are examples of the same general law of diminished oxidation at work. The tuberculous area as it grows begins to be cut off from the blood supply and oxygen and reaches the point of breaking down on this account. At this stage calcareous deposition commences for the same reasons which we have seen holding elsewhere.

Finally, in the calcification of arterial walls in old age and arterio-sclerosis, we see a fine example of the same process of diminished oxidation accompanied by calcareous deposition. The calcareous plaques are formed where the arterioles of the coat of the artery have broken down or become partially obliterated, and the supply of oxygen to the tissues has consequently been decreased, oxidation has become embarrassed, and insoluble calcium salts, the congeners of diminished oxidation, have appeared.

Recent analyses of the calcareous plaques from aortae, made by Drs. O. T. Williams and G. F. N. Joseph in my laboratory, have shown that these consist of mixtures of calcium salts of phosphoric, carbonic, oxalic, and stearic acids, as well as of other products of incomplete oxidation, which are now being more fully investigated.

Accordingly, it is seen that the formation of renal calculi has for its basis a condition of diminished oxidation, in which there appear primarily calcium salts of incompletely oxidized bodies, such as calcium oxalate and calcium urate, associated with calcium phosphate. Further, such diminished oxidation, occurring locally or generally, is seen in many pathological conditions, such as calcium salt deposition in bone in old age, in tuberculous lesions, in gout, in arterio-sclerosis, and generally in calcification processes in the body. The tendency towards such deposition increases with age, and is probably accompanied by an increased alkalinity of the body fluids.

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THE EXAMINATION OF SUSPECTED SMALL-POX:

SOME POINTS OF PRACTICAL IMPORTANCE.

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AN attempt is made in this paper to approach the subject of diagnosis from the point of view of the practitioner who may be called upon to examine, and perhaps forthwith to express his opinion on, a suspected case of small-pox. The subject is considered in the light of the experience gained at the receiving station of the Metropolitan Asylums Board during the London epidemic of 1901-2. It is convenient, therefore, to follow the routine examination to which the patient certified to be suffering from small-pox was subjected at the receiving station during that outbreak, and in doing so to try to emphasize those features of the disease which rose into prominence and gradually acquired a position of major importance as experience in differential diagnosis increased.

The method of examination employed at the receiving station was based upon the recognition of the fact that the most constantly present, the most persistent, and the least variable feature of the disease is found in the distribution of the vesicular rash. The high position which the characteristics of the small-pox distribution occupy in differential diagnosis was first recognized, and has lately been* admirably demonstrated, by the author of a recent work on the diagnosis of small-pox. On his teaching, in its broader aspects, the method of examination followed at the receiving station was based.

* *The Diagnosis of Small-pox.* By T. F. Ricketts, M.D., B.Sc.Lond., M.R.C.P., D.P.H. Illustrated from photographs by J. B. Byles, M.B., B.C.Cantab., F.R.C.S.Eng., D.P.H.

A.—SUBJECTIVE CONDITIONS.

(a) *The Statements of the Patient.*

A method of investigation which assigns a position of major importance to a feature of the disease so purely objective in its nature must tend to deprive the statements of the patient respecting his symptoms of much of their reputed value. It has a similar effect, although not so extreme, on the general history of the case—namely, the movements of the suspect, the source of his infection, his vaccination record, etc. But, even if one avoid any preconception regarding the relative importance of the various symptoms and signs of the disease, it does not require a long experience in dealing with suspected small-pox to prove how unreliable and not infrequently how misleading are the indications derived from subjective conditions.

Small-pox finds the great majority of its victims among the most ignorant of the population. These people resent compulsory examination. They dread an outbreak of the disease, but they object more strongly to the rigid seclusion of the patient and to the life under tiresome medical supervision which follows its recognition. Such conditions combine to produce an individual whose statements are almost always unreliable and at times wilfully misleading. But the failure to obtain assistance of much value in diagnosis from inquiries about symptoms does not depend altogether on the peculiarities of the patients with whom we have to deal. It is associated also with the variability of the symptoms themselves. Some patients who desire to be accurate are unable to recall the details of an illness which was neither recent nor severe. The onset of present day small-pox does not differ in any material respect from the onset of several other acute febrile diseases. It is usually sudden. Headache, vomiting, or nausea and shivering are frequent. General ill-defined aching is a common feature. But the "back-ache," the severe lumbar pain, so often mentioned as one of the most important features of the onset, is not always present. When it occurs, this local pain varies greatly not only in position, but also in severity, in different cases. The patient may complain only of a slight discomfort or stiffness in the neck.

In a feverish attack with sudden onset the presence of severe pain in the back does not necessarily point to small-pox, nor is the absence of this local pain inconsistent with the onset of small-pox of the most virulent type.

The following cases may serve to illustrate this point:

1. A boy, aged 8, had a sudden onset of pain in the abdomen, vomiting, and high fever. There was an indefinite history of contact with small-pox. Twenty-four hours after the onset he was complaining of severe headache and pain in the abdomen but not in the back; there was no skin eruption; the abdominal pain seemed to increase, and the patient became delirious and difficult to control; the abdomen was generally tender, but there appeared to be greater resistance to palpation on the right side than on the left. The abdomen was explored but nothing abnormal was found. *Post mortem* a large retro-peritoneal hæmorrhage was discovered. The illness was almost certainly due to small-pox of the most virulent type, but during life there were no signs on which a diagnosis could be based.

2. A youth, aged 18, was sent to the receiving station from a common lodging-house, where on the same day a case of small-pox had been discovered. His illness had a sudden onset, with chill, headache, severe pain in the back, and vomiting. There was a patch of herpes on the face but no other skin eruption. His condition was due to lobar pneumonia.

3. An educated man, aged 36, was admitted with a vesicular and pustular eruption on the face, trunk, and extremities. He stated that for two to three days before the rash appeared he had suffered from sickness, headache, and pain in the back. The backache he described as so severe that movement was difficult. The eruption was chicken-pox.

It is hardly necessary to discuss the symptoms of invasion at greater length. None of them is peculiar to small-pox. They are important because they indicate the possibility of the presence of an acute infectious disease, and so point to the necessity for complete examination of the skin. The first lesions to appear, as well as the late widely scattered pustules and crusts of a modified small-pox rash, are easily missed if this examination is incomplete.

