the finger which went through all the stages of evolution from a papule to pustule, and on ninth day, developed typical pre-eruptive fever followed after two days, by generalised rash all over the body. Another similar case was quite mild, but the third was an unvaccinated child aged four years, a contact of a smallpox mother, who developed a typical smallpox vesicle on the side of the chest below the axilla and six days after our recognition of the vesicle, he developed fever followed by a fairly severe type of smallpox but survived. This local lesion was positive for variola virus even before the generalised rash occurred.

As regards the localised variola inoculata without generalised rash, the author himself had accidental variolation while digging scabs from a patient. On about fifth day after infection, a deep papule was seen which became a vesicle on the seventh day, and scabbed in another two days. There was no fever or generalised rash associated with this. It was a case of local variola inoculata, but at that time, there were no facilities for culturing the virus.

Eye: There are some, who believe that the portal of entry in

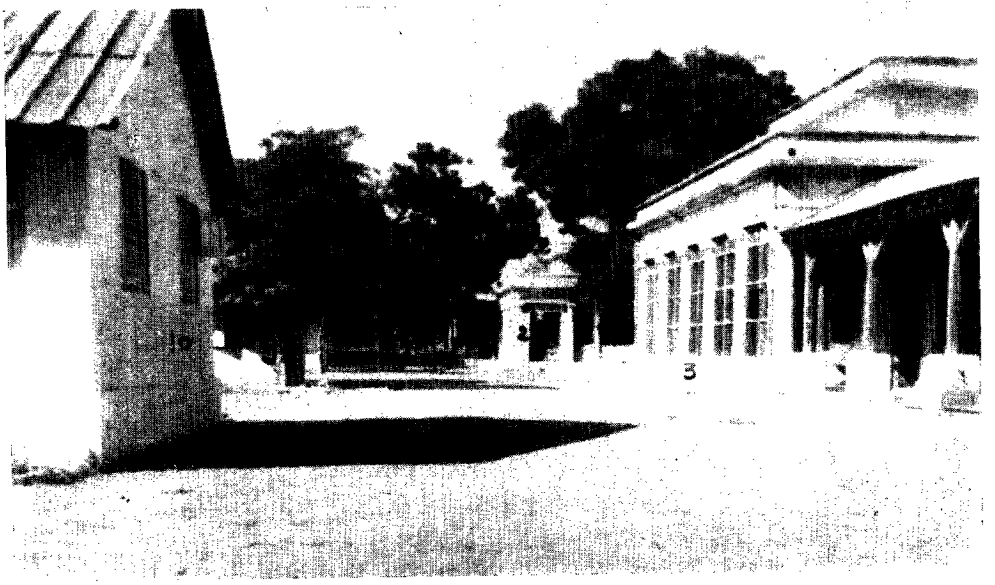
measles may be conjunctiva and hence even in smallpox, this may be possible. In smallpox, it is very difficult to confirm as to which is the portal of entry. There have been several instances where conjunctivitis was the only manifestation of variola infection. Still there were some others, where the conjunctivitis preceded generalised rash by about 8-10 days, and in these cases, whether this is a local infection having nothing to do with the general infection, or whether the conjunctivitis is the result of conjunctiva being the portal of entry, one cannot say. But the fact that these cases are very rare, indicates that the conjunctiva cannot be a portal of entry unless the virus can enter through the conjunctiva without causing any preceptible lesions or changes.

DISSEMINATION OF THE VIRUS IN THE HOST

The fate of the virus after entry into the nasopharynx in the host is still a guess. However, from the experimental evidence available so far with allied viruses in animals, Downie (1959) reviewed and suggested the possibility that the virus of variola enters through the nasopharynx of the susceptible host, multiplies in the cells of mucous membrane of the respiratory tract, produces minimal lesions and quickly passes on into the regional lymphnodes from where it is carried on to the blood producing primary viraemia. This process may take about 48-96 hours. From the blood, very quickly, it disappears into the reticulo endothelial system of various internal organs etc., where it multiplies throughout the incubation period. At the end of the incubation period, it again enters the blood as a 'virus shower' producing secondary viraemia, which corresponds to the first clinical manifestation of the disease namely the fever of smallpox.

Fluorescent antibody studies with vaccinia made by Lawer and his associates (quoted by Westwood 1966) showed that the virus multiplies initially in the cells of broncheoles and alveoli of lungs. Though it is evident that the virus in the lungs finds its way into the blood through regional lymphnodes, yet virus could not be detected at this stage from blood in variola in monkeys (Westwood et al, 1966). However, the same authors were able to detect virus after fourth day from blood in cases of vaccinia in rabbits. In experiments with variola in monkeys (Rao et al, 1968) infected intradermally, virus was isolated from blood in 25 percent of animals on fourth day of infection, i.e. about 48-72 hours before onset of generalised rash on the skin and mucous membranes but very rarely after the appearance of rash.

Inspite of the fact that virus multiplies in large numbers in the lungs and passes through the blood and again multiplies in reticulo endothelial system, yet neither the animals nor hmuan beings, show any signs or symptoms of infection during their incubation period.



13/1. Disposition of Smallpox wards and Non smallpox wards at Infectious Diseases Hospital, Madras

13/2. A typical Household complex in a congested area of Madras

There is no method described so far, to detect at this stage of infection whether a person was infected or not.

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14

Subclinical (Inapparent) Infections

INTRODUCTION

In epidemic outbreaks of several bacterial and viral diseases, occurrence of subclinical infections has been reported. Till recently, there have been no such authentic reports in smallpox. Perhaps, this has been mainly due to our inability to diagnose a case of smallpox, in the absence of rash. For a long time, the thinking has been, that smallpox is only an overt disease with frank rash. It is only recently, that studies have been conducted to probe into the occurrence of inapparent cases in smallpox.

Evidence suggestive of occurrence of subclinical infections in smallpox

Studies on intrafamilial transmission of smallpox (Rao et al, 1968 b) indicated that nearly 60 percent of the unvaccinated, and as high as 98 percent of once vaccinated, escape clinical disease even on close intrafamilial exposure to smallpox. These figures, of course, vary from country to country (Heiner et al, 1969, Nilton Arnt et al, 1970). Further, in several localised outbreaks in closed communities, smallpox was found to spread slowly and steadily (Rao, 1968 a) but never in an explosive manner, and the outbreaks, not infrequently, die out automatically by themselves in course of time, occasionally leaving quite a few unvaccinated and several once vaccinated, unaffected.

There is no doubt that the vaccinal status of a person is the most important factor that determines the type of clinical attack one develops. However, that is not the only factor. Of a series of 3544 smallpox cases amongst the unvaccinated, treated by me, nearly 2.1 percent belonged to the Modified variety, indicating that vaccinal status alone does not modify the course of a disease. The dose of infection, the degree of exposure, the duration of exposure and even the type of exposure to infection which will be discussed later, seem to play quite a significant role. Perhaps, even the nature of the source of the virus to which one is exposed, also may determine the type of attack one develops. We have no data at present, as to what type of determinants

are there, to induce only subclinical infection in some contacts of smallpox cases.

The above epidemiological findings strongly suggest the possibility of occurrence of subclinical infection in close familial contacts of smallpox cases and even among the extra familial contacts in small closed communities.

Detection and diagnosis of subclinical infections

Infection with variola virus, whether it results in the form of either an overt disease with rash, or subclinical infection without any signs and symptoms of smallpox, is invariably followed by, as in other diseases, a rise in the titre of different antibodies in the blood against the variola-vaccinia group of viruses. In the absence of rash, there is no other way of diagnosing a case of smallpox, except by serological response to infection. However, there are certain difficulties encountered in diagnosis of such cases by such means.

A finding of a four-fold rise in antibody titre in paired samples of sera, one collected in early stage of the disease, and the other during the stage of recovery, is always diagnostic of smallpox. But to detect subclinical infection in the contacts of smallpox cases, who do not develop signs and symptoms of the disease, by this method, is not possible. Unless samples are taken from the contacts, as immediately as possible after exposure to primary case, and again after 3 or 4 weeks after exposure, the rise in antibody titre cannot be demonstrated. To find out the day of exposure and to collect two samples of sera from the contacts on the field, are almost impracticable. Further, if such contacts are vaccinated after exposure, as is usually done, the rise in antibody titre may not always mean recent infection with variola, since this antibody response may, as well, be due to vaccination itself. Only because of these inherent limitations, we have not been able to detect and describe the occurrence of subclinical infection in smallpox so far. From a serological study of a single specimen serum, it is not easy to confirm a diagnosis of subclinical infection with smallpox. Downie et al (1969 b) however, have stated that "a positive precipitation test in agar gel, a CF titre of 1:20 or more, or an HI titre of 1:80 or higher, in a single specimen serum, would be suggestive of a recent smallpox infection. Such a result might be of special value in retrospective diagnosis of missed cases, and in detection of minimal or subclinical infection."

How far this statement would be correct and applicable especially in endemic areas (of course Downie's studies were undertaken in endemic areas) has to be carefully considered. Downie et al (1961) found 6 percent (13/213) of the sera from blood bank, as well as cases

of chickenpox, admitted to I. D. Hospital, Madras, but not exposed to smallpox has an HI titre of 1:80 or more. Similarly we have found *(Table* 14.1) about 12 percent (24/197) of sera collected from new staff recruits to Infectious Diseases Hospital, as well as patients suffering from various diseases and not exposed to smallpox, and an HI titre of 1:80 or more. Such being the case it is doubtful whether it would be quite correct to say that it is suggestive of a recent smallpox infection, in persons whose sera show HI titre of 1:80 or more.

Downie et al (1969 a) have also observed, from another study "3 groups of post vaccination sera were studied for vaccinia antibodies by precipitation, HI, CF, and Neutralizing tests. All the sera were negative by Precipitation test, and many by HI and CF tests, but most showed neutralizing activity in serum dilutions of 1:10 or higher".

Table 14.1

Haemagglutination inhibition antibody titre in persons not exposed to Smallpox

Nature of the subjects	Number of Sera tested	HI Titre (Showed as Reciprocal of the Serum Dilutions)						
		<20	20	40	80	160	320	>320
New Staff recruits	97	69	16	6	1	3	2	—
Chickenpox	34	20	4	4	4	2	—	—
Diarrhoeas (including Cholera)	51	30	6	5	3	5	1	1
Mumps	10	8	2	—	—	—	—	—
Measles	2	2	—	—	—	—	—	—
Enteric Fevers	2	—	—	—	1	1	—	—
Allergic Rash	1	—	—	1	—	—	—	—
Total	197	129	28	16	9	11	3	1
Percentage of Totals	100.0	65.5	14.2	8.1	4.6	5.6	1.5	0.5
Number of subjects who gave history of vaccination within one year before	67	41	9	5	4	7	—	1

The WHO Scientific group on smallpox eradication (WHO 1968) has also stated that "the precipitating antibodies are detectable in the sera of convalescent smallpox cases by Precipitation in gel (PIG) technique, at least for 4-6 months. Such antibodies are rarely found in post-vaccination sera."

From the studies of Downie, as well as from the report of WHO Scientific group, it appears that, if any serum gives a positive precipitation in gel, it indicates that person had a recent infection with variola virus. This does not appear to be so simple as that. The above findings, made us study in great detail, the utility of the PIG test in diagnosis of smallpox, especially in retrospective diagnosis of recovered cases, and diagnosis of subclinical infection with smallpox. In one of our studies (Rao et al, 1970) sera of 286 adults were examined for precipitating anibodies by PIG technique by using vaccinia as antigen. Of these subjects 34 had no visible scars of vaccination, 180 had only scars of primary vaccination, and the remaining 72, not only had scars of primary vaccination but also gave history of revaccination and some of them had scars of revaccination too. None of these sera gave positive precipitation by PIG technique either with vaccinia or variola antigen. 98 of these subjects were vaccinated by us with potent freeze dried vaccine and the reactions to vaccination were recorded. Pre-vaccination and post-vaccination sera on the 14th day of vaccination, were collected and tested for precipitating antibodies by PIG technique using vaccinia as well as variola (vesicular fluid of smallpox patients) antigens, and HI antibodies. All the pre-vaccination sera were negative both with vaccinia and variola antigens. 34 percent (33/97) of post-vaccination sera had an HI titre of 1:80 or more. 31 percent (27/87) of the post-vaccination sera gave positive precipitation with vaccinia antigen by PIG technique. With reference to vaccination takes, 50 percent (2/4) of those with 'primary' take, 37.5 percent (21/56) of those with 'major' takes and 10.5 percent (2/19) of those with 'equivocal' takes gave positive precipitation with vaccinia antigen (*Table* 14.2).

This is in contrast with the findings of Downie and his associates and the WHO Scientific group on smallpox. In our study, quite a sizable percentage of post-vaccination sera gave positive precipitation with vaccinia antigen and there was fair amount of correlation between vaccination success rate and positive PIG rate. But surprisingly none of the post-vaccination sera gave positive precipitation with variola antigen by PIG technique.

We have further tested the sera collected from 61 cases of smallpox on different days of the disease for precipitating antibodies by PIG technique using both vaccinia as well as variola antigens and HI antibodies. The results are shown in *Table* 14.3. No precipitating antibodies were detectable on or before 6th day of the disease tested with variola antigen, though 20 percent (1/5) were positive with vaccinia. 50 percent (7/14) of sera collected between 7th and 9th day of disease were positive with variola and 57.1 percent (8/14) with vaccinia. 100 percent (33/33) of sera collected between the 10th and

28th day of the disease were positive with variola antigen and 96.7 percent (29/30) with vaccinia. Even upto 90 days after the onset of the disease, nearly 75 percent of the cases were positive. Between 3 months and 12 months, about 35 percent were positive. As can be seen from the table, there was a good correlation between HI titres and positive precipitation. 100 percent of the sera collected between 10th and 28th day of the disease had HI titre of 1:80 or more.

These results of PIG test on sera of vaccinees (*Table* 14.2) and sera of smallpox patients (*Table* 14.3) suggest that the precipitating antibodies formed as a result of vaccinia infection (post-vaccination sera) precipitate only vaccinia antigen and not variola, whereas the precipitating antibodies formed as a result of variola infection (sera of smallpox patients) precipitate both variola as well as vaccinia antigen.

With this presumption, the validity of which may be questioned, we tested 136 sera of 109 familial contacts of 38 cases of smallpox, collected on different days of exposure to the first case in the family, for precipitating antibodies and HI antibodies. The results are shown in *Table* 14.4. 9.1 percent (6/65) of sera collected before the 24th day of exposure were positive for precipitating antibodies tested with variola antigen and 23.1 percent (15/56) with vaccinia. Of the sera collected between 24th and 90th day of exposure, 47.4 percent (28/59) gave positive precipitation with variola, and 49.1 percent (27/55) with vaccinia. Of the sera collected after 90th day of exposure, but within one year, 28.3 percent (3/11) were positive with variola, and 25 percent (2/8) with vaccinia. 12.9 percent (8/62) of sera collected before the 24th day of exposure, and 63.7 percent (7/11) of those collected after 3 months but within 12 months after exposure, had an HI titre of 1:80 or more, indicating recent infection with variola virus. HI antibodies seem to persist for a longer time than precipitating antibodies. The reason why the 'day 24' was taken as a criterion for comparison was, that in the clinical smallpox cases (*Table* 14.3) it was found that by the 10th day of the disease, i.e., 24th day of infection (10 days of disease plus incubation period) 100 percent of the cases had demonstrable precipitating antibodies. It was therefore expected that maximum number of sera of contacts of smallpox will be positive only after 24th day of exposure, if they are infected.

Despite the fact that not in all contacts in whom sera were collected before 24th day of exposure, a second sample was taken again after 24th day, the total number of contacts who had demonstrable precipitating antibodies with variola antigen, in this study, worked out to 31.2 percent. If our presumption is correct these 31.2 percent of the contacts studied, had subclinical infection with smallpox.

Table 14.2

Results of PIG Test and HI antibody titres in Post-vaccination sera with reference to Vaccinal Take

Type of Vaccination Take	No. of persons studied	PIG Test						H.I. Antibody Titres*					
		With Variola Antigen			With Vaccinia Antigen								
		No. of sera tested	No. +ve	% +ve	No. of sera tested	No. +ve	% +ve	No. of sera tested	80	80-320	320	% of sera with titre of 80 and above	
Primary Take	4	4	0	0.0	4	2	50.0	4	1	2	1	75.0	*HI antibody titres shown as reciprocal of sera dilutions
Major Take	67	61	0	0.0	56	21	37.5	66	43	20	3	34.9	
Equivocal Take	19	18	0	0.0	19	2	10.5	19	12	5	2	36.8	
Take not known	8	8	0	0.0	8	2	25.0	8	8	—	—	0.0	
Total	98	91	0	0.0	87	27	31.0	97	64	27	6	34.0	

Table 14.3

Results of PIG Test and HI antibody titres in Sera of Smallpox Cases

Day of disease when sera were collected	PIG Test						HI Antibody titre*					
	With Variola Antigen			With Vaccinia Antigen								
	No. of sera tested	No. +ve	% +ve	No. of sera tested	No. +ve	% +ve	No. of sera tested	80	80-320	320	Percentage of sera with 80 and more.	
6th day and less	8	0	0.0	5	1	20.0	7	5	2	0	28.6	*Titres shown as the reciprocal of the sera dilutions.
	(3)	(0)	(0)	(3)	(0)	(0.0)	(3)	(3)	(0)	(0)	(0.0)	
7th to 9th day	14	7	50.0	14	8	57.1	13	8	2	3	38.5	
	(0)	(1)	(16.7)	(6)	(2)	(33.3)	(5)	(4)	(1)	(0)	(20.0)	
10th to 28th day	33	33	100.0	30	29	96.7	30	0	14	16	100.0	( )Fatal cases
	(5)	(2)	(40.0)	(5)	(4)	(80.0)	(5)	(1)	(1)	(3)	(80.0)	
29th to 90th day	26	19	73.8	21	16	76.2	21	1	7	13	95.2	
90 days and above	14	5	35.7	14	5	35.7	14	9	2	3	35.7	

Table 14.4

Results of PIG Test and HI antibody titres in Serum of Familial Contacts of Smallpox Cases

Day of Exposure to primary case when sera were collected	No. of sera collected	PIG Test						HI Antibody Titres*				
		With Variola Antigen			With Vaccinia Antigen							
		No. of sera tested	No. +ve	% positive	No. positive of sera tested	No. positive	% positive	No. of sera tested	80	80-320	320	% of sera with HI Titre more than 80
Within 24 days	65	65	6	9.1	65	15	23.1	62	54	8	0	12.9
24th day to 90th	60	59	28	47.4	55	27	49.1	43	32	10	1	25.6
After 90 days	11	11	3	27.3	8	2	25.0	11	4	5	2	63.3

* HI titre is shown as the reciprocal of serum dilutions

Table 14.5 shows the age, sex and vaccinal status of these contacts with subclinical infection. Of the 34 cases of subclinical infection, 20 were males and 14 were females. 5 out of 34, were amongst the unvaccinated which includes 2 children in the age group 0-4 years. (This is surprising), in general, we have found, by this method of detection that for every single 'contact clinical smallpox case' there will be on an average two 'contact subclinical (smallpox) infections' in the familial contacts.

Heiner et al (1971) using a purified antigen derived from *Variola infected cell cultures* found post vaccination sera positive for precipitatig antibodies by PIG technique in 19 out of 25 subjects tested, precipitins being detectable first on 'day 10' after vaccination. This is in quite contrast to our findings, where we did not find even a single post vaccination serum, tested of 91 vaccinees, on the day 14 after vaccination, positive for precipitating antibodies using variola antigen (pooled vesicular fluid of smallpox patient) though 31 percent of them were positive with vaccinia.

Commenting on our study, Heiner et al (1971) have stated "in Rao's study the use of pooled vesicular fluid, apparently provided an antigen of relatively low potency, and this allowed a quantitative distinction to be made between the reactions of smallpox cases, including subclinical cases, and those of vaccinees. However, since this distinction is quantitative, such a test may also yield false positives especially in view of the great variability in the antigenic concentration of different specimens of pools of vesicular fluid. In the present study, in which a more concentrated antigen was used, no distinction could be made in individual cases between the residual post vaccination precipitins, and those due to recent Variola infection".

While agreeing with Heiner and his associates, that the concentration of antigen may play some role and influence the results of PIG test, it is rather difficult to understand why the vesicular fluid of smallpox cases, which we have used, and which in Heiner's opinion is poor in its antigenic concentration, gave a very high positive results with smallpox patients' sera, which are known to contain far higher concentration of antibodies than vaccinees' sera. Further, the results of PIG test, using vesicular fluid and vaccinia antigen on sera of smallpox patients were more or less identical. Under the circumstances, there seems to be no reason, therefore, to suspect the concentration of antigen in vesicular fluid for the different results we had, as regards the serological response of precipitating antibodies, as detected by PIG technique using vaccinia and variola antigens. Only these observations made us feel that there may be some specificity (we may be absolutely wrong) with reference to the antigens used and that, as stated already, the precipitating antibodies formed as a result of vaccinia

Table 14.5

Details of Persons with Subclinical Infection with reference to Age, Sex and Vaccinal Status

Age Groups	Vaccinal Status																
	Unvaccinated			PV only			PV and RV			Total vaccinated			VSNK		Grand Total		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	M	F	T
0—4 years	1	1	2	3	1	4	—	—	—	3	1	4	—	—	4	2	6
5—14 years	—	—	—	3	3	6	—	1	1	3	4	7	—	—	3	4	7
15—44 years	1	1	2	7	5	12	1	1	2	8	6	14	—	—	9	7	16
More than 44	1	—	1	1	—	1	1	—	1	2	—	2	—	—	3	—	3
Not known													1	1	1	1	2
Total	3	2	5	14	9	23	2	2	4	16	11	27	1	1	20	14	34

PV — Primary Vaccination. RV — Revaccination. VSNK — Vaccinal status not known.

infection may not precipitate the variola antigen, whereas the precipitating antibodies formed as a result of variola infection may precipitate both variola, as well as vaccinia antigens. But unfortunately the results of Heiner's study do not corroborate our findings.

It cannot therefore be said definitely, that the antigenic concentration alone is responsible for the differences, which we have observed in serological responses to variola and vaccinia infections.

From the above observations therefore, it is apparent that neither HI titre of 1:80 or more, nor a positive PIG test, in single serum specimens can be taken as a reliable evidence of a recent infection with variola virus to diagnose a case of subclinical infection. However, if there is no history of revaccination, or if the contacts are unvaccinated, these tests may indicate the possibility of subclinical infection. There is a need for further studies on this subject, especially in standardization of the antigen for the purpose of diagnosis of subclinical infection and also for making retrospective diagnosis of recovered cases. Studies have also to be conducted to find out whether there are any differences in the antigenic component between the vaccinia and variola virus, and also in the antibody response, these two viruses induce in man. Till we know more about these aspects, we may not be able to say, that we have a fool-proof method of diagnosis of subclinical infection in smallpox in man. However, there is absolutely no doubt, that not only subclinical cases do occur, but also they occur far more frequently than one would expect.

Epidemiological significance of subclinical infections

The fact is there, that there are twice as many subclinical infections of smallpox as clinical overt cases among the familial contacts of smallpox cases. What is their importance in the epidemiology of the disease? One thing seems to be certain, that they increase the immunity status of the community. Perhaps that explains why, not all the unvaccinated, and majority of once vaccinated, do not develop clinical smallpox even on close intrafamilial exposure. But more important than this is, especially from public health point of view, one would like to know whether or not these persons with subclinical infections form sources of infection for the spread of the disease. In this respect no methodical and scientific studies seem to have been made so far.

While we were studying the serological response of contacts of smallpox cases, we happened to collect throat washings of a few of them and accidentally found that some of these yielded variola virus on culture. Out of 109 contacts studied for subclinical infection, in 37, throat washings were collected and in 16, eye swabs also were collected, on the day of detection of the primary case. In 3 cases, specimens

have been repeated daily for 7 days. Five of the 37 yielded variola virus on culture of the throat washings, and one of the 16 eye swabs was positive for variola virus on culture on CAM. The details of the cases are shown in *Table* 14.6. Though the quantum of virus in the throat washings was not much, since in all these cases the undiluted throat washings produced discrete lesions on CAM, the number of pocks varying between 4 and 50 for 0.1 ml of inoculum, yet it is evident that these contacts did carry the virus in their throats without developing the overt disease later, indicating that they are 'contact carriers'. By our criteria, cases 1, 3 and 5 have proved to be subclinical infections also. We do not know how long these persons have voided the virus. In cases 2, 4 and 5, virus was isolated on 6th to 8th day of exposure to primary case. In case No. 1 the virus was isolated on 30th day of exposure, but in this particular instance, we cannot rule out the possibility of this contact contracting infection from some other source, since there have been several cases of smallpox in the same compound. In case No. 3 there was a secondary case in the same family and it is possible that the contact might have contracted infection from that patient, in which case, virus was isolated from his throat washings on 13th day of exposure. All the 5 have been very close contacts of smallpox cases and all were in the previously vaccinated. Two of the five, had scars of revaccination said to have been done within one year before exposure, in addition to primary vaccination scars.

It is quite possible that some of the other contacts, who are negative in the early days of exposure, might have become positive later for PIG test, and several others, whose throat washings were not cultured might have yielded virus, if investigations have been done methodically. Therefore, it is possible that greater number of subclinical infections might have occurred than presented here, and some more of them might have voided the virus, and even without serological response a good number of contacts might have been carriers. The possibility of persons with 'subclinical infection' as well as 'contact carriers' becoming sources of infection, cannot therefore be definitely ruled out. However, the chances of their being capable of transmitting the disease in endemic countries are rather remote, because even in these few, who were positive, it was found that the quantum of virus voided by them has not been so heavy as to cause damage to the community in endemic areas where one requires heavy dose of infection to get infected. However, the same argument may not hold good in all countries and at all times. One, therefore, has to consider them as potential sources of infection.

