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LECTURE
ON
'CLINICAL STAGES OF SMALLPOX, CHICKENPOX, HERPES'

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INTRODUCTION

Study of the evolution of the disease, through different stages, is of great importance in differential diagnosis of eruptive fevers. Each disease has its own characteristic clinical course. In this short time available, it is impossible for me to describe the clinical course of all the eruptive fevers, which simulate smallpox. Further, it is not even necessary, since most of these diseases can easily be distinguished from smallpox.

The disease, most frequently confused with smallpox, is chickenpox. However, in my experience, I found that there are a few more eruptive fevers which cause problems in diagnosis of smallpox, and they are papular syphilides and generalised vaccinia. Herpes zoster and herpes simplex do also require consideration in the laboratory diagnosis of smallpox, and so will be dealt with separately in this training programme. But the clinical manifestations of these two viruses, very rarely create problems in diagnosis of smallpox. Hence it is proposed, in this talk, to describe the different stages in the clinical course of smallpox and chickenpox in great detail and discuss, how they can be differentiated clinically. Incidentally however, the course of the other diseases viz. herpes simplex, herpes zoster, papular syphilides and generalised vaccinia, to the extent they are likely to be confused with smallpox, will also be outlined.

HISTORICAL BACKGROUND

Smallpox has been known to the ancient physicians, by whatever name it was, as a separate entity, even about 3000 years ago. Same was the case with herpes zoster. It was also recognised as a separate disease by Grecian physicians and was called zona. In the case of chickenpox, it was quite different. For along time, it was confused with smallpox. For the matter of that, Rhazes the famous Egyptian physician of Ninth Century A.D. was reported to have described chickenpox as a mild form of smallpox. Only in the beginning of 19th Century, it was recognised that chickenpox and smallpox were two different diseases altogether. Now, of course, we know, that smallpox is caused by varicellavirus, belonging to the Pox group and
Chickenpox by Herpes virus varicella, belonging to Herpesvirus group of viruses.

Available epidemiological and serological evidence indicate that both Chickenpox and Herpes zoster are only two different clinical manifestations of one disease, caused by V-Z virus. The consensus is that Herpes zoster occurs in adults, who have had Chickenpox in their early childhood. However, not in all cases, we get such a typical history. Zoster is presumed to be the result of reactivation of the V-Z virus, which is supposed to be remaining latent in some parts of the body, especially in posterior nerve root ganglia, or extramedullary ganglia of the cranial nerves, after the primary infection in childhood. The reactivation may follow any physical, chemical, or even psychological trauma or insult, and the virus multiplies and distributes itself on the skin, innervated by the affected nerve roots. The other view about the occurrence of zoster is, that it is the result of re-infection with a heavy dose of V-Z virus in an individual with partial or waning immunity, as a result of the primary infection. This second theory, of course, cannot satisfactorily explain why the reinfecting virus should affect only the nerve roots. However, it is certain, that these two clinical conditions are caused by either one and the same virus or two antigenically identical viruses.

Not much was known about the history of Herpes simplex. During the early part of this century, it was recognised as a separate virus disease nothing to do with the others, and further it was found to be so common an infection that it was estimated that nearly 70 to 80 percent of the adult population may have a high level of neutralising antibodies as a result of this infection in early childhood. Subclinical infections with Herpes simplex are far more common than with others. Herpes simplex is caused by Herpesvirus hominis. This presents a wide variety of clinical manifestations involving mucous membranes, skin, cornea, genitals, gums, central nervous system etc. However, all these do not cause any problems in diagnosis of smallpox. It is only one rare clinical variety viz. Disseminated Herpes simplex, which occurs mostly in premature babies, neonates, infants and children under age of 5 years, that may resemble smallpox. Rarely it occurs in adults too, and some such have been wrongly diagnosed as smallpox.

Syphilis has been one of the ancient diseases known to man. This is one disease that mimics several others. Though, after the discovery
of the antibiotics, the papular and pustular syphilides have become a rarity, yet not infrequently we do come across cases of secondary syphilis with rashes referred to I.D. Hospital as smallpox cases. On a few occasions, even wrong diagnoses have been made by us and therefore one has to bear in mind, syphilis also, in differential diagnosis of smallpox.