(b) *Source of Infection.*

A history of contact with the disease.

The suspicion aroused when the patient attacked by a feverish illness is known to have been exposed to the

infection of small-pox can be tested only by subsequent developments. If the presumption in favour of small-pox is strong enough to justify removal to hospital, it is a wise precaution to vaccinate the patient before he is brought into an area where undoubted small-pox is concentrated.

In this connexion the following figures are of interest: In the twelve months from August 1st, 1901, to July 31st, 1902, 197 patients who were "contacts" were sent to the receiving station, probably on account of a feverish illness, since they had no rash of any sort. Of these, 55 developed the rash of small-pox while they were under observation. In 142 another disease declared itself, or the symptoms passed off with no further development. It is possible that among the latter there may have been a number of abortive attacks of small-pox in which the rash was entirely suppressed.

A few cases occurred in which it seemed probable that the reported contact of the patient with small-pox was based on an error in diagnosis. For example, a seaman developed feverish symptoms and was detained under observation on account of the report that small-pox had occurred recently among the crew of the steamer from which he had been discharged. When his rash appeared it proved to be chicken-pox.

B.—OBJECTIVE CONDITIONS.

(a) General Aspect of the Small-pox Patient.

The conditions grouped under this heading and observed not infrequently in the patient attacked by small-pox are the expression of the prostrating effect of the onset and primary fever. They have frequently been described. Their intensity varies with the severity of the initial symptoms. The small-pox patient whose invasion period has been severe, and whose pain has abated with the beginning of the eruption, gives one the impression that he has passed through an exhausting struggle. His face and his attitude express weariness and apathy. His voice is apt to be low-toned and monotonous. His mental processes are slow, and control over his movements is apt to be defective. For example, his reply to a question may be appreciably delayed, the question may have to be repeated, and his movements are often retarded, tremulous, and jerky. In the presence of such conditions he may assert that he feels much better since the pain has abated. But he will stagger if he tries to walk, and is apt to fall if not supported. It is not suggested that these conditions are peculiar to small-pox; but they are frequently present in severe cases of this disease, and they have their value as indicators. From their association with the stage of the primary fever towards its end, they are at their highest value when, after a day or two of a severe "influenzal" illness, their presence is accompanied by an eruption of "spots," however discrete the eruption may be.

A few examples of a rare type* of case, in which the presence of the signs of prostration becomes of especial value in diagnosis, occurred during the epidemic. A boy, 6 years of age, a contact, was admitted to the receiving station on the first day of his illness. There were four vesicular lesions on the skin, which was covered by verminous petechiae. One vesicle was situated on the back near the lower angle of the right scapula, another on the right flank, a third on the right side of the abdomen, and the fourth on the right thigh. They were flat, white vesicles, measuring about $\frac{1}{4}$ inch in their longest diameter. Those on the trunk were oval; the one on the thigh was irregular in outline. They had a superficial resemblance to the lesions of varicella, but they had a stronger pellicle, and they were larger than the usual chicken-pox vesicle. Each vesicle was set on a slightly raised inflammatory base. All appeared to be of the same age. They developed slowly. On the next day there was little change in their appearance, except a decided increase in size and also in prominence, due to further inflammatory induration of the base. Between the second and third day after admission the general small-pox rash began to appear, and the patient was sent on to the hospital. In this case the signs of prostration were not well marked. But in another patient, a boy 12 years of age, admitted on the second day of his illness, the apathetic facies and general appearance of prostration were very evident. In his case the only lesion present on admission was a large flat vesicle with irregular margin and indurated base situated near the centre of the forehead.

Two cases representing the most fulminant and rapidly fatal type of the disease were sent to the receiving station during the epidemic. Extreme pallor, great restlessness, and frequent outcry on account of severe pain were noted in both patients. One, the case of a boy whose pain seemed to be altogether abdominal, has already been mentioned. The other was a woman, 21 years of age. Her child was in hospital with small-pox. She was admitted at the receiving station on the afternoon of December 6th, 1901, with a history of a sudden onset of great

* These cases seem to be examples of inoculated small-pox. In the first the arrangement of the lesions suggests that the inoculation was brought about by vermin.

severity in the forenoon of the same day. She suffered from continuous nausea and retching, but complained chiefly of a feeling of "weight on the chest," which seemed to interfere seriously with respiration. Her temperature was 101° F. During the night and the following morning her eyes became suffused, cough became very frequent, and the sputum more and more deeply blood-stained. In the evening of December 7th, purpuric spots were noted on the eyelids and on the abdomen and lower part of the back. Subconjunctival haemorrhage also appeared. Death occurred shortly before 6 a.m. on December 8th, less than forty-eight hours after the beginning of her illness. No papules or vesicles were present. The skin remained quite clear until eight or nine hours before death, when haemorrhage began to make its appearance.

In this case the sudden and violent onset after exposure to infection pointed to small-pox. But in cases of this rare type if the history of exposure to infection is wanting, it is hardly likely that the disease will be suspected until its purpuric character reveals itself.

(b) Temperature.

In cases which have been under observation during two or three days of a feverish illness, a fall in temperature associated with the appearance of "spots" on the skin, however few and widely scattered the lesions may be, is an indication of the highest importance.

(c) The Buccal Mucous Membrane.

That small-pox vesicles are apt to occur on the mucous membrane of the mouth is a fact of considerable importance in the recognition of the disease. The soft palate is their favourite site, but if numerous they also invade the hard palate, the cheeks, and the tongue. They appear early in the eruptive period, and may precede the beginning of efflorescence on the skin. Their presence at this early stage becomes of the highest importance in diagnosis, because, on account of the rapidity of their evolution, they can be recognized as vesicles at a time when the lesions on the skin, being recent and small, may not present any features which will suggest a diagnosis of small-pox. But the period during which their assistance is available is short. Situated on a mucous membrane these lesions are naturally shallow; vesiculation is rapid; the pellicle is thin, becomes rapidly macerated, and is easily torn. After rupture of the pellicle it may be possible by the aid of strong illumination to see on the mucous membrane of the palate a slight depression with shreds of the torn pellicle adherent to its margin. But very frequently the rupture of the pellicle is followed by the rapid and complete disappearance of the lesion.

