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SMALLPOX IN TRIPOLITANIA, 1946: AN EPIDEMIOLOGICAL AND CLINICAL STUDY OF 500 CASES, INCLUDING TRIALS OF PENICILLIN TREATMENT

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(With Plates 12 and 13, and 9 Figures in the Text)

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I. INTRODUCTION

Although Burnet (1946) defines epidemiology as 'the natural history of the inter-action between bacterial protein and the host', in the field the host is only part of the problem. The guiding principles in the control of an epidemic may be clear and based on scientific fact, but to gain control environmental, economic, religious and political factors must be taken into account. What may appear to be trivial detail has been included in the following account as it is from this material that effective field control has to be evolved.

There is much confusion as to the use of the word vaccination. In this paper vaccination has the literal meaning of 'to inoculate with the virus of cowpox as a protection against smallpox' (*Shorter Oxford Dictionary*, 2nd ed., 1936). Vaccination may not necessarily produce immunity, and in the absence of vesiculation the operation is termed 'unsuccessful'. When infection with the vaccinia virus takes place the term 'vaccinated successfully' is used.

II. GENERAL BACKGROUND

Tripolitania is a large country situated at the centre of the North African coastline, and has a population of about 800,000 of whom all but 40,000 are Arabs.

Smallpox was probably common more than 20–30 years ago, as about 14 % of persons over 30 years of age gave a history of having had the disease. This statement was borne out by the low incidence of successful vaccination among the older inhabitants.

Although the disease has been common for some years in the contiguous territory of Tunisia, Tripolitania was apparently free from smallpox during the more recent years of the Italian occupation, except for an outbreak which occurred in the desert hinterland 7 years prior to this epidemic.

The level and duration of immunity resulting

from vaccination or from a previous attack of smallpox is known to vary in different races, and it should be noted that the population in Tripolitania is predominantly dark-skinned, a mixture of Arab, Berber and Central African.

The two epidemics of smallpox, in Sirte and Tripoli, to be described occurred in the dry summer months and this fact may have accounted for the low incidence of respiratory complications. The general absence of malaria, dengue and sand-fly fever, and diseases of temperate climates such as colds and influenza made the pre-eruptive pyrexial stage of smallpox easily recognizable even by the patients.

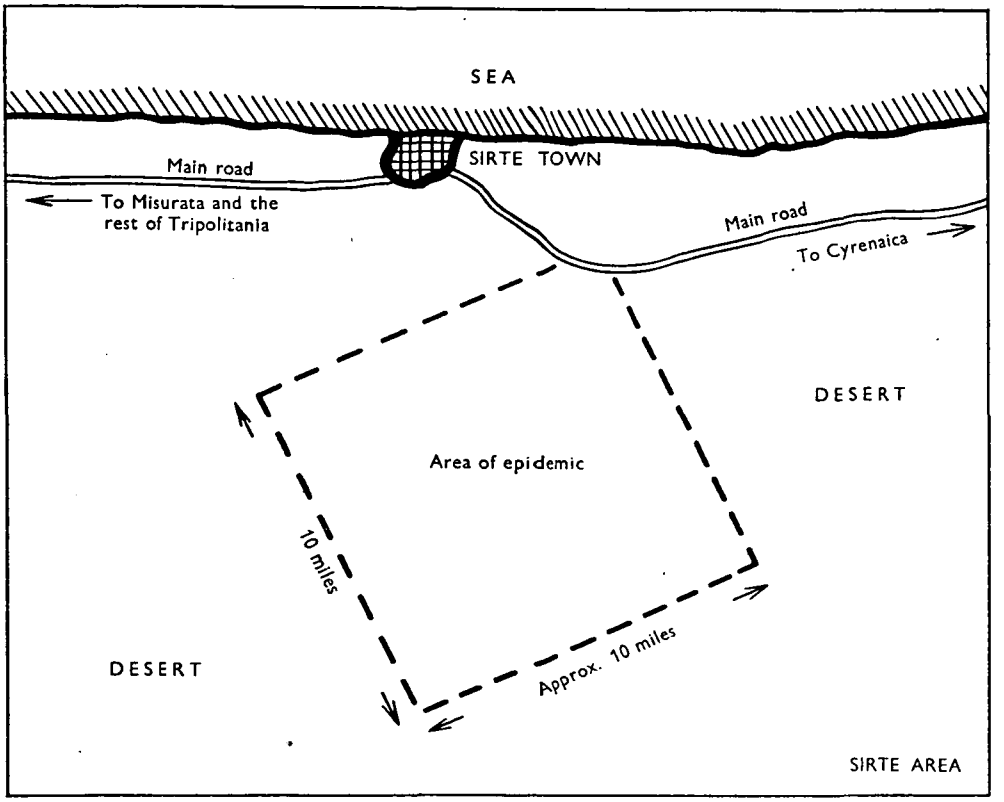

Fig. 1.

III. THE SIRTE EPIDEMIC

The Sirte outbreak was a circumscribed epidemic amongst Bedouin Arabs living in a desert area of approximately 100 square miles. As is common with this type of population the epidemic only came to light when seventeen cases were discovered simultaneously on 26 May, most of them at least 14 days old.

The inhabitants were nomads engaged in grazing sheep and goats and in view of their relative isolation (Text-fig. 1), it was decided to allow the cases to remain in their tents and to leave treatment largely to nature. Vaccination of contacts was commenced immediately, but no attempt was made to isolate the population as the area was too extensive. The inhabitants of the town of Sirte were vaccinated at the same time. For political reasons more stringent measures were inadvisable and the relatively small movement of the older men was not considered too great a risk.

In the first weeks of the campaign the vaccine lymph was not kept cool enough as no refrigerators were available. It was also too old, consisting of the accumulated monthly supplies sent down from Tripoli for the vaccination of passengers from Cyrenaica. The use of this lymph on the contacts of the first cases, with a take rate of only 10%, certainly accounted for the secondary outbreaks between 14 and 22 June.

Tracing contacts was difficult owing to the desert terrain and the fact that the total population of 12,000 was scattered in groups of from three to ten tents, 0·5–5 miles apart.

After much effort lymph, transport and personnel were obtained and intensive vaccination and revaccination were done at intervals of approximately 5 days, some persons being vaccinated

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as many as six times before showing a successful result. Only when fresh lymph was used and a high take rate obtained was it possible to convince the Italian doctor that his old Italian lymph was of no value. Subsequent events show that the attitude of some British medical officers was little better.

'*Expanding ring*' *vaccination.* The vaccination campaign was organized on the supposition that smallpox behaves like other droplet infections and that the maximum incidence would be expected in the family, the chance of infection decreasing as distance from the family centre increased. In each case the family was vaccinated first, then the inhabitants of the surrounding tents together with close contacts such as relatives, next the village or group of tents and so on, the area covered increasing for 5 days, after which revaccination started again at the centre concurrently with a search for cases. The writer calls this method 'Expanding ring' vaccination.

This method was probably the most economical way of covering the area, using as a team an Arab driver and an Arab infirmere (male nurse). In this particular area no trouble was experienced with male nurses vaccinating the Moslem women. However, when three cases occurrred in the town of Sirte itself it was found that the vaccination state of the women was not, for this reason, as high as the Italian doctor had suggested. These cases were isolated in a building in the centre of Sirte, and no further cases occurred there.

All cases in the desert were treated by their relatives in their own tents. No current or terminal disinfection was possible, although the people were advised to expose their tents and belongings to the sun. Being graziers they had in their tents quantities of wool destined for market in Mizerata (Tripolitania), or in Cyrenaica. An order was, therefore, made that all wool for market would be disinfected by steam in Sirte before dispatch. An R.A.M.C. sanitary inspector trained a local Arab inspector to do this work, but it is unlikely that all the wool exported from the area was disinfected. A complete ban on export was impossible for political reasons. However, no cases of smallpox occurred in the contiguous territory from this focus of infection, and the risk of spread of infection from this type of contaminated material is probably less than is usually supposed.

The main coast road between Tripolitania and Cyrenaica continued to be used extensively by military and civilian motor traffic. All staging within 10 miles of Sirte was prohibited and no one was allowed to proceed by road from Sirte without a certificate of successful vaccination or attempted vaccination done more than 14 days previously and within 2 years. Control of tracking by foot or camel across the desert was impracticable. It would, however, have taken over 14 days to reach a settlement or town of any size.

Between 12 May and 24 July, approximately 11 weeks, 68 cases occurred with 12 deaths. Using the 'expanding ring' technique this epidemic covering an area of 100 square miles was completely controlled and no infection spread to other areas, although cases were not isolated and premises were not disinfected.

No cases occurred in persons successfully vaccinated prior to contact. Several people who had suffered from smallpox 40 or 50 years previously gave a good vesicular response to vaccination. Statistics are not available. The total number of vaccinations is estimated at 20,000, but, as most vaccinations were done by Arabs and as it is known that many persons were scarified more than once, it is safe to assume that, while a highly immune population was built up close around the primary and secondary cases, further afield the immune state was progressively less: exactly the state of affairs which should, and did, control an epidemic of this type.

IV. THE TRIPOLI CITY EPIDEMIC

The genesis of the Tripoli City outbreak is given in some detail in Text-fig. 2 to illustrate some of the clinical and administrative problems.

Cases 1 and 2 were a mother and child. Infection was brought from Tunisia by the husband of case 1 who was ostensibly a fisherman, but actually a smuggler. Having, after much perseverence, gained this information from the wife it was not possible to examine the husband to see if he had had an abortive attack, but this seemed the most probable method of infection as the wife and child developed the disease simultaneously.

The woman had a well-marked pre-eruptive fever with meningitic symptoms and was lumbar punctured by the Italian doctor who first saw her. She and the infant were admitted to the infectious diseases block of the Colonial Hospital. The mother had a macular rash which, when seen on the next day, 19 May, showed all the typical signs of an early unmodified papular smallpox eruption. The state of the infant was similar.

The two patients came from the crowded centre of Tripoli and it was decided, as accommodation was available, to isolate home contacts as well as cases at the hospital set up at Busetta, because surveillance of Arab civilians was likely to be difficult and to favour spread by missed cases. The course of events confirmed the value of this policy. The first contacts were admitted to Busetta late on 20 May, the third day of the eruption of patient 1. It was found that they had not been vaccinated. This was contrary to the instructions given when the first case was dis-

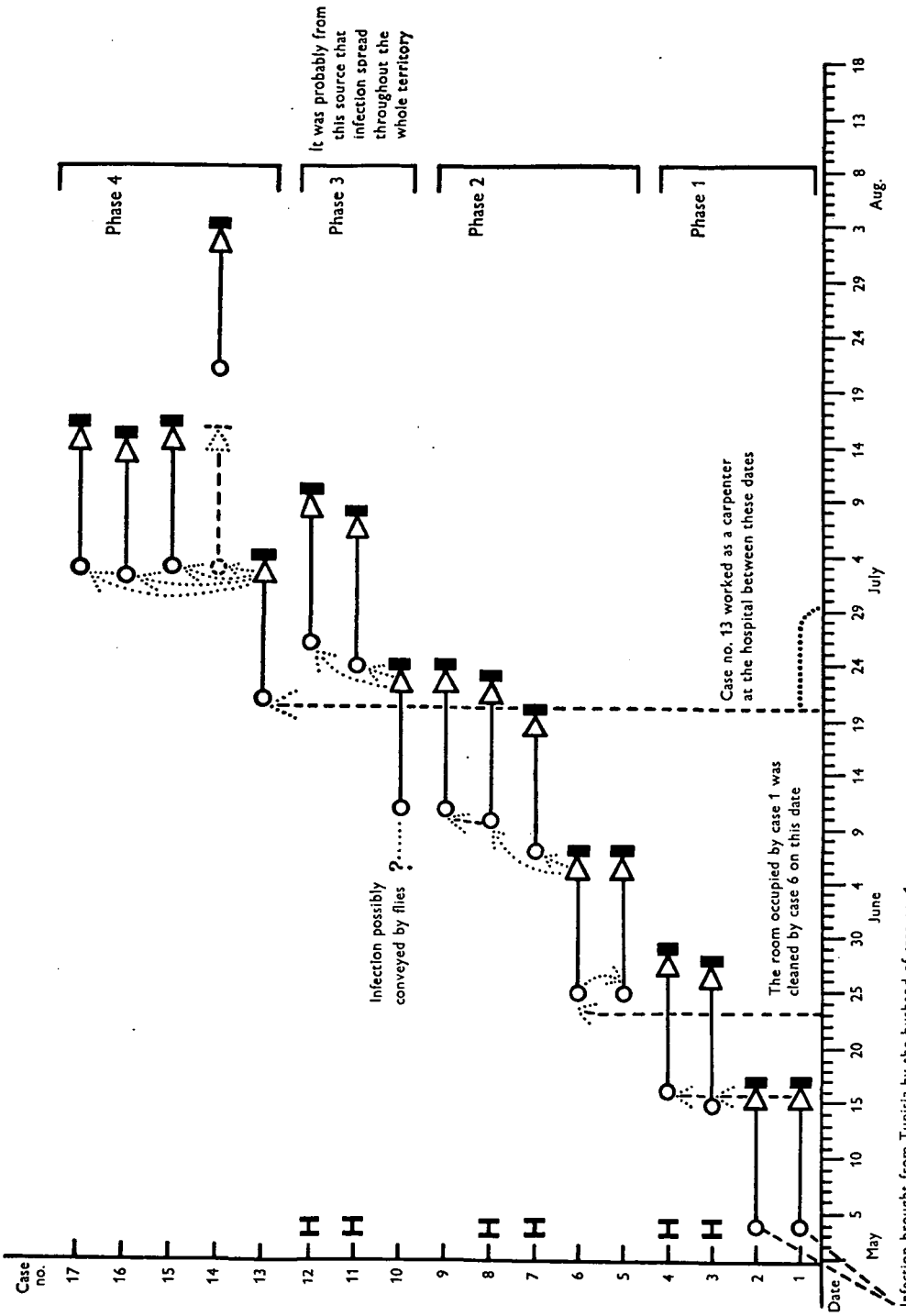

Fig. 2. Diagram showing the genesis of the Tripoli epidemic; with the four 'family' outbreaks. In three the infection was controlled; the fourth, phase 3, was probably the source of the infection that ultimately became widespread. ▮, day of appearance of rash shown; △, duration of pre-eruptive fever; ○, date when infection might have occurred assuming an incubation period of 12 days; H, cases who developed the disease whilst under observation in hospital.