Generalised vaccinia, usually follows primary vaccination and so may not pose as a problem in diagnosis. The question arises only, when it occurs in the exposed contacts of a smallpox case, if there is no history of such an exposure, it is no problem.

in all these diseases, eruptions do occur on the skin and/or mucous membranes, and these lesions evolve through different stages, and finally, on recovery, leave scars either permanent or temporary. For distinguishing one disease from another, therefore a careful study of the clinical course of each of these diseases is essential.

CLINICAL STAGES

Introduction

It is conventional to consider the day of manifestation of the first signs and symptoms in a patient, as the starting point of the clinical course of the disease. It is perfectly true; because a disease can be recognised only then, and not before. However, in dealing with communicable diseases, in public health practice, to a Medical Officer of Health and an Epidemiologist, an infected person is as important as a diseased person. An infected person may not present manifestations of the disease, yet he may be a menace to the health of the community. Even granting that he is not infective during that period, yet he should be kept under active and continuous surveillance, to see that he does not cause any damage to the community. But unfortunately there is no method known so far, to detect an infected person before he develops the disease, and therefore, anyone who gives history of having had the exposure to an case of infectious disease, should be treated as a potential patient till it is proved otherwise.

Under the circumstances, I consider, the stage of incubation as the first stage in the course of the disease, though I may not be, technically absolutely correct. Broadly speaking, therefore, the
Clinical course of these diseases consist of three stages, the stage of incubation, the pre-eruptive stage and the stage of eruption.

**Stage of Incubation**

The incubation period is the time interval between the day of entry of the agent of infection into a host and the day of appearance of the first manifestation of the disease. To determine this period is not easy, because, no one can definitely fix the exact time of infection. If a person is exposed to case of infectious disease, he may get infected on the first day of exposure, or a few days later, or never at all. The day of exposure need not therefore always be the day of infection, and hence it is difficult to determine the actual incubation period. However, if there is a history of a very short and single exposure, and if there is no further continuity in exposure and if such a contact develops the disease, only then, can one justifiably say that the day of exposure was the day of infection. But such histories are rarely available. In the absence of such, the best we can get, is "Exposure to Fever" (E-F) interval, i.e., the time interval between the day of first exposure and the day of appearance of the fever, if fever is the first sign of the disease. This E-F interval is either the same as the incubation period, or in majority of the cases, longer.

The incubation period in Smallpox appears to be fairly constant, about 12 days. However, it may range between 7 and 21 days. Very few single and short exposure case histories are available to fix the actual incubation period. Recently we had one instance. A person happened to travel in a railway compartment, sitting by the side of a case of Smallpox, from Khasipet to Jhansi, about 12 hours journey. At Jhansi, he got out of the compartment for fear of contracting the disease. Exactly on the 12th day of the exposure, he developed fever, and rash of Smallpox three days later. Here, E-F interval was 12 days, and it was the same as the incubation period, since the exposure was single and short and there was no continuity in the exposure.

In a study of about 1300 contacts of 254 Smallpox cases, we found 50 contacts developed the disease. All the 1300 had continuous exposure to their primary cases from the day of onset of fever till...
the day of isolation of the case or death. In these 50 contact
Smallpox cases (secondary cases) the "Fever to Fever" (F-F) interval
i.e., time interval between the day of onset of fever in the primary
case and the day of onset of fever in the secondary case was found
to be ranging between 12 days to 24 days with a mean of 16 days.

Persons incubating Smallpox, for all practical purposes, are absolutely
normal. Whether they can transmit infection to others during this stage,
is a debatable question. However, there appears to be a possibility,
that they could. During the first 72 to 96 hours of incubation,
it is found that the Smallpox virus multiplies in the respiratory
tract before it reaches the reticulo endothelial system through the
blood. While it is multiplying in the respiratory
tract, there is a possibility that such apparently normal persons
incubating the disease, may void the virus either through the
nasopharyngeal droplets or discharges. However, so far, there is no
definite epidemiological or virological evidence to show that they
transmit the infection even in the early stages of the incubation
period.

The incubation period in cases of Chickenpox is reported to be longer
than that of smallpox, ranging between 12 to 21 days, with a mean
of 17 days. Some claim it to be round about 14 days. As in Smallpox,
here also we have the same problem, inability to fix exactly the day
of infection, unless the disease follows a single and short exposure.
Further, in Chickenpox, it is also difficult to find out the exact
day of the manifestation of the first sign of the disease. Some may
have fever, and majority may not have. The first sign, in several
cases, may be the occurrence of the rash itself, and not infrequently,
the first crops of lesions are missed by the patients. This is an
additional difficulty in determining the incubation period of
Chickenpox.