As a differential test between chicken-pox and small-pox the presence of vesicles on the mucous membrane has a limited value. They are probably less common in chicken-pox than in small-pox, and the probability in favour of small-pox increases with their number. But individually the lesions present no features by which they may be distinguished.

(d) The Signs of Previous Vaccination.

In determining whether a rash is or is not due to small-pox a little help may be obtained from inspection of the patient's vaccination marks, if one is careful not to over-estimate their value as negative evidence in diagnosis. The immunity against invasion by small-pox conferred by vaccination does not remain perfect. If not reinforced it undergoes a gradual but progressive diminution, a process which depends mainly on the combination of two factors: (1) the efficiency of the operation, and (2) the time which has elapsed since it was performed. Without an accurate knowledge of both conditions no assistance in diagnosis can be expected. Patients with signs of previous vaccination may be divided into two groups, according to the condition present at the time they come under examination, namely: (1) those with lesions of vaccinia in their active stage (vesicles or pustules); (2) those in whom the active stage has passed (crusts, ulcers, pigmented scars, and white scars).

1. In cases of the first group the operation is evidently both recent and successful. But this condition is of little value as negative evidence in diagnosis. Small-pox and vaccinia can develop together. The evolution of the vaccinal lesion may have been delayed, or the patient may have been vaccinated after exposure to infection. On the other hand, a successful vaccination performed after the

appearance of the suspected rash may be regarded as excluding small-pox.

For example, a boy, 8 years of age, an in-patient of a general hospital, unvaccinated, was sent to the receiving station on account of a very discrete rash. The lesions were situated on the face and on the right leg near the ankle-joint. They were dome-shaped, yellowish-white vesicles. On an assumption that they were the lesions of small-pox, they were evidently well advanced in the pustular stage. The opinion was formed that the rash was not due to small-pox, the patient was vaccinated, and returned to hospital. Six days afterwards he was sent back to the receiving station as it was considered that the possibility of small-pox was not altogether excluded. On readmission the rash was still present. The lesions had not changed in appearance. They were still yellowish-white dome-shaped vesicles. The vaccination was successful. Its lesions were well-formed normal vesicles, a result which was of value as corroborative evidence that the rash in question was not due to small-pox.

The rare type of case known as Generalized Vaccinia or vaccinal eruptive fever may be mentioned in connexion with cases in the first group. One case in which it was suggested that this condition was the cause of the eruption was admitted during the epidemic.

The patient was a young woman, a domestic servant who had been vaccinated along with the rest of the household because small-pox was active in the district. The vaccinal lesions had reached the eighth or ninth day of development. A very discrete pustular eruption was present on the face, trunk, and extremities. The units of the rash varied very much in size, but with this exception the eruption presented no features inconsistent with a mild and modified small-pox rash, and as the patient came from a district in which small-pox was rife, the certificate seemed to be fully justified.

2. In cases of the second group the *crust* or *ulcer* have no features which are peculiar to a successful vaccination, and therefore can afford no reliable means of judging of the efficiency of the operation. With very few exceptions, the statements of patients about the result of vaccination are quite unreliable, because they do not appreciate what is meant by "successful vaccination."

The relationship which has been shown to exist between fatality in small-pox and number of vaccination cicatrices has no practical value when the possibility of *invasion* in individual cases has to be decided. It does not seem likely that a more accurate standard for diagnostic purposes will be attained by attempts to assess the protective value of the scars of individuals attacked by small-pox, since it will never be possible to ascertain what share secondary infections have had in the production of the scar, and since it is unlikely that similar investigations among those who have been exposed to the infection, but have escaped attack by the disease, will ever be recorded.

The following case is of interest as representative of a type of rash presenting difficulty in diagnosis, and as an illustration of associated conditions in which the result of vaccination after the appearance of the suspected rash cannot be expected to afford reliable evidence for or against small-pox:

A girl between 6 and 7 years of age, vaccinated in infancy, was sent to the receiving station on account of a rash, of which the diagnosis lay between chicken-pox and small-pox. The rash was present on the face, trunk, and extremities. There were a few lesions on the forearms and hands, and on the legs and feet. The majority of the lesions had desiccated. A few on the face and extremities were pustular. Two vaccination scars of more than average size were present. The opinion was formed that the rash was chicken-pox. Revaccination at the receiving station was not successful.

(e) *The Cutaneous Signs of Small-pox.*

Small-pox is capable of producing three distinct types of eruption:

1. Erythema.
2. Purpura.
3. Vesicle (the pock).

During the period (commonly called the pre-eruptive stage of the disease) between the onset of the illness and the appearance of the first lesions of the vesicular rash the skin may remain quite free from eruption, or the clinical picture may be dominated by the presence of an erythematous or purpuric rash.

1. *Erythema*.—That difficulty is encountered in the identification of this sign of small-pox is evident from the number of varieties of the rash which are described in the textbooks. The small-pox erythema is said to conceal its identity under many disguises—to appear at one time as a scarlatiniform rash, at another time as a morbilliform

erythema, and at another as an erysipelatoid eruption. In a recent article on the prodromal rashes of small-pox no fewer than seven subdivisions of the condition are recognized. The making of these minute subdivisions is of doubtful value for the purposes of diagnosis. Even in the most simple classification there exists the very important disadvantage associated with the nomenclature which is employed. To one who is unfamiliar with the disease from the want of opportunity of observing it, the use of such terms as "scarlatiniform," "morbilliform," etc., with their definite connotation, must almost inevitably emphasize a likeness which is superficial or confined to one feature of the condition at the expense of distinctions which are often all-important in diagnosis.

The rash occurs most frequently in patches. In the majority of cases it tends to fade rapidly and leaves no trace. It varies in the intensity of its colouring on different parts of the body. Sometimes it seems to migrate. Patches of colour may appear on the chest soon after the onset of the illness and gradually or rapidly fade, while a similar rash makes its appearance on the extremities. These patches are not urticarial in character. The position which this rash occupies as a differential test for small-pox may, perhaps, be most easily indicated if the following features are taken to represent the type:

1. It has no definite unit, but consists of patches which are irregular in contour and vary much in size.
2. It is haphazard in distribution.
3. It is not a raised rash.
4. It does not affect the face.