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covered and vaccination was, therefore, attempted on 21 May, a significant delay.

Of the six contacts who were vaccinated only two gave a successful take, an infant aged 6 months and a girl aged 18 years, although there was no evidence that any of the remainder had ever been vaccinated previously. One contact who gave a negative response was acting as wet-nurse to case 2; she did not develop smallpox although in long contact with the disease. The two contacts with successful vaccinations developed fever, headache and malaise on 25 and 26 May respectively. Three days later in each case a macular rash appeared and became papular and vesicular in the typical smallpox manner. The extent of the eruption in case 3 appeared almost identical with that of case 1, but developed first on the hands, then on the arms, face, trunk and legs in that order, and spread for about 3 days, so that by the fourth day the eruption on the hands was typically vesicular while that on the legs was macular. Vaccination performed on the probable seventh day after infection appeared to cause little modification of the extent of the rash which, however, appeared in atypical parts of the body and matured more quickly. No further cases occurred in this group of contacts and this phase, phase 1, may be said to have been checked by the measures taken.

When cases 1 and 3 were removed from the infectious diseases block of the Tripoli hospital to the smallpox hospital on 20 May the rooms were 'disinfected' by the perfunctory use of a little formalin and shut up until the 23rd when they were opened and cleaned out and the bedding was removed by a nurse. About 12 days later this nurse, who was non-resident, complained of fever and headache and was sent home. She was seen on 10 June, 6 days later, and found to have a very slight smallpox eruption with small, drying-up vesicles.

On the same day a porter from the infectious diseases block was found to have a similar eruption. According to him he had never had anything to do with the room of case 1 or its contents. He was, however, friendly with the nurse and everything points to both having been infected on or about 23 May. Both (cases 5 and 6) had been successfully vaccinated in infancy, but neither had given a vesicular response when revaccinated on the occurrence of case 1.

Case 6 (the nurse) was a married woman with four children who were admitted to the contacts' section of Busetta. Vaccination was performed immediately on admission. These children had been successfully vaccinated in infancy and at 5 years of age and carried definite, but rather superficial, scars. All the present vaccinations were negative. Two of these contacts, cases 7 and 8, developed extremely mild attacks.

One patient, case 7, suddenly felt ill with headache and malaise and the temperature, previously normal, rose rapidly to 103° F. By the second day the temperature had fallen and the patient felt quite well again. On the third day three small superficial, but otherwise characteristic, smallpox lesions appeared, one on the forearm and two on the trunk; there were none on the face, arms, hands or feet. The lesions matured rapidly, so that by the sixth day the scabs had gone and 2 days later it was very difficult to find the sites, the scars being little more than slight depigmentations of the skin such as might occur after any small impetiginous lesions.

The other, case 8, was very similar, occurring 2 days earlier with approximately eighteen discrete lesions.

There are two features which stand out in these cases. One was the very sudden onset; the other was the pre-eruptive phase, no less severe than that of unmodified cases, contrasting with the scanty rash when the patients felt so much better that neither was kept in bed. Both cases, especially the former, could easily have been missed if not under close observation.

Case 9 was a child aged 10 years whose only known contact was sitting next to case 7 at an examination about 6 June. Infection must have taken place by direct transfer on or about the day when case 7 herself acquired the infection from her mother and not, as occurred in practically all the other cases, from a person in the pre-eruptive phase. The mode of infection was probably similar to that of case 5 from case 6. Case 9 was admitted with a rubella-like eruption with a centrifugal distribution, well developed on the face, palms of the hands and soles of the feet, but, in the early stages, relatively scanty on the legs. There was a well-marked rash in the flexures, areas that the proper smallpox eruption usually spares. No vesicular eruption occurred and the case was considered one of *variola sine eruptione*.

Case 9 and her contacts, all of whom had been vaccinated successfully in infancy, were revaccinated; all except case 9 gave a vesicular take. No spread occurred from this focus.

The next case admitted, case 10, was an Arab girl aged 10 years with severe smallpox of 6–8 days duration, who died 5 days after admission. She lived in an Arab village, Amruss, approximately half a mile from the smallpox hospital and, as far as could be ascertained, she had not been near the hospital. Moreover, contact with the staff or patients was unlikely as the hospital had extensive grounds and was surrounded by wire fencing. No member of the staff came from this village.

Fly-proofing of the hospital had not been completed, however, at the time this case occurred, in spite of repeated requests to the appropriate authorities. The hospital was situated in an extensively cultivated area in which fly breeding was

very active and although the walls had been treated with D.D.T. it was difficult to keep the rooms free from flies. The Arab village itself was reasonably clean, but fly 'infestation' of the population was pronounced, the small children having many flies round the eyes, the nose and the corners of the mouth. There is a distinct possibility that flies breeding around the hospital carried the infection to the near-by village where they were likely to go in search of food. In spite of the late stage of admission of case 10 and the late vaccination of the population of the village no further cases were discovered there. Fly-proofing of the hospital was commenced on the 20th and was completed by the 28th so no further spread of the disease by flies from the hospital could have occurred.

When case 10 was admitted the remainder of the family, mother, father and two children were admitted for observation and were vaccinated immediately. All were unvaccinated previously. They were thus vaccinated on approximately the seventh day after contact with case 10 in the pre-eruptive fever stage and all gave a vesicular response. Both the children had typical mild attacks of smallpox; the adults escaped. Pre-eruptive fever was, as before, of sudden onset and out of all proportion to the severity of the ensuing attack.

One of the children, case 12, was of some interest on account of secondarily infected scabies of long standing. A number of lesions on the thighs had apparently been inoculated with vaccinia by scratching the primary vaccination, so that this case presented a mixture of lesions, simple sepsis and scabies with secondary vaccinal lesions at about the seventh day of maturation interspersed with a few smallpox lesions (Pl. 12).

About this time it was rumoured that one of the carpenters who had worked at Busetta from the 20th to the 28th was away sick with a rash. Enquiries made by the M.O.H. of Tripoli from the Italian doctor treating him only elicitated the story that the man had eczema. However, 10 days later he, his wife and three children were admitted to the smallpox hospital. The man had obviously had a mild, modified attack with no more than a dozen abortive pocks, although the pre-eruptive stage had apparently been quite typical.

The wife had a few modified lesions; one child, aged 2, who died, was unvaccinated and had an early confluent eruption and another, aged 8, successfully vaccinated in infancy, had a generalized papular eruption of characteristic distribution. The third child, case 14, had had a morbilliform eruption 2 days previously which the Italian doctor had diagnosed as measles. When seen at Busetta no rash of any kind was present, nor did one develop. The child had been vaccinated in infancy and also 1 year prior to admission and had definite scars from both. At first it was thought that this child might have had an attack of *variola sine eruptione*, but subsequent events showed this to be unlikely.

The third child and the father, who were considered free from infection, were discharged 4 days later. Twelve days from the date of discharge the child was admitted to the Colonial Hospital with fever and, as a precaution, was transferred to Busetta. When seen next day there were signs of broncho-pneumonia at the left base, but no eruption. Penicillin was given and the patient was transferred back to the Colonial Hospital. A vaccination performed previously showed a typical vesicle and was 12 days old. The pyrexia subsided rapidly and by the fourth day a few papules appeared. These were of varying size and erupted over the next 3 or 4 days. They were superficial, but in appearance no different from those of any of the other mild cases. Although so scanty, some appeared on the face and neck and the most characteristic were on the backs of the wrists; there were a few on the lines of the points of pressure of the shoulder blades. There were no lesions at all on the front of the chest or the abdomen.

This case, therefore, presented a diagnostic problem. The first disease with the morbilliform eruption was unlikely to have been smallpox in view of the subsequent vaccination take. Ricketts and Byles (1908) noted on rare occasions successful vaccination up to the third day of the eruption. If this first disease was not smallpox and the second disease was, the child must have escaped infection when she first came into contact with it, but succumbed when she came into contact again a fortnight later. If this view is taken, the morbilliform rash must have been purely coincidental. The second disease started 12 days after successful vaccination which was unexpected, but smallpox could not be excluded. High fever and chest signs followed by a pock eruption of centrifugal distribution 2 days later is difficult to explain otherwise. Vesicular response to vaccination within 1 year of earlier successful vaccination was unusual and suggests a patient who developed very transient immunity. If the case was one of chickenpox it must have been contracted at approximately the time when the other members of the family were first ill. At this time the schools were closed and no other cases had been notified in Tripoli City for many weeks. It could also have been a mild generalized vaccinia, but, unfortunately, laboratory aids to diagnosis were not available.

It is interesting that in this epidemic there were four separate family outbreaks with a relatively high infection rate but, in spite of crowded housing conditions, infection did not become widespread. A similar high family incidence was observed in the Detroit epidemic of variola minor in 1940–1 (Top & Peck, 1943). But for the religious and social

practices of the inhabitants the disease might never have spread beyond these families.

Case 14 was thought to be the last and the smallpox hospital was closed on 12 August when all the patients had been discharged. However, on 26 August it was found that an Arab child had died of smallpox in the Arab section of the city and investigation showed four foci of infection within a hundred yards of each other. There were two cases of a month's duration. The Arab fast of Ramadan had been celebrated during this time and accounted for the concealment of the earliest cases, both males who were probably infected in Amruss, the Arab village. Some mild, ambulant cases must have been missed in the checking done by the Italian M.O.H. and his R.A.M.C. supervisor. Subsequent events once again Italians and Jews, although the risk to them was slight, whereas the Arab population, particularly the women, would not have come and it was upon them that the major incidence fell.

After about 14 days many cases were found in Sugh el Giumaa, a large semi-urban market gardening district on the outskirts of Tripoli, which has a large interchange of population with the Arab section of Tripoli City. The number of patients found was so great that it was soon impossible to admit contacts.

Of the two areas affected, Tripoli City and Sugh el Giumaa, from the former family contacts were admitted to hospital, from the latter they were not. In the former, fairly efficient vaccination was carried out on the Sirte plan; in the latter, due to shortage of female staff and the very large area involved, ring

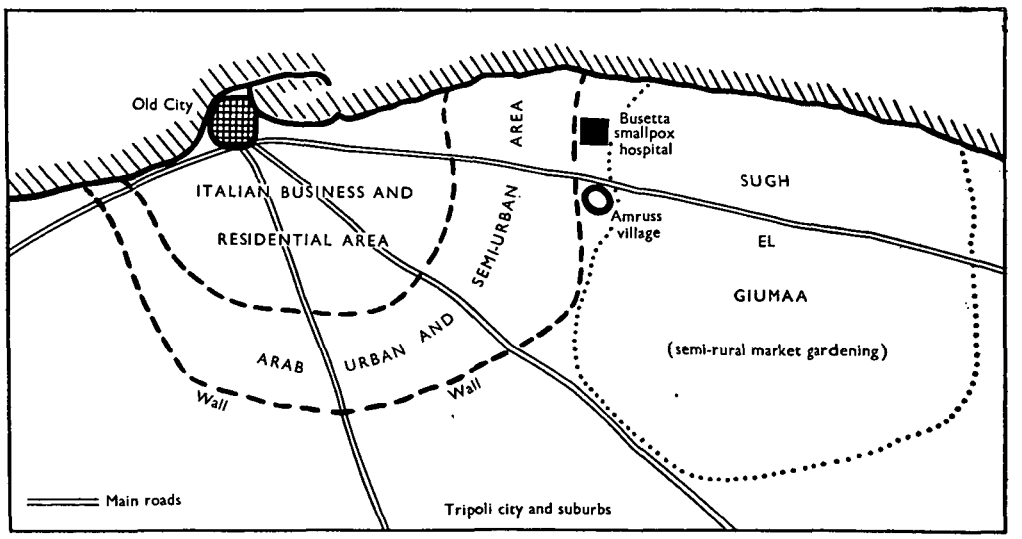

Fig. 3.

pointed to over optimism regarding the vaccination state of the population. The technique of vaccination was not above suspicion and will be mentioned again in the general discussion on vaccination (section VI (*f*)).

From 26 June to 31 September all cases were admitted to hospital together with immediate family contacts. Expanding ring vaccination was introduced and every effort was made to keep the Italian M.O.H. to this plan. Lymph and personnel were so scarce that, apart from any theoretical considerations, the only practical policy was to deal with the area of maximum risk first and in considerable strength, rather than to waste resources attempting the impossible over a wide area. Mass vaccination in the accepted sense is a big undertaking for a population of 125,000. If vaccination centres had been set up they would have been flooded by the vaccination was less complete, particularly the 'follow-up' and secondary vaccination where the primary vaccination had failed. The sequence of events was different in these two areas. Although a number of foci occurred in Tripoli City, they were controlled by ring vaccination, and only in the Old City, where very gross overcrowding occurred, was mass vaccination carried out. Among the population of 125,000 (approximately 20,000 Italians) in Tripoli City 114 cases occurred, an attack rate of 0·91 per 1000; in Sugh el Giumaa with a population of 38,000, 354 known cases occurred, an attack rate of 9·3 per 1000.