Recently, we had some instances, where we were able to calculate roughly
the E-F and F-F intervals. Two cases of Mumps admitted to I.D. Hospital
Madras, got cross infection with chickenpox. In one case, the E-F
interval was 16 days and in the other, 20 days. In another set of
9 secondary cases of chickenpox in the infected families, the F-F
interval was 20 days in 3 cases, 24 days, 21 days, 19 days, 18 days
17 days in one case.
It appears therefore the incubation period of Chickenpox may range between 15 and 24 days on the assumption that a Chickenpox case is infective even from the 1st day of disease. In persons, who develop Chickenpox after exposure to cases of Herpes zoster, which occurs occasionally, the incubation period is reported to be ranging between 7 and 21 days.

There are some, who believe that persons who are incubating chickenpox maybe infective during the last 24 hours of the period, but as in Smallpox, there is no epidemiological or virological evidence to substantiate this view.

In Herpes simplex the incubation period is reported to be very short, ranging from 2 to 7 days with a peak at 4 days. Of course this applies to only primary infections, since in recurrent Herpes, only the latent virus is reactivated by some stimulus. Further, the only manifestation, that creates the problem, is Disseminated form and that follows only primary infections.

Generalised vaccinia follows mostly after primary vaccination. Usually, there is an interval of 7 to 9 days between the vaccination and appearance of the rash which includes the pre-eruptive stage. It is rather difficult to say exactly what the incubation period is, in Generalised vaccinia.

In both Smallpox and Chickenpox, as well as those who are incubating Herpes zoster and Herpes simplex, the persons appear absolutely normal and healthy, and therefore the question of detecting the infected persons from among the normal persons, and differentiating one infection from the other, are absolutely out of question with the present knowledge we have.

Pre-eruptive stage

Signs and symptoms of this stage of the disease are of utmost importance in the clinical diagnosis of eruptive fevers in general. For the matter of that, it is the characteristic symptoms-complex of this stage that differentiates Smallpox from Chickenpox.
There can be Smallpox without rash but there cannot be smallpox without fever preceding the rash. This is true in almost all cases of smallpox. The pre-eruptive stage of smallpox corresponds to the stage of viraemia. The virus which was multiplying in the Reticuloendothelial System through the major portion of the incubation period, flows into the blood stream like a virus shower before it reaches and settles on the skin and mucous membranes producing the specific focal lesions of Smallpox. For localization and development of the focal lesions to such an extent as to make them visible, it will take normally 48 to 72 hours, which corresponds to the pre-eruptive stage. However, in the very severe and fatal cases of Smallpox viz the Early hemorrhagic, the duration of this stage may apparently be prolonged to 96 hours or more, and these cases may even die before the focal lesions appear on the skin.

On the other extreme, in the most modified and the mildest type of smallpox viz. Variola sine eruptione, the pre-eruptive stage is not followed by any rash on the skin. In such cases, the fever comes down to normal by 72 hours and they recover without any visible rash on the skin. Barring these few exceptions which account for only about 3 percent of total number of Smallpox cases, in all others, the rash appears after 2 or 3 days of pre-eruptive stage.

This stage is characterized by varying degrees of fever. The fever may be sudden in its onset, with or without rigor, remains high showing a tendency to drop towards the end of this stage, with the onset of rash. Nearly 95 to 100 percent of the cases, complain of head ache and back ache which may be so severe as to incapacitate them, more than the height of the temperature. The other signs and symptoms commonly associated with this stage, are diarrhoea and/or vomiting in about 80 percent, delirium and/or hallucinations in about 15 percent, sore throat and dry cough in about 15 percent, and abdominal discomfort or colic in about 13 percent of all cases. Children may develop convulsions. Transient rashes of different types have been described to occur, which usually disappear with the onset of focal rash.

In Smallpox, therefore, this stage is associated with regular constitutional symptoms and so form a symptom complex and this pre-eruptive symptom complex or pre-eruptive syndrome, is a 'must' in clinical diagnosis of smallpox. Irrespective of the type of attack that is to follow, the characteristics of the pre-eruptive
stage are always a constant feature in smallpox, though in general the signs and symptoms are more severe with the severe types.