This negative method of setting out the characters of the rash may serve to indicate that in a considerable proportion of its examples the erythema is in itself of little assistance in diagnosis, but acquires importance only from being associated with a purpuric or vesicular eruption, present at the time of examination or superimposed on the erythema during a short period of observation.

The exceptional examples may be considered in two groups: (a) Cases in which the rash, by assuming more positive features, becomes in itself an indicator of considerable value; (b) cases which are apt to be mistaken on account of a resemblance to other more common conditions.

(a)—(1) A rare form which the erythema may assume is exceptional in its tendency to symmetry in distribution. Soon after the onset of the disease brilliant, almost vermilion, patches may appear over the extensor surfaces of the larger joints, the knee, the shoulder, and the elbow, affecting both sides of the body, but usually in an unequal manner. Along with these symmetrical patches others of equal brilliance may be seen on the trunk. Such patches may show at one side a margin where the transition from erythema to unaffected skin is very abrupt. In some cases symmetrical patches occur along the inner margin of the feet or along the radial side of the forearm on the dorsal surfaces.

(2) The onset of the most virulent toxic attack may be accompanied by the appearance of a rash occurring not in patches, but as a continuous sheet of erythema. Usually the face is also affected. This rash is remarkable not only for uniformity and evenness of distribution, but also for its colour, which is frequently brilliant. It can hardly be mistaken for scarlet fever, since it is entirely wanting in the characteristic punctuation. At its first appearance this universal form of the small-pox erythema is not unlike the blush which may be produced on the hands and arms when they are plunged into hot water.

(b) The cases in this group, unlike those mentioned in the preceding paragraphs, cause considerable difficulty in diagnosis on account of the manner in which they mimic more common conditions.

The following case, recently under observation, illustrates very well the difficulty which may be encountered:

A female, aged 18, was admitted to hospital on March 2nd, 1911, under certificate of scarlet fever. The patches of erythema were very distinctly raised. The rash was almost confluent on the forearms and legs, and very discrete on the back and on the front of the chest. Discrete patches were present on the neck, and these extended upwards over the skin of the jaw, and were present on the cheeks. The face, therefore, was affected, but there was only one patch on the forehead, and the circumoral region was free from eruption. There was a history of sickness and headache on the day before admission. Temperature was 99.8° F.

The patient had been labelled scarlet fever probably on

account of the confluent rash on the arms and legs, but there was no evidence anywhere of the characteristic punctate rash. The eruption at first sight had a considerable resemblance to measles, and with a rash so well developed the absence of Koplik's lesions could not be regarded as conclusive negative evidence. There was a slight suffusion of the eyes.

The anomalous character of the rash, which was certainly not the rash of scarlet fever and did not satisfy all the conditions required for measles, led to a closer examination of the condition. In the isolated spot on the forehead there was a small papule; another was found on the cheek near the left side of the nose. Others were found on the arms and back, and one on the right palm. The total number of lesions was under twenty. They were all insignificant, and search had to be made for them. The patient was isolated, and on the following morning the diagnosis was no longer in doubt.

2. *Purpura*.—The poison of small-pox, in common with that of the majority of infections, has the power in some cases of producing extravasation of blood. The condition is dealt with here only as it affects the skin and the more exposed mucous membranes—for example, the mucous membrane of the mouth and the conjunctiva. The severity of the purpuric sign in toxæmia varies within wide limits. There is, for example, the staining, more or less persistent, left not infrequently when an erythema fades. Such staining occurs in some cases of scarlet fever and in many cases of measles. The same condition is seen after some examples of the small-pox erythema. Again, there is the more severe form of purpura, the small, bright red petechiae of the size of a pin's head or smaller, which are also not uncommon as accompaniments of the rash in scarlet fever, in measles, and in some cases of food poisoning. The favourite sites of these petechial lesions are in and about the flexures—for example, in the groin, in the bend of the elbow, and about the armpit. The same condition occurs in some cases of small-pox. Again, the exaggerated tendency to bruising, or to accentuation of the result of slight injuries, seen in diphtheria and in enteric fever, and the still more severe form of purpura in which the lesions are of deep purple colour, of considerable size, and contain an appreciable quantity of blood—the type of lesion to be seen in severe septicaemia and in diseases which, for want of accurate differentiation, are classed as purpuras of different varieties, can all be paralleled in some cases of small-pox; that is to say, the purpuric lesions of small-pox do not differ either in their type or in their arrangement from those found in the other diseases of its class. But this sign of toxæmia is of considerable value in the recognition of the disease; its importance depends altogether on the frequency of its occurrence and on the severity of its manifestations. Small-pox, above all other diseases of its class as we see them in this country, is a purpuric disease. To obtain an estimate of the frequency of the purpuric sign in small-pox, an examination was made (by kind permission of Dr. T. F. Ricketts, Medical Superintendent) of the records of 1,232 consecutive cases of the disease completed in the Metropolitan Asylums Board Hospital during 1901, and it was found that purpuric skin lesions were noted at some time during the attack in 271, or in 22 per cent. A considerable number of these cases first came under observation in the late stages of the attack, at a time when the sign, if it had been present, must have faded completely. Therefore, in regard to this series of cases, 22 per cent. cannot be considered as an overestimate of the frequency of the condition.

Of the severity of the condition in small-pox, the petechial lesions of the flexures afford a good illustration. As they occur in small-pox, they are usually very densely set, and they tend in a marked way to pass beyond the exact line of the flexures. Frequently they extend from the groin upwards over the abdomen and flanks, and from the axilla downwards over its inner and outer walls. A band of scattered petechiae may extend across the abdomen below the umbilicus or across the small of the back.