During September it was pointed out to the Administrators of the Territory that unless Tripoli City and suburbs were put into some form of quarantine it was likely that infection would be conveyed along the lines of communication to other parts of the

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country. This suggestion was not accepted and shortly afterwards infection was detected at a number of places and subsequently became widespread.

Adequate supplies of lymph were becoming available and vaccination was being practised in most parts of the territory. All was voluntary and, therefore, tended to attract the Europeans rather than the Arabs until active cases occurred, when the Arab was keen to be vaccinated. In many areas the women had to be vaccinated in their homes and this often presented difficulties because of the almost universal use of male nurses.

By 31 December 1946, 1450 cases and 118 deaths had occurred in Tripolitania. Most of the cases in outlying parts were nursed in their homes as at Sirte. In the clinical section (p.) the statistics are given of 487 cases classified and treated in hospital under reasonably good conditions. A number of cases not included in this section because of incompleteness of some of the clinical data are, however, included in the analysis of incidence by age and sex shown in Table 1.

Smallpox is a disease with a number of phases which must be fully appreciated if the classification is to succeed. The onset of the illness in all cases is very sudden; even in the mildest without subsequent focal rash there is fever, headache, a considerable degree of malaise and other signs of an acute infection. In all except the fulminating cases the primary toxaemia is much reduced by the third day when the rash appears. From this stage onwards there is a marked difference between the various types, so that in the mildest the symptoms and signs after the pre-eruptive stage may be negligible. Toxaemia accompanying the eruption up to about the twelfth day is the true secondary toxaemia. In cases where pustulation is marked there may be a low-grade toxaemia up to the sixth or seventh day of the rash and this is augmented and gradually replaced by the toxaemia of septic absorption which should be called the tertiary toxaemia. The secondary and tertiary toxaemia in this classification correspond to the older description of secondary toxaemia. Use of penicillin in suppressing suppuration has enabled a more accurate picture to be obtained. This is shown in Text-fig. 4.

Table 1. *Analysis of* 502 *cases by age and sex, and of* 87 *deaths by age, sex and type*

Age group	Cases		Deaths and types																		
	Males	Females	Males	Types 1	2	3	4	5	6	7	8	9	Females	Types 1	2	3	4	5	6	7	8	9
0–5	58	47	17	—	5	5	1	2	3	1	—	—	16	—	9	3	1	3	—	—	—	—
5–10	28	26	6	—	4	2	—	—	—	—	—	—	3	—	3	—	—	—	—	—	—	—
10–15	48	31	6	—	4	2	—	—	—	—	—	—	3	—	2	1	—	—	—	—	—	—
15–20	46	65	7	—	6	1	—	—	—	—	—	—	7	—	5	2	—	—	—	—	—	—
20–25	50	61	5	—	4	1	—	—	—	—	—	—	12	3	9	—	—	—	—	—	—	—
25–30	9	22	0	—	—	—	—	—	—	—	—	—	4	1	1	2	—	—	—	—	—	—
30–35	1	4	0	—	—	—	—	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—
35–40	2	2	0	—	—	—	—	—	—	—	—	—	0	—	—	—	—	—	—	—	—	—
40–	1	1	0	—	—	—	—	—	—	—	—	—	0	—	—	—	—	—	—	—	—	—
Total	243	259	41	0	23	11	1	2	3	1	0	0	46	4	30	8	1	3	0	0	0	0

V. CLINICAL OBSERVATIONS

(*a*) *Classification into nine types*

The system of classification to be described has been used successfully by inexperienced Medical Officers. Provided that the salient characteristics are appreciated, the same classification is given by different Medical Officers and the personal factor, a difficulty in all clinical classifications, is virtually eliminated. It must be emphasized that the classification was used on variola major, modified and unmodified, and primarily on Arab patients. The few European cases were also classified without any difficulty, although some symptoms common among Europeans were not encountered among Arabs. Mania was replaced in Arabs by an anxiety state. Any characteristic national or racial reaction to acute toxaemia should be borne in mind.

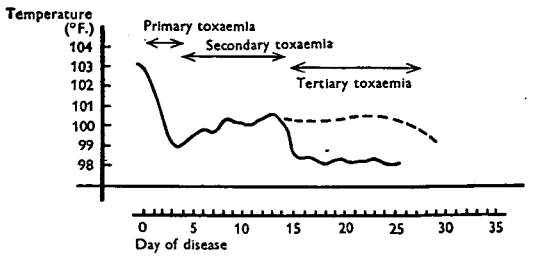

Fig. 4. Diagram showing the three toxaemic phases that may occur in smallpox.

As in Ker's description (1939) in estimating extent of eruption 'attention is paid chiefly to the face and fore-arms as even in the worst confluent cases the

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lesions on the trunk may be quite discrete'. Confluence of lesions on the face and forearms merits the description of confluent; confluence on the face only is described as semi-confluent; no confluence anywhere is described as discrete. On sites of trauma or of old sepsis, or on pressure points due to occupation or dress, local confluent areas may occur and these should be disregarded.

The classification depends on the separation of cases with severe toxaemia, called 'malignant', from cases with slight toxaemia, called 'benign', on the basis of the intensity of secondary toxaemia and on the extent of the eruption.

There are nine types:

1. *Purpura variolosa.*
2. Malignant confluent.
3. Malignant semi-confluent.
4. Benign confluent.
5. Benign semi-confluent.
6. Discrete.
7. Mild.
8. Abortive.
9. *Variola sine eruptione.*

The principal clinical features upon which the classification of the nine types is based are given in Table 2. Additional information is given below.

Type 1, called *purpura variolosa*, is the fulminating type of disease in which the patient exhibits no resistance; it is a rapidly fatal infectious toxaemia. Petechiae are usual within 24 hr. of onset and large haemorrhages occur in the mucous membranes and into the skin. Death often occurs before the rash appears or before it has taken its characteristic form. Early in an epidemic this type of case might be very difficult, if not impossible, to diagnose. Treatment is of no avail and, as in Ricketts' (1908) classification, all cases are fatal.

Type 2 is the malignant confluent. Here the patient experiences the characteristic pre-eruptive malaise and fever and there may be some petechiae or ecchymoses including the classical 'bathing drawers' distribution. With the appearance of the rash the temperature drops and the general condition is often remarkably good considering the

Table 2. *Principal clinical characteristics of the nine types of smallpox*

Type	Name	Secondary fever	Laryngeal lesions	Mental symptoms	Haemorrhages	Rash	Pustulation (untreated)	Extent of eruption	Mortality (%)
1	*Purpura variolosa*	—	±	Anxiety +++	Early, esp. mucous membranes +++	Soft, velvety; often absent	Nil	—	100
2	Malignant confluent	+++	++	++	Late in the skin and mucosa ++	Soft, velvety, hot and tender. Slow evolution, pseudo cropping	Nil	Confluent on face and arms	69
3	Malignant semi-confluent	++	++	++	Late in the skin and mucosa +	Soft, velvety, hot and tender. Slow evolution, pseudo cropping	Nil	Confluent on face only	24
4	Benign confluent	+	±	—	—	Hard, pearly. Normal evolution, uniform on each anatomical part	Severe	Confluent on face and arms	18
5	Benign semi-confluent	+	—	—	—	The same as in type 4	Severe	Confluent on face only	12
6	Discrete	±	—	±	Occasionally in individual vesicles	Usually hard, pearly	Slight	No area confluent. 100–1,000 or more lesions	2·5
7	Mild	—	—	—	—	Hard, pearly. Some lesions may abort	Slight	20–100 lesions	0·7
8	Abortive	—	—	—	—	Pearly. Many macules and papules abort	Nil	Less than 20 lesions	0
9	*Variola sine eruptione*	—	—	—	—	No focal rash	Nil	Nil	0

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ultimate fate of the patient. The eruption appears slowly during the succeeding days and by the fourth to fifth day feels velvety. The rash is frequently not 'classical' and some lesions may not develop fully, not beyond the papular stage. There is persistent hyperaemia around the lesions which is not easily detected in dark-skinned persons. The lesions and the skin around them feel hot, irrespective of the actual temperature of the patient, and are tender to slight pressure. Lesions are best palpated with the palm of the hand on the extensor aspect of the arm. These two characteristics (heat and tenderness) have not, as far as I know, been previously described and have proved of value in the classification of cases. The vesicles, which are often well umbilicated and flattened, due to haemorrhage into the base, appear blueish. Large haemorrhages may also form in the skin. True 'pearly' vesicles followed by pustules do not occur. When drying up between the twelfth and sixteenth days, the eruption has a coppery appearance. If the toxaemic element is very marked large areas of epidermis measuring 8 or 10 sq.in. may slough off leaving the exposed dermis.

A number of severe cases of this type which recovered and which were not given any penicillin had no pus formation in the areas of denuded skin. The condition appears to be a superficial gangrene. Bed sores are difficult to prevent. Classical pock marks are replaced by a thin, papery type of scar similar to that seen after a burn.

Some of the mental symptoms common in Europeans were not present in this series, but the malignant cases were extremely anxious. Involvement of the trachea and larynx is usual and the patient has no appetite and often great difficulty in swallowing. Haemorrhages from the mucous membranes are common. The general condition is strikingly like that of typhus with gradual relentless deterioration. Death usually occurs on the twelfth to fourteenth day. If the patient recovers there is often a crisis on about the twelfth day of the eruption with a sudden fall of temperature and a dramatic improvement in the general condition. Occasionally the temperature comes down by lysis and secondary broncho-pheumonia may appear as a complication.

In the benign types, 4 and 5, the general condition of the patient is often surprisingly good, although there may be great local oedema of the skin and resultant discomfort. The trachea and larynx are not usually involved and the patients are remarkably placid and have an unexpectedly good appetite considering their appearance. The rash is not hot or tender and vesiculates well, giving a classical pearly eruption well set in the skin. Pearly lesions are also seen in types 6–8, although in the last two they tend to be more superficial.

The mild cases, type 7, have from twenty to a few hundred pocks; the abortive, type 8, less than twenty lesions, many of which do not mature properly. *Sine eruptione* cases have no focal eruption and, although there may be a rash, it is usually morbilliform and attacks the flexures, parts most often spared by the focal eruption.

'Illness of contact' has been mentioned by Boul & Corfield (1946) and by other writers. It is doubtful whether this should be regarded as different from *variola sine eruptione*.

It may not be possible to assess confluence until the eruption has matured and, in general, all except fulminating cases should be classified on the sixth to seventh day of the disease. The fever itself is often a good indication of secondary toxaemia; typical temperature charts for the different types are given in Text-fig. 5. Minor variations may occur but they are exceptional.

(1) *Clinical* (b) *Diagnosis*

(i) *Pre-eruptive phase.* It is not proposed to go into all the details of the general symptoms and course of the disease, but there are some points of interest. The pre-eruptive fever and malaise was very definite in all types of case. Sudden onset was noticed in those who were in hospital as contacts and who were, therefore, observed from the very beginning of the illness. Within an hour a person previously feeling well would have malaise and fever very like classical influenza. Back-ache was not a predominant symptom. Prodromal rashes of the 'bathing drawers' type were rarely seen, as many of the severely ill patients were admitted too late for this sign.

Modification by previous successful vaccination did not appear to influence the severity of the pre-eruptive phase, and in all types this syndrome proved of great value in the differential diagnosis of smallpox from chickenpox and lichen urticatus.

(ii) *Eruption.* The rash is also important, and the following points are emphasized. The early rash was mistaken for measles by a number of Italian doctors. The macular rash in smallpox is more uniform in colour than the rash of measles, has a centrifugal distribution and quickly becomes papular. Diagnostic difficulties are much reduced as the papules form, for on palpation they have a characteristic feel which is difficult to describe. The finger can detect that they are deeper in the skin than the more superficial lesions of chickenpox. However, in mild cases modified by successful vaccination the eruption tends to be as superficial as that of chickenpox.

Malignant types, 2 and 3, had rashes which many would consider not typical of smallpox. In these cases the rash was soft and velvety, the pocks were flattened and well umbilicated and interspersed amongst papules which did not develop, so giving

an appearance of cropping. This rash is not really atypical and has been described as occurring in severe cases by Ricketts & Byles (1908) and others.

The distribution is far more important than the actual character of the lesions. The rash generally

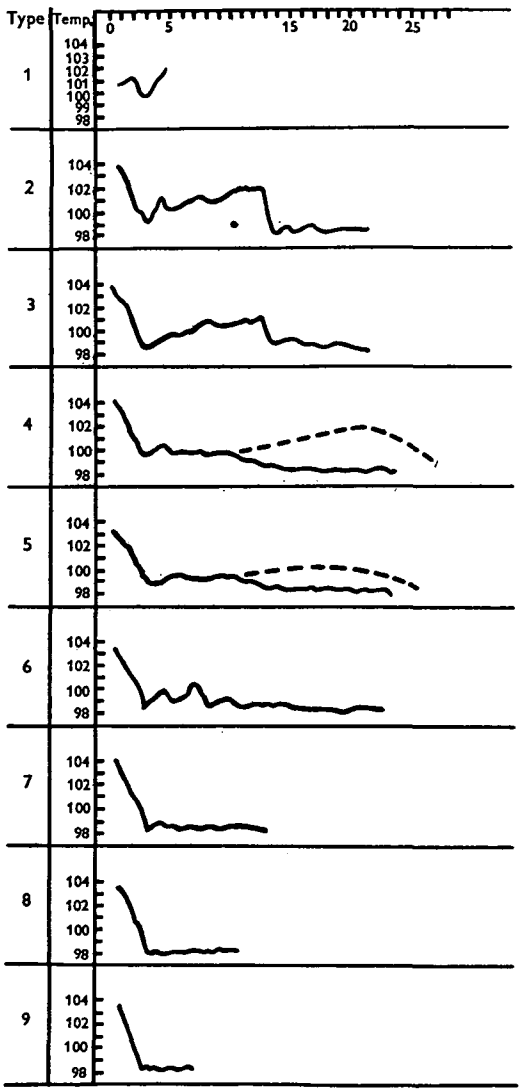

Fig. 5. Temperature charts characteristic of the different types of smallpox

avoided the flexures, and if the axillae did not escape altogether lesions there were relatively sparse. In types 2 to 6, both modified and unmodified, the rash was centrifugal in distribution. When the lesions were very scanty, as in types 7 and 8, this was not always obvious and in a number of abortive cases the rash consisted of from eight to ten lesions, all of which were on the back. A characteristic area in these mild cases was around the wrist, particularly over the lower end of the ulna.