In conclusion, it may be stated that there is sufficient evidence

Table 14.6. Result of virological studies of Throat Washings of Contact Carriers of Smallpox

S. No.	Name	Sex	Age	Relationship to primary case in the family	*Vaccinal Status (number of scars)* PV	RV	Day of exposure to primary case when specimen taken	*PIG* With Variola	*Test* With Vaccinia	HI Antibody Titres @	Results of Cultures
1.	Mrs. P.	F.	26	Mother	4	Not done	30th	+	+	40	TW +ve Original
							*210	—	—	80	undiluted 3, 0, 10
2.	Mrs. L.	F.	22	Mother	4	„ „	6th	—	+	20	TW +ve Original undiluted 3, 2, 10
3.	Mas. J.	M.	12	Brother	4	NS (1Yr)	33rd	+	+	160	TW +ve Original
							*344	—	—	20	undiluted
											El undiluted 61, 48
											eye swab — ve
4.	Miss K.	F.	11	Daughter	4	2 (1Yr)	8th	—	—	10	TW +ve Original
							*338th	—	nd	160	undiluted 4, 2, 0
5.	Mrs. V.	F.	30	Mother	4	1 (6/12)	8th	+	+	40	TW +ve Original undiluted 14, 3, 0 eye swab +ve

TW—Throat washings
PV—Primary Vaccinals
RV—Revaccination
NS—Scars not seen

F. Female
M. Male
El—Egg passed

@ Shown as reciprocal of serum dilution
* No specimens were collected for culture

Note: Figures in culture column indicate the number of pocks on CAM.

to show that subclinical infections do occur in smallpox. These can be diagnosed only by serological studies. There are certain limitations even in this procedure. However, in general, precipitation in gel test and estimation of HI and CF antibodies may help in diagnosis of these. Results of these tests have to be interpreted carefully. The possibility of persons with 'subclinical infection' and 'contact carriers' in smallpox as sources of infection cannot be completely ruled out, though such chances are remote. This is a field in which further studies have to be made.

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15

Factors Influencing The Transmission Pattern

In the previous chapters, the mode of transmission of smallpox was discussed. From the experience of epidemiologists it is noted that the pattern of transmission of smallpox either in a family or in a community is not quite simple and straightforward. It appears to depend upon several factors. For instance, in a study of intrafamilial transmission in 254 infected families (Rao et al, 1968 b) it was found that only in 14 percent of these families, was there transmission of the disease. Further, despite the fact that nearly 9 percent of the familial contacts of these cases were unvaccinated, only about 40 percent of them contracted the disease even on close exposure. Similarly only 2 per cent of the vaccinated contacts became infected. From this it is clear, that though vaccination plays a great role in determining the transmission of disease in a closed community, yet it is not the only factor. As mentioned earlier, the factors that determine the transmission pattern may pertain to the agent of infection, the source of infection, the host, and the environment.

Factors Pertaining to the Agent of Infection

In India, only variola major has been described so far. Epidemiological evidence shows that there is no variola minor in this country. But the fact that the virus of variola major produces different types of clinical disease in different individuals, makes some feel that there may be different strains of the same virus with varying virulence or invasiveness. The clinical and epidemiological evidence, however, clearly indicate, that different hosts respond in different ways to the same agent of infection depending upon individual resistance, immunity etc. Dixon (1962) has suggested that the virus by passage through the skin may lose its virulence to some extent and consequently, the virus contained in the scabs may be less virulent and invasive and therefore, may produce modified attacks even in the unvaccinated. Although there is such a possibility, it requires laboratory confirmation and so far, there is no evidence, either direct or indirect, to prove Dixon's

views. The only factor pertaining to the agent of infection, that determines the disease transmission pattern therefore, is that variola major and variola minor breed true. One does not produce the other in contacts, irrespective of their immunity status.

Factors Pertaining to the Source of Infection

Although a case of smallpox may be infectious throughout the whole course of the illness, the maximum infectivity is usually confined to the early stage. However, not all cases have the same infecting capacity, which again seems to depend upon other factors. The following are some such, which we have observed from our studies.

Clinical Variety: Though the same strain of virus causes different varieties of disease, yet the clinical variety of the primary case seems to play some role in determining the pattern of disease transmission. Our studies on the intrafamilial transmission of smallpox indicated that the severest variety, the 'Haemorrhagic' and the mildest variety the 'Modified' transmitted the disease to the least number of familial contacts. Whereas maximum transmission occurred with the 'Ordinary' and 'Flat' varieties of the disease. It is possible that three factors, may be basically responsible for this type of disease transmission pattern.

Firstly, a patient who is confined to bed because of the severity of the attack, is less likely to come in contact with others except those who attend on him. This may be one of the reasons why the more severe attacks, like Haemorrhagic, transmitted infection to less number of contacts. By the same argument, the more ambulatory case, viz. the Modified, should transmit infection to greater number of contacts but this is not so. This may be because of the second factor which also seems to play a great role viz. the degree of the severity of enanthem that occurs on the nasal and buccal mucous membranes. We had enough evidence to show that transmission occurs mostly through nasopharyngeal droplets which contain large number of virus particles; hence the greater the severity of enanthem the greater is the infectivity of a case. Modified cases, in the majority of instances, do not have enanthem and hence, inspite of their ambulatory nature, they have the least capacity to infect, whereas the Ordinary and Flat varieties satisfy both these two conditions — they have fairly severe enanthem and they are somewhat ambulatory in the early stages of the disease. Thus these two factors play a great part in determining the 'capacity to transmit' of a case. The third factor which may also play a role, is the duration of the patient's stay at home. Since it has been found that cases of smallpox are highly infective between the fourth and seventh day of the disease, it is possible that those cases which are removed to

a hospital, or which die, before fourth day of the disease, may have no time to transmit infection. This is true with the Haemorrhagic cases, which are either fatal early in the course of the disease or are removed to the hospital, because of the haemorrhages, on the first or second day of the disease. Perhaps this is the reason why Haemorrhagic smallpox cases, especially, the Early type, have not been found to infect contacts at home, though there have been some instances, where they caused severe outbreaks in hospitals, especially in non-endemic areas.

Vaccinal Status of the Primary Case. The transmission of disease to contacts was greater with unvaccinated smallpox cases than with the vaccinated. This is not because the unvaccinated usually develop severe disease, since even with the same clinical variety, there seems to be some difference in the extent of transmission between the unvaccinated and the vaccinated. There is no evidence, so far, to show that virus voided from vaccinated smallpox cases is in any way different from the virus voided from an unvaccinated case. However, it is possible that the quantum of virus in the nasopharyngeal droplets may be less in the vaccinated cases and that the virus in the vaccinated cases may be less virulent or invasive. Both these are mere assumptions for which there is no proof. Such epidemiological evidence as we have, suggests that a less number of contacts become infected from a vaccinated smallppox case than from an unvaccinated one. This requires further study.

Clinical Outcome of the Primary Case: Another finding that cannot easily be explained is that for each clinical variety of smallpox, contacts appear to be more readily infected by cases that subsequently prove fatal than by those who survive. This is even more evident where deaths occur at home, as compared with deaths in hospital. In two groups of cases belonging to the same clinical variety, in which the duration of stay at home was almost the same, there was a statistically significant difference in the transmission pattern of the group that died as compared with the group that survived. It looks as though anxiety, fear, stress and strain, as a result of death at home, may play some role because following a death in the home, the transmission was greater amongst the vaccinated adult contacts than in the unvaccinated child contacts.

Age and Sex of the Primary Case: Surprisingly, the age and sex of the primary case have been found to play a significant role in determining the transmission pattern of the disease in contacts. It was found that children of age group 0 to 4 years who develop smallpox transmit infection to a greater number of female than male contacts. Perhaps this stands to reason, because mostly women and girls look after young children when they are sick. More important than this, is that children

of age group 5-14 years, notably males, transmitted infection to a far greater number of contacts than any other age group. The possible explanation for this observation is that children of this age group usually move about freely, rarely confining themselves to bed inspite of sickness, and they also desire other members of the family to stay and play with them continuously. The greater attention that is paid by all members of the family to this age group when they are sick, will also increase their exposure to infection.

Thus we find that the degree of mobility of the patient at home, the degree of severity of the enanthem, the duration of stay of the patient at home before isolation or death, the clinical outcome, the age and sex of the patient, the attachment of the other members of the family to the case, the fear, stress and strain that the disease causes in the contacts at home, all these seem to play a very important role in determining the pattern of the disease transmission in a family. Perhaps these very factors may also play a similar role in the disease transmission in localized communities.

Factors Pertaining to the Host: Though vaccination immunity of the host exposed to infection is the most important determining factor yet it is not uncommon to find several vaccinated contacts of a smallpox case developing the disease and several unvaccinated escaping.

Age: Although the overall incidence of smallpox is very high in the age group 0-4 years, yet amongst the vaccinated members of this age group the disease has the lowest transmission rate of all. In this recent study it was found, that there was not a single case of smallpox amongst 118 vaccinated contacts belonging to this age group inspite of close familial exposure. This shows that primary vaccination done in infancy confers fairly a good amount of protection upto four years. Beyond the age of four, the immunity from primary vaccination wanes slowly, and beyond the age of 14 years, nearly 3 percent of familial contacts vaccinated in infancy contracted the disease. In the unvaccinated, there was not much difference in the disease transmission pattern with reference to different age groups.

Sex: Women belonging to age group 15 to 44 years, seem to be slightly more susceptible to infection irrespective of whether they are vaccinated or not, when compared with men of the same age group. This may perhaps be due to some hormonal disturbances that occur in women of this age group.

Vaccinal Status: People who have been successfully vaccinated primarily and revaccinated successfully not more than two years before exposure rarely develop the disease inspite of close contact. But it has been found that 3 percent of the familial contacts who have both

primary vaccination and marks of successful revaccination said to have been done more than two years previously have developed smallpox.

In our studies the transmission rates in contacts under the age of 14 years were slightly greater amongst those, who had a single primary vaccination scar, than in those with multiple vaccination scars, though the differences were not statistically significant. Successful primary vaccination, even after exposure, seems to reduce the incidence of smallpox as well as to mitigate the severity of the disease to some extent. The single exception is the Haemorrhagic smallpox, which is equally prevalent in both the vaccinated and the unvaccinated.

Degree of Exposure: Though in several non-endemic countries, a casual exposure to smallpox for a few minutes or the mere entry into an infected room may be responsible for transmission of the disease, it has been our experience in Madras, where the basic immunity of the population may perhaps be comparatively high, that it requires adequate, though short, continuous exposure, for infection to occur. In a study of more than 250 exposed unvaccinated contacts, we observed that 32.5 percent of those who slept in the same room as the case, and spent most of their time, day and night with the patient, and 30.6 percent of those who, although slept in the same room as the case, but spent most of the day time away from the house, contracted the disease. Of all other contacts who visited the room frequently but slept outside, only 14.6 percent became infected. From this, it is clear that the greatest transmission results from close and continuous, though short, exposure, particularly at night, when over-crowding is at its maximum, and ventilation and air circulation are at their minimum.

Intercurrent Disease: It is a common clinical experience that persons suffering from disease of the reticulo-endothelial system such as leukemia etc., fare very badly with other virus infections. This is the case with smallpox too. These persons are more susceptible to infection and severe varieties of smallpox. Even a good vaccinal status may not offer enough protection.

Drugs and other forms of Treatment: Persons receiving corticosteroids, immuno-suppressive drugs, deep X-Ray or radium therapy, all of which suppress the defence mechanism, are unable to withstand infection with smallpox and hence are likely to develop very severe types of the disease with, in the majority of cases, a fatal termination. Even a good vaccinal status may not give adequate protection.

Hormonal disturbances: Hormonal disturbances at the time of infection seem to influence considerably the susceptibility of exposed persons. As will be described later, the pregnant are more susceptible

than the non-pregnant, of the same age group. There is some evidence to suggest, that the high level of circulating blood corticosteroids may be responsible for this high susceptibility to infection and death amongst the pregnant women. We have also found that deaths due to smallpox at home which may cause fear, stress, strain and anxiety in contacts are associated with greater transmission of disease amongst the familial adult vaccinated contacts. Perhaps the same hormone may make these vaccinated contacts temporarily susceptible to infection. There may be some other hormones also which may play some role, in determining the disease transmission about which we have little knowledge.

Factors pertaining to Environment

Load of the unvaccinated: There is evidence, that the greater the unvaccinated load in an infected family, the greater is the transmission of the disease to their contacts, not only to the unvaccinated but also to the vaccinated, thus suggesting that the overall immunity level of the family is reduced. A similar phenomenon may determine the transmission of the disease in the community too, since it is found that when the unvaccinated load is low, so also is the transmission rate, but when the load increases beyond a certain level then epidemic conditions prevail, involving the vaccinated as well as the unvaccinated.

Living conditions and over-crowding: It is a common observation that the greater the overcrowding and the less the available living space per person in a family, the greater is the transmission of the disease. However, studies on intrafamilial transmission of smallpox indicate that although the percentage of the unvaccinated is relatively less in the families of higher economic group, yet the smallpox transmission rate amongst them is surprisingly greater to a certain extent when compared to that amongst the unvaccinated in the families of lower income group. It is quite possible that exposure to mild hidden smallpox cases, and close living and exposure to vaccinated persons may produce higher basic immunity level amongst the lower economic group who live in overcrowded tenements, when compared to those of higher economic group who live in independent detached well-ventilated bungalows. Though there is no laboratory confirmation, epidemiological findings suggest this possibility.

Social Factors: Social customs and community or caste barriers also seem to determine the pattern of transmission of smallpox in closed communities. In a recent epidemiological study of an outbreak of smallpox in a village near Madras city, there were some interesting findings (Rao, 1968 a). Two population groups belonging to two

different communities and professions were living together very closely in the same villages. Inspite of their closeness of living, when there was an outbreak of smallpox in one community of Gounders, whose profession was stone cutting and quarrying, the disease has not spread to the other community viz. the Harijans whose profession was agriculture.

Meteorological factors and weather: Though smallpox has been found to be a seasonal disease, we still do not have definite authentic data whether meteorological factors actually influence the disease transmission. In Madras city, we usually experience two peaks, a high peak in February and March and a low peak in August and September of the year. With the onset of monsoon and with increasing humidity, usually the smallpox incidence comes down (Rogers 1926), but this has not been found to be uniformly applicable to the whole country. Moorthy et al (1958) have also suggested that seasonal variation may depend upon the ultra violet ray intensity in sunlight, which changes with seasons. All these theories do not seem to satisfactorily explain the seasonal variation in the incidence of smallpox in India. However, it is possible, that the transmission of disease in a community may be influenced to a certain extent by the meteorological factors, especially the absolute humidity of the atmosphere, which may keep down the infective dust, if at all air plays any role in transfer of infection over long distances, which itself is doubtful. As regards the transmission of disease within the families, our studies indicated that meteorological factors, *perse* do not seem to determine the transmission pattern. However, we have found that the transmission of disease was maximum in winter and rainy months, which of course can definitely be attributed to greater overcrowding within the houses that occurs during these seasons. It is also observed that during these months, there is a greater load of the unvaccinated in the community which is mainly due to the fact that greater number of births occur during the latter half of the year. Hence it appears that the seasonal variation commonly observed in smallpox transmission is more 'man made' than 'natural' and if only every child is vaccinated and protected as soon after birth as possible, the socalled seasonal variation can definitely be proved to be after all a myth.

Thus the transmission of smallpox in a family, a community or a nation seems to be determined by several factors pertaining to the infecting organism, the source of infection, the exposed contacts and the environment. Vaccination immunity of the exposed host is only one amongst them.

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16

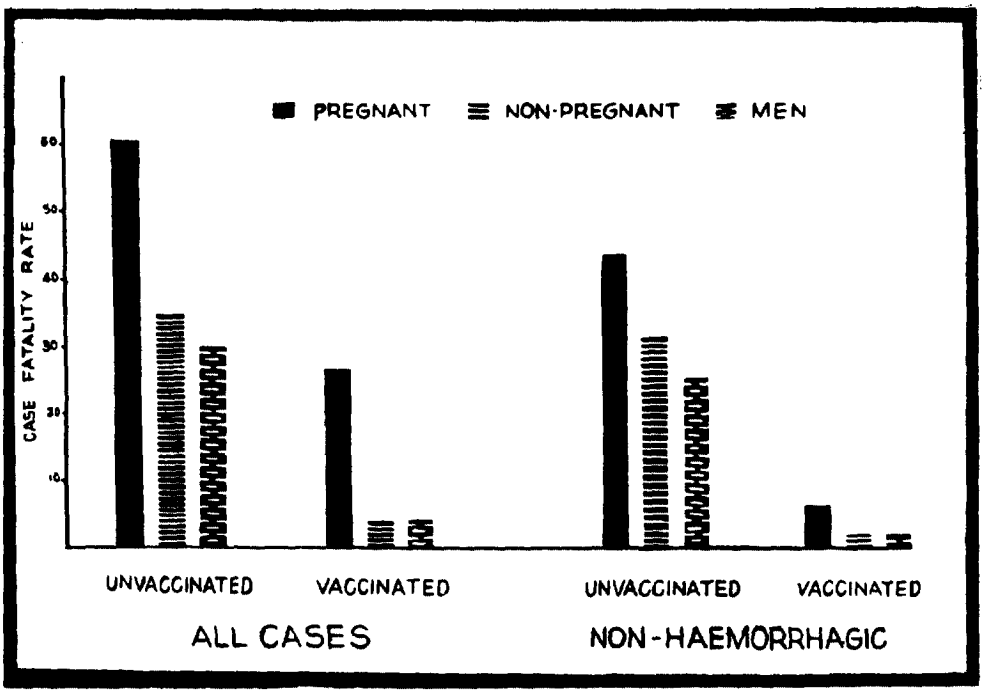
Pregnancy And Smallpox

Smallpox in the pregnant has been a fascinating and intriguing subject both to the obstetricians and physicians. The pregnant, inspite of good vaccinal status, get severe types of smallpox and die. Why they are susceptible inspite of vaccination, is beyond one's comprehension and why they develop such severe types and die is still a riddle with no definite answer.

Since Gregg's (1948) incrimination of rubella, as a factor in the etiology of congenital malformations, great interest has been evinced, during the last two decades, in the effect of other viral and bacterial infections on the life of the mother, of the foetus, on the termination of pregnancy and of course on the occurrence of congenital malformations. But even before Gregg associated maternal rubella with congenital deformities, several authors had observed different types of response in the pregnant to various infections, though they never studied congenital malformations as such.

Williams (1926) held that, with the exception of scarlet fever, pregnancy did not seem to increase the resistance of the body to any other infection. Sprunt et al (1932) observed that pregnancy in rabbits altered the reactivity of 'virus infectious myxomatosis'. Roshan et al (1936) showed that in a large number of rabbits, the pregnant animals were more resistant to vaccinia infection than the non-pregnant. McGoogan (1932), Aycock (1946) and several others reported increased severity of poliomyelitis in the pregnant women. Thus we have many interesting but somewhat conflicting reports regarding pregnancy and infection.

But as regards smallpox in particular, there has been a greater unanimity in the findings of several authors. Marsden (1951) held that association of pregnancy with smallpox was bad both for the mother and the child. Downie (1959) stated that a pregnant woman seemed to fare particularly badly when she contracted the disease. We have also observed from vast clinical experience (Rao et al, 1963) that smallpox in the pregnant is associated with a high rate of premature termination of pregnancy, high foetal and maternal loss. There was enough evidence to show that the 'pregnancy status' as



16/1. Comparison of Case fatality rates in the Pregnant, Men and Non-pregnant women with Smallpox

such, has a disease-enhancing property, with the result that the pregnant are more susceptible to severe types of smallpox inspite of their sound vaccinal status. 50 percent of the Early haemorrhagic type and 65 percent of cases of Haemorrhagic variety in females were in pregnant women (Rao, 1964). These observations leave no doubt that the pregnancy status does enhance the disease.

A study of a series of 389 pregnant women with smallpox confirmed our previous findings regarding the deleterious effect of the disease on the life of the mother, the life of the foetus, and on the termination of pregnancy (*Table* 16.1).

Effect on the Mother: The maternal loss is very high. The overall case fatality rate in pregnant women with smallpox was 33.4 percent, with 27 percent amongst the vaccinated and 61 percent amongst the unvaccinated, as against a case fatality rate of 21.4 percent for all cases with 6 percent and 35 percent respectively among the vaccinated and the unvaccinated. Even successful vaccination does not seem to offer much protection to the pregnant from death due to smallpox.

Effect on Termination of Pregnancy: Although any acute febrile illness in the pregnant is associated with greater tendency to premature termination of pregnancy, in smallpox it is exceptionally high. The termination rate during the course of the disease was 42.3 percent in those women who contracted the disease in the early stages of pregnancy (upto and including 24 weeks). Of those, whose pregnancies did not terminate during the course of the disease, 35 percent had premature termination after discharge from the hospital. Thus nearly 75 percent of women who get smallpox in the early weeks of pregnancy, terminate prematurely.

Amongst women who developed smallpox after the child had become viable but before full term (between 25th to 36th week), 43.4 percent had premature termination during the course of the disease and of the remainder, 13 percent ended in premature termination after recovery. So even in this group of patients, nearly 60 percent had premature termination. In women admitted at full term with smallpox, nearly 90 percent were confined during the course of the disease. We find therefore when a pregnant woman gets smallpox, about 9 percent die before termination, and of those who survive termination, a little more than half, have the termination of pregnancy during the acute phase of the disease itself.

Effect on foetus: The foetal loss is again considerable. Nearly 72 percent of women, who developed smallpox within 25 weeks of pregnancy, had foetal loss which includes abortions and still births either during the course of the disease or immediately after recovery. Simi-

Table 16.1

Smallpox in the Pregnant—Effect on the life of Mother, Foetus and Termination of Pregnancy

	No. of cases	Number died	Case fatality rate	Number died before termination of pregnancy	Number survived termination of pregnancy	Number terminated during the course of the disease	Termination rate	Nature of Termination of pregnancy								Nature of Termination of pregnancy			
								Abortions	Premature		Full term		Number terminated after discharge	Number not traceable	Number traced and followed	Abrotions	Premature		Full term	
									L.B.*	S.B. @	L.B.*	S.B. @					L.B.*	S.B. @	L.B.*	S.B. @
24 weeks and less	137	40	29.2	14	123	52	42.3	52	—	—	—	—	71	34	37	9	1	3	24	—
25 weeks to 36 weeks	148	50	33.8	19	129	56	43.4	—	34	22	—	—	73	27	46	—	2	4	40	—
More than 36 weeks	104	40	38.4	3	101	91	90.1	—	—	—	82	9	10	7	3	—	—	—	3	—
Total	389	130	33.4	36	353	199	53.5	52	34	22	82	9	154	68	86	9	3	7	67	—

L.B.* — Live Births

S.B.@ — Still Births

larly after the child has become viable and before full term (between 25th to 36th week), 39.3 percent had foetal loss during the course of the disease and another 8.7 percent after recovery and discharge. Nearly 48 percent of the terminations therefore resulted in still births. But amongst the cases that were admitted at full term, the still birth rate was only about 10 percent.

Effect on the child: The effect of the maternal disease does not seem to cease with child birth. Nearly 55 percent of the children born alive, died within 15 days after birth, the majority during the first 72 hours of life. The cause of death in these children was not known, though majority were reported to be due to 'want of maternal care', since a good number of mothers die and those who survive are too sick to nurse the babies.

Surprisingly, the incidence of smallpox due to intra-uterine infection is not as high as one would expect. Of 116 live births, that occurred during the course of the disease, there were only 10 cases of congenital smallpox, (Plate 13) where the babies presumably got infected in utero during the viraemia stage, with a 'fever to fever' period (interval between day of onset of fever of the mother and day of onset of fever in the baby after birth) of about 9 to 12 days. Two of these ten cases were premature births and the remaining eight were full term and all of them died, though the clinical attack they had, was not very severe.

Since the placenta is not a barrier to the passage of virus, one might expect all the children born of smallpox mothers to get infected in utero and develop the disease. Most of the terminations occur during the early pre-eruptive stage and so the virus in the blood has every chance of passing through the placenta to the foetus in utero. But it does not seem to happen because only 9 percent of babies were infected in utero. It is not known whether the permeability of the placenta depends upon the degree of virus load in the blood or there is something in the placenta or cord that neutralizes the virus. The fact that none of the 21 children born alive of 84 mothers with Haemorrhagic smallpox (who have intense and continuous viraemia) developed congenital smallpox, suggests that perhaps it is not the load of the virus alone that determines the permeability of the placenta. However, one should not forget that 17 out of these 21 died within a few hours to 72 hours after birth indicating the possibility, that they might have been infected very heavily but they did not survive till presentation of clinical manifestations of the disease. There was no way of finding out whether they were infected or not.

Table 16.2 shows the influence of the clinical variety of the case on the maternal mortality, the termination of pregnancy and the life

of the foetus. The maximum maternal mortality, of course, was with the severest variety — the Haemorrhagic (93.8 percent) and the least with the Modified variety (nil). Similarly, the pregnancy termination rate also was as high as 98.2 percent with Haemorrhagic as against only 25.7 percent with the Modified. Even the foetal loss was highest with the Haemorrhagic and lowest with the Modified. Further with cases of Haemorrhagic smallpox, nearly 81 percent of children born alive of these mothers, died within 72 hours after birth. Thus, the greater the severity of the clinical disease in the mother, the greater are the maternal loss, the premature termination of pregnancy, the foetal loss and neonatal mortality.

Children born of smallpox mothers cannot be expected to have any immunity derived from the mothers since they are born of those who have no immunity at all. Further, most of the confinements occur during the early stage of the disease, when mothers would not have developed any antibodies to transfer to the foetus in utero. All the children born alive who have been vaccinated within first 3 days of life have had successful skin takes. These indicate an absolute lack of immunity among these infants. However, it is surprising that very few infants so born of smallpox mothers contracted the disease either in utero or after birth despite the close exposure to the mother as well as other cases in the ward. This is further discussed under immunology.

The other aspect of smallpox in the pregnant is the influence of pregnancy status on the severity of the disease. For this purpose, the disease pattern in 384 pregnant was compared with that in 1228 non-pregnant women and 1717 men with smallpox in the age group 15-44 years, which is the most susceptible age for pregnancy.

Table 16.3 shows the frequency of the different clinical varieties in these groups of persons with reference to the vaccinal status. The Haemorrhagic smallpox among the vaccinated is nearly seven times more frequent in the pregnant than in the non-pregnant women and men of the same age group. Even among persons with primary as well as revaccination scars, it is nearly eight times more common in the pregnant.

Further, about 22 percent of the total cases in the pregnant were Haemorrhagic as against only 2.8 percent and 2.9 percent respectively in the non-pregnant women and men of the same age group. Even in the vaccinated, a similar high incidence is observed. Only 9 percent of the pregnant cases belonged to the Modified variety, as against 20 to 22 percent amongst the non-pregnant women and men.