The value of the purpuric sign in the differentiation of small-pox may, therefore, be stated as follows: Given an onset of a febrile disorder pointing to the presence of an acute infection and associated with purpura, small-pox should be considered as occupying the first position as a possible cause, and one may go further and say that the probability of the presence of small-pox increases according to the severity of the purpuric lesions as regards both their number and their type. Assuming that this is the position, it seems hardly necessary to separate the so-called

petechial initial or prodromal rash from the other more severe purpuric lesions of the disease, or still further to accentuate the difficulties of diagnosis by describing a so-called haemorrhagic variety of small-pox as if it were to be classed by itself, the descriptive method so constantly adopted by writers on this disease. One can hardly avoid forming the opinion that some at least of the missed cases of small-pox, and most certainly those rare and virulent examples (by *virulent* meaning of high infective power as well as deadly to the individual) which have the purpuric sign as their outstanding feature, would not escape if these facts were fully recognized. Several missed cases belonging to this type which had been labelled "blood poisoning" came under notice during the epidemic of 1901-2. Each acted as a centre from which infection spread, and from one of them more than twenty patients contracted the disease by direct contact.

3. *The Vesicle or Pock*.—The influence of the high infective power which seems to be possessed by cases of the type just referred to is limited by the rarity of the type, by the complete prostration of the patient, and by the termination, which is almost invariably rapidly fatal. The majority of the population possesses some degree of immunity. Most are susceptible to attack by the disease, but not to death. The febrile disturbance, the pain, and the other more or less severe toxæmic effects of the invasion frequently subside with the appearance of the pocks, and the severity of the later stages of the attack, in the uncomplicated case, depends entirely on the number of the pocks and on the manner of their evolution. Therefore, in many of the cases occurring in a partially protected population, the illness is over with the appearance of the peculiar rash, the patient is able to resume his usual life, and may become an active agent in the spread of infection. The presence of a few "spots" or "pimples" may not cause remark. From one-third to one-half of all cases, a proportion which depends on the prevailing epidemic type, belong to this class. Therefore, there is a very considerable number of cases in which diagnosis must be based on the characteristics of the peculiar rash of small-pox, and on these alone.

In discussing these characteristics one may view the rash from two different standpoints. One may lay stress on the features of the individual lesion, the unit of the rash, or one may consider the whole rash, the multiple rather than the unit, attaching the greater importance to the collective features of the lesions, namely, the very important tendency they have to group themselves on some areas of the skin surface more than on others, and the less important relationship which is gradually established between one group and another as the lesions pass on through the successive stages of their evolution.

The collective features of the lesions have the greater value in diagnosis. The unit of the rash is a gross inflammatory focus, which passes through several stages in the course of its life-history. Appearing first as a macule which very rapidly becomes a papule, the typical lesion advances steadily through vesicular and pustular stages to the formation of a crust, which on separating leaves a scar. *This quality of continuous change inherent in the lesion is of considerable assistance in diagnosis.* It is very useful in many difficult discrete eruptions which may be under observation on suspicion of small-pox. But the lesions are subject to accidental disturbances—for example, to injury by the patient himself, a factor which may have considerable influence on the very discrete rash. Their evolution is influenced by a lowering of the general physical condition of the patient—for example, by old age or previous ill health, and it is affected also by the presence in the patient of a degree of immunity against the disease.

On the other hand, the more important of the collective features of the lesions depend much less closely on the personal factor in observation. They begin to appear with the beginnings of the eruption. They become fully established when efflorescence is completed, and they must remain as unchanging evidence as long as the rash lasts.

I.—THE FEATURES OF THE LESION OR UNIT.

It has been pointed out that the pathology of the lesion is essentially the life-history of a vesicle. In this life-history there are two stages: (a) *A stage of progression or formation leading up to full vesicular development, and*

passing almost imperceptibly into the second stage: (b) *the stage of retrogression*, which begins with the onset of purulent change in the contents of the vesicle, and terminates with the separation of the crust. The peculiar features of this inflammatory process are found:

- (1) In its deep-seated origin;
- (2) In its intense and localized character; and
- (3) In the acuteness of its course.

In the typical lesion clinical evidence of these features begins to appear as soon as the papular element is recognizable. It attains its greatest prominence when vesicle formation becomes apparent. It gradually declines as pustulation advances, until in the end it has almost completely disappeared.

(a) *The Stage of Progression or Formation.*

The early macule has no characteristic features, but this stage of the lesion is so transient that usually in practice one can recognize a distinctly papular condition in the lesion which appears on inspection to be a simple macule. It will usually be noted that the papule does not involve the whole macule of which the outer part is the areola. The pain which is frequently associated with the beginning of this process is of considerable importance in diagnosis. It is described by the patient as a pricking sensation, and it may be produced or increased by pressure on the area in which the lesion is growing. It is to be ascribed to the intrusion of the process on the true skin, and being associated with the presence of a papule it indicates a deep-seated, localized, and intense inflammation. This pain is accentuated on parts where the lesion is bound down by the thickness and density of the outer strata of the epidermis. Therefore, in some cases, it is of value in locating lesions which may be present but scarcely visible on the palms and soles. At the same time further evidence of the depth of the lesion and of its localized character may be obtained in passing the finger over it, at first lightly and then more heavily. With light pressure the lesion may be scarcely appreciable, or it is felt as a slight elevation with gradual slope and a considerable area. With firmer pressure it seems to assume a smaller size and to acquire a sharper outline. This evidence also is more easily appreciated where the epidermis is thick and dense, or where the lesion can be pressed against the bone. As growth goes on the greater prominence which the lesion acquires on parts where the skin is of finer texture becomes more and more accentuated. The major part of the growth of the papule is the result of serous exudation. As this exudation goes on the tension of the lesion increases, and by a systematic examination of the rash at this early stage some lesions may be found in which this condition of tension can be demonstrated by means of a small lens. Under the lens the erythematous area in which the lesion is situated may be seen to resolve itself into three zones. The margin of the tiny lesion is marked by a narrow ring of a tint distinctly paler than the area within it, or the much more extensive and irregular area outside it which forms the areola. As the central area increases in diameter it loses its colour, and at last, when the vesicle is quite apparent to the eye, the anaemic marginal ring becomes merged in the translucent pellicle of the lesion. At this stage, as before, the degree of prominence of the typical lesion depends on the character of the outer strata of the epidermis. Where the skin is of finer texture the vesicle stands well out from the surface. It can be grasped, but it cannot be ruptured by pressure, and attempts to rupture it cause considerable pain. The sensation of unyielding solidity imparted by a lesion which appears to be a translucent vesicle is a feature of very considerable importance in differentiation. Where the outer strata are dense the lesion scarcely rises above its surroundings. The vesicle situated, for example, on the palm cannot be grasped, and is much less refractile than the lesion on other parts. It appears as a small, dark, almost black area, in striking contrast to its well-defined marginal ring.