In contrast to smallpox, in Chickenpox, virtually, it can be stated that there is no pre-eruptive stage. Very few cases give a history of fever preceding the rash. In majority of cases, rash is the first manifestation noticed by the patient and fever may follow. In a few, the first crops of lesions may be associated with fever, the rash and fever occurring simultaneously. They may have slight headache, malaise, and indisposition, a few hours before the appearance of rash. However, there are a few, who actually give definite history of 2 or 3 days of fever preceding the rash, though not associated with constitutional symptoms. On careful examination of such patients, one will find 2 or 3 crops of lesions on their back, which, the patients might not have noticed, to explain the so-called pre-eruptive fever. This absence of the pre-eruptive syndrome in Chickenpox differentiates most of them from Smallpox.

As in the case of Chickenpox, there is no pre-eruptive fever in Herpes Zoster too, but majority of cases complain of either irritation or shooting pain along the nerve roots affected, 24 to 36 hours before the focal rash appears. These cases are not likely to be confused with Smallpox.

In the rare cases of Disseminated Herpes simplex, a pre-eruptive stage has been described. This is usually associated with primary infection, mostly in children, but rarely, in adults also. In the reported cases, they were associated with constitutional symptoms like head ache, severe back ache, vomiting, diarrhoea etc., lasting for 2 or 3 days before the appearance of the rash. With this kind of history, these cases are likely to be misdiagnosed as Smallpox. However, these are usually associated with severe stomatitis, which is rare in Smallpox.

Not infrequently, cases of Pemphigus vulgaris give a definite pre-eruptive history of fever with constitutional symptoms, which are almost similar to those of smallpox, lasting 3 or 4 days before the appearance of the lesions on the skin. With this type of history, cases are likely to be mistaken for Smallpox and in a few instances we have committed such mistakes.
After primary vaccination, usually the child develops fever on or about 5th day and in cases developing Generalised vaccinia, the lesions are usually seen on the skin, between 7th and 10th day. There is therefore a definite pre-eruptive stage with fever of 3 or 4 days duration. With that type of history, there is every likelihood of such cases getting confused with Smallpox, especially when they occur amongst the contacts of case of Smallpox. However, the constitutional symptoms so characteristic of the pre-eruptive stage of smallpox are, to a great extent, absent in the case of Generalised vaccinia.

**Stage of Eruption**

It is in this stage, that the confusion starts in diagnosis of smallpox. Careful study, however, of the lesions will certainly help in majority of cases. In studying the rash, one should observe, the order of appearance of the rash, the distribution of rash, the characteristics of the individual lesions, and their evolution. In addition, the study of the general condition of the patient throughout the course of the disease is also of great importance.

**Order of appearance:**

In Smallpox, enanthem, when present, is the first to appear. The tongue, the palate and the nasopharynx are the frequent sites, where the lesions are noticed as minute spots, a few to 24 hours before the appearance of rash on the skin. Other mucous membranes are also involved but the lesions may not be easily visible. It should be, however, remembered that not in all cases, does the enanthem occur.

As regards the exanthem, it is on the face, the first lesions usually appear, especially on the forehead, as angry looking macules. The rash then rapidly spreads on to the upper extremeties, trunk, and then the lower extremeties and the whole process may take about 24 to 36 hours. However, this order of appearance may be absent in about 15 percent of the cases.

In Chickenpox on the other hand, the first lesions seem to appear on the trunk, especially on the back, which are often missed by the patient. Following this, the lesions may appear on the neck, the face and then the extremeties. Almost every day, a fresh crop of
Lesions appears adding to the total number of lesions on the body. This may go on, for about 4 to 7 days. Almost 50 to 60 percent of the cases do have exanthem, and when present, need not always precede the exanthem, it may follow.

Unions Herpes zoster is associated with generalised rash on the body, it needs no consideration in differential diagnosis of smallpox. But no infrequently, Herpes zoster, is associated with rash as in Chickenpox. It is not so rare as the books describe.

In such cases, generally, the local zoster lesions precede the general rash. In a few instances, however, the general rash may be followed by the local zoster lesions. Whatever it is, as long as there are lesions distributed along a nerve root, and the general lesions resemble those of Chickenpox, it poses no problem.