The same is the case with prognosis. *Figure* 16.1 clearly shows that both in the vaccinated as well as the unvaccinated, the case fatality

Table 16.2

Smallpox in the Pregnant—Effect of Clinical Variety on the Life of Mother, Foetus on termination of Pregnancy

CLINICAL VARIETY	Number of cases	Number died	Case fatality rate	Number died before termination of pregnancy	Number survived termination of pregnancy	Number terminated during the course of the disease	Termination rate	Nature of Termination of pregnancy during the course of the disease					Number terminated after discharge	Number not traceable	Number traced and followed	Nature of termination of pregnancy after discharge of the patient.				
								Abortions	Premature		Full term					Abortions	Premature		Full term	
									L. B.*	S. B.@	L. B.*	S. B.@					L. B.*	S. B.@	L. B.*	S. B.@
Haemorrhagic	84	83	93.8	29	55	54	98.2	19	6	9	15	5	1	1	—	—	—	—	—	—
Flat	13	11	84.6	3	10	9	90.0	—	2	1	6	—	1	—	—	—	—	—	1	—
Ordinary	251	35	13.9	4	247	125	50.6	33	26	12	50	4	122	50	72	9	2	4	56	1
Modified	36	—		—	36	9	25.0	—	1	1	7	—	27	16	11	—	1	1	9	—

L. B.* — Live Birth S. B.@ — Still Birth

Table 16.3

Distribution of Principal Clinical Varieties of Smallpox in the Pregnant, Men and Non-Pregnant Women

Vaccinal Status	Pregnancy Status	Number of Cases studied	CLINICAL VARIETIES			
			Haemorrhagic	Flat	Ordinary	Modified
Unvaccinated	Pregnant	10	50.0	—	50.0	—
	Non-Pregnant	21	—	—	100.0	—
	Men	17	5.9	5.9	88.2	—
Unsuccessfully Vaccinated	Pregnant	60	30.0	5.0	65.0	—
	Non-Pregnant	200	6.5	7.0	85.0	1.5
	Men	216	6.9	1.8	90.4	0.9
Primarily vaccinated after exposure.	Pregnant	2	—	—	100.0	—
	Non-Pregnant	18	—	5.5	89.0	5.5
	Men	9	—	—	77.8	22.2
With primary Vaccination scars	Pregnant	299	19.4	3.3	66.3	11.0
	Non-Pregnant	960	2.3	1.5	71.9	24.3
	Men	1404	2.3	0.7	72.8	24.2
With primary and revaccination Scars	Pregnant	13	23.1	—	53.8	23.1
	Non-Pregnant	29	—	—	58.6	41.4
	Men	71	2.8	—	59.2	38.0
TOTAL	Pregnant	384	21.9	3.4	65.3	9.4
	Non-Pregnant	1228	2.8	2.4	74.5	20.3
	Men	1717	2.9	0.9	74.6	21.6

*Frequency of clinical varieties is shown as percentage of the total cases in that particular group.

rates are far greater in the pregnant than in the non-pregnant and men of the same age group. This increased fatality is not due solely to the increased number of Haemorrhagic cases among the pregnant. The case fatality rates were higher even in the non-haemorrhagic varieties, as can be seen from the Figure. The reasons for the high susceptibility of the pregnant to severe types of disease and high fatality in the pregnant are not quite clear.

Under similar conditions of vaccinal status, the pregnant fare worse than their counterparts, the non-pregnant women and the men. Does this mean that, inspite of vaccination, they either do not develop antibodies to protect them from an attack of smallpox, or even if they develop antibodies, they become temporarily susceptible during pregnancy? This is further discussed in the next chapter.

Gamzell (1953) measuring the blood levels of 17-hydroxycorticosteroids in pregnant women, observed that they were elevated during pregnancy and that the levels dropped to normal within 6 days after parturition. Robinson et al (1955) examined the blood of 101 pregnant women at different stages of pregnancy and compared the levels of steroid hormones in their blood with those of normal subjects as well as non-pregnant women with some pathological conditions. They found that the steroid levels in the pregnant are elevated significantly during pregnancy, though in several, the levels were fairly high even 6 to 9 weeks post partum.

The disease enhancing property of the steroids is well documented. Schwartzman (1950) produced marked acceleration of poliomyelitis infection in mice and an extraordinary enhancement of susceptibility to infection in hamsters giving rise to a virulent and uniformly fatal disease. Rose et al (1952) found diminished local inflammatory reaction with experimental intradermal vaccination in rabbits, but increased quantity of virus in the blood and internal organs in animals to whom cortisone had been administered. Similarly Bugbee (1960) found that cortisone has definite disease enhancing property on vaccinia in rabbits. Aranson and Schwartzman (1953) confirmed the relationship between the susceptibility to infection and cortisone. No one seems to know definitely the mode of action of this hormone on the disease process. One thing seems to be certain, it does not have anything to do with the virus as such. Hence the only possible effect would be perhaps its effect on the defensive mechanism of the host.

Perhaps the high level of corticosteroids in the blood of pregnant women may, therefore, be responsible for the occurrence of severe varieties of the disease and a very high fatality in the pregnant with smallpox. Further, the fact that non-susceptible animals like the hamster (Schwartzman) was made susceptible to poliomyelitis, makes one

wonder whether corticosteroids make even an immune person susceptible to infection and disease, as happens to the pregnant who have been vaccinated. With these ideas in mind studies were made regarding disease-enhancing property of cortisone in experimental variola in monkeys (Rao et al, 1968).

The disease which is almost non-fatal in monkeys was invariably fatal in cortisonised monkeys. Both the local and general lesions were severe in the cortisonised. The cortisonised animals developed bloody diarrhoea, which were absent in the controls. Virological studies showed that there was a persistant viraemia in the cortisonised, till the day of death, whereas in the control animals, virus could not be isolated after the onset of rash. Autopsies done, showed that almost all the internal organs of the cortisonised, yielded plenty of virus and, further, varying degrees of haemorrhages were found in the lungs and mucous membrane of the gastro-intestinal tract, whereas the control animals did not present any haemorrhagic manifestations. The variolated pregnant monkey behaved in the same way and presented the same appearance as the cortisonised animal. She aborted on the sixth day. She developed the most severe local lesion as well as general rash. Virus was isolated from the blood till the day of death. Autopsy of the animal showed extensive haemorrhages into the lungs and gastro-intestinal tract and also all the internal organs were loaded with virus.

Thus cortisone has been shown to enhance the disease of variola in monkeys. Adequate doses of cortisone before and after variolation produced a fatal form of smallpox, associated with internal as well as external haemorrhages. Pregnant monkey and cortisonised monkey reacted to smallpox infection in the same way as a pregnant woman with smallpox. The mechanism by which cortisone enhances the disease is still vague.

However, it seems certain that at least one of the important factors that is responsible for enhancement of disease in the pregnant is the high level of circulating steroid hormones in them. There may be some other factors too, but our knowledge about this subject is very meagre.

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17

Immunity In Smallpox

The immunity of individuals is the most important epidemiological factor that determines the transmission of disease either in a family or a community. The entry into, and establishment of the agent of infection in the tissues of a host is 'infection'. The 'infected' person need not always be a 'diseased' person. A person may be infected yet he may not present always the clinical manifestations of the disease. But a disease cannot occur without infection. Further, the results of infection may vary from person to person to a very great extent. The organism may gain entry and a foothold and multiply, and yet it may not be able to produce an apparent disease in certain hosts, because of the high resistance the hosts have. In some others, it may multiply and produce the disease and the host may recover from it, if he develops the defensive forces to counteract the infection. Lastly the infecting organism may multiply in large numbers, breaking down all the resistance of the host, and as a result, the host may develop a very severe clinical disease and die. Thus the clinical response depends upon the resistence or immunity of the host to the invading organism. The former word is used in a more comprehensive manner to cover all the factors that make the host resist the infection, or to mitigate the severity of the disease, and the latter is applied only to the resistance due to the presence of specific antibodies to the specific antigen or the invading organism.

Though vaccination and an attack of smallpox are the only two methods by which a person can develop immunity against that disease, yet we know that some persons who have neither been vaccinated nor had an attack of smallpox do escape the disease even on close exposure. The actual mechanism of immunity is complicated and poorly understood. It is not proposed to discuss the various theories about the immunity mechanism in smallpox in great detail.

Inspite of the extensive knowledge that has been acquired about the antigenic structure of vaccinia virus, and to a limited extent, of the variola virus, yet the actual role these various antigenic components play in the immune mechanism is not known. All these antigenic

components seem not to invoke, by themselves, any immunity. It has been found that the injection of enormous quantities of killed vaccinia virus into an animal did not confer much benefit, and that only vaccination with a living virus produces maximum immunity. Whether this difference in immune response is due to the fact that the immunizing substances are destroyed by the procedure employed in killing the virus, or whether living virus which multiplies in the tissues can alone produce the factors which set up immune response in the host, is still not understood. From the studies made by various authors, of smallpox virus, there seem to be three possible explanations for acquired resistance; firstly, through the mediation of humoral antibodies, secondly, by the modification in some way of susceptible cells to resist viral proliferation, and lastly through a state of allergic activity or delayed hypersensitivity. Each of these explanations has experimental evidence both 'for' as well as 'against', with the result that we still do not know how resistance to infection is actually developed or even how recovery from infection occurs.

The fact that injection of prepared antibodies (hyperimmune vaccinia gammaglobulin) either before or immedidately after infection, reduces the incidence of the disease among the exposed contacts, shows that virus inhibition by inhibiting antibodies in the circulation, does play some role either in resisting the infection or in preventing the disease in the infected. This inhibition, of course, may be only partial in the majority of cases, perhaps depending upon the intensity of viraemia (virus load in the blood) and the concentration of circulating antibodies present in the blood at the stage of viraemia. These antibodies therefore, in some way, seem to enable the host to resist infection and prevent the development of disease. Perhaps this is the most acceptable explanation of the mechanism of immunity. But unfortunately, it does not seem to explain the whole immune mechanism. Several instances have been reported, where agammaglobulinaemic and hypogammaglobulinaemic children after recovery from any virus disease, developed resistance to that virus without any demonstrable antibodies in their blood. This raises a fundamental question, whether development of antibodies is really essential for recovery from infection or disease and even for resistance against reinfection.

Several workers showed, by experimental evidence, some kind of altered receptivity of cells of immune animals to infection. For instance the cornea of immune animals, thoroughly washed of free aqueous humor, was found to be partially resistant to infection with vaccinia virus. Similarly, it has been shown that vaccination, which fails to take when done on or near the site of previous vaccination, 'takes' on change of site. But against this experimental evidence, vaccinia virus has been recovered from the tissues of immune rabbits for

periods ranging from a few weeks to months after infection. We have also found smallpox lesions actually occurring on vaccination scars. But these observations may not actually deny the existence of cellular immunity, because there is no real evidence so far to suggest that antibodies can destroy virus. What actual role, be it cellular or humoral, antibodies play in the immune mechanism is not known.

The possible role of allergic activity or delayed hypersensitivity status in resistance to infection has not got much supporting evidence, though in virus infections, where the virus is an intracellular parasite, one might imagine that the hypersensitivity state may have a more protective role than in case of bacterial agents. But the fact that injection of killed vaccinia virus, which produces a high level of hypersensitivity, induces very little immunity shows that this may not play a very important role in the immune mechanism.

In short, our knowledge about the mechanism of immunity in smallpox infection is still obscure. So far, there is no definite evidence of any kind, to suggest that the antibodies by themselves actually destroy the virus. How these antibodies function in protecting the cells from the virus — whether they destroy the virus, either free or intracellular, or whether they inhibit the virus multiplication within the cells or whether they prevent the virus from entering into the cells is not known. Incidentally, we also do not know the optimum level of antibodies and which type of antibodies that are required in resisting the infection of variola. All these problems require further studies.

The immunity against smallpox may be 'natural' or 'acquired'.

NATURAL IMMUNITY

This, in fact should be called natural resistance. It is a state of insusceptibility to the disease even without the presence of specific antibodies against smallpox. Natural immunity is one, that is not acquired. Very little is known about the mechanism by which one can develop this resistance without antibodies.

Species immunity: There is no doubt that smallpox has an affinity only for certain species of animals. Besides human beings, smallpox occurs naturally only in monkeys, which may get infected from human beings. Even in the laboratory, the monkey is the only animal in which the disease similar to that in man, can be induced. Surprisingly, even animals which are quite susceptible to vaccinia are not susceptible to variola, though both viruses are antigenically similar in several respects. Hence there seems to be some 'species immunity' against smallpox, the monkey and the man being the most susceptible.

Racial immunity: There is no evidence available so far, to show that any particular race, nationality or community has some special predeliction or insusceptibility to smallpox. On exposure to infection, every unprotected person irrespective of race, creed or nationality has the same chance of contracting the disease. Thus there is nothing like 'racial immunity' against smallpox.

Genetic immunity: Presence of blood group substances present in the red blood cells is under genetic control. There has been a lot of speculation that persons belonging to certain serological groups are more resistant to smallpox than those belonging to other groups. Pettenkoffer et al (1960) have stated that persons belonging to blood groups O and B, who possess anti-A antibody, would be more resistant to smallpox. They founded their theory on their findings, that egg-grown vaccinia virus possessed blood group A-like substance, and they inferred that variola virus also may possess such substance.

Pettenkoffer et al (1962) have further observed that the existence of a relatively high proportion of group B individuals in India can be explained by the fact that they had survival advantage over others in this country, where smallpox has been endemic for centuries. They also found in their retrospective studies in India, of persons who had had smallpox, persons belonging to groups B and O suffered a less severe form of pitting than those belonging to groups A and AB.

Weiner and Springer (1962) contesting the findings of Pettenkoffer, stated that the blood group A-like substance found by the latter in egg grown vaccinia virus, is probably derived from chick embryo itself and has nothing to do with vaccinia virus at all. According to them, even egg grown influenza virus possesses the same substance. Haris et al (1963) have shown that extracts of normal chick embryo contained this antigen, and further, vaccinia virus grown on the infected rabbit tissue does not possess this substance. They also found that antisera prepared against blood group A substance as such, has no neutralizing capacity against vaccinia virus.

Downie et al (1965) comparing the blood groups of 337 smallpox patients with those of 27,142 blood donors (from the blood bank) concluded "although the total number of smallpox cases was small, the blood group distribution amongst them does not suggest that the presence of anti-A substance is associated with resistance to smallpox. Further, comparison of smallpox patients possessing anti-A antibody (groups B and O) with those who did not (groups A and AB), in relation to severity of illness shows no essential differences". Vogel et al (1960) suggested that the possession of anti-A antibody might lessen viraemia in smallpox, but Downie et al (1965) stated "that the frequency of Haemorrhagic smallpox cases (where viraemia is

severe and persistant) in group B patients does not confirm Vogel's hypothesis".

Individual immunity: In a highly susceptible population exposed to infection under identical conditions, certain individuals do not get infected even though they have had no previous exposure, which cannot be explained easily. Perhaps several non-specific mechanisms also operate and minimize the chances of virus entering and multiplying in the human host. Similarly, as stated already, hormonal factors may play some role in making well immunized persons susceptible to infection.

ACQUIRED IMMUNITY

Immunity may be acquired after birth either passively or actively. Unlike the natural immunity (natural resistance), this acquired immunity is a specific immunity as a result of the presence of specific antibodies to the infecting organisms and/or its antigens.

Passive: This is a state of temporary insusceptibility to infection due to the presence of circulating antibodies passively administered either artificially or transmitted through the placenta to the offspring. Since these antibodies break up constantly without fresh ones being formed, they disappear rapidly conferring only a temporary protection.

Transplacental passive transfer of antibodies: It is generally felt that if the mother has antibodies to any particular infection, they are passively transferred through the placenta to the foetus *in utero*. In the baby, for some weeks after birth, these antibodies may persist conferring temporary protection.

It is thought that this mode of transfer depends upon the thickness of the placenta. For instance in certain animals like the cow, sheep, pig, horse etc., in whom the placenta is thick, consisting of many layers, the entire transfer of antibodies seem to occur through the first milk or colostrum, which contains a high concentration of antibodies. On the other hand in human beings, in whom the placenta is thin and easily permeable, it is assumed that most of the antibodies are transferred through the placenta. It is now felt that it is neither the thickness of placenta nor the size of the antibody molecule alone, that determines the transfer. There may be several other factors, including the selective capacity of the placenta for certain antibodies.

Further, it has been found that in certain instances, the placenta draws and transfers the antibodies to the foetus even at the expense of the mother with the result that there is greater concentration of antibodies in blood of the cord at confinement, and even in the baby after birth, than that in the corresponding mother. Cruickshank (1963) says that "this greater concentration of antibody, in particular diptheria

antibody, staphylococcal and streptococcal antihaemolysins, in infant or cord blood than in corresponding maternal blood cannot be explained". Similarly we have found in our studies (Rao et al, 1969) greater concentration of antibodies against vaccinia in the cord blood and baby's blood at birth than in corresponding bloods of mothers who have been successfully revaccinated during pregnancy.

This may perhaps explain why pregnant women get smallpox inspite of successful recent revaccination and also why babies born of smallpox mothers, and who are kept in smallpox wards do not develop smallpox so easily.

We have also found that it is only the HI antibodies that are concentrated in cord blood and babies' blood with almost complete absence in the mother's at the time of confinement, whereas the concentration of neutralizing antibody was more or less the same in the mother as in the baby, though about 30 percent of the babies had a higher concentration of neutralising antibodies than what their corresponding mothers had. Does this mean that the placenta has some selective capacity for concentrating HI, but not neutralizing antibodies? If that is so, it raises another more important question; which of these two antibodies protect against smallpox? Are HI antibodies more important than neutralizing? So far, they have never been thought so. The pregnant, who have high level of neutralizing antibody but very little or no HI antibody, seems to be more susceptible to smallpox inspite of successful vaccination. Similarly babies (born of smallpox mothers) who have fairly high cocentration of both neutralizing as well as HI antibodies at birth, are generally found to be non-susceptible to smallpox atleast for a short period of time. Since it has been found that HI antibodies disappear very early and that smallpox incidence in unvaccinated children is fairly high after one month, it appears that HI antibodies are perhaps as important as neutralizing antibodies in the prevention of smallpox. However, this requires further study and elucidation to throw some light on the protective power of the different types of antibodies.

For how long do these passively transferred antibodies protect the child after birth? *Figure* 17/1 shows the proportionate distribution of smallpox cases in the unvaccinated with reference to age groups. As can be seen from this and *Table* 17.1, 59 percent of the total unvaccinated cases were in the age group 0 to 4 years and of these cases, only 1.8 percent were under 30 days. (*Fig.* 17/2), whereas nearly 26 percent of the cases occurred in the age group 1 to 12 months. Further, majority of the cases under the age of 30 days were congenital smallpox with infection occurring *in Utero* and the disease developed within 14 days after birth. It is true, therefore, that the lowest incidence of

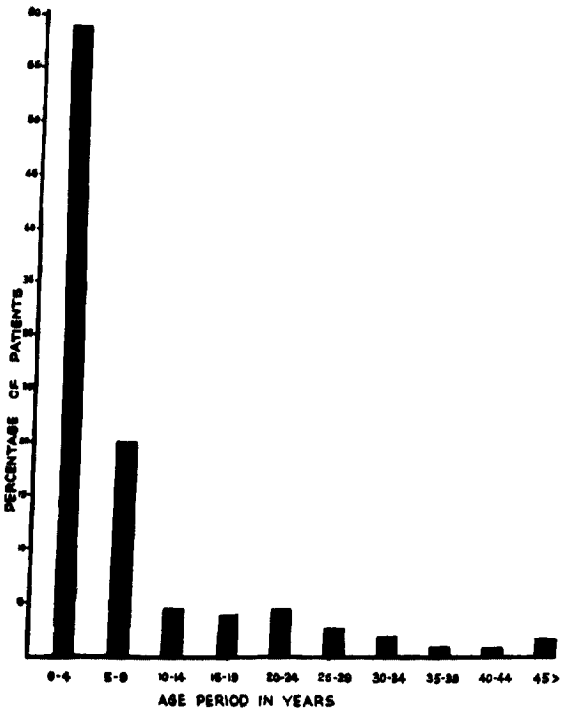
smallpox in the unvaccinated children was under the age of 30 days, beyond which it increased with age reaching the maximum in the age group 13 to 24 months. This indicates that if any protection at all is conferred by transplacentally transferred antibodies, it is unlikely to last more than a month.

Vaccinia Immune Gammaglobulin: As in the case of bacterial diseases, prepared antibodies can be administered to those persons who have been infected with smallpox and in whom there is no time for the individual to develop antibodies by active immunization. These antibodies are administered in the form of concentrated preparation viz., gammaglobulin which is prepared from the plasma of recently successfully vaccinated adult human donors.

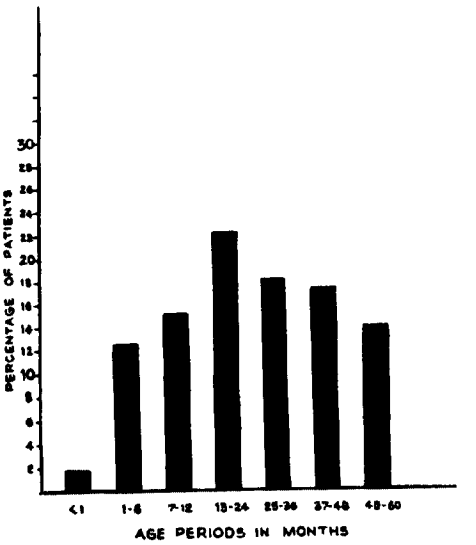
Extensive work has been carried out with vaccinia immune gammaglobulin in the prophylaxis of smallpox by several workers, notably by Kempe and his associates (1961). These authors have found in their studies that five out of 326 exposed contacts treated with vaccinia immune gammaglobulin developed smallpox as against 21 out of 379 control contacts. Both the treated as well as control groups, of course, were vaccinated after exposure. In their opinion the difference "can be regarded as significant in the sense that a reduction in the incidence of smallpox of the order of 70 percent can be expected in the contacts by giving vaccinia immune gammaglobulin".

Of course prophylaxis with vaccinia immune gammaglobulin cannot and will not replace routine vaccination. This will be useful only in those who are infected. These antibodies disappear very quickly and hence confer protection only temporarily, just enough to tide over the emergency. Since one does not know who is infected and who is not, simultaneous active immunization by vaccination has to be done. It is almost impossible to use this procedure on a mass scale in endemic areas, since vaccinia immune gamaglobulin is not produced commercially. This may have some practical application in protecting the infants and pregnant women who, when exposed to infection, are likely to develop severe attacks. Another group of population, especially in non--endemic areas, are the hospital staff, who are exposed to smallpox unknowingly and in whom vaccination at such a late stage of incubation may not help. Downie et al (1961) found a far greater antibody concentration in the sera of recovered smallpox patients and so it is possible that gammaglobulin prepared from the plasma of convalescent smallpox patients may contain a far higher concentration of antibodies and that such variola immune gammaglobulin may be far superior to vaccinia immune gammaglobulin.