(b) *The Stage of Retrogression.*

The formative stage of the vesicle merges almost imperceptibly in the retrogressive stage. With continuous increase of the lesion, both in size and in prominence, its contents gradually become opalescent, opaque white, and

yellow when pustulation is completed. Swelling of the surrounding skin and induration of the margin of the lesion accompany this change; therefore the lesion becomes less definitely localized. As it fills out with pus, the outer layers of the epidermis are stretched and thinned and the remaining intercellular connexions are broken down; therefore the sensation of unyielding solidity imparted by the vesicle is lost. The lesion becomes superficial and can be easily ruptured. Its tendency is to rupture, collapse, or dry up and form a crust. Small-pox crusts may be yellow or dark brown; they may be circular or of irregular outline; they may be flat or dome-shaped. In some lesions the margin of the dome-shaped crust is overlapped by the surrounding skin, giving it the appearance of a "jewel in its setting" (Kaposi). None of these features is peculiar to the small-pox crust. The differentiation of the fully-developed pustule and of the crust depends entirely on such evidence as can be obtained that the origin of the process was deep-seated. Where the outer strata of the epidermis are dense, as on palms and soles, the pustule frequently fails to break through. Its contents are partially absorbed, and the remainder, with the thick pellicle, forms the deep-seated crust or "seed" so well known as the last remains of the small-pox rash.

Therefore the latter stages of the lesion are clinically retrogressive. The peculiar features of the process gradually become concealed, and, in the end, the differentiation of the lesion depends almost entirely on its locality.

The conditions which interfere with this process of evolution are important, but they are not in every respect a hindrance to diagnosis.

1. *Accidental injury to the lesion*—for example, by the patient himself—may entirely destroy its characteristic features. The importance which such injuries may assume in a very discrete rash has already been referred to.

2. *The presence in the patient of a degree of protection against the disease.* The clinical effect of partial immunity is twofold. The severity of the rash is lessened

- (1) By decrease in the number of its lesions, and
- (2) By decrease in the severity of the local inflammatory process.

In regard to diagnosis the latter factor is the more important. It is associated with a shortening of the period of evolution. As a result there is a general decrease in the size of the lesions and also an accentuation of the variation in size which is present even in the unmodified rash. Vesiculation does not involve the whole lesion. The vesicle, pustule, and crust are small and may appear as if set on the top of the papule. From want of evidence throughout the process, its true nature as a deep-seated vesical formation may not be recognized. On the other hand, in most cases some lesions are to be found which conform more closely to type, and in every case the lesions situated in the thickened epidermis of the hands and feet appear to be less profoundly modified than those on other parts of the body. In addition, in many puzzling discrete eruptions, observation for a short period by demonstrating the rapidity with which the lesions hasten through their evolution will satisfactorily differentiate the small-pox rash from many other conditions—for example, from the papular rash sometimes resulting from mosquito bites, from severe acne, from a pustular syphilide, from impetigo, and from some drug rashes.

3. *The lowering of the general physical condition of the patient, for example, by old age or previous ill health.* From the point of view of diagnosis this condition is the most important. Under its influence the lesion develops badly. The period of eruption tends to be prolonged. The early lesion is less definitely localized, and the vesicle, as it grows, tends to become irregular in outline, flat and flaccid, to increase in area, but not much in prominence. Except for its area, there may be nothing which can distinguish it from severe types of the lesion of chicken-pox. One feature of such a lesion, and not the least important, is its tendency to linger in its evolution, a tendency which in some cases lessens the value of the assistance expected from a short period of observation. The mild, very discrete rash, found with considerable frequency in the old and infirm, may be overlooked when it is, as it may be, entirely composed of this type of lesion. An interesting series of such cases occurred during the

1901-2 epidemic in one of the large metropolitan infirmaries. This type of lesion occurs also in the severe rash of the badly-nourished infant, and in the rash of the adult worn out by disease, by hard living, or by the severity of the invasion period of his attack; but in these cases the nature of the condition is less likely to be missed since it is so frequently associated with very obvious signs of toxæmia.

II.—THE COLLECTIVE FEATURES OF THE LESIONS.

1. *The Tendency the Lesions have to Group Themselves on some Areas of the Skin more than on others.*—It has long been recognized that the lesions of the vesicular rash of small-pox tend to cluster about an area subjected to pressure, or where a local irritant has been applied. The classical illustration of the induction of such an artificial and local increase in the density of the lesions is the effect produced by the mustard plaster, applied, it may be, for the pain of the invasion period.

Other illustrations may be given, such as the increased incidence of the rash on the buttocks and upper parts of the thighs in the neglected baby, the marking out by the lesions of the line of pressure of a garter, or the line of a scratch, their tendency to cluster round sores caused by vermin, round recent vaccination lesions, round the nipple of the nursing mother, especially if a fissure is present, and so on.

It has also long been recognized that in the great majority of small-pox eruptions the evident natural tendency of the lesions is to prefer the skin of the face and extremities to that of the trunk; that on the trunk they favour the back more than the front, and the front of the chest more than the abdomen; and also that they tend to avoid the lower parts of the abdominal wall, and especially the flexures of the groins, the site of election of the petechial lesions. These natural distinctions in distribution strike the eye at once in many severe discrete or semiconfluent eruptions. They are seen to the greatest perfection in this type of rash occurring in the unvaccinated child.

Dr. T. F. Ricketts has shown that a common factor is concerned in the production of all these variations in the density of the lesions, not only of the artificial variations induced by the mustard plaster, the garter, etc., but also of the seemingly natural variation in grouping so easily recognized in many of the more severe small-pox eruptions. This common factor is exposure to irritation. He shows that its influence is at work in controlling the disposition of the rash over every part of the skin surface. He has demonstrated not only that the presence of this factor determines a greater incidence of the rash on the part of the skin surface so exposed, relative to other parts, but also that its absence—that is, freedom from irritation or protection against irritation—determines a slighter incidence of the rash on the part so protected relative to other parts. The latter effect can be shown by direct experiment.