In Disseminated Herpes simplex, as per the published reports, the rash seems to appear on the hands and feet and then spread on to the trunk, but there may not be any particular order of appearance.

In Generalised vaccinia and Secondary syphilis there appears to be no particular order of appearance of rash.

Distribution of rash:

The rash in smallpox has a fairly characteristic distribution. The rash is relatively more dense on the face and the extremities than on the trunk (centripetal distribution). On the extremities, the rash is more dense on the distal portions, than on the proximal; more on the extensor aspects, than on the flexor; more on the convexities, than on the concavities. The axillae are less frequently involved than the folds (Ricketts' sign).

Palms and soles are more frequently involved in smallpox than in chickenpox. On the trunk, the rash is relatively more dense on the back than on the front; on the front, it is more on the chest, than on the abdomen; on the abdomen, it is more on the upper half than on the lower half.

Presence of lesions in the palms and soles, and absence of lesions in the axillae are not diagnostic of smallpox as some books suggest,
because in several cases of chickenpox we do find rash in palms and soles, and the axillae also are free.

This kind of typical distribution is found only in about 80 percent of all cases. Almost all cases belonging to the ordinary variety, about 80 percent of the flat variety, and about 50 percent of the modified variety, may present this type of distribution. It is not wise, therefore, to completely rely on the distribution alone for diagnosis of smallpox. The characteristic distribution, when present, may certainly help.

In Chickenpox, in general the rash tends to be more dense on the trunk than on the extremities (centripetal). Yet there are several exceptions. I am inclined, to feel, that in Chickenpox, the rash, by and large, has no typical distribution, as the rash of Smallpox has. The distribution character seems to depend, more on the number of crops of lesions, that the patient develops than on anything else. Quite a sizable number of cases of Chickenpox, have lesions in the palms and soles, notably in palms.

In Herpes zoster the lesions occur unilaterally on the skin innervated by the affected nerve roots and so the confusion between smallpox and this disease does not arise. When it is associated with generalized lesions on the body, they have the same type of distribution as those of Chickenpox. On the other hand, Herpes zoster has been confused with Herpes simplex, when the latter confines itself along a nerve root, as it does sometimes.

There does not seem to be any characteristic distribution of the rash in the Disseminated form of Herpes simplex, though it has been noticed, that in the few cases reported the rash has been mostly on the extremities.

The Syphilitic rash can take any form of distribution. We have been cases of papular and pustular syphilides with the typical centrifugal distribution like that of Smallpox, causing difficulties in diagnosis.

In Generalized Vaccinia again there does not seem to be any definite type of distribution. The lesions are usually uniformly distributed all over the body, though recently we have had a case where the rash
was almost confluent on the back, with only a few lesions on the extremities.

Characteristics of the lesions:

In diagnosis of Smallpox, perhaps these characteristics are far more important than even the distribution or the order of appearance.

From the data available from Madras, it was found that 50 per cent of all Smallpox cases belonged to the Ordinary variety, 15 per cent to the Modified, 4 per cent to the Flat and 3 per cent to the Haemorrhagic varieties. Of course, this was irrespective of the vaccinal status. Therefore let us consider the characteristics of the lesions of the most common variety, the Ordinary, and discuss variations in the other varieties, if there are any.

The lesions in the Ordinary variety are deep seated, and are in the skin, more or less circular in shape, shotty to the feel and can be rolled between the fingers without any fear of rupturing them. They are raised above the skin, are multilocular and present true umbilication, i.e., a central depression with a black spot without loss of potency of the vesicle. This umbilication is the result of loss of fluid tension and pulling in, of the fibrinous threads within, which separate the vesicle into different compartments. Usually the lesions are not surrounded by any erythematous areaola.

The most important characteristic, that distinguishes it from Chickenpox, is the absence of pleomorphism. In Smallpox, at a particular time and at a particular site, all the lesions will be found in one and the same stage of evolution, whereas in Chickenpox they are found in different stages of evolution. At times, one may find, in Smallpox, lesions in different sizes but not different stages. This should not be confused with pleomorphism.