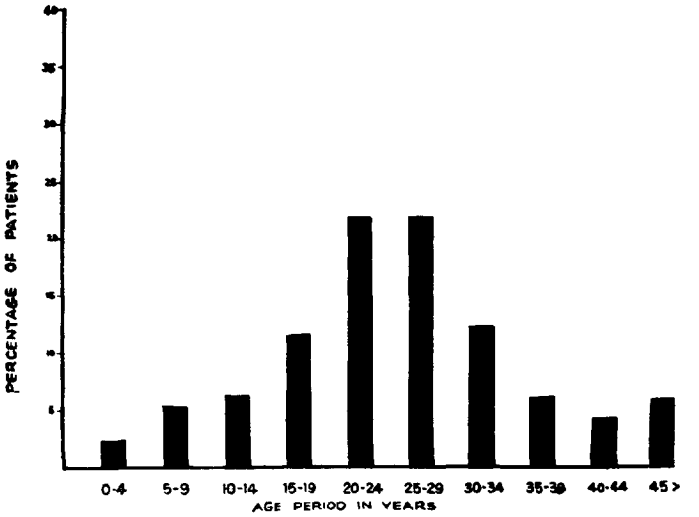
The use of vaccinia immune gammaglobulin has become almost a routine prophylactic measure in several countries, where complications



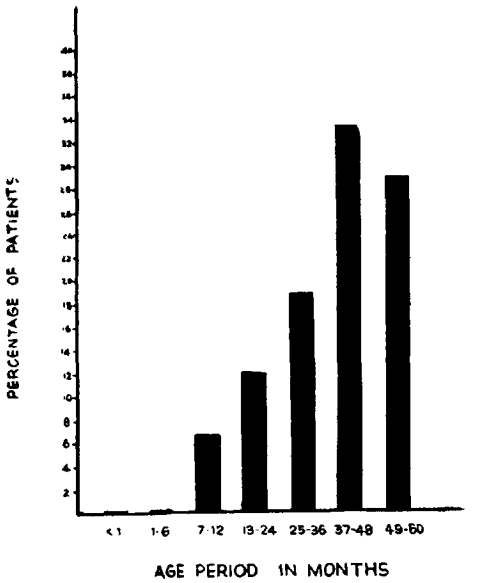
17/1. Distribution of Smallpox cases amongst the Unvaccinated by Age group



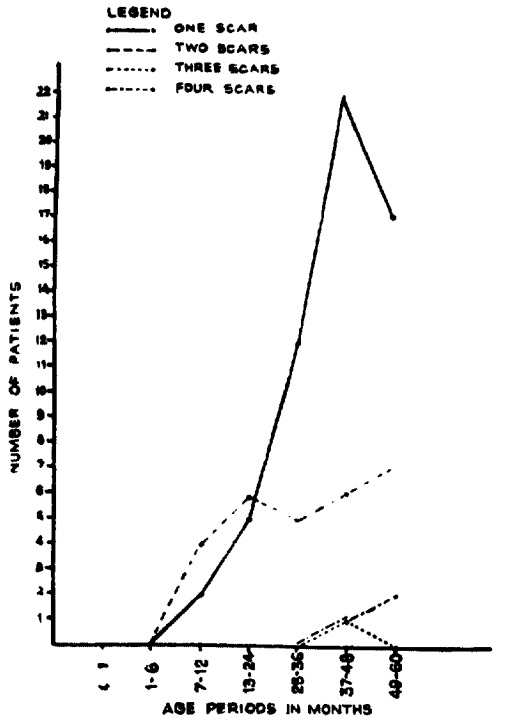
17/2. Distribution of Smallpox cases amongst the Unvaccinated in the Age group 0-4 years by Age in months



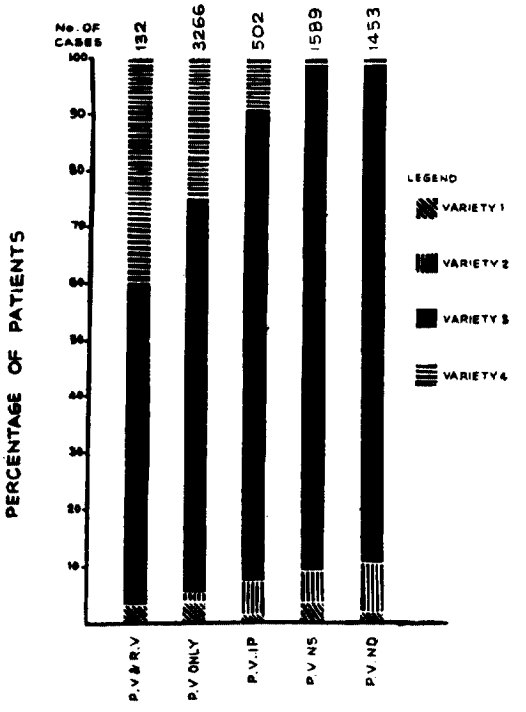
17/3. Distribution of Smallpox cases amongst the Vaccinated by Age group



17/4. Distribution of Smallpox cases amongst Vaccinated in the Age group 0-4 years by Age in months



17/5. Distribution of Smallpox cases amongst the Vaccinated in the Age group 0-4 years by the number of Primary vaccination scars



17/6. Distribution of Smallpox cases by Vaccinal status and Clinical variety

Table 17.1

Distribution of Principal Clinical Varieties of Smallpox cases amongst the Unvaccinated, by Age

Clinical Variety		Number of cases	AGE GROUPS 0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45 and above.
Haemorrhagic	C	85	24	5	4	7	18	10	3	1	2	11
	D	84	24	5	4	7	18	9	3	1	2	11
Flat	C	236	169	32	4	5	7	5	5	1	—	8
	D	232	157	32	3	5	7	5	5	1	—	7
Ordinary	C	3147	1837	665	145	130	132	83	50	30	30	45
	D	954	681	120	11	20	39	24	12	14	10	23
Modified	C	75	61	6	1	1	4	1	—	1	—	1
	D	—	—	—	—	—	—	—	—	—	—	—
TOTAL	C	3544	2091	708	154	143	161	99	58	33	32	55
	PDF	100.0	59.0	20.0	4.4	4.1	4.5	2.8	1.6	0.9	0.9	1.8
	CFR	35.8	41.7	22.2	11.7	22.4	39.8	38.0	34.5	48.0	37.0	61.5

C = Cases D = Deaths PDF = Proportionate distribution Frequency CFR = Case fatality rate.

due to vaccination are far greater in number than cases of smallpox. After the onset of complications in the vaccinees following vaccination, and after the appearence of clinical manifestations in cases of smallpox, utility of administration of vaccinia immune gammaglobulni is doubtful.

Active immunity: As against passive immunity, this is a state of resistance built up by the individual by an experience with the infecting, or an antigenically similar organism. In immunity against smallpox, it may be an experience with variola virus (attack immunity) or with vaccinia virus (vaccination).

i. Attack immunity: Smallpox is one of the diseases that is known for its production of solid immunity after an attack. Second attacks of smallpox are rather rare. In our experience they occurred at the rate of 1 in 1000 cases. They are far more common in women, the average interval between the two attacks being about 15-20 years. It is quite possible, the frequency may be a little more than what we have observed, since invariably second attacks which are very mild may have missed isolation. Second attacks are never fatal, though Dixon has reported 25 per cent case fatality amongst them, a little more even than the mortality rate of the first attacks! Of course only the presence of pitting on the face was taken as evidence of the first attack by us and not the history. All second attacks were diagnosed clinically by the author himself and confirmed also by the laboratory.

Immunity after an attack of smallpox lasts long as evidenced by persistance of high level of neutralizing antibodies even for several years. But it is not difficult to vaccinate these persons successfully, even after one year, with a potent vaccine. "Major takes' can be obtained in recovered cases of smallpox within one to two years. This may mean nothing. Definitely it does not mean that they have become susceptible to smallpox so quickly. It is possible to get 'major takes' with vaccination on the skin, even in the presence of high level of circulating antibodies. It is also possible that variola may not offer so much protection against vaccinia as it does against variola. Whatever it is, it is certain that immunity after smallpox persists for a period of 10 to 15 years though second attacks during that period have been described to occur rarely.

There is another question that often crops up, and that is whether the degree of antibody response after an attack of smallpox depends upon the severity of the clinical type of attack. Though it does not appear to be possible, yet it merits consideration. Further, what will be the type of antibody response in a case of smallpox, who had primary vaccination in infancy compared to that in one who has never been vaccinated? Does this attack of smallpox, in the previously vaccinated

person act as a booster and raise the antibody level to a far higher concentration than that in the un-vaccinated? Similarly in an unvaccinated person, does a Modified attack produce the same degree of antibody concentration as an Ordinary confluent attack does? These are of some practical significance requiring careful and detailed investigations.

ii. Active immunization — Vaccination: Till Edward Jenner discovered vaccination, variolation which was in vogue in certain countries, was the only method employed to prevent smallpox. Smallpox was so rampant in pre-Jennerian days that, it is said that the public health bulletins in the United Kingdom were mentioning the 'number of persons in a locality yet to get smallpox' and not 'those who had' the disease. From this and such other historical data in other countries, one can easily visualize the occurrence of the disease in those days. Most of the adult population would have comprised only of those who had an attack of smallpox in infancy and survived. Smallpox was mostly a disease of childhood at that time.

But the picture has changed after the discovery of vaccination. With a good number of children protected at a young age, there has been a definite shift in the age incidence of smallpox to higher age groups. Jenner thought that vaccination protected a person life long from smallpox. But very soon it was realized that it was not so. At the beginning of this century there was a strong belief that it protected a person for not less than 7 years. Now, we are inclined to believe that protection conferred by vaccination may last about 2 to 5 years. In endemic areas, nearly 50 percent of the total cases of smallpox are found to occur among the adults, who have been vaccinated once in infancy. Thus it is clear that, after all, vaccination is not infallible. It has its own limitations.

Immunity after primary vaccination: It is very difficult to say how long immunity lasts after primary vaccination. Even if the concentration of different antibodies is estimated in children after primary vaccination at varying intervals, one still does not know which of the antibodies does really protect against smallpox, and what is the optimum level of circulating antibody that is necessary to protect against the disease on exposure. In the absence of these data, it is not possible to state categorically the duration of immunity after vaccination. Further, the presence or absence of antibodies alone does not seem to determine the susceptibility to infection. However, it has been found that after primary vaccination, both neutralizing as well as HI antibodies appear by about 2 weeks in almost all persons with successful takes, though the CF antibodies may appear a little later. The neutralizing antibodies may be detectable even upto 20 years after primary vaccination though there may be individual variations. But the HI

and CF antibodies usually disappear within a year. *Table* 17.2 and *Figure* 17/3 indicate the proportionate distribution of cases occurring in the vaccinated with reference to age. As is evident, the lowest incidence was in the age group 0 to 4 years, and it increased with increasing age upto 30 years, beyond which it came down again. It indicates that the protection after primary vaccination is quite good upto 4 years of age beyond which it wanes rather slowly upto the age of 14, and then rapidly up to 30 years. The fall after 30 years may be due to the fact that the majority above that age have been revaccinated several times though no scars were seen, or the population distribution itself has the same trend.

Figure 17/4 shows the break-down of the cases that have occurred in the vaccinated belonging to the age group 0 to 4 years. There were no cases in the vaccinated up to the age of 6 months. About 7 percent of the cases occurred in the age group 7 to 12 months and there after the frequency increased with age rather rapidly after 36 months. Barring some exceptional cases (which will be discussed later) the immunity after primary vaccination seems to be fairly solid for about 24 months and fair upto 4 years.

Considering it from a different angle, in an actual study of familial contacts exposed to infection within the family, we have noted that there was no transmission of smallpox even on close exposure in 118 vaccinated children under the age of 5 years, and very little upto the age of 14. There were only two cases among smallpox contacts out of 327 vaccinated contacts aged 0-14 years, whereas there were 11 contact smallpox cases out of 590 adults beyond the age of 14 years. This study shows that upto the age of 4 years the primary vaccination protects a person well, even on close exposure, and beyond 14 years the protection is likely to wane.

Immunity and number of primary vaccination scars: This has been a controversial subject. Old authors observed that there was some correlation between the number of primary vaccination scars and the occurrence of smallpox. But virologists and immunologists feel that there cannot be any correlation, since the vaccination is done with a living virus which multiplies rapidly.

Since it is possible that a number of children are revaccinated either successfuly or unsuccessfully, after the age of 5 years let us take only the age group 0-4 years. *Figure* 17/5 shows the distribution of smallpox amongst the vaccinated children belonging to the age group 0-4 years with reference to the number of scars of primary vaccination done in infancy, i.e., within 6 months of birth. 96 percent of the total cases in this age group were in children with two scars or less. Further, there was no case of smallpox in children under the age of

Table 17.2

Distribution of Principal Clinical Varieties of Smallpox Cases amongst the Vaccinated, by age

Clinical Variety		Number of Cases	Age group in years									
			0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45 +
Haemorrhagic	C	115	1	6	1	9	22	28	24	6	11	7
	D	108	1	6	1	9	22	28	20	6	9	6
	CFR	100.0	100.0	100.0	100.0	100.0	100.0	100.0	83.8	100.0	81.8	85.7
Flat	C	45	3	2	—	2	5	13	5	4	6	5
	D	30	3	2	—	2	2	8	4	3	3	3
	CFR	66.7	100.0	100.0	—	100.0	40.0	61.6	80.0	75.0	50.0	60.0
Ordinary	C	2377	52	88	137	268	524	564	300	158	108	168
	D	76	10	3	1	4	9	15	9	7	5	13
	CFR	3.2	19.2	3.4	0.7	1.5	1.6	2.6	3.0	4.4	4.6	7.7
Modified	C	861	34	74	72	120	209	160	98	39	24	31
	D	—	—	—	—	—	—	—	—	—	—	—
	CFR	—	—	—	—	—	—	—	—	—	—	—
Total	C	3398	90	180	210	399	760	765	427	207	149	211
	PD	100.0	2.7	5.3	6.2	11.7	22.4	22.5	12.5	6.1	4.4	6.2
	CFR	6.3	15.6	6.1	0.9	3.8	4.3	6.7	7.7	7.7	11.4	10.4

C=Cases D=Deaths PD=Proportionate Distribution by age CFR=Case Fatality Rate

36 months who had 3 or 4 scars. Thus there is a suggestion that protection is greater in children with multiple insertions than in those with a single insertion.

Immunity as a result of primary vaccination after exposure to smallpox: It is stated often that vaccination, if done, within the first 24 to 72 hours after exposure to smallpox, may ward off the attack. There is little evidence to confirm this, since no one knows who was infected and who was not. *Figure* 17/6 shows the frequency of different clinical varieties in the unvaccinated, unsuccessfully vaccinated, and those vaccinated for the first time after exposure. These suggest that vaccination after exposure may mitigate the severity of attack.

Regarding the actual warding off the attack, it is difficult to have controlled studies since the contacts are invariably vaccinated as soon as a case is notified, but we (Rao et al, 1968) had the opportunity to make some observations. Although our figures were not statistically significant, yet they did indicate that successful vaccination after exposure may reduce the incidence of smallpox in the exposed contacts to a certain extent.

Immunity after revaccination: Studies on incidence of smallpox with reference to vaccinal status in intrafamilial contacts exposed to smallpox, have shown (Rao et al, 1968) that there was no case of smallpox in 212 familial contacts who had both primary vaccination and successful revaccination within 2 years before exposure, but there was one case among 30 contacts who had primary vaccination and successful revaccination more than 2 years before exposure (in this instance it was 3 years and it was with liquid lymph).

In general, therefore, it can be stated that a successful revaccination in a person who has been previously vaccinated in infancy usually protects against smallpox for several years, and certainly for 2 to 3 years. There are, of course, several exceptions to this.

Vaccination immunity and severity of the disease: *Table* 17.3 shows the frequency of clinical varieties in each group according to vaccinal status. Nearly 40 percent of all cases that occurred in persons presenting evidence of both successful primary and revaccination were Modified in contrast to only about 25 percent of caes in persons vaccinated only once in infancy, and only one percent in those who were never vaccinated. There were no cases at all belonging to the Flat variety in persons who had both primary vaccination as well as revaccination scars and cases of Flat variety were even less prevalent in the once-vaccinated when compared to the unvaccinated.

There is no significant difference in the frequency of clinical varieties and the number of primary vaccination scars, if all the age groups are considered. But taking into consideration only children upto the

Table 17.3

Distribution of Principal Clinical Varieties of Smallpox Cases by Vaccinal Status

Vaccinal Status	Clinical Varieties								Total	
	Haemorrhagic		Flat		Ordinary		Modified			
	Cases	Frequency	Cases	Frequency	Cases	Frequency	Cases	Frequency	Cases	Frequency
Unvaccinated	22	1.5	120	8.3	1296	89.2	15	1.0	1453	100.0
Unsuccessfully Vaccinated	59	3.7	88	5.5	1425	89.7	16	1.1	1589	100.0
Primary Vaccination after exposure to smallpox	4	0.8	28	5.6	426	84.8	44	8.8	502	100.0
With scars of Primary vaccination	111	3.4	45	1.4	2302	70.5	808	24.7	3266	100.0
With scars of primary and revaccination	4	3.0	—	—	75	56.8	53	40.2	132	100.0

*Frequency shown as percentage of total in that group.

age of 10 years (*Table* 17.4) severe varieties of smallpox, with exception of the Haemorrhagic variety, are far less in persons with more than two scars and further, only 20.4 percent of the single scar group were Modified as against 35 to 62 percent in multiple scar group. There were no Flat cases at all in those with more than two scars.

The data indicate that the greater the number of primary vaccination scars, the greater is the protection against severe varieties of smallpox upto the age of 10 years, the exception being the Haemorrhagic variety.

Among persons who had no evidence of vaccination scars, the cases who had successful primary vaccination even after exposure (*Table* 17.3) fared slightly better, since 8.8 percent of such cases followed a modified course in contrast to only 1 percent of the cases who were unsuccessfully vaccinated or never vaccinated.

The exception to all these is the Haemorrhagic variety in whom the picture is different. This variety of smallpox occurred in a slightly greater proportion amongst the vaccinated persons than in the unvaccinated. Even amongst the unvaccinated, it was more frequent in the 'unsuccessfully vaccinated' than in the 'never vaccinated' or 'successfully vaccinated for the first time after exposure'. Even in persons who had both primary as well as revaccination scars, 3 percent were Haemorrhagic suggesting that vaccination and even successful revaccination does not seem to offer as much protection against this variety of smallpox as they do, against the non-haemorrhagic.

Vaccination immunity and prognosis: As has been already stated, in general, the vaccinated have greater chances of survival when compared to the unvaccinated. But the age, sex and hormonal disturbances also influence the prognosis of a case besides vaccinal status. The protection from death by smallpox due to vaccination immunity is not absolute. As with morbidity, the immune barrier is broken by several of these factors and the patients inspite of good vaccinal status may succumb to the disease in such circumstances.

Corticosteroids and immunity: It has been shown in the previous chapter that when an adequately cortisonised monkey is variolated, it develops very severe fatal disease indicating that a high level of cortisone at the time of infection with variola virus does enhance the disease in an animal. The same mechanism seems to work in the pregnant women also who have a very high level of corticosteroids in their circulation. There are two aspects to this question. Firstly, does a high level of circulating corticosteroids make even an immune person temporarily susceptible to variola infection? Though Schwartzman has reported that cortisone can make a non-susceptible animal susceptible to polio infection, yet from our studies we have not found that

Table 17.4

Distribution of Principal Clinical Varieties of Smallpox Cases amongst the Vaccinated in the Age Group 0-9 years, by the number of Primary Vaccination Scars

Primary Vaccination Scars	Clinical Varieties								Total	
	Haemorrhagic		Flat		Ordinary		Modified			
	Cases	Frequency	Cases	Frequency	Cases	Frequency	Cases	Frequency	Cases	Frequency
One	3	2.8	4	3.7	79	73.1	22	20.4	108	100.0
Two	1	1.2	1	1.2	39	47.0	42	50.6	83	100.0
Three	—	—	—	—	14	63.6	8	36.4	22	100.0
Four	3	5.7	—	—	17	32.1	33	62.2	53	100.0
Total	7	2.6	5	1.9	149	56.0	105	39.5	166	100.0

cortisone can make an immunized animal susceptible when it is challenged with variola virus. Though this requires further study, yet it looks as though the greater susceptibility of the pregnant women, inspite of vaccination may not be due to the high level of cortisone. Perhaps the increased susceptibility, as explained, might be due to the disappearance of certain type of humoral antibodies that are formed after vaccination and their transference through the placenta to the offspring. It is not known whether the cortisone plays any role even in this phenomenon of transfer of antibodies from the blood of the mother and their concentration in the foetus. Perhaps it is the placenta that is responsible for this kind of selective transference of their antibodies. More work has to be done to explain this mechanism.

The second aspect of the question is, how does cortisone enhance the disease when once the infection has occurred? Does it interfere or delay the development of antibodies? The fact that tissue cultures treated with cortisone have yielded increased quantities of virus (Kilbourn, 1957; Holden et al, 1962) indicates that cortisone, probably does not enhance the disease by suppression of antibody formation. Similarly preliminary experiments done by us with variola in monkeys, showed that there is not much difference in the antibody concentration between the cortisonised monkeys and control monkeys estimated at the time of death of the cortisonised monkeys. These experiments have shown that the cortisonised monkeys have died of intense viraemia thereby indicating that cortisone probably has acted in some way to see that multiplication of virus is not inhibited. The fact that the control monkeys survived without any demonstrable antibodies up to the day corresponding to the day of death in cortisonised monkeys, indicates that antibodies were not, perhaps, so important for recovery of control animals.

"Isacs believed that interferon may be more important than antibodies in recovery from virus infections, since the latter appear too late to influence the primary infection." (Rhodes and Rooyan 1962) On the other hand he has stated that interferon is produced at the right time to influence this stage, and that there is some evidence that interferon production is suppressed by cortisone. Kilbourn et al (1961) also found that pretreatment of eggs with cortisone inhibits the production of interferon when embryonated eggs are infected with influenza virus. If, therefore, interferon plays any such role in recovery from variola, it may explain how cortisone, while suppressing the interferon formation, enhances the disease. Perhaps this is the mode of action how cortisone in the pregnant women, makes the disease so severe and why cortisonised monkeys invariably die of smallpox.

Squires and Mcfadzean (1966) found that the "mean survival time in mice (infected with variola virus) given one dose of cortisone (50 mg)

subcutaneously, with oral M&B 7714 for 4 days was 9.0 days compared to 13.1 days when no steroids were administered". This shows that cortisone may even interfere with antiviral activity of the drugs too.

Infection occurring in a person having high level of steroids in the blood, is therefore likely to take a severe form, due probably to the interference with the interferon formation by the hormone concerned. It is also possible that cortisone may interfere with other defence mechanisms as well.

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SECTION—3

CONTROL

18

Introduction

No discovery made in recent years has saved so many millions of lives from a dreaded disease as 'vaccination against smallpox'. One can never imagine what would have been the fate of the world today, if only Edward Jenner has not discovered vaccination. But inspite of the fact that we have been having such a potent tool with us, for more than 150 years, it is a pity, that smallpox still persists as a problem to us. It is not because, that vaccination was ineffective, but it is because our knowledge about smallpox and its control has been rather imperfect. In recent times, however, we gained better understanding of the disease and its spread, and methodology of control. Several countries in the world, by effective vaccination were able to wipe out the disease from their midst, but some how, it is still lingering tenaciously in the countries of South East Asia, Africa and South America. In these days of jet travel, no country which is free from smallpox can consider itself to be safe, since the infection can be imported at any time from endemic areas. Though United States has been spared of these importations during the last two decades, yet this has become quite a common feature in the continent and United Kingdom.

Realising the gravity of the situation, the eleventh World Health Assembly in 1958, proposed that smallpox eradication programme should be undertaken on global basis simultaneously in all the countries, especially in endemic areas, with the final aim of eliminating the disease once and for all from the whole world. Following the resolution, several countries including India, have started the programme and quite a good number of them have even succeeded in their attempts to eliminate the disease from their countries. But unfortunately, a large number of cases are still being reported from the region of South East Asia. The problem of eradication of smallpox from the whole world is not so easy as one would think. There are several reasons for this continued persistence of the disease in these areas, but mainly, want of adequate potent vaccine, lack of adequate technical assistance, resources and personnel etc., played a great role in the initial failures of the programme.

Having reviewed and carefully considered all these problems facing some of the developing countries, the nineteenth World Health Assembly in 1966, reaffirming their intention of pursuing global eradication of smallpox, unanimously declared "this programme to be a major objective of the Organization", and appropriated funds especially for this purpose, and called upon the member governments and other organizations to provide additional support.

Of all infectious diseases, smallpox is one, that can definitely be eradicated for the following reasons:

1. Man is the only host so far known.
2. Transmission occurs from man to man only, without any intermediary host or vector.
3. Transmission occurs mostly by very close contact, and it is not a highly contagious disease producing explosive epidemics.
4. Cases can easily be detected by the presence of rash on the skin. Subclinical cases are not only rare, but also are of not much epidemiological importance.
5. The infective phase is mostly confined to the acute stage of the disease, which is of short duration.
6. An attack of smallpox confers an almost life long solid immunity and second attacks are extremely rare.
7. The incubation period of the disease is more or less constant and short and not more than two to three weeks.
8. Antigenically, there is only one virus to deal with.

Such being the case "global eradication of smallpox is well within the bounds of possibilty" (WHO 1968). The President of the twentieth World Health Assembly, Dr. Gunarathne, has rightly stated that 'the eradication of smallpox is within our reach, the achievement of this important undertaking now depends exclusively on our will and determination'. With such a will and determination, on the part of the member countries of the World Health Organization, there is no reason why this dreaded disease cannot be eliminated from the world once for all, in the next few years to come.

Smallpox eradication has been clearly defined by the World Health Organization Scientific Group (WHO — 1968) as "the elimination of clinical infection by variola virus. As there is no carrier state in smallpox, and subclinical infections are rare, and since no animal reservoirs of disease are known, the absence of clinical apparent human case can be assumed to signify the absence of naturally ocurring smallpox". This definition, of course, presupposes every country to have a good and effective case reporting and detection system, to

reveal the presence of every case of smallpox. Without this basic administrative and organizational set up, this definition has no meaning, since a country may be smallpox-free according to the reports reaching the administrators, although unreported cases may still be occurring. Therefore, all the countries should develop and maintain a well organised reporting system so that no case of smallpox is missed; and with such a set up, if any country, by its eradication programme reports 'NIL' cases of smallpox continuously for at least a period of two years, only then, it attains the 'smallpox free status' as defined by the scientific group.

The main objective of elimination of 'clinical infection' can be achieved by an energetic programme of organization and execution, which envisages, raising the immunity level of the population to such a point as is necessary to interrupt the transmission of disease in a community, which can be done by a quick and effective vaccination of the population in a locality. But this is only one component of the programme. The other component, which is in no way less important than vaccination, is surveillance which includes detection, isolation and treatment of every case of smallpox. Unless every source of infection is removed and isolated from the community, however effective the vaccination programme may be, the disease cannot be 'eliminated'. Any programme which does not give due importance and prominence to this second component, is likely to be ineffective in the long run. Hence an eradication programme should comprise of mass vaccination, surveillance and the institution of immediate effective containment measures.

In the next three chapters, some broad outlines of the organizational aspects of smallpox eradication programme in endemic areas, especially urban areas, will be discussed from the experience gained by the author, in implementation of the smallpox eradication programme in Madras city since 1963.

In areas in which smallpox is highly endemic, mass vaccination, the first component of the programme, may be executed in four phases, whereas the second component of surveillance and containment measures will have to be enforced throughout all phases of the programme with the same vigour. There is no rigid demarcation between one phase and the other. In a programme of such magnitude, in a vast country like India, for practical convenience and operational efficiency, phasing of the programme is very important. These phases are (i) the preparatory (ii) the attack (iii) the consolidation and (iv) the maintenance. Any haphazard, ill-planned and ill-organized programme will always end in failure, resulting in enormous waste of money, energy and man power.

In any public health programme, the 'preparatory phase' is a 'must'. The operational personnel have to be prepared well in advance, people should be prepared to accept the programme, and all the tools and equipment for the programme have to be obtained and collected far in advance. Without proper preparation, a programme is likely to go only half way and end there.

The second phase of operations, the 'attack phase' consists of a large scale, simultaneous attack on all fronts, to vaccinate every available person in a locality, as quickly as possible, by employing an army of well trained vaccinators, so as to boost up quickly the immunity status of the population, to a very high level. Concurrently, care should be taken to see that not even a single case of smallpox escapes the notice of the public health authorities. The programme will continue to be in this phase, as long as the annual incidence of smallpox reported is more than 5 per 100,000 population, and also as long as more than 20 percent of the population have no scars of vaccination.

The second phase is followed by the third, viz., the 'consolidation'. The achievements so far are, that the annual incidence of smallpox has been brought down to less than 5 cases per 100,000 population, and 80 percent of all sections of population have scars of vaccination, done at one time or other. It is almost impossible for any organization to vaccinate 100 percent of the population and detect every single case of smallpox in one phase of operation alone. During this consolidation phase therefore, not only mopping up and vaccination of missed persons should be undertaken but also all vulnerable groups should be protected, so as to see that there are no pockets of susceptibles any where. The aim in this phase is to see that every unvaccinated person is vaccinated, and that the locality becomes smallpox free and remains so, for a continuous period of not less than two years. Only then, will the area be fit to enter the next and the last phase of the programme, the 'maintenance'.