Variations in distribution were found due to trauma or to some peculiarity of pressure. One case, a woman, had a confluent eruption over the whole of the abdomen, although the chest was practically clear and the rash was not confluent elsewhere. This was probably due to some traumatizing treatment given during the pre-eruptive stage or to some peculiarity of dress.

When the rash did not appear simultaneously over the whole body it usually proceeded in the order, face, arms, hands, trunk and legs. In the unmodified disease, apart from the abortive papules that occurred in types 2 and 3, the lesions in any anatomical part of the body were the same and cropping, such as occurs in chickenpox, was not seen. This rule does not hold good for smallpox modified by successful vaccination.

Umbilication was well marked in types 2 and 3, but only appeared late in the pearly types, or not at all. In this series of cases umbilication, loculation and other features of an individual lesion were of little diagnostic value.

(iii) *Smallpox modified by successful vaccination.* There was a tendency for the incubation period to be prolonged, but the pre-eruptive fever was true to type and usually as severe as in the unmodified case. The temperature dropped to normal and the eruption appeared on the third day. Sometimes in abortive (type 8) cases this was delayed to the fourth or even to the fifth day, when a few papules appeared of which only a small proportion became vesicular.

Types 1–3 usually occurred when the last successful vaccination had been at least 20–30 years previously and modification hardly existed; types 4 and 5 were not seen when successful vaccination had been performed prior to contact. The characteristic types in vaccinated persons were 6–8, and in these the rash usually showed a centrifugal distribution. Where the lesions were very sparse it was necessary, in order to ascertain their relative distribution, to count them and, even then, often no great difference was found between the trunk and the limbs. Cropping was almost always present and there could be as much as 3 days between crops on the same anatomical part. The rash matured more rapidly and abortion of some lesions was usual, particularly in the later crops. Smallpox modified by vaccination may be extremely difficult to diagnose, but both the pre-eruptive phase and the characteristics of the eruption must be taken into account.

(iv) *Unusual clinical features.* In two cases, one successfully vaccinated and one unvaccinated, the focal eruption, which had developed as far as the early papular stage, was completely arrested and never became vesicular. Superficial desquamation

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followed leaving no scarring and only very slight temporary pigmentary changes, as though a sensitized, but tardy, immunity mechanism had come into action.

There was only one case of probable second attack of smallpox. An old man who had had smallpox in childhood visited Tripoli and then returned to his isolated village many miles away. There was no smallpox in the village, but 12 days after returning he developed a high fever lasting 2 days and then recovered. There was no evidence of the presence of malaria, dengue or sand-fly fever. About 12 days after his febrile attack the old man's son developed a fever and subsequently had a typical smallpox eruption, a circumstance which is strong presumptive evidence that the father's disease was smallpox.

Two patients, both adolescents, died with encephalitic symptoms, one on the twelfth and the other on the fourteenth day of the disease.

(2) *Laboratory aids to diagnosis*

No laboratory aids were available at the commencement of the epidemic, but after a few months Captain J. Anderson, R.A.M.C., arrived in the territory and took material from many early cases. Smears from papules and early vesicles were stained, using the technique of van Rooyen & Illingworth (1944), and examined for elementary bodies. After some initial difficulty with precipitation of stain the technique was mastered and from smears taken from over a hundred early cases elementary bodies were seen. The density of these varied and was less in the very early papules and in later vesicles where the onset of cellular infiltration tended to spoil the picture. Unfortunately, no cases of chickenpox were available for comparison, but smears taken from other vesicular skin diseases gave negative results.

(*c*) *Prognosis*

The typing of cases was of value in prognosis and in treatment, the mortality of the different types falling from types 1 to 9. As pointed out by Ricketts & Byles (1908) and others, smallpox patients either die on the first or second day in the fulminating type, between the twelfth and fourteenth day from toxaemia, or from sepsis or bed sores in the third week or later.

Young infants did badly, irrespective of the type of the disease, and all the deaths in types 5–7 were in infants under 1 year of age. Broncho-pneumonia supervened early, whether due to the smallpox virus or other organisms is not known, but penicillin as a prophylactic or as treatment did not appear very effective. Bad feeding and mismanagement by the mother was probably a contributory factor. Wherever possible babies suffering from smallpox were breast fed, even if their mothers had the disease, as long as the general condition of the mother permitted. The mortality in children under 1 year was 55 % and under 5 years 28·5 %, as against a general mortality of 18 % (Table 3).

Table 3. *Relationship between age and mortality in all types*

Age group	No. of cases	No. of deaths	Mortality (%)
Under 1 year	36	20	55·5
Over 1 year and under 5 years	80	13	16·2
Over 5 years	371	55	14·8
Total	487	88	18·1

Apart from pregnant women and infants, mortality was related to type and not to age or sex. Table 1 shows, however, that very few patients in the whole series were over 40 years of age. The overall mortality rate of 18 % for those treated in hospital was little different from the crude mortality rate of the cases left in their tents during the Sirte epidemic.

(*d*) *Complications*

Some of the most serious complications were those affecting the eye. These were most severe and frequent in types 2 and 3, but occasionally eye lesions of some severity occurred in types 6 and 7. Patients suffering from the latter types often had old trachoma or the scar of a previous eye injury, and this suggested that previous eye disease might pre-dispose to the fixation of virus in the eye with consequent serious injury. The eye conditions were closely studied by Captain J. Macbeth, R.A.M.C., who, it is understood, will be publishing a paper on the eye complications in smallpox.

Scarring, an important sequel to smallpox, particularly in women, was found to vary according to the type of disease. In the malignant types, 2 and 3, with no treatment at all, frank pustulation never occurred, the flattened vesicular stage dried up and scaled, leaving a thin papery scar like that following a burn. Types 4–6 gave characteristic pock scars in some cases, even when sepsis had been suppressed by penicillin treatment. Keloidal scarring was common amongst the negroid patients. Cases of 'mild' and 'abortive' types, both unmodified and modified by vaccination, tended to have very superficial scabs and, particularly in the modified cases, it was difficult to find the sites of the lesions 3 or 4 weeks later. After some months they would probably be quite invisible.

(*e*) *Treatment*

1. *General*

A review of the text-books shows that a great variety of treatment has been given from time to time, none of which appears to have any definite

effect on the disease itself. Symptomatic treatment is very varied and, apart from treatment of complications, seems limited to local measures with the object of reducing the irritation of the eruption.

The heroic treatment given in Korea to American soldiers (Boeck, 1946) included intravenous injections as a substitute for food in all severe cases, vitamins, intravenous plasma and whole blood, oxygen therapy, sulfadiazine for pulmonary and penicillin for septic complications. In spite of this barrage of treatment thirteen cases out of thirty-seven died and 'usually in haemorrhagic cases' (probably types 2 and 3) 'no treatment employed was of any avail'. During the Sirte and Tripoli epidemics, in the absence of any treatment, the mortality of this type of case appeared to be little different.

In the present series general treatment was of necessity simple, but it is felt that over-treatment with useless remedies is only likely to exhaust the patient. Types 2 and 3 were hard to feed due to difficulty in swallowing caused by painful pharyngeal lesions. Fluids were required in large quantities, but could usually be taken by mouth. These patients were very restless and the use of mattresses on the floor solved many of the nursing problems. The mild cases, types 7 and 8, were not kept confined to bed. Irritation of the skin was an uncommon cause of complaint and even the infants did not scratch their lesions noticeably. Possibly the Arab's experience of insect pests has lowered his irritation threshold.

No permanganate baths were used (Harries & Mitman, 1947), the skin being kept dry until desquamation started. At this stage daily showers were encouraged particularly to soften the skin to facilitate the removal of 'seeds', lesions 'situated in the soles of the feet where the thick cuticle of the sole lies over them and they do not interrupt its level surface'. (Ricketts & Byles, 1908).

After the pre-eruptive toxaemia had passed, all patients, except those of types 2 and 3, ate well, including those of type 4 although they had confluent eruptions. Similar observations were made in the Edinburgh epidemic in 1942 (Clark, 1944).

Minor sepsis and boils were treated on orthodox lines; secondary impetigo responded well to penicillin cream, and lanoline was used on the tender atrophic scars of the malignant types, and also for secondary eczema which sometimes occurred on the face.

(2) *Penicillin therapy*

Penicillin in doses of 30,000 units 4-hourly was used early in the epidemic. At first all severe cases received it, but when it was realized that prognosis could not be based solely on the extent of the rash, cases were classified and the use of penicillin confined to certain types.

In fifty patients classified as types 2 or 3, penicillin in doses up to 1½ million units over 7 or 8 days had no demonstrable effect on the general condition, temperature or outcome, whereas among fifty-one cases classified as types 4 and 5 with a few type 6, penicillin treatment appeared to prevent pustulation and with it tertiary fever due to sepsis.

Frank pulmonary complications were rare in adults, but it seems unlikely that penicillin would have much effect in such a complication occurring in types 2 or 3. All young infants, except those with the mildest infections, received penicillin as a prophylactic against respiratory complications, but terminal broncho-pneumonia was common amongst thirty-six cases under 1 year of age, and the mortality rate of 55 % does not suggest any great benefit from this treatment. No statistics are available for untreated controls.

In the light of this experience penicillin was used as a routine on types 4 and 5 and on many type 6 cases. Fifty-one cases of these types were treated with penicillin, but at times penicillin was not available and, therefore, 105 similar cases had no such treatment. The observations which follow are based on a comparison of these two series of cases.

Penicillin therapy was usually started on the fifth day of the rash when the vesicles were about to become pustular, the lesions on the face and the backs of the arms being the deciding areas. As far as could be seen early administration of the drug had no effect in modifying the papular or vesicular stages and was, therefore, wasteful. A standard dosage of 30,000 units every 4 hr. was given to all patients of all ages because of the unskilled nursing staff. Treatment usually lasted 3–4 days and dosages of 400,000 to 750,000 units were usual, the lower dosage being used in the type 6 cases, often the successfully vaccinated patients in whom it is usual for the lesions to mature more rapidly. The effect was dramatic. Full, pearly-white, tense vesicles showed rapid absorption of fluid, becoming flattened and dry within 72 hr. After 3 or 4 days on penicillin the lesions were completely flattened and copper coloured, there was no smell and no sign of any suppuration, the roof of the vesicle together with a small plaque of dried serum separating from the skin and leaving a clear epithelialized area. There was a complete absence of the yellow pustule and subsequent dirty yellow scab of dried serum and pus. Epithelialization was often so good that it was hoped that as a result of treatment scarring would be much reduced. While close observation of all cases showed very superficial scarring and depigmentation the ultimate appearance after weathering can only be surmised.

It is of interest to note that the malignant cases who survived showed a diffused atrophic type of scar instead of the classical deep pock marks. Many of the patients were of negro stock, among whom

keloidal scarring with a raised, instead of a pitted, scar was common. Penicillin did not appear to affect this.

The pathology of the uncomplicated smallpox vesicle is primarily in the epithelium. Most lesions show some inflammation and cellular infiltration of the underlying dermis. Bacterial infection of the vesicle probably greatly increases the sub-epithelium damage and destroys more epithelium, so increasing granulation and scarring. A few deep lesions of this kind occasionally occur in chickenpox, but they are characteristic rather of smallpox pustules. In mild and modified smallpox the lesions are more superficial and unless secondarily infected scarring may be minimal, amounting to little beyond loss of pigment. In abortive cases it may be impossible to pick out the sites of the lesions after some weeks.

In view of the variations occurring naturally in smallpox caution should be used in judging the power of penicillin to prevent scarring. Practically all the cases in this series were in dark-skinned persons and, although the few Europeans appeared to show minimal scarring, observations on a larger series of white persons and on the effect of weathering on treated and untreated cases should be studied. If penicillin prevents pock marks in smallpox it should do the same in vaccinia, which should be capable of test.

The duration of stay in hospital was slightly shorter in those treated with penicillin than in those of a similar type treated without it, but the results are not statistically significant. They are of little use in assessing the value of penicillin, as the criterion determining stay in hospital was, rightly or wrongly, the disappearance of all 'seeds' from the hands and feet. Arabs walk bare-foot, so the skin of the feet is very thick and hard and it was tedious having to wait for them to be free of these lesions. Frequently odd 'seeds' were dug out with a scalpel, the area treated with tincture of iodine and the patient sent home.

Incidence of septic complications in the two series of cases of types 4–6 was not high and, although this was possibly due to the current cleaning and disinfection practice in the wards, other epidemics with a low incidence of septic complications have been recorded. However, there were no septic complications in the fifty-one cases treated with penicillin, as against nine in the 105 comparable cases treated without. Presumably more serious complications such as pyaemia are less likely when penicillin is used. None occurred in this series.

The value of penicillin in smallpox may be summarised thus:

(1) Penicillin has no effect on the virus or on the symptoms resulting from acute viraemia.

(2) The value of penicillin as a prophylactic against broncho-pneumonia in infants is very doubtful. Definite pneumonia at any age is a complication which should be treated with sulphonamides or penicillin as the case merits. As far as can be seen results will be in keeping with those expected of a serious complication in a patient who is already suffering from a serious virus infection.