In the Late Haemorrhagic type of cases, the lesions may be of two types, the Ordinary or the Flat. In the former case, the lesions have the same typical characteristics of those of the Ordinary variety described above and in the latter case, the more frequent of the two, the lesions have the characteristics of those of the Flat variety of smallpox which are described below.
in the flat variety of smallpox, the lesions are a little superficial (though not so superficial as those of Chickenpox) and are not much raised above the skin. During the vesicular stage, when they should normally be raised and projecting on the skin, the lesions flatten out, remain almost buried in the skin. They are neither multilocular in nature nor do they present true umbilication, since the potency of the vesicle is lost due to haemorrhages occurring into the bases of the lesions invariably. Some lesions may have an erythematous areola around.

In cases belonging to the Modified variety they have all the characteristics of the Ordinary variety, but sometimes, they appear to be more superficial. They may not present umbilication because they start scabbing in the vesicular stage itself and not infrequently, there may be a tendency to pleomorphism.

In several cases, the number of lesions may be so few that it may cause difficulties in diagnosis. We have seen cases with one lesion and 3 lesions, yet, Variola virus could be isolated from them. On other extreme cases have occurred throughout ranging when confluent rash was seen on the body, yet the course was modified with all lesions scabbing before 10th day. These cases do cause difficulties in diagnosis.

Unlike in Smallpox, the lesions of Chickenpox are quite superficial and are on the skin. They are more or less oval in shape, not shotty to the feel and are likely to be ruptured easily with slightest pressure. They are raised on the skin, unilocular in nature without any umbilication. Some lesions appear as fine clear water or dew drops on a lotus leaf. Some may present a false umbilication, a result of rupture of the vesicle, with a central depression, with a puckered appearance around, with the loss of potency of the lesions. In majority of the cases, the lesions are surrounded by an erythematous areola, which may persist, at times even after the scab is formed. But the most important characteristic feature is the pleomorphism. At a particular time, at a particular site, one finds lesions in different stages of evolution, and this is the result of the fact that in Chickenpox, unlike in Smallpox, the lesions appear in crops.
In a few cases, the lesions may not be so typical. The lesions are not raised, do not appear as clear vesicles, instead, they have a tendency to flatten out and remain flush with the skin as in the flat variety of Smallpox. Sometimes, these lesions may have haemorrhages into their bases. However, there is no evidence to show that these cases belong to a different type of Chickenpox. Anyhow this requires further investigation. In the very rare cases of Haemorrhagic Chickenpox, the lesions have a tendency to flatten, with haemorrhages occurring into their bases and these are associated with haemorrhages into the different mucous membranes, the commonest being epistaxis. Another variety of chickenpox that is occasionally seen is the Bullous variety. In these cases, big bulli are seen, which usually become infected with bacteria and therefore appear as bags of pus. In some cases these bulli are as big as big sized lemons. They rupture leaving extensive raw areas of skin.

There are no special characteristics of the lesions of Herpes Zoster. The general lesions are similar to those of chickenpox and the local lesions are usually big in size. They are confluent and get distributed along the affected nerve root.

The vesicles of the Disseminated Herpes simplex are reported to be deep set in the skin, like those of smallpox and are surrounded by a definite crimson colored area.

The lesions of Generalised Vaccinia are almost like those of smallpox, but usually somewhat bigger in size, otherwise indistinguishable from smallpox.

The papules of Secondary syphilis are hard, coppery hue in color, slightly raised above the skin, do not usually vesiculate. When a needle is passed through the papule, it will not split the lesion, as it does the papule of Smallpox or Chickenpox. This test, we call it "Needle test" is useful in differentiating the papules of syphilis from those of other diseases. The lesions have no erythema around.

Evolution of lesions:

The evolution of lesions in Smallpox is much slower than in Chickenpox.
On the mucous membranes, however, the exanthem evolves more rapidly. The lesions appear as macules, which evolve very quickly in about 48 to 72 hours, into papules and vesicles, which ulcerate liberating large quantities of virus. They heal also quickly, leaving no scars, in about 4 to 6 days. In a few instances however, they may take longer time, and we have isolated the virus from the throat washings of smallpox cases with the exanthem even up to 15 days.