Having attained smallpox-free status for a period of more than two years the immunity level in the population as well as smallpox-free status have to be continuously maintained by periodical vaccination till the disease has been completely eliminated from the whole world. Any hasty action taken to enter into this last phase while neighbouring states and countries are still reporting cases of smallpox, is beset with danger. Atleast geographically contiguous areas should be smallpox-free, before any locality enters the maintenance phase. Experience of programme in some of the states in India have shown clearly, the importance of this statement.

If the phasing of the whole eradication programme is organised in such a way as described, the ultimate objective can be achieved in a methodical and scientific way, so that there will be no recrudescence of the disease at any time in future.

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19

Vaccination

Technical Considerations

Prior to Jenner's discovery of vaccination, variolation was in vogue in different countries in different forms. Dixon (1962) has described vividly in his book "smallpox", the history of various methods employed for protection against the disease in those days, and also how Jenner gave us the most valuable tool against the disease.

It is said, that vaccination was first introduced in India even within four to five years after discovery by Jenner. But it took such a long time for the people to accept it. Even now, there is some resistance, rather indifference, amongst the people in general, to vaccination. However, in recent years, the public co-operation has not been wanting and vaccination is being accepted as a rule. Even in rural areas, vaccination is generally popular, though some people may not know even the purpose for which it is done.

Vaccination is introduction of vaccinia virus into the basal layers of epidermis of the skin. Being an antigenically similar virus, vaccinia confers immunity aganist the allied virus, variola. What exactly was the origin of the vaccinia virus is anybody's guess. Though some feel, that is was derived from cow pox virus, yet there is a widespread opinion, that vaccinia virus is actually a derivative of variola virus, modified by passage in the laboratory. However, vaccinia is a disease which does not occur in nature, unless it is artificially introduced by means of vaccination into animals or human beings, whereas variola and cowpox are naturally occurring diseases in their respective susceptible hosts. Variola and vaccinia though antigenically similar, produce defferent responses in different hosts. For the matter of that, as has been stated already, certain animals which are susceptible to vaccinia are non-susceptible to variola.

Since variolation is dangerous in several respects, it is prohibited legally in all countries including India. Not only a high percentage of variolated persons develop actual disease and die, but also these persons spread the disease in a community, like the naturally occurring human smallpox cases. Therefore, vaccination has, more or less,

completely replaced variolation all over the world, though it is reported, that it is still practiced in a few areas unauthorisedly.

Smallpox Vaccines

Smallpox vaccine consists of infectious particles of live attenuated vaccinia virus. The most commonly used vaccine is dermal vaccine which contains vaccinia virus propagated on the skin of susceptible animals, usually the sheep, the bufallo or cow calf. Certain countries also use avian vaccine which is prepared from vaccinia virus propagated on the chorio allantoic membrane of developing chick embryo. Prepapration of vaccines containing vaccinia virus propagated on tissue culture, is still in experimental stage.

In smallpox-free countries, it has been found that there are more deaths due to vaccination than due to smallpox in recent years. Hence several types of vaccines containing inactivated vaccinia virus are being tried to see whether they can be used to protect against smallpox without producing complications. This inactivation is usually done by heat, formaldehyde, UV rays etc., but the consensus is that these killed vaccines do not confer enough immunity against smallpox and currently, they are being used as pre-immunization vaccination which is followed by regular vaccination with live virus. It is claimed that this procedure has minimised complications of vaccination. Results of recent studies made in our laboratory to find out the effectiveness of inactivated variola virus in conferring protection against smallpox infection in monkeys, indicate that it does not induce any appreciable antibody response. Monkeys so immunised, developed clinical smallpox on challenge with live variola virus, even within a month or two of immunization. Therefore, like inactivated vaccinia virus, the inactivated variola virus also does not appear to have any place in protection against smallpox.

The vaccines may be either in the form of liquid (glycerolated) or freeze dried powder. As regards the potency, purity etc., certain specific standards have been prescribed by the WHO. A good potent vaccine should produce, on vaccination, local infection in the skin, and the virus should multiply inducing antibody response in the vaccinee. The WHO requirements also stipulate, besides potency, that the vaccine prepared should be stable, and be free from any pathogenic organisms other than vaccinia virus. Different strains of vaccinia virus are being employed for the manufacture of smallpox vaccine, in different institutions. Some of them may be less reactogenic, but may be highly immunogenic. In general, therefore, such strains as those which produce less aggressive skin reactions but a high antibody response are often preferred for manufacture of vaccine lymph.

In countries with smallpox, what is required is a good potent vaccine, which confers immunity against smallpox for at least a few years. To produce a successful take and consequent good antibody response, vaccine should be potent at the time of its application to the hand of the vaccinee. It is true that several countries still use liquid vaccine, which may be potent at the time of manufacture and may retain the same potency to a great extent if properly stored at —20°C always. But it loses its potency rapidly in tropical countries especially, where the storage and transport facilities are poor or almost nil, and where the atmospheric temperature during the greater part of the year is very high. Use of such liquid vaccine therefore in such countries under such conditions, should not be encouraged. Even under ideal conditions of storage, it was found from the studies in Madras (Hobdey et al, 1961) that freeze dried vaccine gave far higher success rate even on revaccination than the liquid vaccine. The advantage of the freeze dried vaccine is, that it retains its potency even at 37°C for a few days to a month as long as it is not reconstituted.

If it is reconstituted, only just before vaccination on the field, the vaccination can definitely be expected to have been done with a potent vaccine. After reconstitution, however, it should be used immediately and any vaccine left over should be discarded. Simply because, there is no smallpox prevalent in those countries where the liquid vaccine is still in use, it cannot be cited as an argument for continuing the use of liquid vaccine in countries, where there is smallpox. In formulating the vaccination policies in endemic areas, whatever be the practical difficulties, only freeze dried vaccine shall be used to eradicate smallpox.

Experience in Madras proved this beyond any doubt. When liquid vaccine was in use for decades, smallpox continued to occur annually in thousands, despite the fact that hundreds of thousands of vaccinations were being done, but after the introduction of freeze dried vaccine since 1963, there has been a rapid and dramatic decline in the incidence of the disease and there is no doubt that it has been mostly due to the use of potent freeze dried vaccine.

Contraindications of Vaccination

Though several new chemoprophylactic drugs have come into the field, and much publicity has been given in certain countries about their utility in prevention of smallpox, yet none of them can replace smallpox vaccination and there is nothing, other than vaccination, that can asssure freedom from smallpox.

In non-endemic areas much has been talked about contraindications to vaccination. The circumstances and conditions there, are quite different from those prevailing in endemic areas, where there is always

a constant threat of smallpox. It may be true, that in countries like United States, there were more deaths due to smallpox vaccination than those with smallpox, but the same may not be true in other non-endemic countries. For instance in United Kingdom, it is reported that there were 723 cases of smallpox with 111 deaths (Editor, 'The Lancet', 1970) since 1950. I think there would not have been so many deaths due to vaccination during the same period. On the subject of contraindications, and formulating vaccination policies, therefore, each country has to weigh the pros and cons, regarding the dangers due to vaccination *vis-a-vis* dangers due to smallpox. Criteria applicable to one country are not applicable to others. Especially in countries of South East Asia, where variola major with high mortality, is the greatest problem, they cannot think of any contraindications to vaccination because anything is preferable to death due to smallpox. All aspects pertaining to this subject have been carefully considered at great length by the WHO Scientific Group on Smallpox Eradication in 1967, and they have rightly concluded, that there is no absolute contraindication for vaccination in countries with smallpox. From the experience of mass vaccination in India, during the last decade there have been no reports of any unusual number of serious complications due to vaccination, to warrant withholding of vaccination in any person. However, let us consider the common conditions that are often cited as contraindications by several authorities on smallpox especially in non-endemic countries, and see whether the same hold good in endemic countries. The following are some such oft-quoted conditions.

Acute illness: At the Infectious Diseases Hospital, Madras, it has been the practice to vaccinate all patients suffering from different diseases, who were admitted to the Hospital either at the time of admission, or definitely a day or two later. This is the precaution that was being taken to prevent cross infection with smallpox in the Hospital. During the years 1963-70, 32,315 cases of chickenpox, 14,203 of measles, 1,420 of mumps, 36,559 of cholera and choleraic diarrhoeas and 10,786 cases of other miscellaneous diseases were vaccinated and there was not even a single case of serious complication occurring amongst them. A few of these had local severe reactions especially in the early days when, for the first time USSR Freeze dried vaccine was used. In the earlier years, majority of the measles cases were unprotected children, and they were all vaccinated during their acute illness, with successful takes, but with no complications. Further, all suspected cases of smallpox and cases of eruptive fever, who were under observation awaiting confirmation of diagonsis, were all vaccinated at the time of admission. There is no harm in vaccinating smallpox patients, but there is a positive harm in not vaccinating non-smallpox patient admitted to Infectious Diseases Hospital. Sometimes, vaccination itself

was used as a diagnostic method. Vaccination done on a smallpox case after the onset of rash, rarely results in a successful take. Hence a successful take occurring in a case of eruptive fever as a result of vaccination done after the rash has appeared, can usually rule out the diagnosis of smallpox, though a 'no take' may mean nothing. If I remember right, in 1948 or 1949 about 500 patients suffering from serious acute illnesses, including diseases like Diphtheria, post-peurperal septicemia, tetanus etc., as well as chronic illness like diabetes have been reported to have been vaccinated at Infectious Diseases Hospital, Detroit, when a suspected case of smallpox was admitted. It was stated that majority of these vaccinations were successful and none of them developed any complications. This procedure followed for the last one decade at Madras, was responsible for the very negligible incidence of cross infection in the Hospital. Inspite of the fact that smallpox wards were separated from other wards, only by a small distance of about 20 to 30 feet, only 7 cases of smallpox presumably due to cross infection within the hospital, have occurred amongst a total of 123,522 non-smallpox cases treated during the years 1959-70. During the same period 17,169 cases of smallpox were treated simultaneously. Therefore, this policy of vaccinating all non-smallpox patients as well as suspected cases of smallpox immediately after admission to Infectious Diseases Hospitals should be encouraged in all endemic areas, where smallpox cases as well as cases of other infectious diseases are usually admitted to such hospitals.

Eczema: Eczema is considered as one of the important contraindications for vaccination in non-endemic areas, because of the complication, 'eczema vaccinatum', that is likely to occur. Thousands of vaccinations are being done in Madras year after year, and eczema is not stipulated as a contraindication. As long as the vaccination site is clean and healthy, children are vaccinated, even though they have eczematous patches elsewhere on the body. Experience has shown that this complication, eczema vaccinatum, is very rare in Madras and hence Eczema need not be considered as a contraindication at all in endemic areas. There have been no report of deaths due to Eczema vaccinatum at all in Madras city.

Persons suffering from tumors of Reticulo Endothelial system and those who are under treatment with immunosuppressive drugs, Corticosteroids or radiation therapy.

A famous paediatrician once remarked: "I do not mind giving a false certificate of vaccination but can never dare vaccinate a patient suffering from leukemia." Here again in the mass vaccination programme that is being conducted in India, it is almost impossible to find out who is suffering from leukemia etc., or who are under treat-

ment with immuno-suppressive drugs, steroids and radiation therapy, but yet the number of complications after vaccination that have been reported in this mass programme of millions of vaccinations done so far, have been absolutely negligible. Hence it is doubtful whether vaccination in this kind of patients is really so dangerous as one thinks. On the other hand, these patients if they are exposed to smallpox, do develop very severe types of disesase and die even.

Pregnancy: Enough has been stated about pregnancy and smallpox, and the risk of severe types of smallpox occurring amongst them with a high fatality rate. Though in non-endemic areas, pregnancy has been cited as one of the contraindications, in endemic countries where there is the greatest risk of exposure to smallpox, pregnancy is more a positive indication for vaccination and even repeat vaccination, rather than a contraindication. They are the most important vulnerable targets for smallpox and special priority should be given to vaccination of the pregnant.

Let us see what exactly are the oft quoted dangers that vaccination may cause to pregnant women. So far there have been very few cases (about 25) of foetal vaccinia reported in the world, as a result of vaccination during pregnancy. Unfortunately no reliable data regarding the number of vaccinations done amongst the pregnant are available. It must be running into hundreds of thousands, and so the incidence of foetal vaccinia must have been very insignificant. Another important point, that should be born in mind, is that almost all these 25 cases have occurred as a result of primary vaccination. Primary vaccination is invariably accompanied by viraemia and the placenta is no barrier to vaccinia virus. One should therefore normally expect foetal vaccinia in all the pregnant, in whom vaccination was done during pregnancy. But, for reasons not clearly known, it does not happen. Very rarely foetus gets infected. So far no case of foetal vaccinia seems to have been reported from India. In maternity and child welfare centres of Madras Corporation, about 30,000 antenatal cases are attended to, annually, and most of them are usually vaccinated as a routine, and so far, not even a single case of foetal vaccinia has been observed. Of course very rarely, pregnant women in endemic areas come for primary vaccination and therefore even the minimum risk of foetal loss due to foetal vaccinia does not exist in India.

Considering therefore, the risk the pregnant woman faces on exposure to smallpox in endemic countries, the risk the foetus faces with vaccinia infection, on vaccination of the pregnant is absolutely negligible. Therefore, in all endemic areas the pregnant women must be protected irrespective of their previous vaccinal status and period of gestation. There is far greater risk to the mother if she is not vaccinated, than the risk to the foetus, if she is vaccinated.

In short, therefore, there is no absolute contraindication in endemic areas to vaccination, except, as stated by the WHO scientific group on smallpox eradication, 'a person who is actually dying', since the death, if it occurs, may wrongly be attributed to vaccination. Recently a few articles written by some experts on smallpox from non endemic areas, explaining the dangers of vaccination and discouraging routine vaccination, have appeared in journals which have wide circulation in India. Naturally, these are likely to create fear in the minds of people, who have some doubts about the vaccination. It is for smallpox workers and public health administrators, to explain to the people, educate them about the risks of smallpox and its dangers in endemic areas and the need for vaccination.

However, even in endemic areas, in smallpox free cities or states if there is no immediate risk of exposure to smallpox, the Medical officer of Health can use his discretion and postpone vaccination in persons with the above contraindications temporarily. But he has to be careful in using his discretion, since smallpox infection can be imported any time from a neighbouring state or city, when he will be taking a great risk in exposing these persons to smallpox.

AGE FOR PRIMARY VACCINATION AND FREQUENCY OF REVACCINATION

This is a controversial subject. The immunization schedule varies from country to country. Hitherto it was the impression that complications after vaccination, especially the post-vaccinial encephalitis, occurs when primary vaccination is done in older children. It looks as though this theory does not hold good now. In some countries nowadays, they vaccinate children in the age group 1-2 years, and in some others, primary vaccination is done even at the school going age. Ideas seem to change from time to time and differ from country to country. In countries, where smallpox is the problem, the answer to this question is simple. Vaccinate every child at birth, or atleast, as early after birth as possible. From the clinical experience we have, the least occurrence of smallpox amongst the unvaccinated is only under one month of age. Beyond one month, not only the incidence, but even the mortality is high. If at all there is passive immunity as a result of transplacental transmission of antibodies, at best it will last only a month, and not beyond that. Therefore, every child shall have to be vaccinated immediately after birth or definitely before the end of first month of life. This policy of vaccination may be at great variance from that followed in other countries, and perhaps it is even against all the tenets of teachings on immunology. A pilot study was conducted in Madras (Ramachandra Rao et al 1963) in 1959-60 when, about 2,500 new-borns were vaccinated on the

third day after birth before they were discharged from the hospital. At that time, for want of freeze dried vaccine, only liquid lymph was used. The case success rate was 82 percent. None of these neonatal vaccinees had any complications attributable to vaccination, on the other hand, the local reactions in these babies have been uniformly milder. All the babies that have been vaccinated have been followed over a period of two years and more. During these two years. Madras city was having an epidemic of smallpox. Of the 2,500 babies vaccinated at birth, 36 were actually exposed to smallpox in their own families within 2 years after vaccination. Of these 36, 4 had no scars of neonatal vaccination, and 3 of these developed severe varieties of smallpox and died. Of the remaining 32 babies, who had scars of neonatal vaccination, 3 developed Modified smallpox and survived. This study has therefore clearly shown that babies can successfully be vaccinated even at the age of 3 days, that such vaccinations confer protection against smallpox, that no take on neonatal vaccination does not mean immunity but it means either bad technique or bad lymph, and that neonatal vaccination is safe and not accompanied by any complications.

Based on this experience, we have made it a routine feature now to encourage neonatal vaccination on babies born in Corporation maternity homes. In all Government Maternity Hospitals, and major private lying-in hospitals in Madras also, neonatal vaccinations are being done on most of the babies now. In urban areas, where majority of births occur in institutions, public health administrators find it very difficult to track down these children for vaccination after discharge from the institutions. Though legal provisions are there, that every child has to be vaccinated before the end of the 6th month of life, yet in practice, nearly 50 percent of children born in institutions are not at all traceable in time for vaccination. This procedure of neonatal vaccination, has eliminated these administrative difficulties, and has resulted in a far better primary vaccination coverage. The success rate is now as high as 99 percent to 100 percent just like infant vaccination, because of use of freeze dried vaccine, as against 82 percent with the liquid vaccine.

Irrespective of the fact whether it is neonatal vaccination at birth, or infant vaccination later, as long as there is smallpox in the country, revaccination also has to be done every 3 years to ensure safety from smallpox. Some workers, even in endemic countries, feel that the routine revaccination is not absolutely essential for eradication of smallpox, if there is 100 percent coverage of primary vaccination. I am afraid, this is not a correct step to be taken in Eradication programme. It is quite common to find adults, who had primary vaccination about 15-20 years before, as susceptible to small-

pox, as the unvaccinated. When Madras city was reporting thousands of cases of smallpox annually, nearly 85 percent of the total cases of smallpox amongst the 'once vaccinated' belonged to the age group 15 and above. If only there was a good revaccination drive at that time, I am sure all these could have been definitely prevented. Further to ensure 100 percent coverage of all unvaccinated is almost an impossible task in any country, therefore no such risk can be taken at the time, when smallpox still persists in endemic countries. In countries like India, with several states and cities at different stages of control of disease, to give up or relax revaccination programme, even in smallpox free cities or states, rather prematurely, is beset with dangers.

Site for Vaccination: Skin at any site, can be used for vaccination, but for practical convenience, skin on the outer aspect of the arm is used for primary vaccination, since most of the children can wear sleevless frocks or shirts. In adults, in whom it is rather difficult to get at that site, especially in women, in countries like India, the flexor aspect of the forearm is usually preferred for vaccination. In several countries, primary as well as revaccinations are done on the upper arm itself. Selection of site, is a matter of convenience to suit the acceptance of the people. However, upper extremity is to be preferred to the lower, since the former can easily be kept free from dust and is also easily accessible.

Preparation of the Vaccination Site: In the past, there has been a feeling amongst the vaccinators and physicians, that the vaccination site has to be prepared as though it is for a surgical operation. In several countries, alcohol, acetone etc., have been used to clean the site. In India, where these are not easily available, the vaccination site is cleansed with soap and water and dried with a clean towel. Now it has been clearly demonstrated that all these procedures are not only unwarranted, but also may be positively harmful. The World Health Organization Scientific group on smallpox Eradication in their report (WHO 1968) has stated "unless the selected site is obviously dirty no treatment of the skin is needed; disinfectants inactivate vaccinia virus more efficiently than they kill the bacteria; cleansing may create slight aberrations which can get infected with vaccinia virus to form satellite pocks. If the area is obviously dirty, it should be gently wiped with a cloth or cotton wool moistened with water and permitted to dry". Thus the best skin preparation perhaps is none at all.

Vaccination Methods: There are several vaccination techniques in vogue, but the vaccination with rotary lancet is unique for India and Pakistan only. The multiple pressure and the scratch method

are the methods employed in several countries. Recently, multiple puncture method with bifurcated needle and vaccination with jet injector have come into use. Whatever be the technique employed, in the hands of a good vaccinator, any method will give high success rate. Details of various methods of vaccinations are described in Handbook on smallpox eradication (WHO 1967) to which readers are referred.

The rotary lancet technique is considered by several, as highly traumatic, when compared to other methods. If the vaccinator is properly trained, the trauma with rotary lancet can certainly be minimised and it can be as atraumatic as other methods. On the other hand, there are a few positive advantages with the rotary lancet. Firstly, even an illiterate vaccinator can be trained in no time; secondly, the vaccination insertion as such, is standardised because the diameter of the disc is constant; thirdly, the central needle in the disc is just a little longer than the peripheral needles and is blunt and hence cannot go deeper and when all the peripheral needles touch the skin, it gives an indication that the vaccinator has gone to the correct depth and one single rotation of the disc in the drop of lymph implants the virus at the right place.

The multiple pressure method is more difficult to learn, and the technique varies from person to person, depending upon the pressure he employs, which cannot be regulated, and further the size of the insertion also again may be variable.

In the scratch method, the depth and the length of the scratch are likely to vary from person to person.

The new method of multiple puncture with bifurcated needle is good and the greatest advantage with this, is economy of vaccine. This requires some training for persons who are not used to it. To get at the correct depth, one requires practice. It is the method of choice recommended by the World Health Organization and accepted by several countries including India. It is simple, safe and far less traumatic than other methods. It has also been found that the success rates with this technique have been uniformly high and it requires minimum amount of vaccine. As far as endemic countries are concerned, where the conservation of vaccine is essential, especially when the production of vaccine is low, this method should replace all others as early as possible.

Jet injector is good, painless and very rapid when compared to all others. Recent work showed that high success rates can be achieved even with less potent vaccine and the immune response to such vaccination is reported to be as good as that achieved with other vaccination techniques. But it is not economical unless there

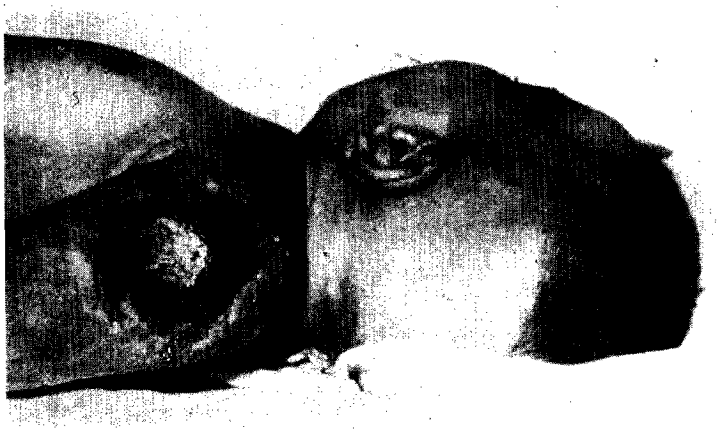
tries like India, there is no harm in giving some antiseptic powder for local application. It will, in no way, affect the vaccination take, but on the other hand, it will satisfy the people and at the same time prevent local septic complications and tetanus. If there is lot of oozing, and if there is a risk of contamination of clothes with the infective materials, loose dry dressing may be applied.

Reactions After Vaccination: Though old books describe four types of reactions as 'vaccinal' 'vaccinoid' 'immune' and 'immediate' takes, the World Health Organization Scientific group on smallpox eradication programme have amended the classification of these reactions. A 'successful primary vaccination' is one, in which a typical Jennerian vesicle appears after three to five days, which becomes pustular by about eighth day, scabs of in about two to three weeks, leaving a typical vaccination scar. But the interpretation of the reactions to revaccination is rather difficult. Since it has been found in certain revaccinees, that a lesion can occur without active multiplication of the vaccinia virus at the site, the scientific group, after careful consideration, has classified the reactions to revaccination into two, the 'Major' reaction i.e. a reaction where "on examination after one week, a vesicular or a pustular lesion or an area of definite induration or congestion surrounding a central lesion which may be scab or ulcer" is manifest and any other reaction is termed as 'Equivocal' reaction. A major reaction is the result of active multiplication of virus, whereas an equivocal reaction may occur in previously vaccinated persons, whose high level of immunity inhibits the virus multiplication or it may also follow insertion of inactivated vaccinia, or vaccination with poor technique. The cutaneous response which may be observed in equivocal reactions is the consequence of the hyper sensitivity to vaccinia protein. Though about half of equivocal reactions are followed by antibody response yet immunity in others, cannot be assumed and hence it is necessary that the vaccination should be repeated in all such persons".

Vaccination take Rates: The success rate of vaccination, mostly depends upon the technique of vaccination, the potency of the vaccine at the time of its use, and the immunity status of the vaccinee.

If the technique is good and the vaccine is of high potency the success rate should be in the order of 95 percent to 100 percent in primary vaccination. If the success rate is less than 95 percent a thorough probe is absolutely necessary into the technique of vaccination and also the potency of the vaccine used on the field.

With revaccination, it is rather difficult to give any definite opinion as to the success rate that can be expected, since it varies from locality to locality, depending upon the immunity status of the popu-



19/1. A Fatal case of Progressive vaccinia

lation. It may not be difficult to get a major reaction on revaccination in any person who had not been vaccinated successfully about an year before, provided the technique is good and vaccine is potent. There have been instances, where major reactions have been obtained even within one year after successful revaccination. However, on an average 40 percent to 50 percent success rates can be achieved in revaccination of the population. 95 percent to 100 percent success takes on primary vaccination may be achieved even with less potent vaccine but to get a fairly high success rate on revaccination, it is essential that vaccine should be of high potency satisfying international standards.

COMPLICATIONS AFTER VACCINATION

Introduction of vaccinia virus naturally results in occurrence of the local disease-vaccinia. If there is no multiplication and occurrence of local vaccinia, the desired effect, viz. the antibody response and protection against smallpox, would not be achieved. Vaccination is usually followed by a local lesion, which may sometimes become necrotic associated with regional lymphadenopathy and constitutional symptoms like fever etc. Very rarely, any serious complications are observed. When compared to the benefit derived by this vaccination, viz. protetion against the highly fatal disease, the occasional risks of complications due to vaccination are minimal. The incidence of these complications also varies greatly from country to country and the following are some of the common complications observed.

Local infection: Apart from the aggressive type of local skin takes with necrotic deep lesions, which may follow the use of certain strains of vaccinia virus, sometimes secondary bacterial infection may occur in the vaccinated sites resulting in severe local reactions which may occasionally develop even into cellulitis. Application of extraneous infective materials like cowdung etc. also produces local septic complications as well as tetanus. But proper technique and good aftercare of the vaccination site, usually prevent these complications.