Table 4. *Thirteen cases of smallpox in mothers and infants*

	Mother												
Case ...	1	2	3	4	5	6	7	8	9	10	11	12	13
Type of disease	3	6	2D	3	2	2D	2	7	5	8	6	6	7
Vaccination state	10y +	—	—	—	—	—	—	8y +	—	AC +	10y +	AC +	15y +
	Child												
Type of disease	2	6	2D	6	2D	8	7	7	7	3D	2D	6	3D
Vaccination state	—	AC +	AC +	—	—	AC +	U −	—	—	—	U −	AC +	—

y, years since successful vaccination; D, fatal case; U, intra-uterine infection; +, successful vaccination; −, vaccination not performed or unsuccessful; AC+, successful vaccination after contact.

(3) Penicillin will completely control suppuration when due to penicillin-sensitive organisms in types 4–6, in which the eruption almost invariably passes through a pustular stage. The general condition of the patient is much improved and septic complications such as boils and abscesses do not occur.

(4) The use of penicillin does not prevent serious eye complications involving loss of sight or loss of the complete eye.

(*f*) *Smallpox in mothers and babies*

Table 4 shows thirteen cases of smallpox in mothers and in their infants under 1 year of age, including two cases of intra-uterine infection with live births. The type of infection in mother and child was the same in six, in four the severity in the mother was very much greater than that in the infant, and in three the infant's disease was more severe than that of the mother. In the last group the mothers had been vaccinated successfully, one after contact, but all had mild, modified attacks. The vaccination state of the infants who had milder

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attacks than their mothers was different; one had a positive vaccination done after contact, with a very small vesicular response, after four previous unsuccessful attempts; one had been vaccinated three times, all without success, and one had never been vaccinated. In the remaining case, in which there was intra-uterine infection, the infant had a type 7 attack and the mother a fatal type 2.

Three cases of intra-uterine infection were seen. In one the infant was born dead with the eruption in the vesicular stage corresponding to the seventh or eighth day of the disease. This showed that the infant was infected during the pre-eruptive stage of the disease in the mother, assuming an incubation period of 12 days. Two infants were born during the early stage of the disease in the mother; one developed the eruption on the seventh day of life, on the thirteenth day after the pre-eruptive fever in the mother; the other on the ninth day of life, the twelfth day after the pre-eruptive fever of the mother. These cases are of interest in suggesting that transplacental infection occurs during the pre-eruptive fever and not before.

(g) *Smallpox in pregnant women*

In all except one case, a type 7, infected pregnant women (3 months or over) miscarried or went into premature labour. Uterine haemorrhage was not uncommon in the non-pregnant malignant cases and would suggest that the virus has a specific effect on the uterus. Pregnant women did badly, their mortality being 40 % compared with 12 % in non-pregnant women of the same age group. The difference of 28 %, with a standard error of 12, is probably a real one. Pregnant women also showed a higher proportion of severe cases. Of the four type 1, fulminating, cases all were women of whom three were pregnant.

VI. EPIDEMIOLOGY

(a) *Incidence*

Text-fig. 6 shows the weekly incidence of smallpox in Tripoli City and the neighbouring Sugh el Giumaa from the start of the epidemic until 31 December 1946, the period covered in this review. The total population was about 800,000 of whom all but 40,000 were Arabs. The incidence in the non-Arab population was very small as the ordinary Italian colonists had been vaccinated on entering the territory and the majority of Italian infants were also vaccinated during the Italian regime.

(b) *The fate of contacts*

As accommodation was available it was decided to admit to hospital immediate family contacts of the cases occurring in the cramped confines of Tripoli. The only exceptions were males who were over 40 years of age and who had been vaccinated recently. The communal type of house in Sugh el Giumaa and the large size of the families made it impossible to admit contacts from the rural areas, the populations of which served as a comparative group.

Nearly 300 persons, mostly women and children, who had all been in contact with infected persons, were kept under observation. It can be assumed that under Arab living conditions the virus must have been inhaled by all these persons and massive infection was more than likely. Table 5 shows the fate of 288 contacts of whom thirty-seven developed smallpox of varying severity. A large number who

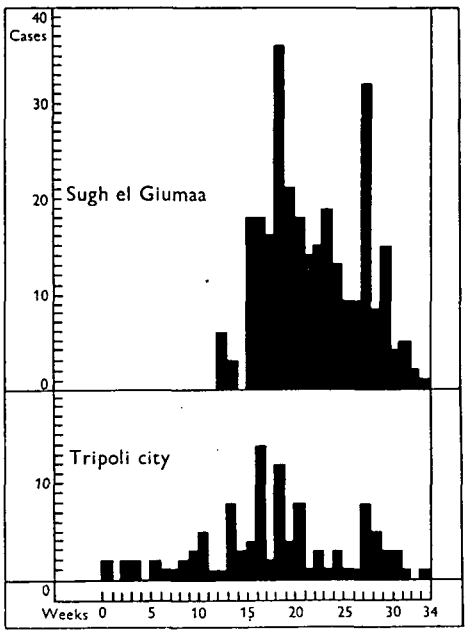

Fig. 6. Weekly incidence of smallpox in Tripoli City and Sugh el Giumaa for 35 weeks (1946).

had no history of vaccination did not develop even mild clinical smallpox. Of particular interest is the almost complete immunity of persons over 40 years of age, and the relatively large proportion, 14 %, over 30 years of age admitting to a previous attack of smallpox. This is in keeping with the history of the territory and offers an explanation of the age incidence in the epidemic (Table 1).

Although the numbers in the various groups are not large they reveal certain trends. In the group under 5 years of age, of fifty-nine contacts twenty-two (37 %) developed smallpox. While no contacts in this group who had had a successful vaccination prior to contact developed smallpox, approximately half of those who had had a successful vaccination

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Table 5. *Fate of contacts*

Age group	Male	Female	Total	Immunological classification and fate: V− BC V− AC Sm	V− BC V− AC Nil	V− BC V+ AC Sm	V− BC V+ AC Nil	V+ BC V+ AC Sm	V+ BC V+ AC Nil	V+ BC V− AC Sm	V+ BC V− AC Nil	History of previous smallpox Sm	History of previous smallpox Nil	Totals Sm	Totals Nil
0–5	32	27	59	5	6	17	15	0	1	0	15	0	0	22	37
5–10	3	14	17	0	2	5	5	1	1	0	3	0	0	6	11
10–15	3	6	9	0	2	3	2	0	0	1	1	0	0	4	5
15–20	1	6	7	0	0	0	1	0	2	1	3	0	0	1	6
20–25	5	19	24	0	9	0	3	1	3	0	8	0	0	1	23
25–30	1	17	18	0	17	0	0	0	0	0	0	0	1	0	18
30–35	0	22	22	0	11	0	2	0	0	0	6	0	3	0	22
35–40	0	28	28	0	11	1	3	0	0	0	9	0	4	1	27
40–	6	98	104	0	68	0	7	0	0	0	15	0	14	0	104

Sm, attacked by smallpox; Nil, not attacked by smallpox; V+, vesicular response to vaccination; V−, vaccination unsuccessful; BC, before contact; AC, after contact. E.g. V− BC means vaccination before contact unsuccessful; V+ AC vaccination after contact successful (vesicular). All contacts are assumed to have been exposed to massive infection.

after contact developed the disease. Of those who were vaccinated with an unsuccessful result approximately half developed smallpox. The apparent absence of success in vaccination in approximately one-fifth of this group is not easy to explain as the vaccinations were done in hospital with fresh lymph, although admittedly by the nursing staff. A relatively high proportion were young infants a few days or weeks old, although infants were successfully vaccinated on the day of birth.

The age group 5–10 is very small, but shows a similar trend. With advancing age the picture changes and there is an ever decreasing incidence of smallpox and an apparent increase in refractoriness to vaccination, the number of successful vaccinations in the age group over 35 being very small. The picture is not unlike that which occurred in the eighteenth century in this country when smallpox was endemic and largely a disease of childhood, the adult population being immune after clinical or subclinical attacks.

The 288 contacts were not an unselected sample of the population, as about fifty-five cases, mostly under 25 years of age, had been removed from amongst them. However, 160 adults over the age of 25 who remained in contact with the disease for many days did not contract smallpox, although they had not been successfully vaccinated. It is not certain that determined revaccination would have been unsuccessful or that these persons would have escaped a further epidemic, but if, as is probable, they were for the most part truly immune the population at risk in this epidemic must have possessed a higher degree of immunity than would be expected in an English population.

Amongst the Italian population the distribution of cases was quite different, 60 % occurring in patients over 30 years of age. Children and young adults escaped because they had been successfully vaccinated in infancy or childhood.

Contacts were put in the same ward with convalescent cases, but if they developed the disease it was 12–13 days after contact, prior to admission with a patient in the pre-eruptive stage. This suggests that sufficient immunity must be possessed by those who escape smallpox after contact with the disease in the pre-eruptive stage to resist further infection, or that the infectivity of the late eruptive stages is much less than is generally supposed. Early experience in this epidemic suggested that those who escaped clinical infection after first contact would escape after further contact. Later experience showed that this was not always true and that smallpox behaves like other droplet infections in which the attack is dependent on the size of the infecting dose and the immunity level. However, it would be unreasonable to suppose that persons resident in a smallpox hospital were not exposed to considerable risk of infection, even if the scabs are of low infectivity.

(c) *Spread of infection*

Although transcutaneous infection has been recorded in the naturally occurring disease, the normal method of infection is by inhalation of the virus. There would appear to be four possible routes:

(i) Virus from the nose and throat contained in droplets exhaled by patients.

(ii) Virus carried by dust from the clothing, bedding or immediate surroundings of a patient, on which respiratory droplets have dried.

(iii) The virus from the cutaneous lesions, particularly the scabs, and the dust obtained therefrom.

(iv) Virus from any of these three sources con-

veyed by flies to the eye, nose or mouth of a susceptible person or to food.

There seems no reason to suppose that the macular, papular or vesicular lesions which are intra-cuticular can in themselves be infectious, although the patient himself or his clothing may be infectious at this time by material from the respiratory tract.

Experience in Sirte suggested that fomites were not an important source of spread and the more detailed observations in Tripoli suggested that the period of greatest infectivity was during the pre-eruptive fever. Text-fig. 2 shows the first four stages of the Tripoli outbreak in which the secondary cases in the families affected could be traced to contact with the original case during the pre-eruptive phase. Text-fig. 7 shows the daily incidence in the village of Henscir and in area 1 in Tripoli City. Groups of cases occurred approximately every 13 days, although late scabbing cases were present during this time, mixing with all and sundry. The over-crowded Arab Mass vaccination was not carried out except in the Old City of Tripoli where there was gross over-crowding. Compulsory vaccination was not introduced.

In Sugh el Giumaa patients were isolated, but, because of the difficulty of finding some of them in the larger area, they were admitted later in the disease. Isolation of close family contacts was not possible from this area and disinfection of premises could not be undertaken. Text-fig. 6 shows the difference in the weekly notifications from these two areas.

The guiding principle in the control of smallpox should be to build a barrier of immunes around the infectious persons. If cases are hidden and the people are non-co-operative, as in the Sugh el Giumaa area, this policy cannot prevent infection being introduced into other areas. It was certainly because of the movement of infected persons from this area to other parts of Tripolitania that the infection became widespread.

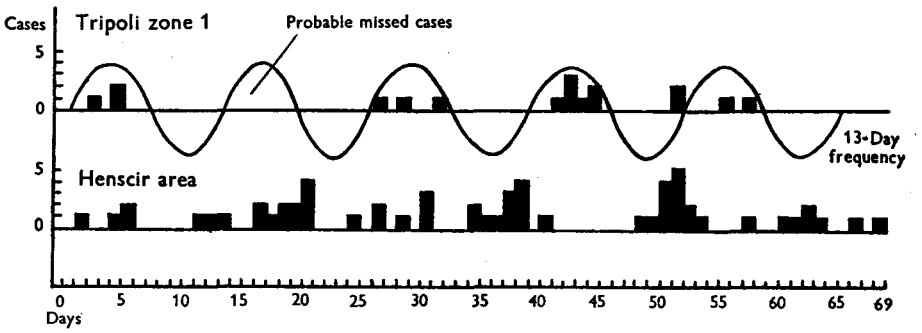

Fig. 7. Diagram showing grouping of cases at about 13-day intervals in the daily notifications of cases in Tripoli zone 1 and in the Henscir area.

way of life should be ideal for the spread of infection from dried scabs if these were highly infectious. Had the airborne dust from dried scabs been a major source of infection a gradual increase in the number of cases once the primary cases had begun to scab, would have been expected, instead of the periodic incidence with an interval of approximately 13 days.

Although infection was most probably introduced into Amruss village by flies, flies are unlikely to be vectors of importance in the general spread within a community unless living conditions are very primitive; even then, direct droplet spread is probably more effective.

(*d*) *Control policy*

As described in Section III, the control of the smallpox epidemic in Sirte was effected by contact vaccination on the 'expanding ring' principle. Control in Tripoli was based on isolation of cases, isolation of immediate family contacts for 14 days from the date of onset of the infecting case and routine disinfection of premises by Italian methods.

(*e*) *Hospitalization*

The first case of smallpox in Tripoli was diagnosed in the infectious disease block of the main Tripoli hospital which had 1100 beds. A small derelict Italian military hospital at Busetta on the outskirts of Tripoli had previously been earmarked as a smallpox hospital. The buildings were fairly well isolated, being half a mile from the nearest village of any size. Unfortunately, a main camel road ran past the gate, but the whole area was liberally surrounded with barbed wire and there were large notices in Arabic, Italian and English. The patients were moved in within 24 hr. and alterations and some services completed later.