On the skin, the lesions appear as macules, which look like flea bites on the 3rd or 4th day of the fever, towards the end of the pre-eruptive stage. In about 24 to 36 hours they get raised over the skin and develop into papules. The papules of smallpox, unlike those of syphilis, are really early vesicles and so are not hard. Fluid collects within, raising the skin over the papules, and turns them into vesicles in about 48 to 72 hours. The fluid in the vesicles is opalescent and is not clear as in the vesicles of Chickenpox. In the next 48 hours, the fluid becomes turbid and opaque, giving the appearance of a pustule. These pustules usually contain only tissue debris and not frank pus. Not infrequently, the contents are even sterile. For 3 or 4 days, the pustules mature, when on or about 14 day of fever it resolution starts. The lesions start scabbing usually between 14th to 21st day of fever and complete by about 30th day or more, at times. These scabs are deep seated unlike in chickenpox. However, they separate off from all parts of the body easily, except from the palms and soles of the feet, where they may have to be dug out with a needle. The scabs are usually dark brown in color. All this descriptions holds good mostly to the Ordinary variety of Smallpox. Even in that variety, there may be great variation in the timing of the different stages of evolution and this is mainly determined by the vaccinal status of the patient as well as the type of attack.

In the Early haemorrhagic type, usually the patients may not survive so long as to allow the lesions to evolve beyond the maculo-papular stage. In the Late haemorrhagic types among the survivals, the evolution of lesions depends upon the nature of the lesions, flat or ordinary.
In the flat variety of smallpox, the lesions evolve into the vesicular stage like the ordinary, then they flatten out and there is no further evolution into pustular stage. In survivors scabbing starts early, without going through the pustular stage, and therefore the evolution in general, may be a little more rapid than in the ordinary variety. The scabs in this variety of smallpox are somewhat superficial and thin. Further the scabs are of varying sizes and some may be so small as the size of pin-head and are very difficult to find. The scabs of the flat variety are somewhat purplish in color as against the dark brown color of the scabs of the ordinary variety.

In the modified variety, the lesions evolve very rapidly. The scabbing starts even during the vesicular stage, skipping over the pustular stage, and at times, the scabbing may be completed even long before the 10th day of fever. The scabs are quite superficial and separate of very easily.

Unlike in smallpox, the evolution of lesions is more rapid in chickenpox. Starting as macules, in a matter of few hours to 12 hours, the lesions become papules, and vesicles in another 24 hours. The vesicles are clear covered with a thin skin and appear like clear drops of water. At times, due to secondary bacterial infection, as a result of rupture of the lesions, the fluid may become turbid and vesicles appear as pustules. Otherwise, the lesions usually resolve in 4-5 days and scab. Successive crops occur which usually do not exceed 5 or 6 in number though in rare instances, more number of crops may occur, when not infrequently the later crops may not evolve through all stages but scab off more quickly. The scabs of chickenpox are superficial and thin and they easily separate off from the body. However, in palms and soles, when the lesions occur, the scabs may have to be dug out.

In rare cases of Haemorrhagic chickenpox, there may not be much difference in the nature of timing of the stages of evolution but in the bullous variety, with the bulli may get infected with bacteria, and these may take quite a long time to heal. They usually do not scab since invariably the skin of these bulli peels of leaving extensive raw areas of the skin.
The lesions of *Herpes zoster* like those of chickenpox, rapidly evolve up to vesicular stage, beyond which it takes longer time to scab. Some times successive crops occur at the same place on the affected skin. For the scabbing to complete, it may take about 10-12 days. As far as the lesions on the body are concerned, when they are present, they evolve in the same manner as those of Chickenpox. The scabs in the case of Herpes zoster are superficial and separate off quite easily.

In the reported cases of *Disseminated Herpes simplex*, it was noted that the evolution of lesions was more or less similar to that of Smallpox, and in the case reported by Kipling and Downie the lesions seemed to have scabbed off or or about 12th day of the disease.

In the *Papular syphilides*, one of the characteristics features, which differentiate from Smallpox and Chickenpox, is the absence of evolution beyond the papular stage. In the untreated cases the papules continue to remain for quite a few days, and slowly scale off without scabbing. There have been instances however, where the vesiculo pustular stage has been noticed, in which case these pustules take quite a long time to scab.

In *Generalised vaccinia*, the lesions seem to evolve in the same manner as those of smallpox, through all the stages of evolution.