Auto Vaccinia: If vaccinia virus is transferred from the vaccinated site to other areas by scratching, it is likely that, at all such infected sites, the virus may multiply producing lesions and these autoinoculated lesions may go through the usual evolution, leaving vaccination scars. Post-vaccinial conjunctivitis is not uncommon as a result of such inoculation into the eye (Kempe et al, 1969). This complication can be avoided if vaccination is done either at birth or within a month after birth.

Exanthematous reactions: Several types of rashes after vaccination are occasionally seen. Mostly they are of urticarial type, probably as a result of allergy to the calf protein, which is present in the vaccine.

These rashes usually disappear with appropriate antihisteaminic therapy. These are rare after neonatal vaccination.

Generalised vaccinia: Though rare, it is not infrequently seen after the primary vaccination. There has been no instance of this complication following neonatal vaccination in Madras city. The transient viraemia, which follows the primary vaccination, may result in localisation of the virus at various places on the skin resulting in generalised vaccinia. Usually, the rash is seen round about the seventh to ninth day after vaccination. The lesions are similar to those of smallpox, from which it is rather difficult to distinguish. Especially when primary vaccination has been done in contacts, who are exposed to smallpox in the family, the difficulty in diagonsis between smallpox and generalised vaccinia arises, and this has been discussed under differential diagnosis.

Eczema vaccinatum: It is a very rare complication and is the result of implantation of the virus in eczematous areas on the skin. This is considered as one of the important serious complications of vaccination in non-endemic countries where a few fatalities also have been reported. We have never come across any fatal cases of eczema vaccinatum in Madras during the last 10 years of our programme. Further, this again is an avoidable complication, since neonatal vaccinations are not usually followed by eczema vaccinatum.

Progressive vaccinia: This complication is very infrequent in India. Though rare in other countries too, yet it is considered as one of the few fatal complications of vaccination. It is supposed to occur in immunologically defective persons as in agammaglobulinaemic children, or persons with tumors of the reticuloendothelial system (leukemia, multiple myeloma etc.) or in persons who are under treatment with immunosuppressive drugs, or corticosteroids, or radiation therapy. Why this particular complication is rare in this country is not known. It is quite possible that most of the congenitally defective agammaglobulinaemic children die with various bacterial infections even before they get vaccinated. Very few cases of this complication are reporetd from India. There was one report from Calcutta some years ago and recently we have seen one such fatal case in Madras (Fig. 19/1). In this instance his brother also was reported to have died of similar complication about 4 years ago.

Post-vaccinial encephalitis. It is one of the serious complications occurring about seven to ten days after primary vaccination. It is very rare after revaccination. The frequency of occurrence of post-vaccinial encephalitis varies from country to country so much, that it is hard to believe whether there are any definite criteria even for diagnosis of this condition. Even these criteria seem to vary from physi-

cian to physician. Our knowledge about the pathogenesis of the complication itself is meagre. We do not still definitely know whether all cases diagnosed as post-vaccinial encephalitis, do have really demyelination and whether, even if it is present, it is really due to vaccinia virus itself. However, applying the usual criteria of diagnosis, there have been only 28 cases with 13 deaths (Mahendra Singh, 1970) due to this complication reported in India out of nearly 141 million primary vaccinations done since 1963. Of course, this is definitely an underestimate due to defective notification. In Madras city alone, out of nearly 700,000 primary vaccinations done during the last 8 years, there have been 7 deaths due to post-vaccinial encephalitis, giving a rate of 1 death for every 100,000 primary vaccinations. This again has been found to be very rare after neonatal vaccination.

Post-vaccinial osteomyelitis: This is another rare complication. Recently there was one case reported from Vellore, but there was no definite proof that Osteomyelitis was the result of vaccinia infection, because no virus was isolated from the site. This might as well have been due to secondary infection.

The common fatal complications viz. progressive vaccinia, post-vaccinial encephalitis, eczema vaccinatum and generalised vaccinia are mostly associated with primary vaccinations and not with revaccinations. In Madras city where the registration of deaths is more or less complete, there were only 8 deaths due to these complications out of nearly 900,000 primary vaccinations done, during a period of 9 years from 1963-71. But it should be carefully noted that during the same period, as against 8 deaths due to vaccination, there were 1,270 deaths due to smallpox and further, about 3,200 persons who survived smallpox, suffered from some disability or deformity or disfiguration. In countries therefore, where smallpox is a constant threat and several thousands are dying of smallpox annually, and several hundreds of thousands are suffering from the after-effects of smallpox, a few fatalities due to complications of vaccination occurring out of millions of vaccination done, are of less consequence. For the matter of that, even these few fatal vaccinial complications can definitely be prevented, if routine vaccination programme viz. vaccination at birth and revaccination every three years, is followed till the last case of smallpox is wiped out from the country.

In general, the fatal complications of vaccination in United States and United Kingdom, occur approximately in one for every million primary vaccinations. (WHO — 1967). Though the number of complications and fatalities are few, yet in such non-endemic countries with the disappearance of smallpox, they find greater morbidity and mortality due to this preventive immunization, rather than with small-

pox itself. Since endemic countries have not attained that smallpox-free status, and is not likely to attain that status for some more years to come, the complications after vaccination should be considered as negligible and unimportant. Vaccination, therefore, at all costs, should be strictly enforced.

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Vaccination

Operational Considerations

Mass vaccination is one of the two important components of eradication programme. Unless it is well-organised and systematically done, the programme is likely to fail. In any such gigantic programme, there are bound to be defects and failures in the initial stages, but the efficiency of an organization depends solely upon the programme officer who, by learning lessons from every failure, rectifies the defects and improves the organizational procedures. This can be done only by periodically reviewing and assessing the work done at every stage of operation. It was considered, therefore, useful to narrate a few of our experiences in the control programme of smallpox, our shortcomings, failures and how they have been overcome, before actually discussing the organizational procedure of mass vaccination in an urban smallpox eradication programme. *Figure* 20/1 shows the trend of smallpox incidence during the last 35 years in Madras city. It is evident that, barring an occasional year here and there, the city has been experiencing heavy incidence of the disease ranging from a few hundreds to some thousands annually. Especially during the last 10 years, when the notification was considerably improved, there has been no year with less than 1000 cases reported, till the National Smallpox Eradication Programme has been started. This has been the state of affairs duirng the last several decades, despite the fact that the city has been having a band of vaccinators, who have been doing hundreds of thousands of vaccinations annually. Further, primary vaccination by the age of six months, and revaccination every four years, are compulsory. Notification and isolation of every case of smallpox, registration of every birth occurring within the city limits, are also compulsory. Inspite of all these, smallpox persisted. Evidently no one has studied the possible reasons for such persistence of the disease.

Pilot Project of 1961 in Madras: After the World Health Assembly has resolved in 1958 to eliminate smallpox from whole world,

India too, as a member country, has taken up the task of eradicating the disease. As a pilot study, one district in each of the States of the country and a few cities have been taken in 1961. Madras city was one such. The purpose of this project was to assess the magnitude of the problem, to find out the methodology in organization and execution of the programme, and to know the needs of the nation-wide programme by projecting the results obtained from the execution of the pilot projects in these selected areas.

The aim and goal are the same, to "eliminate clinical infection" of smallpox in the local areas taken up. The methodology proposed was to achieve 80 percent vaccination coverage of the population in the area, in the shortest time possible. It was thought that 80 percent vaccination coverage would suffice to interrupt the disease transmission. In Madras city, this target was achieved in five to six months, by an intensive vaccination drive by specially appointed staff, besides the permanent vaccinators. But unfortunately, the target alone was achieved but not the ultimate goal of "eliminating the clinical infection." The disease still persisted even after this intensive vaccination drive, indicating that the programme failed. The same was the experience in some of the other States in the country also, where pilot projects were underatken.

A little introspection shows the reasons for this failure. Our assumptions and presumptions might have been wrong. Our methods of organization and execution might have been defective or the failure might have been the result of the combination of both.

Is the presumption that 80 percent vaccination coverage of the population in a locality is sufficient to interrupt the transmission correct? If so, what are its limitations? A careful scrutiny of age distribution of smallpox cases admitted to Infectious Diseases Hospital those days, showed that a little more than half the number of cases were amongst the unvaccinated, and the remaining were those, who were mostly adults, and who were vaccinated successfully only once in their infancy. This observation indicates clearly that the immediate targets for smallpox attack were the unvaccinated, and those who were never revaccinated for years. This was not surprising, because vaccination records always showed that the population easily accessible to vaccination, viz. the school children, the office staff, the industrial workers etc., were the persons who were vaccinated year after year. Even in pilot project, when the target was fixed as 80 percent coverage of population, again to get at that figure, the same groups of people were evidently vaccinated, and majority of the unvaccinated, who composed of the new-born, the pre-school children, slum dwellers, migratory and floating population, who have been evad-

ing vaccination all along, still escaped, with the result that these groups formed a sizable unprotected susceptible population in the community. Hence to interrupt the transmission of disease, 80 percent immunity level in the community may be sufficient, provided it is a uniform coverage of all sections of the population. Hence one of the lessons that has been learnt of the failure of the programme was, that it is not the overall vaccination coverage, but a uniform coverage of all sections of the population in all sectors of the city, that interrupts the disease transmission.

To those who have seen thousands of cases of smallpox, it will not be a revelation that the 'vaccinated' are quite different from the 'protected'. Simple vaccination does not confer protection, unless it is a successful vaccination. Nearly two-thirds of cases of smallpox, admitted in those days, were amongst those who were vaccinated several times but unsuccessfully i.e., they did not have any scars of vaccination. A vaccination which has not 'taken' is as good as 'no vaccination'. Not only the lay people, but even the medical profession, were under the false impression that 'takes' follow only primary vaccination, and that subsequent vaccinations, as a rule do not result in successful takes; and further, a 'no take' was even considered as a sign of immunity against the disease. These false ideas made people complacent, and this was mainly responsible for the failure of the pilot project. Even the vaccinators were ignorant of this fact, with the result, they were not even taking the elementary precautions they should take for revaccination, not only regarding the technique, but also as regards the quality of vaccine used. The result was that majority of the smallpox cases in adults were amongst those who were unsuccessfully revaccinated. These indicate, therefore, to attain our objective of elimination of smallpox, even 80 percent uniform coverage of all sections of the population in all sectors of the city alone would not suffice, unless such coverage is a successful vaccination coverage. Though priority should be given to the protection of the unvaccinated, yet adults, who were vaccinated successfully only in infancy and not revaccinated successfully again, should not be forgotten, since one successful infant vaccination alone, will not protect an individual throughout the life.

A successful vaccination depends on the potency of the vaccine used at the time of vaccination. All these years, and during the pilot project, only liquid lymph was used. As stated already, however potent, the vaccine may be at the time of manufacture, yet at the time of vaccination, the potency of liquid lymph, rapidly deteriorates under conditions prevailing in this country. Though the take rate was not bad with primary vaccination during the pilot project, yet the revaccination success rate was as low as 10 percent or even less. Hence

partly, the failure of the pilot programme was due to the use of ineffective vaccine.

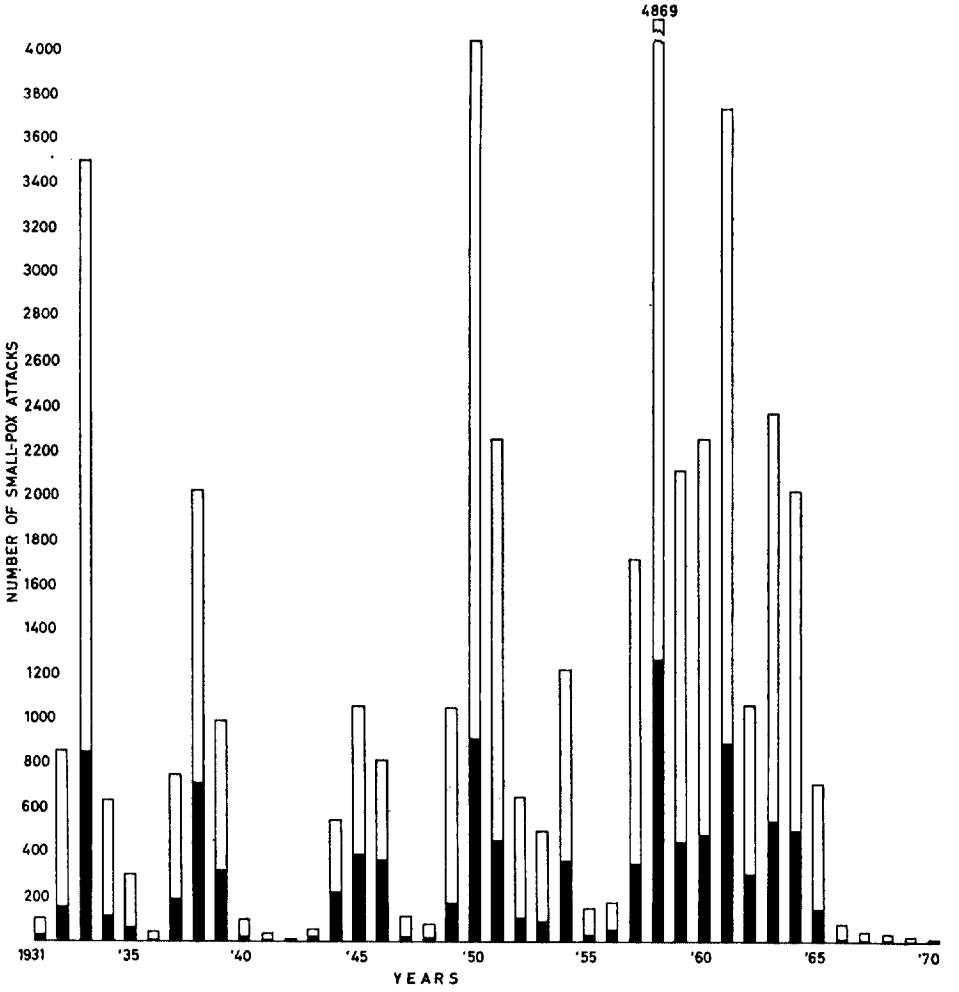
In a programme like this, complete reliance and sheer dependence on the reports received from the field staff, is always dangerous. It is not uncommon to find unscrupulous staff boosting up figures of vaccination by manipulating and producing bogus records. To get a correct picture of the work done, there should be an effective supervision at every stage of operation, not only in the maintenance of records but also the storage of vaccine, the technique of vaccination etc., etc. This most important aspect of the programme, viz, effective supervision, was completely overlooked during the pilot project and there is no wonder the programme failed.

Stress was laid all along on vaccination and vaccination coverage alone. After all, even vaccination has its own limitations. No importance was given or rather not much emphasis was laid on detection, isolation and treatment of all cases of smallpox. Whatever may be the efficacy of vaccination as a prophylactic agent for smallpox, unless every source of infection is removed from the community, and effective and immediate containment measures are taken to prevent further spread of infection, even vaccination by itself may not help in eliminating the clinical infection. This particular component of smallpox eradication, which will be discussed in greater detail in the next chapter, was not given its due importance in the pilot project, with the result several cases of smallpox were hidden in their houses, and they maintained the chain of transmission of infection amongst the susceptibles.

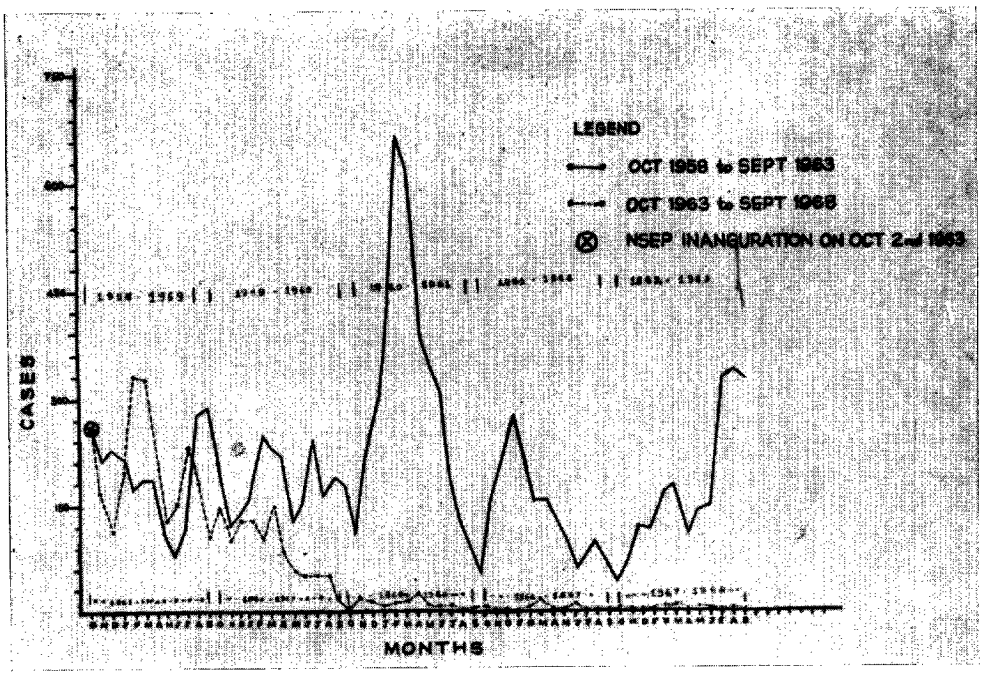
These were, in short, the defects in the programme of the pilot project. With this experience in the background, and on the basis of observations made above, a well organised systematic mass vaccination programme was started in 1963. There was a dramatic decline gradually but significantly, in the incidence of smallpox from 2,000 and odd cases in 1963 to 26 cases in 1968, and four in 1969 (*Figure* 20.2 and *Table* 20.1). Since 1970, the city has maintanied a "smallpox free" status. By keeping up the tempo of vaccination programme, it is hoped, the city would continue to be smallpox free.

Broad outlines of the organization and methodology of an urban smallpox eradication programme, based on the experience gained in Madras, is described here.

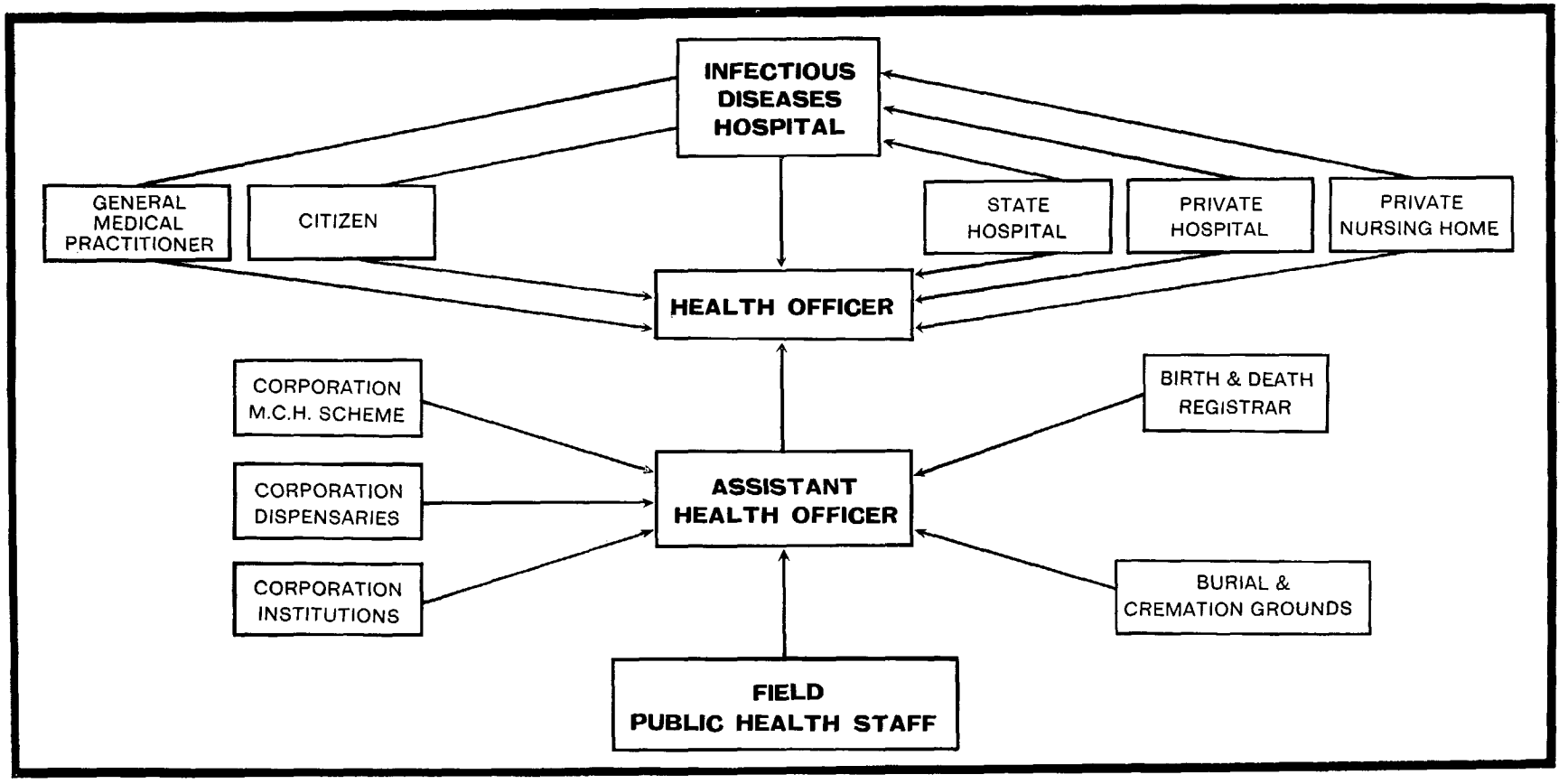
Aims of Smallpox Eradication Programme: The objective and the final aim of the programme has to be clearly spelt out. The final aim is not mass vaccination but it is "elimination of clinical infection with smallpox" from the city. As a preliminary step, the aim is to interrupt the transmission of the disease when cases occur. Elimination



20/1. Smallpox incidence in Madras City



20/2. Monthly Smallpox incidence in Madras City during 60 months before and 60 months after the launching of Smallpox Eradication Programme



21/1. Schematic representation of reporting system of Smallpox Cases in Madras City

Table 20.1

Smallpox Incidence in Madras City

Year	Attacks	Deaths	Primary Vaccinations done	Revaccinations done
1958	4869	1260	56,472	439,681
1959	2138	443	51,910	236,369
1960	2248	462	54,650	417,555
1961	3737	852	64,001	646,419
1962	1476	300	55,900	280,828
1963	2378	577	61,427	319,799
1964	2201	491	53,750	255,958
1965	730	156	52,354	157,520
1966	75	14	72,881	602,651
1967	38	9	103,000	424,371
1968	26	8	107,963	305,095
1969	4	1	92,878	211,771
1970	1*	Nil	103,391	332,243
1971	Nil	Nil		

October 2, 1963 — Inauguration of NSEP.

* Imported

of infection or eradication comes only at the final stage of the programme, till then, it should be considered as "smallpox control" only. This control can be achieved only if there is a high level of immunity in the local population. The number of susceptibles in the population should be brought down to such a low level, that further transmission from a case cannot occur and that it is not possible for the disease to sustain itself in the community. But what exactly is that level, is not known, and further, it may vary from locality to locality depending, especially on the endemicity of the disease, the density of population, the degree of overcrowding, the conditions of living, the birth rate, the extent of migratory and floating population, degree of immigration etc.

Methods of approach. To attain effective control of the disease and to interrupt transmission, the principal methods of approach are:

i. to vaccinate all the unvaccinated (*those who do not have any scars of vaccination*) irrespective of age, successfully with potent vaccine and a good technique, and

ii. to see that atleast 80 percent of all sections of the population in all sectors of the city are successfully vaccinated with potent vaccine and good technique *irrespective of their previous vaccinal status.*

These, if achieved, will leave no person unvaccinated and in addition a good majority of all others not only have primary vaccination scars but also scars of revaccination, and this will definitely interrupt the transmission of infection of smallpox. This, along with effective surveillance and containment measures, will eliminate smallpox from the locality in the end.

Organizational Procedure

The preparatory phase: Advance planning is one of the essential prerequisites in the execution of any extensive public health programme. All the participants in the programme should be well prepared and trained only then, the programme will yield good results.

There are mainly three aspects to be considered in this phase, the training of the staff, the collection of all equipment necessary for the programme, and the preparation of the people.

Training of the staff: In a developing country like India, it is impossible to get well qualified persons for this temporary work and perhaps there is no need even. A young energetic boy or a girl with minimum knowledge of English and a good knowledge of the local dialect, should be quite sufficient. Training should consist of basic knowledge of smallpox, its causation, clinical features and complications, how it spreads and how it can be prevented, manufacture of smallpox vaccine, how it should be stored, reconstituted and used, methods of vaccination techniques, reading of reactions of vaccination, recognition of complication of vaccination etc. In addition to this technical knowledge, they should be trained, as to how to behave and how to conduct themselves with the public. This is very important since any misbehaviour of misconduct or wrong approach on the part of the vaccinator towards the public, may spoil the whole programme itself. Not only the vaccinator but also other categories of staff in the programme have to be given all this basic training. Perhaps a period of 2 to 4 weeks may be sufficient.

Collection of equipment: For a successful programme, and to maintain its continuity, not only there should be no dearth in supply of equipment, but also such supplies should be continuous without a break. The important things in a mass vaccination programme are, adequate stocks of freeze dried vaccine, facilities for its storage and transport, vaccination kit boxes for vaccinators, and health education equipment. Of course spares should be always available in reserve for replacements. It is better to have, in a big city, a few sub-depots which can indent on the main depot of their *fortnightly* requirements of vaccine. Though it is not absolutely essential for the sub-depots to have refrigerators, the central depot should have facilities of refrigera-

tion and for storing adequate quantities of freeze dried vaccine, which would be sufficient for at least three months and the vaccine stocks should be replenished by indenting on the national organization, far in advance, before stocks get exhausted.

Vaccinators should be provided with convenient and handy kit boxes, to carry the vaccine and vaccination equipment. The vaccinator should see every morning, before he leaves for work, that his kit box contains every thing needed for vaccination. Any article that requires replacement should be replaced then and there, so as to see that work is not dislocated.