There was no difficulty in removing the town Arab into hospital, but those in the rural areas were more difficult to run to earth and tended to be admitted later. The hospital staff was the greatest problem. No European trained nurses were available and so a staff was formed of Arab and Jewish (Tripolitanian) nurses and ward maids, almost all of whom had no

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experience of infectious disease, let alone smallpox. Some of the girls of 15 and 16 years of age, quite untrained in nursing, were very eager to learn and eventually two or three of them gave most of the penicillin injections. Great credit is due to the late Captain La Ferla, R.A.M.C., who assisted the writer in the early stages and whose knowledge of Italian and Arabic made the training of the staff possible.

Much of the actual nursing of patients was done by relatives, mothers and grandmothers, who were admitted with the patients, a plan which overcame tribal and religious difficulties although these were never of great importance. The hospital staff was, consequently, very small—eight female and three male nurses and two ambulance drivers. All staff and their families were adequately vaccinated and most of the staff lived in their own homes, working 48 hr. at the hospital between intervals of going home. They wore hospital gowns and head gear, but no masks or special shoes. Before leaving the hospital they were supposed to have shower baths, but it is doubtful whether this 'disinfection' was carried out very faithfully. However, no cases of smallpox could be traced to the staff or their families, all of whom lived in an area of the town which remained virtually uninfected. Due to the difficulty of obtaining staff, isolation of personnel at the hospital was quite impossible and, if attempted, would almost certainly have led to surreptitious visitors who would have been likely to spread infection.

The principal meals taken at the smallpox hospital were cooked in the kitchen of the main hospital in Tripoli and brought out three times a day, so avoiding a large increase in staff and stores accommodation. Although unorthodox, this arrangement worked well and no infection occurred in any of the main hospital staff, except a dresser in the eye department who had no contact with the kitchens and who lived in one of the infected areas of Tripoli. The staff were all vaccinated and had been revaccinated at the commencement of the epidemic.

Laundering was done on the premises after disinfection in an Army disinfector. Laundry awaiting disinfection was kept in bins with formalin. Linen stained with discharges was difficult to clean, the stains possibly being fixed by the formalin and steaming.

No visitors were allowed to any of the patients, all seriously ill cases having relatives admitted with them.

The general structure of the building was good, concrete with terazzo floors, except in the men's block. The rooms were well lit and ventilated and all windows and external doors were eventually 'fly-proofed'. Furniture was minimal and, as many of the patients preferred to sleep on a mattress on the floor, beds often were not used.

The female ward which housed all the women and children had nine small rooms, each suitable for three or four adults. There was one ward suitable for ten and a very large ward which occasionally housed as many as 100 cases or contacts, a high proportion of whom were young children. The small rooms were used during the early stages of the disease and for the patients who were very ill, and as soon as vacated they were fumigated with formalin and thoroughly cleaned. This procedure is thought to have contributed to the low incidence of septic skin complications. It was noticed that in the men's block, which for the most part had rough concrete floors and no small cubicles and in which this routine of disinfection and cleaning was impossible, the incidence of minor sepsis was higher.

(*f*) *Vaccination*

As already stated in Section III, in the earlier stages of the epidemic the Italian doctors were over optimistic about the vaccination state of the population and the success of the vaccinations. The rapid deterioration of lymph at high temperatures was not appreciated and antiseptics, such as alcohol and acetone, were used lavishly. Later the use of any antiseptic on the skin was prohibited. The vast majority of vaccinations were done by Arab male nurses and the technique was reasonably good. It was not usual to wash the skin of the arm and three insertions, at least 1 in. apart, were made. The Arab vaccinators made rather deep scratches and bleeding sometimes occurred. In spite of the known effect of blood on the activity of lymph this is not regarded as a severe fault; on the contrary it is felt that under the rushed conditions of field vaccinations it is better to make sure that susceptible cells have been exposed by drawing a little blood, than to scarify too lightly. Goodall (1942) reported a slightly higher take rate in vaccinations where a little blood was drawn than in those where it was not, and vaccinations seemed to take very well even when quite deep incisions were made. Three scratches $\frac{3}{8}$–$\frac{1}{2}$ in., were made and were repeated if possible at the end of 5 days. Contacts in hospital were revaccinated at 2-day intervals, vaccination being repeated three times before being regarded as unsuccessful.

Vesiculation was taken as the sole criterion of successful vaccination, all other reactions being regarded as negative. The scar of primary vaccination is definite and a history of primary vaccination should be disregarded if no scar is present. On revaccination in persons with a fairly high immunity very small, but definite, vesicles not unlike those in highly modified smallpox occurred occasionally. These left such an indefinite scar that it was difficult to find the site after some months.

A number of persons on whom vaccination was attempted gave unsuccessful results even when this

was repeated many times. Although in a number of cases smallpox subsequently developed and, therefore, successful vaccination should have been possible, there were occasions when repeated vaccinations were negative, although other vaccinations done at the same time were positive. Subsequent contact with smallpox produced the disease, although often in a mild form, which suggests that a person may have a relatively high immunity to the vaccinia virus when inoculated through the skin while immunity to the smallpox virus entering through the respiratory tract may be less complete. This emphasizes the important point that, even when lymph and technique are satisfactory, repeated unsuccessful vaccination is no guarantee of immunity to smallpox.

Over 100,000 vaccinations must have been done, but it is not possible to give the exact number. No cases of post-vaccinal encephalitis were reported.

(g) The effect of vaccination on the disease

(1) *Mortality*

Table 6 shows the mortality among all cases, the mortality among those vaccinated unsuccessfully, and the mortality among those who were vaccinated successfully after contact. The most striking fact is that in this epidemic there were no deaths in persons who had been vaccinated successfully prior to contact.

(2) *Morbidity*

The relationship between vaccination history and the clinical type of the disease is shown in Table 7. In persons vaccinated successfully after contact the cases are divided into three groups according to whether vaccination was performed between 1 and 5 days, 6 and 10 days, or over 10 days after contact. It will be seen that twenty-one cases of smallpox

Table 6. *Mortality according to vaccination state*

	Never vaccinated	Vaccinated unsuccessfully	Vaccinated successfully (days after contact) 1–5	6–10	10+	Vaccinated successfully (days before contact) 0–1	2–5	6–10	10+	Vaccinated successfully before and after contact
Total cases	132	167	21	31	4	3	6	78	36	9
Total deaths	34	48	0	6	1	0	0	0	0	0
Mortality (%)	25·7	28·7	0	19·3	25	0	0	0	0	0

Table 7. *Relation between vaccination history and clinical type in* 487 *cases*

Clinical type	Mortality (%) (all cases)	Never vaccinated	Vaccinated after contact: unsuccessful	Successful days vaccinated after contact: 1–5	6–10	10+	Vaccinated successfully before contact Within (yr.): 0–1	1–5	5–10	10+	Vaccinated successfully before and after contact*	Total in each type
1	100	2 D2	2 D2	—	—	—	—	—	—	—	—	4
2	69	39 D24	34 D27	—	5 D4	1 D0	—	—	1	—	—	80
3	24	20 D4	44 D13	—	6 D1	—	—	—	—	4	1 (8 y 5)	75
4	18	8 D1	2 D1	—	1 D0	—	—	—	—	—	—	11
5	12	27 D1	16 D4	—	0 D0	—	—	—	—	—	—	43
6	2·5	29 D1	57 D1	3 D0	4 D1	2 D0	—	—	10	9	1 (8 y 8)	115
7	0·7	7 D1	12 D0	11 D0	13 D0	1 D0	1	3	64	23	5 (8 y 11, 8 y 9, 8 y 11, 8 y 6, 8 y 10)	140
8	0	—	—	7 D0	2 D0	—	2	2	2	—	1 (6 y 4)	16
9	0	—	—	—	—	—	—	1	1	—	1 (2 y 7)	3

* Of the figures and letter 'y' in brackets, the figure preceding the letter refers to the number of years between previous successful vaccination and contact, and the figure after the y refers to the day of the incubation period when vaccination was performed giving a vesicular response. D0, D2 etc. indicate the number of deaths in a group.

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occurred in persons who were successfully vaccinated within 5 days of contact. All these cases were mild (types 6–8), and there were no deaths. Successful vaccination, even done as soon after contact as this, therefore, is no guarantee of complete protection although there may be a guarantee against death.

When successful vaccination is performed between the sixth and tenth days after contact the type of disease does not appear to be significantly different from that occurring in unvaccinated persons and, although half the contacts may escape altogether (Table 5), if the disease does occur it may well be severe or fatal. Mortality in this particular group was 19·3%.

The conclusions to be drawn from Tables 5 and 7 are:

(1) Vaccination after contact is no guarantee of protection from attack, although some reduction in severity may occur.

(2) The longer the interval between contact and vaccination the less the chance of any modification.

(3) In this particular population there were no deaths in those successfully vaccinated within the last 10 years, and the majority of cases in this group were very mild.

There is a progressive shift of type from 8 to 6 and even up to 3 and 2 as the period from the last successful vaccination lengthens. The relatively short period of absolute immunity would appear to be in keeping with other observations on the duration of vaccinal protection in coloured races (Boyd, 1945).

One abortive type 8 case in which successful vaccination had occurred 3 months previously is of considerable interest as the vaccination, though undoubtedly positive, had left only a small scar $\frac{1}{8}$ in. in diameter. The patient was an infant of 1 year of age and the number of smallpox lesions was about 6. There was no difficulty in the clinical diagnosis and, although some of the lesions aborted, stained smears showed typical elementary bodies. This was probably a case with a fair level of natural immunity 'boosted' by a successful vaccination which, although 'primary', was of a modified type and the resultant immunity was not sufficient to overcome the massive infection to which the child was exposed. This again emphasizes the occasional difference between immunity to vaccination and immunity to smallpox.

It is not possible to produce any statistical evidence concerning the effect of the number of vaccinal scars on the type of disease. The impression was gained, however, that multiple insertions give a higher degree of immunity which lasts longer. In this series all cases of smallpox occurring in persons vaccinated successfully before contact showed differences in distribution and rate of maturation of the skin lesions, characteristic of the description 'modified' and discussed in detail under diagnosis.

The fact that partial immunity renders it more difficult to 'boost' the immunity by vaccination is in marked contrast to the ease with which immunity to bacterial infections such as diphtheria can be raised from a previous significant level.

VII. DISCUSSION

(a) *Classification*

In reading accounts of smallpox epidemics and the various methods of treatment it is often difficult to assess the exact severity of cases from the descriptions given. Cases are usually classified as confluent or non-confluent and the impression is obtained that to many clinicians the rash is the sole criterion of severity. Smallpox must, however, be regarded as a general virus infection affecting many organs. The skin lesions are only one manifestation of localization and may actually be a relatively favourable one, for in the most virulent type of infection, where the resistance of the patient is negligible, a fatal acute toxaemia without any focal eruption occurs, similar to fulminating meningococcal or leptospiral infections.

The terms malignant and benign are used in their literal sense. Benign confluent may hardly seem descriptive of a type of disease with a mortality of 18%, but the prognosis is very much better than that of malignant confluent with a mortality of 69%. The description 'toxaemic' is undesirable as all types have the pre-eruptive toxaemia, and the description 'haemorrhagic' has been omitted because, although massive haemorrhages only occur in types 1–3, even in mild cases small haemorrhages may be seen at the base of vesicles, giving rise to some confusion in the description of the case.

Using the classification now recommended it is possible to take case histories from the literature on smallpox, such as Ricketts's great book (1908), and to predict the eventual outcome. Many cases regarded as exceptional, such as the dramatic recovery of some confluent cases under certain forms of treatment, can be shown to be entirely in keeping with the prognosis of the particular type.

(b) *Spread of infection*

Smallpox has been regarded as one of the most infectious of all the common fevers, even to the extent of possible aerial spread over considerable distances. Argument still takes place over the latter point.

Experience in this epidemic leads me to believe that contact with a case in the pre-eruptive phase is the most important cause of spread in families. The dust from droplets can cause isolated cases and may account for infection of nursing and sanitary staff who have had no actual contact with the patient.

Although Downie (1947) has shown that the virus can be isolated from scabs and crusts after many months, I can find no evidence that the virus in this

state is of any real epidemiological importance. The dust from respiratory droplets in which the virus is in contact with dried mucus appears to have a different epidemiological significance from the dust of dried scabs in which the virus is presumably surrounded by serum exudate, possibly containing viral antibodies. It is possible that the virus has been modified in some way by passage through the human skin compared with the virus from the respiratory tract which has had no such passage. The hot, dry climate of Tripolitania may have been a factor in the survival time of virus outside the body. Literature on the subject of the infectivity of scabs has to be examined in the light of the general acceptance of this method of spread at the time when it was written. It is probable that insufficient consideration has been given to the possibility of the introduction of infection by persons with subclinical or minimal attacks.

In this connexion Egyptian Public Health Officials (personal discussion) relate how the introduction of smallpox into Egypt by returning Mecca pilgrims was reduced when all personal belongings were disinfected, compared with previous years when they were not. The Egyptian authorities pay great attention to the disinfection of clothing and even to jewellery and metal articles. One cannot but feel that the persons rather than the gifts from Mecca were more likely to be the source of infection. This seems all the more probable as the Mecca pilgrims have all been vaccinated at some time and are more likely to have very mild and, therefore, missed attacks. There can be no question that the modified and extremely mild case can be highly infectious in the pre-eruptive phase. This is borne out by the family tragedies seen in this and other epidemics where the husband, vaccinated successfully 8 or 10 years previously, has a highly modified attack which is unrecognized and gives rise to unmodified and often fatal attacks in the wife and children.