The term "irritation" as applied to this factor must be interpreted in a wide manner. As Ricketts says: "The operative causes are manifold, but the most potent factors are exposure to air and friction with clothing, and to their efficacy every case of small-pox is a testimonial."

The working of this general law is easily seen in the seemingly natural variations in the incidence of the lesions, which have been so long recognized. The face, so constantly exposed to the weather, never escapes from eruption, and almost without exception suffers more severely than other parts. The hands also, from continuous exposure and constant use, almost never escape. The feet, exposed to friction in walking and having a range of movement a little less free than the hands, are almost always invaded, but a little less constantly, and on an average less severely than the hands. The back, being liable to considerable friction from the clothing, shows a denser crop of lesions than the front of the trunk, where the friction is less, and the flexure of the groin and the walls of the armpit, the parts of the skin surface where protection from exposure and friction is most complete, are very frequently avoided by the vesicular rash. It is to be noted that the same principles apply in considering the details of the distribution of the lesions. For example, the more prominent parts of any region—for instance, of the face—are prone, other things being equal, to be more

severely affected than the less prominent parts or the hollows.

The application of the test of the small-pox distribution to a suspected rash therefore implies a search to discover the working of this law, and it is essential to its value as a differential test to assume that the theoretical conditions which determine the site of the lesion are not influenced by any degree of immunity against the disease. Let me illustrate shortly, from the experience of the 1901-2 epidemic, some of the difficulties which seem to arise in the differentiation of small-pox, and how they are overcome by the application of this test.

(a) Severe Eruptions.

I have pointed out that the severe discrete or semiconfluent small-pox eruption in which the gross inequalities in the distribution of the rash are very apparent is not usually missed. But a mistake in the other direction—the certification of severe non-small-pox eruptions composed of units more or less closely simulating the small-pox lesion—is not infrequent. Difficulty in these cases seems to arise on account of the severity which the eruption may assume on the face, on the trunk, and even on the upper parts of the extremities, and the error is due to want of appreciation of the fact that the forearms and hands and the legs and feet, if not entirely devoid of rash, as often happens, are at least comparatively free from the eruption. The great majority of the cases of chicken-pox and of the syphilitic eruptions certified as small-pox belong to this group.

In a similar way the great majority of the severe measles eruptions and other erythemata, which are not infrequently mistaken for small-pox on account of the papular condition of the rash, may be excluded. Almost without exception, these rashes are almost confluent on the face, trunk, and upper parts of the extremities, and thin out on the forearms and hands and on the legs and feet.

(b) Mild Discrete Eruptions.

In the great majority of mild discrete small-pox eruptions the working of the general law is not less evident than in the severe discrete and semiconfluent attacks. If any distinction can be made, the advantage seems to lie usually on the side of the more discrete eruption. The gross inequalities in density seem to become more emphasized the more discrete the rash. The only reason for considering mild discrete eruptions under a separate heading is that in a minority of small-pox cases of this type the complementary factor of freedom from irritation or protection against irritation acquires considerable importance in its effect on the distribution. The distinction between freedom from irritation and protection against irritation is rather one of degree than of actual difference, but it is convenient for purposes of illustration. The former is the result of the patient's occupation and station in life. For example, the costermonger's feet may be found to be more severely affected than his hands, and the hands of the manual labourer will attract the lesions to a greater degree than the hands of the costermonger, and to a still greater degree than the hands of the shopwalker. But if each is living his usual life previous to the attack of small-pox, the face will carry its usual proportion of eruption, and the general disturbance in the gross inequalities of the distribution will rarely cause much difficulty. On the other hand, if the patient previous to his attack has been living a life in which he is protected from irritation, this general disturbance may be considerable. This happens most conspicuously in the chronic invalid, especially if he has been bedridden for some time. It is a frequent feature of the rash of the old and infirm, and in these cases it may be sufficiently powerful to mask the typical gross inequalities in the density of the lesions. A very scanty eruption is the rule in cases of this type. But the face very rarely escapes, although the hands and the feet are occasionally free from eruption. The most remarkable series of cases admitted during the 1901-2 epidemic belonged to this class. They were female inmates of a large infirmary, and several had for years been living the infirm life. In the majority lesions were present on the hands and feet as well as on the face. But in a few the total number of lesions was less than twenty;

the feet and hands were almost or quite free, and the trunk carried the majority of the lesions. In some of the latter cases it was easily noted that the lesions on the trunk were grouped at the waist, following the line of pressure of the band of the dress.

2. One or two points of minor importance may be noted among the collective features of the lesions.

Eruption begins at the end of the second or on the third day of the illness. It is probable that the same condition which determines the relative density of the rash when efflorescence is completed also determines the part of the skin surface on which the lesions will first appear. In the majority of cases this part will naturally be the face, followed by the distal parts of the forearms and the hands. But definite local irritation may be sufficient to interfere with this usual sequence. For example, a washerwoman admitted as a contact developed a rash which had its densest setting on the arms and hands, and it was on these parts that the first lesions were seen.

In practice an opportunity of observing the beginnings of the eruption is not frequent. The eruptive period is not usually prolonged, and within a few hours of the appearance of the first lesions others will be found on every region of the skin. No assistance in diagnosis can be expected from attempts to discover a sequence in the invasion of the various regions if the eruption is well advanced or completed. But the appearance of lesions on the extremities as well as on the face, and particularly the invasion of the hands or feet, very soon after the beginning of the eruption, is an observation of the highest importance in the differentiation of small-pox.

As evolution progresses the lesions which were the first to appear will naturally maintain their priority. In the severe, unmodified eruption the natural sequence in the invasion of regions is continued throughout the evolution. At any time it will be seen that the lesions on the face are most advanced. Those on the trunk and upper parts of the extremities are usually next in order, followed by the lesions on the forearms and hands, and then by those on the legs and feet. But this sequence can at best only apply to the majority of the lesions on any region. It is easily observed in the severe, unmodified eruption, on account of the enormous mass of the lesions and of the regularity and completeness of the stages of their evolution. In the discrete and modified rash efflorescence is more rapidly completed, and priority of one region over another in invasion or during evolution may not be evident. That is to say, in the cases in which difficulty in diagnosis is apt to arise, this feature of the typical eruption may not be available for differentiation.