Education of the people, as will be described later, is of paramount importance for success of the programme. Health education is a science and an art. All the equipment that is needed for the education like megamikes, cine and slide-projectors, tape-recorder etc., should be procured. Recorded songs in favourite tunes on smallpox and its control, film strips and projection slides etc., have to be prepared and got ready far in advance before starting the programme. A separate vehicle to transport these, to various parts of the city, preferably equipped with an electricity generator so as to cater the needs even in non-electrified areas, has to be provided for.

Preparation of the People: If people are educated in various health problems, and the role they and their families have to play as active participants in the execution of various health programmes, every programme will naturally succeed. The greatest weakness of the health administrator is, that he assumes that the people know what he is doing, and what he proposes to do, and blames them if the co-operation of the public is wanting. This kind of presumption is quite wrong in many instances. Before starting any programme, for the matter of that, even in execution of day to day public health activities, the administrator should explain to the people the problem, its solution, and how it is going to be solved. He should also explain to the people, what is expected of them in successfully carrying out the programme. If people are so educated and taken into confidence by the administrator, I am sure, such programme will never end in failure. In smallpox eradication programme, the role of the people is very simple. They have to be prepared to accept the programme as their own, and this can be done only by a proper effective pre-programme health education, as well as concurrent health education by persons who are competent to do it. Such education cannot be done by each and every one, except by a qualified and trained health educator.

A thorough understanding of all sections of the people, their social structure, educational level and religious beliefs, their grievances and personal difficulties etc., is absolutely necessary. A rational approach

to the people naturally depends upon these fundamental data gathered in advance, by the health educator. In addition, he should have some basic knowledge about smallpox and its control as the vaccination staff. He should also have an idea of what the people should know, in order to enlist their willing co-operation in the programme, since he is expected to transmit that message to the common man. He should explain to the people that smallpox is a dangerous disease producing death in about a quarter of the people who get it, and disfiguration, deformity and disability in others, and that successful vaccination alone, can prevent smallpox. It should also be emphasised that this disease has been completely eradicated from several countries only by successful vaccination programme and notification and isolation of every case of smallpox.

This health education can be imparted by several methods. Mass education by broadcasting, press, addressing public meetings, school gatherings, workers' group meetings etc., may be employed. Enactment of dramas and puppet shows, depicting the dangers of smallpox and how to prevent them, conducting Katha Kalakshepams may also be employed to transmit the message. Involvement of local leaders and arranging small group discussions in individual localities, have been found to be quite useful in enlightening the public. Several voluntary organizations like Guild of services, Lions Club, Rotary Club, Red Cross and other social welfare organizations may also be actively involved to educate the people. In highly resistant cases, perhaps individual and personal contact by the health educator would yield results. Publicity materials like posters, brochures, handbills explaining the basic problems and their solution may have to be used to inform the public about the programme. By such various methods, if people are prepared far in advance, not only there will be a good start for the programme but also it will gain momentum rapidly.

The attack phase: The main objective of this phase, is to see that the number of susceptibles in the city is brought down to the lowest possible level, so that the smallpox transmission is interrupted. This involves vaccination of the whole population in the shortest time possible. There are three aspects that should be considered in this phase of operation—staffing, operational procedure and assessment.

Staffing: *Figure* 20/3 shows the minimum staffing pattern required for one million population. The whole programme should be under the administrative control of the Medical Officer of Health. He should be given complete authority and freedom to plan, organize and execute the programme without any interference what-so-ever. The programme should be well financed from the beginning. Since it is possible for the disease to be transmitted from urban to rural areas

and vice versa, the Medical Officer of Health and State smallpox eradication programme officer should work in collaboration, as otherwise the control measures will be ineffective.

Under the Medical Officer of Health, a special city programme officer, solely for the programme, should be there at the rate of one per million. Broad outlines of operational procedures should be clearly drafted and the programme officer should be given the freedom not only to execute them, but also to modify them in minor detail, to suit the circumstances and conditions, in a particular locality.

The duties of the various other categories of staff as shown in the figure should be clearly specified and allotted to them.

Health educator: He will be responsible for organizing the programme and preparing the people in preparatory phase and also to do concurrent health education during all the phases of the programme. He would also deal with cases of individual resistance, which are referred to him. Prosecution of offenders shall be done only as a last resort. The educator should use all his ingenuity to coax people. There lies the importance and significance of a qualified health educator.

The vaccination supervisor: He should preferably be a senior qualified sanitary inspector, with experience in public health administration and with the capacity to control the staff and extract work from them. His duties shall include the supplies of vaccine and supervision of its storage and distribution, supervision of the work of the verifiers and the vaccinators at every stage of operation. He should be honest, sincere and hard working. The success of the whole programme lies on the supervisor and the supervision he does on the subordinate staff. In short, he is responsible for the quality of the work.

Verifier: He should be a qualified sanitary inspector. His duties include verification of vaccinations done by the vaccinator, reading and recording of the vaccination reactions, vaccination of persons missed by the vaccinator, and also secondary vaccination of persons who have been unsuccessfully vaccinated. Verification is a very important component of the work. As has been stated, simple vaccination will never reduce the smallpox incidence and the number of susceptibles in the community, but only successful vaccination does.

Vaccinator: A vaccinator, at the rate of one per 10,000 population should be able to do about 40 to 50 vaccinations per day if not more. However, it depends upon the method of vaccination programme. In our experience by the method of 'house to house approach', though it was possible to do 70 to 80 vaccinations per day, the average did not work out more than 50. If the vaccinator is not given much scriptory work, he may be able to do more. Further, if people are well prepared

and motivated to accept the programme far in advance, work of the vaccinator will be simplified, and he may do greater number of vaccinations. The staff should arrange their work to suit the convenience of the people and not their own personal convenience. For instance, in slums and labour colonies, it may be possible to get people for vaccination only late in the evening after they return from work. In such areas, evening and night vaccination (dusk work) has to be arranged. Similarly, office-going staff may prefer vaccination on holidays. For such persons the vaccinator should fix up engagements previously and work on Sundays and holidays. The vaccinator may also have to make one or two revisits to ensure proper and complete coverage.

Operational procedure: Irrespective of methods, the aim is the same, to have 80 percent uniform coverage of all sections of the population in every sector of the city. This can be done by several ways.

Vaccination of groups collected at a series of different localities: After intense advance preparation, vaccination centres are located at different places in the city, in street corners, market places, schools and other places of congregation. People are notified about this location and are requested to come and get vaccinated. Vaccinations are done on all persons who visit the place. Simple recording system is employed without any elaborate data, giving mostly the particulars of age group of vaccinees etc. Only a tally sheet is used to record the vaccinations. For purposes of identification of the vaccinees, the fingertip of the vaccinee is dipped in a solution of silver nitrate, which leaves an indelible mark. The advantages of this system are its simplicity, and rapidity, but the greatest disadvantage is that people who are reluctant to get vaccinated continue to escape vaccination.

This was, what has been happening in Madras city all these years, People who evade vaccination always evaded. Even though a rapid coverage can be achieved by this method, this should be followed by assessment of successful vaccination coverage, as well as mopping up of missed people, by going house to house. This method may be good in well educated and enlightened population, but was found to be a failure in Madras.

Vaccination conducted in established local health services: This method is always followed in most of the urban areas for routine vaccination. The offices of the registrars of births and deaths, the offices of the vaccinators, the municipal free dispensaries, maternity and child welfare centres etc., offer vaccination to all those who come there. As in the first method, there again, unless people realise their responsibilities and actually take interest in the programme, one cannot expect uniform coverage of the population. This method, like the previous

one will always leave pockets of susceptible people, at different places in the city, which remain as dangerous spots.

Vaccination done by a systematic house to house visits: This is the method followed in Madras programme with a fairly good results. No doubt, it is time consuming, but in the attack phase, in any endemic area like Madras city, this is, by far, the best method. This method will help in better successful and more uniform coverage. The methodology employed in Madras scheme of operation is described here.

The city is divided into two districts, each roughly with a population of million. Each district is divided into 5 circles and each circle into 10 divisions, each division with a population of roughly 20 thousands. In the first round, the unit of operation taken, is one single division in each district, i.e. all the 100 vaccinators, 20 verifiers, 20 supervisors and one health educator of the district are placed in one division at one time for mass vaccination. Before the division is taken for work, intensive publicity is given by use of megamikes fitted in health education van. In our programme a musician-cum-composer was employed to compose songs and sing, to attract people around the vehicle. Then he announced the details of the programme, so that the people of the locality were well prepared in advance. Other publicity media like distribution of pamphlets and handbills were also used. Leaders of the locality, and also the peoples' representatives in the city council, were actively involved in the campaign.

Each vaccinator is given a particular street and specific number of houses for vaccination. He is supplied with a family register, sufficient for 50 families (a sample of such register is seen in Annex 1). The vaccinator is given two days' time for complete enumeration of the whole population in his jurisdiction, and recording the same in the family register. He would inform the people the exact time and date of his proposed visit to the house for vaccination. He would also fix engagements with those persons who wanted different times to suit their convenience. After enumeration is over, vaccination is done of all the available persons and necessary entries made in the family register. The vaccinator is to take only his daily requirements of vaccine from the sub-depots and reconstitute the vaccine at vaccination site only. All the vaccine that has been reconstituted is utilised the same day by doing as many primary vaccinations and revaccinations as possible. Any reconstituted vaccine left over, is invariably discarded.

After he finishes the vaccination of allotted number of houses, he tears of the carbon copies of the family register and hands over the original register to the verifier. After the whole division is covered

by all the vaccinators, they move enmass to the next division and repeat the same operations.

The verifier starts his work about five to seven days after the vaccinator leaves. His duty is to verify all vaccinations, enter the results of vaccination in the family registers, vaccinate those who had no successful takes, and those who have been missed by the vaccinator both for vaccination as well as enumeration, and to keep the family register upto date.

The aim should be as far as possible, to verify 100 percent of primary vaccinations and to achieve 100 percent success rate in primary vaccination. As regards the revaccination attempts are to be made to verify at least 60 to 70 percent, and of these a minimum of 70 to 75 percent success rate is to be aimed at, during the attack phase, so that there will be a uniform 80 percent successful (biological) coverage of the population. During the verification, if any low success rate is brought to the notice of the supervisors and the programme officer, they shall immediately investigate into the causes for such low success rate. If this is found only with any particular vaccinator then it is evident that there is something wrong with his technique of vaccination, whereas if that particular batch of vaccine gives low success rate in the hands of several vaccinators, it indicates that vaccine is defective. In all such cases the vaccine has to be withdrawn immediately, and sent to reference laboratory for potency test. If the vaccinator is at fault with the technique, action has to be taken to see that his technique is improved.

The supervisor of vaccination, of course supervises the work of the verifiers as well as vaccinators at every stage of operation. He is also to help the health educator and the programme officer in maintenance of records, compilation of reports and their despatch.

Since this programme is done according to fixed time schedule, there is bound to be some left overs of unvaccinated, which cannot be helped. But it is possible to have easily 70 percent uniform vaccination coverage even according to this time schedule.

In our experience, since we have taken both the districts simultaneously, the first round of operation took a period of 18 months, and a vaccination coverage of 70 percent of the population only was achieved, and the successful vaccination coverage (biological coverage) was only 50 percent. A second round of operation was conducted immediately after the first round. The procedure was the same as was in first round, except that there was no enumeration done prior to the vaccination. The unit of operation was again only one division. Rapid house to house vaccination of missed people, new borns and immigrants was done in 6 months in the whole city. This raised the vaccination

coverage to nearly 90 percent and the biological coverage to 60 percent. Third round of mopping up was undertaken. An area of 10 divisions of a circle was taken as the unit of operation i.e. all the vaccinators were divided amongst the 10 circles. Simultaneously, every circle was taken for mopping up. This took another 6 months and with this third round of operation i.e. in a total period of 2 years and six months of the attack phase, the overall vaccination coverage has gone to more than 100 percent (because of the repeat vaccinations) and the biological coverage has reached to 75 to 80 percent by which time, the impact of the programme was very much felt with the result that the smallpox incidence has come down very rapidly to a remarkable low level.

In this programme of mass vaccination, a target for vaccination should be fixed for each vaccinator, with reference to primary vaccinations. Knowing fully well, that there would be plenty of unvaccinated children left over from the previous years, to cover this backlog, a primary vaccination target of 8 percent is fixed (as against a birth rate of only 4 percent) in the first year of operation. In the subsequent years, the target is reduced to 5 percent to cover up not only all the city births but also the unvaccinated immigrants from outside the city. This method of approach worked fairly well in our programme and the success of this method was seen in the fall of smallpox incidence itself.

Vaccination of migratory population: In urban areas, floating and homeless population are problems. These persons will be moving frequently from place to place and it is impossible to maintain any family registers for these cases and do systematic vaccination. A separate squad—flying squad—consisting of one supervisor and 5 vaccinators can be employed to vaccinate such people. To catch them for vaccination itself is difficult, and so verification of these vaccination may be impracticable. Such people move even, as soon as the vaccination is over. A simple tally sheet record showing the age and sex of the vaccinees would suffice for this kind of migratory, floating population and platform dwellers. Flying squad can be organized by periodically drafting vaccinators from the staff of smallpox eradication programme without disturbing the programme much.

Assessment: To achieve success in the programme, there should be always a concurrent assessment at every stage. Though this was not done methodically by an independent agency in Madras programme, yet the programme officer himself along with the supervisors was continuously checking the work and success rates. For the matter of that, when the success rate of the primary vaccination was falling down uniformly with certain batches of vaccine, this was brought to the notice of the National authorities and it was found that that particular batch

of lymph had not retained the required potency at the time of operation. However, a periodic independent assessment would be very helpful in such kind of programmes. Here again, there are several methods of assessment. The simplest method is the one described by the World Health Organization in their Handbook on smallpox eradication programme (WHO, 1967). This method "the pock mark and scar survey" may be employed even by the officers themselves, or officers of the contiguous district may come, and do independent assessment in a matter of two or three days, which would give a fair idea of the vaccination coverage of the population as well as smallpox incidence. This is further discussed under the consolidation phase.

The Consolidation phase: When the annual incidence of smallpox in a particular area has come down to less than 5 cases per hundred thousand population, and 80 percent of the people in all sectors of the area bear marks of vaccination done at one time or other, that particular locality enters the consolidation phase. The criteria fixed thus, are quite adequate but yet, separate staff for vaccination purposes should be maintained at least at a reduced strength from what it was during the attack phase. This particular aspect has to be emphasised because, there is always the tendency on the part of the local authorities to completely disband the special vaccination staff when the number of smallpox cases come down. The object of this phase is to see that the 'smallpox-free' status is achieved. Again, as in the attack phase, there are three aspects to be considered in this programme—staffing, operational procedure and assessment.

Staffing: Since 80 percent of the population have vaccination scars before the city could enter into this consolidation phase, though separate staff for this programme are essential to be continued during the third phase of operation, yet the actual number can be reduced. In Madras, barring the health educator and the programme officer, all other staff were reduced by 50 percent, which means that there was one vaccinator in charge of 20,000 population, instead of 10,000. But this could be effected because we had enough permanent vaccinators on our rolls at the rate of one vaccinator for 40,000 population. If such services are not available, the temporary eradication staff working under the attack phase, should be retained *in toto*. Duties of the staff are the same as in attack phase.

Operational procedure: During this period of operation, the vaccination work can conveniently be divided between the smallpox eradication programme staff and permanent vaccinators, so that there will be greater involvement of the basic health services in the programme, from now onwards, in order to facilitate their taking over the whole programme in the succeeding phase, viz. the maintenance. At least in

Madras programme, the work of the vaccination has been divided between these two categories of staff.

The objectives of this phase can be achieved by vaccinating all the unvaccinated and revaccinating the whole population once in four or five years. Since it has been found that, when infection is imported, the first case is usually in the unvaccinated person, from whom only, on close exposure, intrafamilial vaccinated contacts may get infected, it is necessary as a first line of defence, that all unvaccinated persons are protected immediately. If that is ensured, there is very little possibility of transmission of infection occurring even from an imported case. It is therefore advisable to allot separately the work of primary vaccination to a particular category of staff. The staffing pattern should be such that there is at least one vaccinator for 20,000 population for primary vaccination work, so that such vaccinator may have to do roughly 1,000 primary vaccinations annually. This does not mean that he should do 4 or 5 primary vaccinations per day and keep quiet and waste the remaining vaccine. Along with primary vaccination, he also has to do revaccinations. But the main responsibility of doing primary vaccination is his. These vaccinators who are responsible for primary vaccination, should maintain registers (unprotected children register) of all children who are born in the city. With that register in hand, they must go to the respective houses and see that all city births are protected before the age of one month. In addition, house to house visits have to be done systematically to detect unprotected children who have migrated into the city. Special emphasis should be laid on slums, where there is the possibility of accumulation of susceptibles and where the conditions of living are very bad.

Neonatal vaccination has to be encouraged, and every health visitor or staff nurse attached to maternity and child welfare home, should do primary vaccination of children born in these homes, before the mother and baby are discharged. In case, where neonatal vaccinations, are not done, the responsibility of the primary vaccination of all the childern born under the care of the maternity and child welfare scheme, whether the confinement occurred in the maternity home or under domiciliary care, should be fixed on the Medical Officer as well as Health visitor in charge of the maternity home. This will ensure quite a good coverage of most of the children born in the city. Anyhow, the ultimate aim should be to see that there are no unvaccinated children beyond the age of one month.

As regards revaccination, the area of jurisdiction of vaccinator may be divided into four or five sectors, and each sector has to be vaccinated once a year, by rotation. If there are vaccinators at the rate of one for 40,000 population it is not difficult for him to do 10,000 revaccinations

a year. During their visit to houses, if they detect unvaccinated persons, they must immediately protect them and inform their counterparts in the smallpox eradication programme. In this way, unvaccinated persons of the whole district, and one-fourth or one-fifth of the total population would be vaccinated every year, and at the end of four or five years, the second full round of vaccination of the whole city would be accomplished, the first one having been done during the attack phase. Though some feel that revaccination of 25 percent of the population is not absolutely necessary in the consolidation phase, yet it is felt that it is advisable to insist on this, till the whole nation enters the consolidation phase. Especially in urban areas, which are connected by air and rail traffic both with other cities as well as countries, I am afraid, besides one complete round of vaccination of all people in the attack phase, one more round of revaccination during the consolidation phase would be ideal to eliminate clinical infection of smallpox.

Assessment: The assessment, both concurrent as well as independent, is more important, essential and informative during consolidation phase, than in the attack phase. This, if it is independent, would help in a long way, in moulding and correcting the operational procedure in the execution of the programme. Since the number of cases of smallpox have been brought down considerably to a low figure in this phase of operation, and the basic immunity of the people in general has been raised very high, it is to his own interests, that the programme officer should know as to the areas and pockets of population which are still not yet effectively covered by vaccination. This information can conveniently be obtained by a method of rapid assessment. Further, this would help the officer in getting also the information regarding the extent of under-notification of smallpox in the city.

The method of assessment recommended by World Health Organization viz. 'scar/pock mark survey' is a very simple and effective tool which can rapidly give the officer some realistic information regarding the vaccinal status of the people in each locality. It can be done on an adhoc basis to get rapid results though not very accurate, or it can be done in an elaborate scientific and statistically recognised method by employing sampling designs.

In view of the fact, that over 80 percent of cases of smallpox usually occur in the age group 0-14 years, and the transmission of infection is greater in this vulnerable group, this method of assessment is recommended to be undertaken only in this specific population. To have a correct picture of the vaccinal status of the population in each sector of the city, it is better to have this survey done separately in each division, or in a sector consisting of a small group

of contiguous divisions. It is estimated that roughly 40 percent of the population comes under the age group 0-14 years. For example if a particular division has a population of 20,000, it is estimated that 8,000 people will be of this age group 0-14. So as to be meaningful, a survey of at least 5 percent of the susceptible population, i.e. 400 children of this age group 0-14, have to be examined. Assuming, on an average, a family consists of 5 members, 2 of these are likely to fall in the age group 0-14 years. Hence to get at 400 children of this age group, roughly 200 families have to be surveyed in each sector or division. An additional 40 families i.e., 240 may be surveyed to allow for absenteeism so that in the end we will get not less than 400 children under survey. Selection of these 240 families for survey in the selected sector, can be done either with the help of table of random numbers, or alternatively by lottery from a pool of slips with the number of houses written on them.

The survey consists of examination of all children of this age group 0-14 in evrey family, selected at random by the methods described. Firstly, the child has to be examined, whether he or she has pock marks on the face. If the child has, an entry should be made in the tally sheet of the survey form (Annex 2) under Column 'P' in the corresponding age group. Secondly, if the child has no pock marks, the child has to be examined for vaccination scars. If the scars of vaccination are found, an entry has to be made in the corresponding age group under the column 'X' of the tally sheet. Thirdly, if the child has no vaccination marks, or has marks which are not quite clear whether they are the result of vaccination or not, the child should be treated as unvaccinated, and an entry has to be made in the corresponding age group, under the column 'O'. Thus, after examining 400 children of this age group, all the forms are to be collected and the results compiled. Finally, the total number of children under the three sub-age groups viz. 0-1, 1-4 and 5-14 with reference to their vaccinal status have to be arrived at.

The interpretation of the results so obtained is very important. For example, if there are any children in the age group 0-1 years, with pock marks, we can calculate estimated number of cases of smallpox that might have occurred during the preceding one year for the whole population from this survey, and compare it with the actual notification of the disease. This will give an idea of under-notification of smallpox in the city.

Secondly, if the percentage of the unvaccinated in the age groups 1-4 and 5-14 is found very high, this reflects on the vaccination programme indicating that there is a heavy backlog, and that children are not being protected by primary vaccination in infancy. If the pro-

gramme has been successful in any area, there should not be more than 20 percent unvaccinated in the 0-1 year group, and more than 2 to 3 percent in the other age groups. Depending upon the locality and depending upon the results of survey, the programme officer can rectify the defects in the programme and also change the strategy. Such of those localities, where the survey shows that the vaccination coverage is very poor, more number of vaccinators can be drafted and a rapid vaccination drive can be instituted.

These surveys can be conducted not only in static population but also in migratory and homeless platform dwellers. At least in a static population, who live in *pucca* residences, family registers have been maintained during the attack phase, so that one is aware of the vaccination coverage. But as stated already, for migratory population and for those people who live on pavements, no family registers are maintained and no verification is also done of the vaccination. To find out, therefore, the vaccination coverage and the immunity status of these kinds of population, the scar/pock mark survey is the only method. Results of such scar/pock mark surveys conducted in Madras city during consolidation phase in the static population, migratory population and amongst the platform dwellers are shown in the *Table* 20.2.

Unless the city is free from clinical smallpox for a consecutive period of 24 months and unless more than 80 percent of the population of all sections of all sectors of the city have vaccination marks, the city cannot be declared fit to enter the next phase, viz. the maintenance phase. To these conditions, I personally add that 'unless not less than 40 percent of the adult population have revaccination scars also' this would be an additional safeguard to be considered before the area enters the maintenance phase and the whole programme of vaccination is handed over to basic health services which are always very meagre.

The maintenance phase: Having attained 'smallpox-free' status for a continuous period of more than 2 years and having protected successfully more than 80 percent of the population with vaccination, done at one time or other, and having protected at least 40 percent of the population, by not only primary vaccination but also revaccination, the city is fit to enter the maintenance phase, provided it has got basic health services consisting of vaccinators at least at the rate of one for 40,000 population. The objectives of this phase are to maintain the 'smallpox-free' status and to maintain the basic immunity of the population at a high level. These can be achieved by vaccinating all the new-borns without exception, prefarably before the end of one month. The vaccination has to be repeated to all children on entry

Table 20.2

Results of Scar/Pock Mark Survey Conducted in Madras City

Year	No. of surveys made	Results of Survey							
		0-1 years		1-4 years		5-14 years		0-14 years	
		No. of persons examined	% without scar	No. of persons examined	% without scar	No. of persons examined	% without scar	No. of persons examined	% without scar
1967	1	465	27.0	1,620	3.5	2,196	1.6	4,281	5.0
1968	4	6,713	19.0	19,073	1.5	35.966	0.4	61,752	2.7
1968 (PD)	1	225	21.4	688	2.4	1,046	1.3	1,939	3.9
1968 (MP)	1	36	36.2	108	13.0	168	4.3	310	11.0
1969	4	1,189	28.9	2,983	2.7	5,330	0.9	9,502	5.0

PD=Platform dwellers MP=Migratory population.

into the school at the age of five to seven years, and after that, again at the time of employment. If military service is compulsory in any country, vaccination may have to be done at entry into service. Thus vaccination four times in the life of a person would be more than adequate to confer protection when the whole country is almost free from smallpox. Of course, all these measures are in addition to the rigid enforcement surveillance and containment measures which will be described in the next chapter.

REFERENCE

1 World Health Organization (1967) Handbook for Smallpox Eradication Programme in Endemic Areas.

Annex. 1: Specimen form of the Family Register

CORPORATION OF MADRAS No.

Smallpox Eradication Programme

Division No.....Street No.....

Name of Street and House Number.....

Name of Father or Guardian.....Occupation.....

Serial No.	Name of Child or person	Sex	Age	Occupation	Age at which the primary Vccn. was done	No. of Scars of Primary Vaccn.	Date of last Re-Vaccination	Results	Date of Vaccination in Project year	Results	Date of Secondary Vaccns. done after Primary or Re-Vaccinations	Results of Sec. Vaccn.	Remarks
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
14													
15													

SP 14

21

Surveillance and Containment Measures

The second but a very important component of the eradication programme is 'surveillance and containment measures'. This includes "schemes for prompt detection and reporting of all suspected smallpox cases, immediate institution of appropriate containment measures, concurrent analysis and interpretation of the reported data and distribution of this information to the responsible local, national and international authorities." (WHO, 1968).

Unless these measures are effective and well organized, one does not know the actual data regarding the occurrence of disease. It is wrong to assume that these measures are only secondary to vaccination. On the other hand, vaccination and surveillance, are supplementary to each other, and go hand in hand in the execution of the eradication programme. It is a recognised fact that reporting of smallpox cases is very defective in several countries, notably in endemic areas. A good surveillance machinery should therefore be set up, right from the beginning of the programme. Though it may not be quite effective during the attack phase, when the number of cases reported is very high, but its value would be very much greater and its importance would be felt during the consolidation and maintenance phases, when greater emphasis has to be laid on this component of the programme, than even on the vaccination.