I feel that the infectivity of smallpox has been exaggerated, insufficient stress having been laid on the importance of the susceptibility of the population. It is well known that streptococci may be distributed widely in hospital wards, but only under certain conditions, such as in a burns or plastic surgery ward, will the incidence of clinical streptococcal infections be sufficiently high to give a general picture of high infectivity. On the other hand, if the smallpox virus were disseminated in a ward to the same extent as the streptococci and the occupants were susceptible, the incidence of clinical smallpox would be high, giving the appearance of extreme infectivity. Unrecognized smallpox has been nursed in military hospitals for many days without any spread of infection. The population on such an occasion is largely immune, giving the picture of a disease less infectious than the common cold. Infectivity in the epidemiological sense is really a combined measure of dissemination and host immunity. The probable times of active dissemination of virus and, therefore, periods of maximum risk to susceptible persons are shown in the diagram in Text-fig. 8.

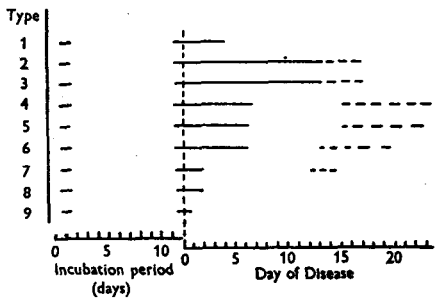


Fig. 8. Times during the incubation period and the clinical attack when the case is likely to be infectious. The continuous line indicates the duration of infection; the interrupted line covers the period when scabbing occurs but this is of doubtful importance.

Passive transfer can probably occur from a case on the first day of the incubation period, a purely mechanical transfer, very close personal contact being essential. In this epidemic there were two cases with fairly definite evidence of spread in this way. Spread of infection from person to person by passive transfer where the persons themselves are immune, as in meningococcal or poliomyelitis carriers, is possible, but unlikely. It would account for the otherwise unaccountable spread of the disease over large distances without the intermediary of recognized patients. Very mild undiagnosed cases are probably more capable of doing the same thing.

The period of greatest infectivity, due to the quantity and possibly also the quality of virus liberated by the patient, would appear to be from the commencement of the pre-eruptive fever. There seems to be no evidence that a patient incubating smallpox is infectious between about the third and ninth days of the incubation period, and I have allowed contacts of cases to attend to urgent business within this period without any evidence of spread, although they subsequently developed an attack.

The length of the respiratory infectious period is of importance in the control of the disease, but varies in the different types of case. Types 2 and 3 have laryngeal and pharyngeal lesions which form shallow ulcers and there is a heavy secondary viraemia. The saliva and respiratory mucus is heavily infected and infection probably persists to the thirteenth or fourteenth day of the disease. Whether the virus is present in the sputum of secondary pneumonia after

this stage is not known, but is unlikely. The mild and, particularly, abortive and *sine eruptione* cases are non-infectious by the seventh day of the disease and can be discharged from hospital.

Droplet infected dust is produced around the patient during the infectious stage and, in the absence of current disinfection, may persist for a considerable time.

(c) *Vaccination*

No work was done on the multiple pressure. method, but the general impression gained was that, given attention to technique and material and a serious realization that the operative skill of the vaccinator was a major factor, the actual method of vaccination was of less importance.

Experience in Tripoli and subsequently elsewhere gave a strong impression that the average young doctor, as represented by the intake into the Army in 1945 and later, had little knowledge of vaccination technique. Some had never actually performed a vaccination during their medical training or since, and the experience of many seemed to be limited to the vaccination of other students during a pathology course.

It is a pity that the word vaccinate has its present rather indefinite meaning, or that some other expression cannot be used for vaccination resulting in a vesicle which alone can be regarded as evidence of the development of sufficient immunity. As pointed out by Marsden (1946) the date of the development of the vesicle is more important than the day the operation is performed.

All doctors, nurses, and health visitors whose work is likely to bring them in contact with smallpox should be vaccinated and re-vaccinated at intervals depending on the risk, but not exceeding 5 years. No Health Department has the right to preach public health to the community without practising upon its own staff one of the soundest procedures in preventive medicine.

(d) *Control*

Contact of a susceptible person with the smallpox virus usually results in clinical infection, but this is not always so. The size of the infecting dose is probably more important than previously supposed. Observations in this epidemic, as in Detroit (Top & Peck, 1943), have shown that smallpox is first and foremost a family disease and, although contact with people outside the family may be considerable, the incidence outside the home of the primary case is small compared with the incidence in the family. Similarly to other respiratory infections numerous secondary foci develop in the families of the chance cases that may occur in a community. It is, therefore, suggested that for smallpox to occur the degree of contact as well as the size of the infecting dose has to be of a magnitude related to the immunity of the population at risk. The high degree of immunity in the Tripolitanian population also supports the view that subclinical infection must occur more frequently than is commonly supposed.

There has been a tendency in the past to vaccinate very large numbers of people on the occurrence of a few cases of smallpox, and the administrative difficulties, the cost and the complications from mass vaccination may be more important than the disease itself. Recently in New York, a State in which, nominally at least, there is compulsory vaccination, 7½ million persons were vaccinated at the rate of 250,000 a day on the occurrence of three cases of smallpox. This seems to be panic action in the extreme. Until lately mass vaccination was also done in the United Kingdom and it was possible to read of numbers of persons queuing for hours in the cold waiting to be vaccinated on the occurrence of only a few cases. Under the conditions of a mass vaccination campaign it is probable that the number of successful takes may often be very low, so that mass vaccination may not produce such a high proportion of immunes as is generally supposed. The credit for stopping an epidemic ascribed to mass vaccination may, in some instances, be undeserved. A simple barrier of immunes is more important. The infectivity amongst the general population is not so great as among close family contacts. The amount of movement of population around the infected persons and social and economic conditions are important.

The experience in one military unit in Tripoli illustrates some of these points. In a group of 300 men living in one large multi-storied block one soldier was found to be suffering from highly modified smallpox on the fourth day of the disease. On paper the unit was 100% up to date with vaccination (2-year intervals). However, on revaccination with lymph of known potency by an experienced officer approximately 20% of the unit showed a vesicular take and were, presumably, also susceptible to smallpox. Infection had been introduced by an Arab 'boy' employed in cleaning and general duties, who was suffering from a highly modified attack and had remained at work the whole time. Opportunity for widespread infection was present, but no secondary cases were found, although careful search was made.

Smallpox has been introduced into the United Kingdom on a number of occasions in the past few years and there has been some surprise that, without mass vaccination, and often in the absence of any definite control measures, infection has not become widespread. This is, however, no new phenomenon as many small epidemics were recorded in the late nineteenth century, even in densely crowded parts of London where, similarly, infection did not spread

and where it was reasonably certain that the population was not sufficiently well vaccinated to be immune.

(*e*) *Laboratory aids to diagnosis*

The main conclusions on the value of the examination of smears for elementary bodies are as follows:

(1) All cases of smallpox examined showed typical stained elementary bodies.

(2) Other skin diseases which were examined (not including chickenpox) were negative.

(3) In no case was a positive result found, even in the most trivial abortive type, where the diagnosis was not relatively straightforward to experienced clinicians during an epidemic.

It is necessary for an experienced person to take and stain the preparation and the stain must be in good condition. The test is likely to be of limited value in the diagnosis of sporadic cases in Great Britain as it depends on the chance of a pathologist practised in its performance having the necessary stains ready and tested when cases occur.

Egg culture (Downie, 1947) may ultimately prove to be of considerable value in proving the diagnosis of doubtful cases, but, unfortunately, the M.O.H. or other consultant who is called to see a patient must make a reasonable provisional diagnosis on the spot to determine the necessary administrative action. This may be most difficult in the highly modified case.

(*f*) *Pathogenesis*

The natural history of smallpox is not completely known, but it is reasonably certain that the virus enters through the nose or throat and is probably present locally for a few hours. From then until the twelfth day it does not appear to be present in the respiratory mucus, or in the blood, but must be in some, presumably intracellular, situation multiplying.

At about the twelfth day the virus seems to be liberated suddenly into the blood stream giving rise to the pre-eruptive syndrome, intrauterine infections, and possibly direct stimulation of the uterine muscle. If the amount of virus is very great massive infection of all the tissues occurs, resulting in the type I case. In most cases, however, it is distributed in the capillary bed of the skin, mucous membranes and other structures, but there is a considerable variation in the susceptibility of the different tissues. The skin is affected in almost all types of the disease and the mucous membranes are particularly affected in the malignant types, whereas the pleura and peritoneum are rarely affected in any type. This localization of virus during the eruptive phase is regarded as an important part of the mechanism of immunity and further reference will be made to it.

In the malignant type there appears to be a secondary growth or development of virus in the skin and mucous membranes and probably other organs, concurrently with the secondary toxaemic state. If the patient survives this severe phase a climax is reached about the twelfth or thirteenth day, the temperature drops quite suddenly and there is great improvement in the general condition. There are, therefore, two phases of development of the virus in the severe case. In the less severe case where the host-parasite balance is less in favour of the parasite, the secondary or eruptive phase of the disease consists in the localization of the virus almost entirely in the skin and neutralization would appear to be effected there.

Although in the less severe cases the virus probably grows and multiplies in the skin lesions, toxaemia or viraemia of the type seen in the malignant case does not occur. Whereas in the malignant case the virus is presumably neutralized at the time of the crisis by some antibody reaction, in the non-malignant type the virus is, in effect, extruded from the body in the crusts and scabs and can be isolated and grown on various living materials. From epidemiological considerations it is felt that this virus must be different in its invasive power from the virus obtained from the body in the earlier stages of the disease. The Chinese practice of inducing variolation by instilling smallpox scab material into the nostrils rather supports this idea as, presumably, the disease induced in this way is usually less severe than that occurring naturally.

(*g*) *Immunity*

(1) *The mechanism of immunity*

Any theory of immunity in smallpox must attempt to explain:

(*a*) The different types of the disease, including haemorrhagic, malignant and benign, the rashes associated with them and the different case mortalities.

(*b*) The variation in extent and maturation of the rash, such as the distinction between few lesions with normal maturation and many lesions with accelerated maturation.

(*c*) Modification of the rash in type and rate of maturation associated with previous successful vaccination.

(*d*) The mechanism of the immunity produced by vaccination, including the development of vaccinia during the incubation period of smallpox.

There appear to be three distinct forms of immunity, anti-invasion, anti-dissemination and local skin immunity. The anti-invasion immunity determines whether or not the virus entering the nose and throat will in fact multiply and produce the pre-eruptive fever, the primary smallpox syndrome. This is probably the same as the 'toxaemic' immunity to which Wilkinson referred (1942) as produced by vaccination. This immunity determines whether or not infection will occur and in immunes is at a level

sufficiently high to prevent tissue invasion. Possibly it is a local cellular immunity of the respiratory mucous membrane. It is produced by successful vaccination, but declines relatively quickly while the other forms of immunity may still be present; its loss accounts for types 7, 8 and 9 occurring in subjects vaccinated between 5 and 10 years previously. Following an actual attack of smallpox this type of immunity is much more persistant.

The anti-invasion immunity seems to be a fairly independent factor and, generally, is complete or absent, resulting in complete resistance or infection. This view is supported by the equally severe pre-eruptive syndromes in all types of case. However, in the 'illness of contact' the anti-invasion immunity is presumably not sufficient to prevent some primary localization of the virus and its multiplication. The 'virus shower' which occurs on the twelfth day accompanied by characteristic symptoms is very rapidly neutralized by the highly sensitized immunity mechanism. This neutralization accounts for the very short attack and the slight infectivity. In highly immune persons the 'illness of contact' may also have an allergic element in its causation. Possibly the peculiar morbilliform eruption, principally in the flexures, which sometimes occurs as a prodromal rash in very mild cases may be an allergic phenomenon due to the delayed action of this immunity mechanism, coupled with a high skin immunity.

The second form of immunity is concerned with the dissemination of virus in the secondary phase. The degree of this immunity affects both the skin and mucous membranes, for when the anti-dissemination factor is low types 2 and 3 occur with gangrenous necrosis of the skin, no pock localization, destruction of the capillaries and consequent massive haemorrhages into the skin and other organs. The intense viraemia which is built up during the secondary phase in the malignant cases reaches a level at about the tenth day which often results in death from toxaemia or massive haemorrhages. Associated with this viraemia is the absence of pus formation in the skin and other tissues. It is not known whether this is a specific effect on the haemopoeitic tissues, although the total white counts tend to be low. Burnet (1945) has suggested that the toxaemia and fatal outcome of smallpox of the more severe kind might be due to super-added streptococcal infection of the skin, but in the cases here reported the clinical picture had all the appearance of being due to the virus of smallpox alone. In this particular type of case penicillin has no effect whatsoever on temperature, toxaemia, appearance of the skin, or outcome and therefore it seems likely that streptococci play no part.

The third form of immunity is the cutaneous affinity for and neutralization of virus and would appear to be a true local virus and antibody reaction taking place specifically in the skin. Skin immunity in smallpox sufficiently high to prevent successful inoculation with vaccinia is not produced until the rash is fairly well developed, about the third day (Ricketts & Byles, 1908).

In the benign cases, even if confluent, once vesiculation has occurred the general condition begins to improve, but in malignant cases steady deterioration continues and the skin does not appear to be capable of fixing and neutralizing virus. There are two reasons for this inability; the skin is slightly refractory as the basal skin immunity is above 'zero', and the massive dissemination of virus due to the absence of the systemic anti-dissemination factor results in the physical destruction of the skin. This would explain the well-recognized fact that smallpox occurring in persons who have been vaccinated successfully 20–30 years before produces a higher proportion of cases of the malignant type. In such persons anti-invasion and anti-dissemination immunity will almost certainly be non-existent, whereas some slight skin immunity is usually present as shown by the slightly modified type of vaccination take.

There is a fairly high level of both anti-dissemination and skin immunity in type 6. Type 7 occurs when the anti-dissemination factor is sufficiently high to prevent all signs of secondary toxaemia and is rare amongst unvaccinated persons. When it does occur the eruption is sparse, but is not modified and usually passes through all the stages of development.