**Scars:**

Smallpox invariably leaves permanent scars. But the depth of the scars and the permanency seem to determined by the type of attack, the vaccinal status of the patient, and perhaps the sex, and the age also. In general, the scars are more or less permanent and deep seated in all cases of Ordinary variety. In the case of Flat and the Modified, a sizable number of cases may not have permanent disfiguration. In a follow up of about 120 cases of survivals of smallpox among the 1965 admissions to Infectious Diseases Hospital, Madras about 30 percent had no visible scars on the face by 1961. Studies made in Africa also indicate the same. We have also found that permanent scars are more common with Ordinary variety and more frequent in the unvaccinated, the youngest age groups and the female sex.

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The scars after Chickenpox usually are not permanent. Further they are more superficial than Smallpox. Perhaps up to 6 to 12 months one may be able to recognise these scars in severe cases of Chickenpox. Normally, no scars will be visible by 6 months. In the case of Herpes zoster due to the confluence of the local lesion on the skin the affected nerve root, a permanent disfiguration may be noticed, through superficial, for a few years.

In the case of Herpes simplex, no information is available to my knowledge, whether the lesions leave permanent scarring or not, when the disease takes a disseminated form.

In secondary syphilis the Papular syphilides may not leave any permanent disfiguration. But in the case of pustular syphilides it may be different. Recently we have had a case, in which even 4 months after the attack, extensive scars and some of them quite deep simulating smallpox were found. In this particular instance, even the distribution of the scars was similar to that of Smallpox except that there was no involvement of the face. In the palms and soles, however, besides a few scars, there was extensive pigmentation. Investigations showed that it was not a case of smallpox, but a case of pustular syphilides.

The rash of Generalised vaccinia may have scars. However, they may not leave any permanent pitting as in cases of smallpox. But I must say that my experience with the follow up of Generalised vaccinia cases is unlimited.

General Condition of the patient during the course of the disease:
In the fever of the pre-eruptive stage tends to come down with the onset of focal rash. In all cases, except the Modified, and a few of the Ordinary discrete type, the temperature tends to rise again in the vesicular pustular stage of the disease. The constitutional symptoms and toxemia are quite severe in Haemorrhagic type, the Flat types and the confluent types of the Ordinary variety especially amongst the unvaccinated. In addition the Haemorrhagic cases develop haemorrhages into the skin and/or mucous membranes during the course of the disease.

In Chickenpox though there is no pre-eruptive at fever, in some cases
every crop of lesions may be associated with rise in temperature and therefore they may have fever every day, till no more fresh crops occur. The constitutional symptoms during the course of the disease are very mild or nil. In cases of Haemorrhagic chickenpox, however, the patients may be toxic and in cases of bullous variety if the bull become septic, the patients may develop septicemia associated with constitutional symptoms.

The course of the Herpes zoster is usually uneventful except for the severe shooting pain in a few cases along the nerve roots affected.

In Disseminated Herpes simplex the fever may continue during the course of the disease and constitutional symptoms may also be as severe as in smallpox.

Cases of Secondary syphilis, normally, are afebrile without any constitutional symptoms.

Especially in young infants, Generalised vaccinia may be associated with constitutional symptoms and fever which may subside when scabbing starts.

CONCLUSION

Though I have discussed the clinical stages in the course of these six diseases, yet, as I have stated earlier, the commonest disease that is confused with Smallpox is Chickenpox. Especially the Modified and atypical smallpox may be mistaken for chickenpox and severe forms of chickenpox for smallpox. All others can easily be excluded if careful observation and clinical examinations are made of the patients. To arrive at the diagnosis, eliciting of correct history is as important as clinical examination. Broadly speaking, there are three types of history that are required to be recorded viz. history of exposure, history of susceptibility and history of onset of the disease. In eliciting history one has to be tactful and put leading questions to get correct answers.

The clinical examination of the case has to be done thoroughly taking into consideration all the aspects that have been described...
but the most important features that distinguish smallpox from others, are

1. a definite pre-eruptive syndrome
2. the depth of the lesions and
3. the absence of pleomorphism.

This diagnostic triad must be there, in all cases of smallpox. All other characteristics of the disease, like distribution, evolution of the lesion etc may help further, in arriving at the diagnosis. In spite of all these, there may be a few cases, which require confirmation by the laboratory investigations.

As a clinician, a practitioner of preventive medicine and a laboratory worker, I would like to say emphatically that, one should not forget that the laboratory results are there, only to confirm the clinical findings and not to substitute them. There are several extraneous factors which determine the accuracy of the results of laboratory investigations and therefore these results should be taken only as additional aids to diagnosis.