Notification

Sources of Reporting: Correct notification of any communicable disease had dual purpose to serve, firstly, to take effective immediate containment measures and secondly, to assess the magnitude of the problem.

No disease can be controlled effectively, unless every single case is notified. But unfortunately, it is the experience in several countries, that notification of smallpox is always poor. The public should be properly educated on the importance of notification even during the preparatory phase. With such awakening, created by health education, one may expect better voluntary reporting from the people.

Besides this, the Medical officers of Health should have a proper organizational channel of reporting from various reporting centres.

If in any particular area, notification of smallpox is not compulsory, it should be made so, by an enactment of legislation, which should also vest the Medical officer of Health, with powers to invoke penal provisions, if necessary, against the offenders.

The reporting system of Madras, is diagramatically represented in *Figure* 21/4. As can be seen from the diagram, the Infection Diseases Hospital is the main reporting centre, because nearly three-fourths of cases of smallpox admitted to Infectious Diseases Hospital are all voluntary. Most of the urban areas are expected to have Infectious Diseases Hospitals. Since a hospital of this type is more a public health institution, it should be under the direct administrative control of Medical officer of Health. Along with compulsory notification, provision for isolation facilities should be made available and isolation of smallpox should be made legally compulsory too. All the cases admitted thus to the Infectious Diseases Hospital, should immediately be notified to the Medical officer of Health and also the local health staff responsible for that particular locality, from where the cases have been removed. All communications should be made by telephone so as to avoid unnecessary delay in transmission of information, and in taking appropriate measures.

It should be made obligatory that all medical institutions, irrespective of the fact whether they are run by the Government, Local body or a Private Organization, shall notify every case of smallpox to the Medical officer of Health and shall remove the cases to the Infectious Diseases Hospital.

All categories of public health field staff, during their daily rounds of their wards, and routine house visiting, should be on the look out for occurrence of smallpox cases, and should be made responsible for notification of such. Similarly, all public health institutions, like free dispensaries, maternity and child welfare centres, etc. should also take up the responsibiltiy of notification of smallpox coming to their notice.

Another set of important institutions, which shall notify smallpox cases are burial and cremation grounds. These institutions should be under the direct control of the Medical officer of Health. The caretakers in charge of these burial grounds must examine carefully every dead body and notify all instances, where they suspect that the death was due to some eruptive fever. The body shall not be disposed unless a competent person inspects the body and certifies whether the death was due to smallpox or not. In Madras, during the consolidation phase, we have gone a step further and insisted, that all such dead

bodies should be sent to Infectious Diseases Hospital for expert opinion and laboratory confirmation. During the years 1965-67 in Madras city, 21 such deaths due to smallpox were detected at the burial grounds. This helped in detection of cases of smallpox at least after death. From these, several hidden cases have been traced. The burial grounds therefore are important sources of information and in any eradication programme, there should be a very strict and rigid control of the disposal of dead especially so, when such bodies of persons who die of smallpox are usually taken to burial grounds in the nights to avoid detection.

An appeal has to be made to all general medical practitioners to notify all cases of eruptive fevers coming to their notice and remove them to Infectious Diseases Hospital for expert diagnosis. Though experience of several Medical officers of Health has been that the response from the general practitioners has been uniformly poor, yet an attempt has to be made in this direction.

If all these channels of reporting are utilised, one can expect better and more effective notification of smallpox cases and this would help and go a long way in the control of smallpox.

Amount of data to be collected: The data in the notification form should be the bearest minimum possible. The most important information required, are the name, age, sex, residential address and the vaccinal status of the patient. A specimen form used in Madras is shown in Annex 1.

Regularity and Supervision of Reporting: This question usually does not arise in urban areas, where there will be a hospital for isolation and treatment of cases. If there is no such hospital, there should be some effective machinery to supervise the reporting centres and see that the staff in charge of these centres are making honest and sincere attempts to detect and report the cases daily in the prescribed form to the higher authorities. Absence of reporting should not be considered as an indication of absence of cases. A 'nil' report should be insisted upon from the reporting centres, only then, can one be sure of atleast to a certain extent, the reliability of such reports. However, in urban areas only an Infectious Diseases Hospital will ensure the best and accurate notification.

Cross notification: In national and international programmes like this, no city or a state or, for the matter of that, a country, can remain isolated. It is very common, that infection is transmitted from one area to an adjacent area, from urban to rural and vice versa, and in these days of rapid travel, the infection can be imported in no time from state to state or even country to country. Hence it is essential that there should be a cross notification. If a case has come from a particular area, either with disease or during incubation period, the

local authorities shall try to get all the information necessary about the movements of the patient within a period of three weeks preceding onset of the disease, and shall intimate the same to the concerned health authorities, so that they can try to trace the source of infection, and take effective containment measures in those areas.

Transmission of data: The collected data regarding occurrence of smallpox, the age, sex and the vaccinal status of the patients should be transmitted weekly, monthly, quarterly and annually to the local authorities of the adjacent districts, the State Health Directorate, the National Health Directorate and World Health Organization and other International organizations. In certain areas, it is necessary that the port health authorities, and defence services also should be informed regarding smallpox incidence.

Interpretation of data and action: Mere collection of data and filing them, will not help in any programme. This basic information collected should be analysed and interpreted. The conclusions so drawn, should be utilised in perfecting the execution of the programme. For example, age distribution of smallpox cases with reference to vaccinal status, may give a clue, as to which segment of the population, that should be given top priority, for vaccination. Similarly an unusual increase in the incidence of smallpox in a particular locality must be enquired into thoroughly, and action should be taken to mobilise the staff and put them in that particular locality, to see that the infection does not spread. For the matter of that, failure of the pilot project in Madras city, and interpretation and analysis of the various reasons for the failure made us to enquire into the various shortcomings in our programme and lacunae in the methodology. These have helped us later in organizing the programme on a more sound footing, which has resulted in greater success.

Diagnosis

Diagnosis, that too correct diagnosis, is very important in control of smallpox, though one should not wait for the confirmation of the diagnosis, in taking control measures. For instance, a few cases of smallpox misdiagnosed as chickenpox or some other diseases will naturally delay in initiating the vaccination programme and isolation of contacts with the result, much damage may be done in the community by the time, one realises that it was smallpox. Similarly the converse is also true. If a wrong diagnosis of smallpox is made on cases which are not, not only unnecessary scare is produced with resulting administrative difficulties (which may sometimes be helpful in endemic areas to push up vaccination drive) but also a lot of money, energy and vaccine will be wasted, in mobilising the staff for vaccination of persons

who are exposed to disease, which cannot be prevented by such vaccination. Before initiating large scale control measures, it is therefore, necessary to find out definitely as to the nature of the disease, one is dealing with. Diagnosis can be made correctly in majority of instances, by an experienced physician but in all doubtful cases, laboratory aid should be sought for. Simple laboratory methods have already described and they should be availed of, to get at the correct diagnosis.

Containment Measures

Staff: There should be separate staff (Epidemiological and 'Fire-fighting' team) for undertaking containment measures, so as not to disturb the regular programme, whenever cases occur. It is better to have a qualified epidemiologist in charge of the unit in any urban area with a population of over one million. He should have a team consisting of a supervisor and 5 vaccinators for every million population to attend to surveillance and containment measures.

Of course if the number of cases is high, even such units may not be able to do effective work, but during the consolidation phase and maintenance phase, these units shall be responsible for all the containment measures for every case of smallpox notified. Even if a local authority cannot afford an epidemiologist, at least the epidemiological unit of this type with a senior supervisor and vaccinators is essential for enforcing containment measures. When there is no case of smallpox, they can help the other staff in vaccination programme.

Measures of Control

i. Isolation and treatment: When notification is made legally compulsory, it is the responsibility of local authority to make provision for isolation and treatment of smallpox cases. Whatever be the greatest effective tool we may have, for prevention of smallpox, viz., the vaccination, yet until and unless the source of infection is removed away from the community, all the control measures are likely to fail since our methods may not be hundred percent effective and fool proof. It is therefore essential that isolation facilities should be provided for, in every urban area.

The word isolation, in public health practice, means well, but amongst the public, this is always associated with ill-conceived notions. The word 'isolation hospital' itself is frightful to people. Though it is a public heath institution, yet it is like any other hospital, where persons suffering from infectious or communicable diseases are not simply be isolated but also treated like persons suffering from any other disease. That taboo and stigma attached to isolation hospital should be removed

by redesignating them as either Infectious Diseases Hospitals or Fever Hospitals, and by making them as attractive as any other hospitals if not more, by providing upto-date modern amenities for care and treatment of cases of infectious diseases.

Special stress is laid on the word 'treatment'. The treatment does not mean the usual treatment given until 'clinical recovery'. Here treatment in public health practice means, until the patient is 'free from infection'. This is very important in smallpox. These hospitals therefore have to be all the more attractive, since cases have to remain there, for greater length of time after clinical recovery. In case of smallpox, no patient shall be discharged till the last scab separates off.

Hence isolation and treatment play important role in the control of smallpox. Every source of infection should be detected, isolated and treated till he or she is free from infection. Further, the Infectious Diseases Hospital itself, should not be a source of infection. Every effort should be made to see that no cross infection occurs in the hospital itself. In the absence of a hospital for smallpox, home isolation is ideal. The patient should not be allowed to leave the house till the last scab separates off and no one is allowed to come into the house except his family members who should be protected immediately after the notification is done.

ii. Disinfection: As has been stated earlier, variola virus is highly resistant to the usual methods of disinfection. All the excretions, secretions and discharges of smallpox patients contain virus and hence are potentially infectious and their proper disposal is very important.

By far, the best method of disinfection is by heat. Incineration of all that could be burnt, boiling of all that could be boiled usually are satisfactory methods of disinfection of infected materials. If chemical disinfectants are to be employed, fomites and infected linen that can be washed, should be carefully collected without much agitation and soaked in 1 in 40 dilution of white fluid or any other coal tar disinfectant, (phenolic compounds) overnight and washed and dried in hot sun. Chlorine compounds like bleaching powder in concentration which leaves free chlorine of 25 ppm or more, after the chlorine demand has been satisfied, is a useful disinfectant, but the clothes may get bleached or get spoiled by this method.

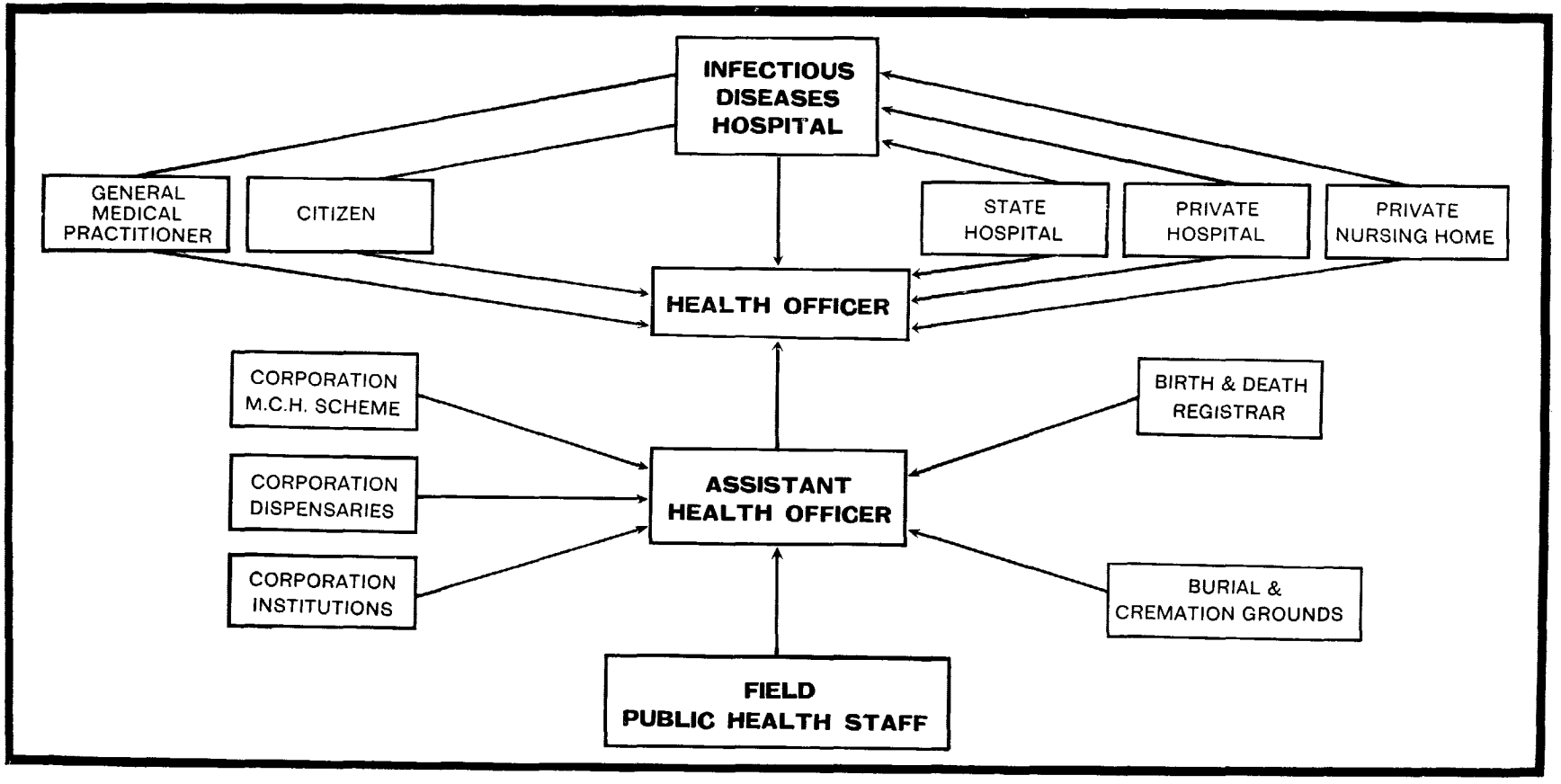
Similarly, chloramines have been found to have virucidal properties. Quarternary ammonium compounds and formalin also have been reported to have disinfectant properties against this virus. Whatever be the disinfectant used, a minimum of four to six hours contact seems to be necessary. Laboratory experiments have shown that exposure to direct sun for 2 to 4 hours seems to destroy the virus in most of the fomites.

Infected rooms should be handled carefully. Fumigation with formaldehyde may help in disinfecting the atmosphere. Fogging with hygroscopic virucidal disinfectant like glycols may help to a certain extent for space disinfection, but their utility is doubtful. Dry sweeping which contaminates the atmosphere, should be avoided at all costs. Disinfectant solutions may be sprayed on the ground and on the walls, and allowed to remain in contact for enough time, followed by thorough washing with copious supply of water or disinfectant lotion. The room is allowed to dry by opening all doors and windows.

In infected houses, immediately after the isolation or death of a patient, the whole premises is thoroughly disinfected and walls are hot lime washed. In case of thatched huts, in addition, the thatched roof is removed to allow the sun light to enter. As far as possible, all infected linen is destroyed, or exposed to direct sun for about 2 to 4 hours. Care should be taken to see that no linen is allowed to be used unless it is properly disinfected. Though there are no prescribed virucidal disinfectants, the procedure described above is practicable and is fairly satisfactory.

iii. Quarantine: Quarantine of contacts in endemic areas, does not serve the purpose intended. Probably it is a wasteful procedure to keep any of the contacts off their work, since none of these people can be restricted from moving out of the houses, and there seems to be no need to impose such restriction. On the other hand, if the familial contacts are allowed to continue their occupation, they can be detected more easily at the first sign of sickness, than if they are allowed to remain at home. A close watch, and routine daily examination of the contacts is necessary, and is more than sufficient. Any one showing the earliest sign of fever should be isolated for observation for smallpox. Unnecessary restrictions of the contacts in no way, helps in better control of the disease.

iv. Tracing the source of infection: Though this is a very important measure in control of the disease in endemic areas, it has been found to be very difficult. As described elsewhere, cases are hidden by such ingenious methods that it is very difficult to find them. However, every attempt has to be made to get at the source and isolate every case and see that the source of infection is removed, only then the vaccination programme that is to follow, will be successful. Sometimes the source might be dead, it is therefore necessary to verify the registers at the burial grounds, and registers of birth and death registrars, and see whether there were deaths under suspicious circumstances, where cause of death due to smallpox, was purposely withheld. A usual index in detection, that would be helpful is, for every case of death due to smallpox, generally there are three or four recovered cases, since the



21/1. Schematic representation of reporting system of Smallpox Cases in Madras City

overall case fatality rate of smallpox is still about 20 percent. On such broad presumption, one should make a search for hidden cases. Similarly, all available data regarding the contacts in the family, in the household complex, with particulars regarding the sex, age and vaccinal status along with information regarding the housing condition, living conditions, occupation, economic status, etc., have to be collected by the epidemiological unit. These data may be helpful in epidemiological studies of this disease. A sample form (Annex 2) shows the data to be collected.

v. Vaccination: Whether or not, vaccination prevents the disease in persons after exposure, yet as soon as a case of smallpox is detected. all the familial and household contacts have to be vaccinated immediately, with a potent vaccine and a good technique. People in about 20 houses or about 100 yards all around the infected house should be protected within 24 hours by a successful vaccination without fail, as an extra precautionary measure, irrespective of their previous vaccination status. Along with the vaccination drive, every effort should be made to detect all hidden cases of smallpox and isolate them. If cases occur in large numbers, all people in the locality should be immediately protected by a successful vaccination.

When cases are many, perhaps it may be rather impracticable to enforce these surveillance and containment measures rigidly, but when the incidence falls down, every case has to be investigated thoroughly and the source of infection, detected, surveillance and effective containment measures should be enforced. This is the only way by which the transmission of infection can definitely be interrupted. These are of great importance in the consolidation and maintenance phase.

With the phasing of mass vaccination programme and successful coverage of the entire population and ensuring that all the unvaccinated are protected at least once, and effective containment measures are enforced there is no doubt that any country can eradicate the disease in 5 years.

REFERENCE

1. World Health Organization (1968) Technical Report Series 393.

Annex 1: Specimen Form containing the data to be collected and transmitted along with Notification of Smallpox.

CORPORATION OF MADRAS

Health Department

Infectious Diseases Hospital, Madras Report No.....

REPORT OF SMALLPOX on the.....day of..... 197

Name.....Age.....Sex.....Religion .....

Occupation.....Place of Birth.....

Residence:—

Door No.....Street.....Division.....

Date of onset of	Fever Rash	Type of Attack	Modified Ordinary Flat Haemorrhagic	Imported Indigenous Mofussil

Date of Discharge

Date of Death

[P.T.O.]

Annex 1:

Vaccinated and evidenced by the presence of one or more vaccination Cicatrix	Stated to have been successfully vaccinated but no vaccination Cicartrix present	Stated to be unvaccinated or vaccinated unsucessfully and no Vaccination Cicatrix present	Previously Unvaccinated but vaccinated during incubation period of smallpox	Stated to have been successfully revaccinated (probable date)
No. of Marks			No. of Marks	No. of Marks
(Probable date)	Date	Date	Date	Date

Probable source of Infection

Name of Notifying Officer & designation

Annex 2: Epidemiological Investigation Form

A. Index Case

Name Sex Age

Residential Address

Discharge

D/Attack D/Admission Date of _____

Death

Home isolation

Notified by Hospital isolation

Occupation Family Income

Place of work or School (if student)

Vaccinal Status Number of marks Date of Vaccination

Primary Vaccination

Last re-Vaccination

Vaccination after Exposure.

B. Housing Condition:

Nature of construction

Independent house or housing complex

Number of persons in the family

Number of tenants in the household

Number of persons in the household

C. Contacts—Familial

S.No.	Name	Age	Sex	Relationship	PV/RV	VIP	Remarks
1							
2							
3							
4							
5							

Extrafamilial Vaccinated Unvaccinated

Adults

Children

(P.T.O.)

D. Source of infection

1. Is or was there any similar case or death due to similar disease in the family/house/locality/place of work? If yes, date of attack of the case or cases. Is that case related to index case? If so, how?

2. How long has the index case been living in this house?
   If less than 3 weeks, give the previous address.
   Is there any case in that address or locality?

3. Has he gone out of this place during the last 3 weeks prior to the date of attack?
   If yes, when and where? Give the various addresses and how long he stayed in each of those places?
   Did he come in contact with any similar case during his journey? If so, where, how and when?

4. Has any one come from outside to his residence?
   If yes, when and from where? How long he or she stayed here, and whether that person was suffering from similar disease?

5. When was the last case in the locality?
   Is there any direct or indirect connection between the last case in the locality and this present index case?

E. Summary of the results of investigations

F. Nature of containment measures taken

1. Isolation of the case
2. Disinfection of the premises and fomites
3. Vaccination
4. Surveillance of contacts

G. Follow up measures

	Date of visit	Remarks
1.		
2.		
3.		

22

Smallpox Eradication And After

There are fair chances of making smallpox a disease of the past. It is most likely that the world will see the end of this disease in another decade, as contemplated by the World Health Organization, if not earlier. But this does not mean that we can afford to forget about smallpox and vaccination after ten years. It is rather unsafe to be completely complacent about it when once the clinical infection is eliminated from the globe. I am afraid, we may have to be on the alert even for some more years to come, especially when our knowledge about the disease and its transmission is still obscure in its various aspects.

We have similar experience with Malaria. After intensive battle with the disease, we have eradicated it from various parts of the world. Several hyper-endemic areas have entered the so-called maintenance phase, but already reports are being received that Malaria is showing itself again.

Same is the case with Plague. It was quiescent for a good number of years, but now and then it increases in incidence. Even, new hosts are being discovered in endemic areas. This, no doubt is the result of relaxation of all efforts, after the so-called control of the disease, and our imperfect knowledge about the epidemiology of the disease itself.

But the question is, can this happen with smallpox? Our ultimate aim now is only to "eliminate the clinical infection with variola virus" and not eliminate "variola virus" itself. Virus can remain dormant at several places and for several years without producing clinical infection. It is humanly impossible to eliminate all the variola virus that may be hiding in every nook and corner of the world. Laboratories may have virus, several infected material hidden somewhere may contain the virus for varying periods of time. Of course if proper and effective containment measures are taken, it is quite possible that these may not act as sources of infection, but one cannot be sure! Hence any type of relaxation after eradication may result in a catastrophe, and what all we have been doing, and may do in the coming ten

years, would go to waste, if after a lull of "no-smallpox" period, suddenly it shows itself again.

There is still another possibility, which we are overlooking, namely, the role of some non-human hosts as reservoirs of infection. We are basing our present programme on a presumption that there are no non-human reservoirs. We know fully well, monkey gets smallpox by introduction of variola virus by several routes. We also know that a monkey can get smallpox on exposure to another monkey suffering from the disease. There is no reason why monkey cannot get smallpox from man, and man from a monkey too.

We are also assuming that smallpox may not occur naturally in monkeys but only monkeypox does. Our knowledge about the relationship between monkeypox and smallpox is very meagre or almost nil. Whether man can get monkeypox on exposure, if so what is the type of disease he gets also is not known. However 4 cases of human beings infected with monkeypox (WHO, 1971) have been reported. With so many questions unanswered, and with such imperfect knowledge about the possible reservoirs of infection in non-human hosts, it is rather unsafe to take it for granted, that everything would be alright, and that we can forget about smallpox, once we 'eliminate clinical infection in human beings'. Of course our immediate goal may be to interrupt the transmission by creating an effective immune barrier and also by isolating every human case of smallpox and taking immediate containment measures to prevent further spread of infection. Yet, it is worthwhile to do intensive studies, on this paricular aspect of the disease, simultaneously along with eradication programme especially with reference to smallpox and monkeypox, and the possibility of monkeys and other animals acting as reservoirs of infection of human variola and the possibility of human beings getting infection with monkeypox if these two diseases are completely different.

Apart from the study of these long range possibilities of reintroduction of infection due to animal reservoirs when the general immunity of population goes down, even immediately, there is enough scope for study of various epidemiological, immunological and virological aspects of smallpox. As has been discussed under various chapters, there are several gaps in our knowledge about the disease. The pattern of spread of infection in the community, the routes of transport of infection from urban to rural areas and vice versa, and various modes of transmission of infection are still obscure, and there is plenty of scope for further studies in the field of epidemiology.

On the immunological side, the nature and level of antibodies which protect against the disease are still not definitely known. Further, one does not know, whether the immune response after an

attack of Variola is the same or whether it varies with, and depends upon the clinical type of attack and the previous vaccinal status. Several studies are being conducted. Still we have some more problems, like the number of insertions and immune response, immunity after primary vaccination and revaccination, the role of interferon and immunity, the influence of steroid hormones on immunity, requiring elucidation. A more intriguing problem still is the pregnancy and vaccination, pregnancy and smallpox and the influence of placenta on immunity of the mother.

As regards the virus itself, there is a lot of confusion in our minds about virulence and invasiveness of different virus isolates from different sources from the patient, and virus from patients of different clinical types etc. This requires further study.

The subject of chemotherapy and chemoprophylaxis is a separate entity by itself. Though nothing promising has come out so far, it opened a new field in antiviral therapy. Several new drugs are coming into the field which require trials on patients. Though we may eradicate smallpox yet these antiviral drugs may be useful against other viral diseases as well.

Antiviral properties of some indigenous herbs of the country are being studied. Preliminary reports indicate that one of two have shown some promising results in 'in vitro' studies on variola and vaccinia virus. Whether these will be useful in chemotherapy and chemoprophylaxis or not, it is felt that they can be used as good virucidal disinfectants and this is another field where extensive work has to be done.

Information obtained from all these studies, should be of immense value to the eradication programme itself. To presume that there is no need for further study of the disease since we are likely to eradicate it in another decade, is wrong. Every effort should be made and enough funds have to be provided for research on various aspects of smallpox, simultaneously along with eradication programme. The findings of various studies will be supplementing the efforts of eradication programme and will lead to more effective and rapid success and incidentally perhaps, they will help not only to eliminate "clinical infection" but also to eliminate "variola virus" itself from the globe. Let us fervently hope, that we will succeed in our efforts and really make smallpox a disease of the past.

REFERENCE

1. World Health Organization Smallpox Surveillance No. 56 April 1971.

SUBJECT INDEX