When vaccination or variolation is performed virus is inoculated into the skin, grows in this tissue first and not until relatively late in the development of the vesicle and pustule does the subject become immune to the inoculation of smallpox virus into the nose or throat. It would appear that the time sequence of events in vaccination is the reverse of that occurring in smallpox. As the skin immunity rises the skin becomes more and more refractory to the inoculation of vaccinia virus which passes from the skin into the blood stream, as evidenced by the occasional occurrence of generalized vaccinia in man and its common occurrence in experimental animals. The very rareness of this complication in man suggests that if a viraemia occurs it is more in the nature of a bacteraemia than a septicaemia. Immunity sufficient to modify the eruption occurs before immunity sufficient to prevent attack. Twenty-one cases vaccinated successfully after contact with smallpox between the first and fifth days of the incubation period were of types 6, 7 and 8, whereas in thirty-one cases where vaccination was performed between the sixth and tenth days eleven were types 2 and 3 and there were five deaths.

The figures in Table 7 also show that anti-invasion and anti-dissemination immunity are lost sooner than the skin-immunity factor. In this series of

cases all those who had had successful vaccination at any time showed some element of modification in the eruption, although five of the cases, types 2 and 3, showed no difference in general severity from similar unvaccinated cases. There were, however, no deaths. The skin-immunity reaction probably never declines to the level of the unvaccinated and uninfected subject.

According to Ricketts positive vaccination can occur late in the disease, even when done on the second and third day of the eruption. This can be explained by the complete dissociation between the systemic immunity mechanisms, anti-invasion and anti-dissemination, and the skin-immunity mechanism. As far as can be determined, once vesiculation has occurred in the skin, that is on the third or fourth day of the rash, vaccination will be impossible.

Previous successful vaccination, which does not usually modify the pre-eruptive fever, causes considerable change in the affinity of the skin even when dissemination is fairly widespread, as in type 6. More rapid maturation of the skin lesions occurs, showing a sensitized immunity mechanism. All variations are seen down to the abortive case where the lesions may not become vesicular.

Entry of the virus through the skin as in vaccination or variolation is likely to produce immunological changes of different type or magnitude from those produced in the natural disease with entry by the respiratory tract. The course of events in inoculated smallpox of historical fame and also in generalized vaccinia suggests that, depending on the type of infective agent and the level of immunity in the host, the inoculated disease can approach closer and closer to the natural disease, but a transcutaneous infection will always be different from the respiratory one. Generally modern vaccination with calf lymph gives an entirely local lesion furthest removed from the natural disease. The higher incidence of general vaccinia in vaccination with egg culture lymph (Marsden, 1946) suggests a disease a little nearer to that occurring naturally. Probably the immunity produced is also greater.

In successful vaccination the natural affinity of the skin for virus is neutralized by a successful take. It is well known that some people are difficult, perhaps impossible, to vaccinate, but they can still contract smallpox and when this occurs the disease should be of a severe type, 1, 2 or 3, or a very mild type, 7 or 8. Experience shows that this is so. In some persons, however, successful vaccination may not result in the skin affinity being neutralized completely in all parts of the body; the antibody mechanism may be saturated and the skin refractory to further virus at the site of the inoculation, but successful vaccinations may be made on other parts of the body (Horgan & Haseeb, 1944).

An attempt is made in the model in Pl. 13 to show the three immunity factors in smallpox, their relation to the nine types and to the completely immune state.

(2) *The source of immunity*

Immunity to smallpox as in other diseases may be acquired as the result of successful vaccination or naturally through previous contact with the virus resulting in clinical or subclinical infection. Natural immunity has long been suspected because mild attacks sometimes develop in persons who could not possibly have acquired immunity, but definite evidence of its existence has not been obtained.

The following information is presented to suggest the presence of natural immunity in this particular population. In Text-fig. 9 are two series, one of 132 and the other of 167 cases of smallpox, comparable in age and sex distribution. They occurred during the course of the epidemic, many from the Sugh el Giumaa area, and, taking into consideration the close contact associated with the Arab way of life, it is probable that they were all exposed to similar infection.

Group 1 had never been vaccinated and group 2 had had vaccination performed, but the operation did not result in vesicle formation and was, therefore, regarded as unsuccessful. Assuming that the application of lymph to the arm without the formation of a vesicle does not affect the immunological state of the subject, the same proportion of cases of the different types 1–9 would be expected in these two groups. The two series are, however, different to a degree that is unlikely to have occurred by chance. I am indebted to Dr B. L. Welch, Reader in Statistics, Department of Mathematics, University of Leeds, for the examination of the figures, and he has shown that the χ^2 value is equal to 15·52 where the 1% significance level for the number of degrees of freedom in the series is 13·28.

It seems reasonable to assume that the group who have never been vaccinated represents a random sample of those in this particular population who contracted smallpox. Since group 2 also contracted smallpox it is correct to say that both groups were susceptible, but they were not susceptible in the same way as they gave a substantially different number of cases in each type.

From the point of view of immunity the only difference would appear to be that when group 2 were vaccinated in Tripoli, 1946, the operation was not successful. No doubt, with persistence many, possibly most, could have been successfully vaccinated, but the facts suggest that these persons were refractory to vaccination as performed at the time. No difference in the two groups would be expected if this failure were due to technique. It is, therefore, suggested that group 2 had some basal immunity

which showed itself by a degree of refractoriness to vaccination and a difference in the type of smallpox experienced.

If this change of type distribution is a significant measure of immunity a group of persons known to have some slight immunity should show a similar

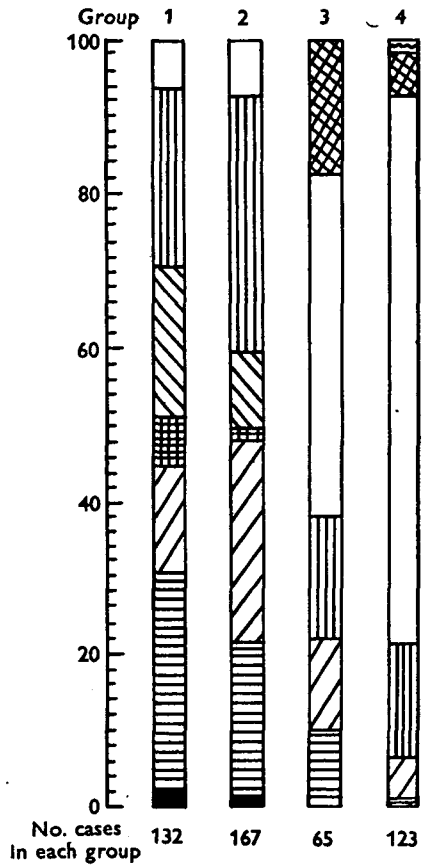
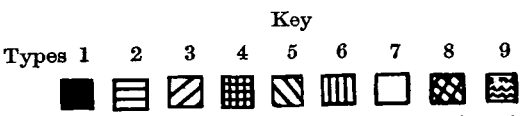


Fig. 9. Diagram showing the incidence of the nine types of smallpox in four groups with different vaccination histories. Each group is standardized to 100.



Group 1. Never vaccinated. Group 2. Vaccinated unsuccessfully. Group 3. Vaccinated successfully after contact. Group 4. Vaccinated successfully some years before contact.

type of change. A third group of smallpox cases where vaccination was positive after contact was standardized to 100 and compared with groups 1 and 2. Examination was also made of a fourth group in which vaccination had been performed successfully, usually some years before contact. It can be seen that there is a regular change in distribution which in groups 3 and 4 is known to be due to some form of immunity. There is just a possibility that in a small proportion of cases this immunity is due to old subclinical infection, but, in view of the age distribution with 80 % under 25 and the history of the territory, there was fairly conclusive evidence that almost all were certain to lack previous contact. It is concluded, therefore, that the immunity in group 2 most probably represents some degree of natural immunity.

In spite of the small series, the incidence of smallpox in mothers and their young infants also lends some support to the idea that this particular population had some immunity of a natural type. It would be unwise, however, to assume that all races and populations possess this immunity, or to the same degree.

VIII. SUMMARY

1. The field epidemiology is described of two epidemics of smallpox which occurred in Tripolitania during 1946.

2. Control was effected by the 'expanding ring' method instead of mass vaccination of the population.

3. Five hundred cases were admitted to hospital and statistics are given of mortality in relation to age, sex and vaccination state.

4. A new clinical classification is described which enables a reliable prognosis to be made and provides a guide to treatment.

5. Controlled experiments were made on the use of penicillin in treatment. Although it is without effect on the viraemia and in general does not significantly affect mortality, it has the power of suppressing suppuration and reducing the effect of secondary sepsis. It also minimizes the amount of permanent scarring of the skin.

6. Evidence is presented to show that the period of maximum infectivity is the stage of the pre-eruptive fever. The mildest cases are infectious, but only for a short time.

The virus contained in dried scabs is not considered to be an important source of infection; it may, be modified in some way by passage through the skin.

7. Although not protected by successful vaccination many contacts showed a considerable resistance to infection. Amongst the older people this may have been due to previous clinical or subclinical attacks. Amongst the younger persons evidence is produced to show that many were relatively refractory to vaccination and experienced the disease in a different way, suggesting that there is natural partial immunity to smallpox in this particular population.

8. The complex problem of immunity in smallpox is discussed, and it is suggested that three factors

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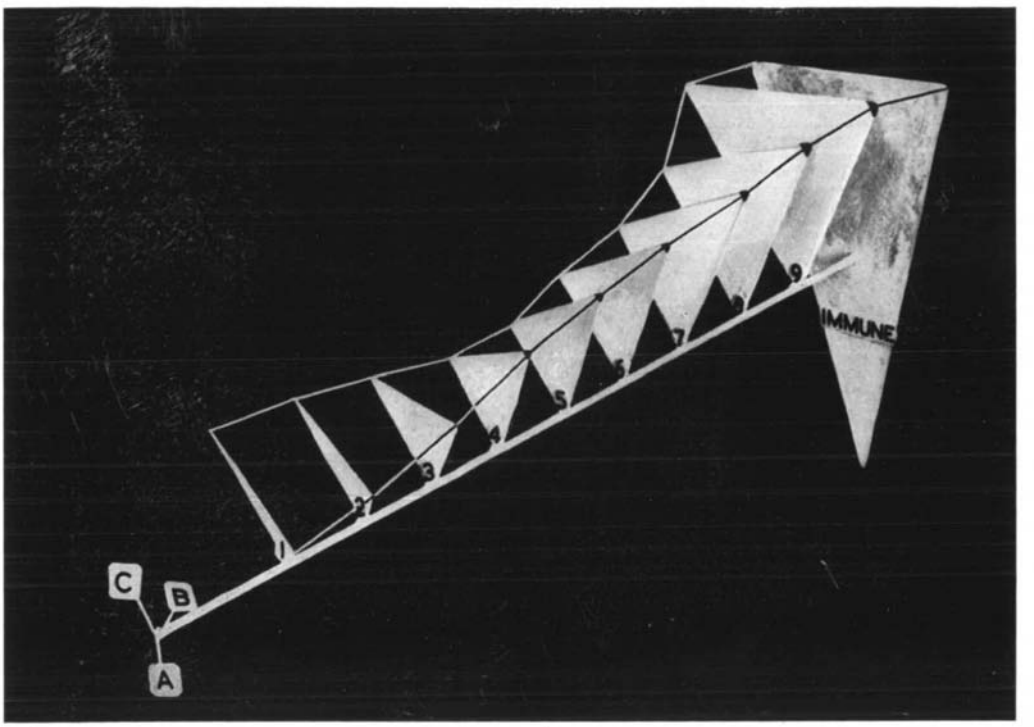

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operate, an anti-invasion factor, an anti-dissemination factor and a local skin immunity mechanism. A photograph is given of a model made to show the interaction of these three factors in producing the immunity levels which determine the type of disease. It also accounts for the immunity reactions in vaccinia and in smallpox in the vaccinated subject, both when vaccinated successfully during the incubation period of smallpox and when vaccinated successfully some time prior to contact.

It was perhaps unfortunate that this work had to be done under Service conditions without access to literature such as Ricketts & Byles's (1908) classic *The Diagnosis of Smallpox*, or Marsden's works, particularly his review of vaccination (1946). The lack of authoritative guidance, however, was compensated for by the enthusiasm of all concerned.

I am especially grateful to Lt.-Col. W. McN. Graves-Morris, R.A.M.C., P.M.O. Tripolitania, for allowing me the opportunity to experiment and to use such a large proportion of the territory's supply of penicillin.

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EXPLANATION OF PLATES 12 AND 13

PLATE 12

Photograph showing two children with smallpox modified by successful vaccination during the incubation period. The nearer child had a successful vaccination at the same stage as that of the further child. On the left knee and thigh can be seen the lesions of scabies and old secondary impetigo. On the inner aspect of the thigh are two impetiginous lesions which have been inoculated with vaccinia by the child scratching and are at about the twelfth or thirteenth day of development. Slightly higher up the thigh is the pearly vesicle of smallpox about at the fourth day of the eruption.

PLATE 13

Photograph of a model made to show the interaction of the three immunity factors which determines the immune state and the nine types of smallpox. In the model the three vectors *A*, *B* and *C* represent anti-invasion, anti-dissemination and skin-immunity factors respectively. The units of measurement are arbitrary and for convenience of demonstration the value of the skin-immunity factor has been made appreciably above zero in all types, but the area of each triangle represents the summation or the resultant immunity. The horizontal bar indicates the threshold between clinical immunity and infection. In the immune state part of the vector triangle is below this bar whereas when the disease occurs, as in types 1–9, the vector triangle is wholly above the bar.

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