Reference has already been made to the way in which the persistence of the lesion is influenced by the texture of the epidermis at its site. The importance of this condition in the examination of "contacts" and "suspects" is obvious.

3. In conclusion, a few examples may be given from cases sent to the receiving station during the epidemic, to illustrate the importance of the assistance afforded in the differentiation of the disease by the presence of more than one of the three types of skin eruption at the time of examination, or as a result of subsequent development during a short period of observation.

1. A girl, 11 years old, vaccinated in infancy, whose father, brother, and sister were in hospital with small-pox, developed a patchy erythema on the day before her admission. On admission, her temperature was 98.6° and pulse 96. An erythematous rash, consisting of patches of varying size, of irregular shape, and scarcely raised above the surrounding unaffected skin, was present on the trunk and extremities. The colour of the patches varied considerably. It was a bright scarlet on the buttocks, thighs, legs, and upper arms, and a dull pink on trunk and forearms. Next day most of it had faded, leaving no trace, but a few fresh patches had appeared on the upper part of the back. On the same day one small papule, which rapidly crusted, was noted on the right forearm.

2. A man admitted with a history of three days' illness had an erythematous rash consisting of a few large and brilliant patches of irregular shape and varying size, but with well-defined margin, situated on the trunk and on both knees. Within one of the areas on the trunk there was a dark, almost black, papular lesion surrounded by a purpuric areola.

3. A hotel waiter had the history of a very sudden and severe onset in the early morning of the day of his admission. On admission, in the forenoon, a brilliant erythematous rash covered the whole body. It was evenly spread over every part, and everywhere it faded completely on pressure. Towards evening it was noted that the rash was losing in brightness; it

became dusky. In the groins and on the adjacent abdominal wall it no longer faded completely, but definite small red petechiae remained when pressure was applied. Next morning these lesions had greatly increased in number and larger, deep purple purpuric lesions were scattered over the trunk and face.

4. Another man was admitted with an erythema of very similar characters to the last case. During three days' observation the rash gradually faded, leaving no staining. No purpuric lesions and no vesicular rash developed.

5. A man admitted on the second day of his illness had a rash, which on first sight appeared to be a brilliant erythema. It affected the groins, the adjacent abdominal wall, the walls of the armpits, and, to a less extent, the flanks. It was almost vermilion in colour. On close examination it was seen to be made up of small, very closely set petechiae. Next morning the rash had passed further on to the abdominal wall and over the walls of the axillae. The flanks were also more thickly covered, and petechiae were present on the back and on the forearms. On the following morning—fourth day of illness—a dense crop of papules was present on the face, the small petechial rash had faded to a red-brown colour, and larger deep purple purpuric lesions were scattered over the area in the groins, abdomen, and flanks, which the petechial rash had occupied. The patient was sent to the hospital. He died on the tenth day of his illness.

In cases of this virulent type, which have as their outstanding feature the early and rapid development of a severe purpura, the patient may die before the vesicular rash has had time to appear. More frequently life is prolonged sufficiently to allow this rash to pass through the earlier stages of its evolution. In the latter cases the further development of the clinical picture depends on the severity of the toxæmic manifestation.

Purpuric lesions in increasing severity may continue to be the predominant feature of the case, while here and there on the trunk and extremities there may be found a few vesicular lesions of the flat, badly-developing type, which has been referred to in a previous paragraph. Frequently hæmorrhage occurs below, around, or into these isolated vesicles. In such cases it seems as if the widespread and excessive purpura replaced the greater part of the vesicular rash. In other cases the purpuric manifestation may partially subside, while the skin of the face, of the hands, and forearms, and, to a less extent, of the legs and feet, becomes swollen. On the forehead it is felt to be thickened and less freely movable than is normal. This change is due to the rise of a very densely-set vesicular rash, in which the units are "so closely crowded the one against the other" (Kaposi), that individual lesions cannot be distinguished on the face and can hardly be separated on the hands and arms. In these cases the skin of palms and soles is tense and may be very tender. As its evolution advances, the vesicular rash gradually assumes a more and more conspicuous position, and, if life is further prolonged, confluent vesiculation occurs, resulting in the formation on face, trunk, and extremities of large flat blebs, which may be torn during the patient's restless delirium. In the end there may be seen all over the body large areas of raw surface exuding blood-stained serum, interspersed with patches of unbroken opaque white pellicle and large and small purpuric lesions.

6. A man who had been admitted to a fever hospital on certificate of scarlet fever was sent to the receiving station for observation. He had a petechial rash in the groins and on the adjacent parts of the abdominal wall. Petechiae were present on the flanks and on the walls of the armpits. The majority of the lesions were bright red points, but scattered over the area there were a few of larger size and deep purple colour. During three days' observation there was no development towards small-pox. A case with very similar features occurred later in the epidemic, and the history of both suggested that the condition was due to food poisoning.

~ The persistence of the staining left by a petechial rash in the groins and armpits is at times of considerable assistance in difficult discrete pustular or crusted eruptions.

7. In a girl, 5 years of age, a contact, there were present on admission several large circular purpuric lesions situated on the trunk and thighs. In colour they were deep purple or almost black and varied from one-fourth to one-eighth of an inch in diameter. The vesicular rash began to appear in the evening of the day of admission.

8. A homeless and destitute man had, on admission, a discrete vesicular rash. The lesions generally varied much in size and were of the badly-developing type. This condition was noticed particularly on the legs, where each vesicle was surrounded by a narrow bright red purpuric ring. No other purpuric lesions were present.

This accidental purpuric condition is seen in the vagrant class, in the debilitated, and in those who have not been confined to bed during the earlier stages of the disease. If limited to the legs and feet it is not necessarily of serious significance. In similar circumstances it occurs occasionally on the lower extremities in varicella.

I am indebted to Dr. W. McConnel Wanklyn for much kind assistance and for permission to quote several of the cases referred to throughout the paper.