

SOME OBSERVATIONS ON THE IMMUNITY AND DISABILITY CAUSED BY VACCINIA

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I. INTRODUCTION.

THESE investigations were made at Greenwich Hospital School, where all the new entrants are vaccinated against small-pox. Up to September, 1928, the calf lymph was inserted by means of two or three "cross-hatched" scarifications. In September, 1928, a technique consisting of one insertion with the minimal amount of trauma was substituted. The method chosen was that called "multiple pressure or prick" technique as recommended and described by Leake (1927) of the U.S. Public Health Service.

The inhabitants of this school are a fairly homogeneous social group, since their fathers are almost all old naval or marine ratings. Their age at entry is 11 to 13 years. About three-quarters of the boys have been vaccinated in infancy; therefore these new entrants formed a good sample for the examination of the effects of revaccination 12 years after primary infantile vaccination. Each batch of "new boys" after being vaccinated were examined daily by the same observer (S. F. D.), and the reactions to the calf lymph were classified according as the inflammatory areola round the site of insertion reached its maximum (*a*) within 3 days, (*b*) from the fourth to seventh day, or (*c*) later. According to Leake's terminology these three classes of reaction are termed (*a*) Immediate, (*b*) Accelerated and (*c*) Primary. (Observe carefully the distinction between a "primary reaction" and a "primary vaccination.") This classification is entirely arbitrary, there is no sharp line of demarcation between the three types of reaction which merge into each other. Thus those reactions which attain their maximum about the end of the third day, or beginning of the fourth, might sometimes be classed as "immediate" by one, and "accelerated" by another, observer. Similarly reactions reaching their acme about the seventh or eighth day might, according to personal bias, be classed either "accelerated" or "primary." In this series the personal equation has remained constant and, although another observer might have recorded a slightly different set of frequencies, yet it is unlikely these differences would have been of such an order or kind as to affect seriously the main conclusions drawn from this investigation. It must also be borne in mind that the criterion used in this

classification of vaccine reactions is the time taken by each specific lesion to reach the maximum area of redness—the condition of the vesicle and actual area of the lesion varies in individual cases, irrespective of the class of reaction. Although generally the size and severity of the reaction varies inversely with its rate of development, yet, not infrequently one subject will produce an “accelerated” reaction with a maximum intensity on the fifth or sixth day, which is larger and more intense than the “primary” reaction of another subject which may not have reached its acme until the tenth or eleventh day.

The typical immediate reaction (a small unbroken papule with an areola about 10 mm. in diameter) obviously indicates immunity to vesicular vaccinia; whether it indicates immunity to variola is not under discussion. Therefore those boys who gave immediate reactions in this investigation are conveniently termed “immunes.”

The vaccine employed in this work was obtained from the Government Lymph Establishment, and was always used within a week of its receipt.

II. IMMUNITY AND BATCH OF CALF LYMPH.

Table I gives the percentages of immediate reactions among 329 *successful second* vaccinations, performed on the average 12 years after a *first vaccination*

Table I. *Revaccination at 11–13 years of age after primary vaccination in infancy.*

Date of revaccination	Sept. 1928	Oct. 1928	Jan. 1929	Feb. 1929	Apl. 1929	Sept. 1929	Oct. 1929	Jan. 1930	Total
No. tested	44	45	33	35	44	48	38	42	329
No. “immune”	18	16	6	8	14	24	16	20	122
% “immune”	40	36	18	23	32	50	42	48	37
P.E. % ±	4·2	4·8	4·5	4·7	4·7	4·8	5·3	5·1	1·8

“Immune” = maximum vaccinia areola within 3 days.

in infancy which left obvious scars. A few subjects who had been primarily vaccinated or revaccinated since infancy and before joining the school, and a few who did not “take” at all on revaccination, were excluded from this group. It will be noted that the frequency of immunes among these revaccinated subjects varied significantly in the eight sub-groups. The reason for this is unknown, but it might have been partly due to variations in the potency of the different batches of lymph used. Force (1927) and Thomas (1926) both state they obtained more immediate reactions when using a less potent lymph. The percentage of immunes in the whole group was 37, but varied between 18 and 50 per cent. in the sub-groups.

III. IMMUNITY AND NUMBER OF OLD SCARS.

In Table II the same sample has been arranged according to the number of scars resulting from the primary infantile vaccination and, in addition, the reactions of 102 boys with no history or marks of a previous vaccination are given along the top line.

Table II shows that:

(1) Immune reactions were about two-and-a-half times as frequent in boys with two or more scars as in those with one.

(2) There was no significant difference in the frequency of immediate reactions recorded among boys with two, three, or four, marks. The numbers of those boys with two and three marks were, however, relatively small.

Table II. *Type of vaccinia reaction according to number of old scars.*

No. old scars of infantile vaccination	Reactions			Total	% "immune"
	Primary	Accelerated	Immediate		
0	98	4	0	102	Nil
1	15	96	23	124	19 ± 2.3
2	4	22	18	44	41 ± 4.9
3	0	23	23	46	50 ± 4.9
4	2	55	58	115	50 ± 3.1
Total re- vaccination	21	196	122	329	37 ± 1.8

P.E. % immune diff.: 1 scar and total revaccination = 3.0.

" " " 2 or more scars and total revaccination = 2.9.

Therefore these differences are statistically significant.

(3) Only four cases of presumably primary vaccination at 12 years of age gave an "accelerated" reaction—none gave an "immediate" reaction.

(4) Of 168 boys with one or two marks, 11.3 per cent. gave a primary reaction, whereas in only 1.2 per cent. of the 161 boys with three or four scars was the maximum effect delayed beyond the seventh day.

Table II shows that at Greenwich Hospital School the rapidity of the development of the vaccinia lesions at the age of 12 was greatest in the sub-groups who had more than one insertion of lymph in infancy, and least among the boys who had never been vaccinated before.

IV. IMMUNITY AND AREA OF SCAR TISSUE.

The question arises whether it is the number of marks, or the total area of scar tissue, which is most closely associated with the probability of obtaining an immediate reaction on revaccination. Of course, other factors being equal, two or more scars will, in general, cover a greater area than one. The point, however, is whether it is the area *per se*, irrespective of the number of scars, which is the factor determining the larger proportion of immunes among the groups with multiple scars. To elucidate this point it is necessary to compare groups with the same number of scars but different areas of total scar tissue. The scars of the last three batches of new entrants shown in Table I were measured, and the results, together with type of reaction and number of scars, are summarised in Table III. The group with a single scar, over 4 sq. cm. in area, did not give a greater proportion of immune reactions than boys with single scars less than 2 sq. cm. in area. Boys with four marks, but less than 6 sq. cm. of scar tissue, gave a higher proportion of immune reactions than "four scar" boys with more than 9 sq. cm. In the bottom line of Table III

the average area of a single scar in each group is given. Two interesting facts emerge: (1) the mean area of a single scar was smaller, the greater the number of old vaccination marks; (2) on the average, those subjects, who gave immune reactions on revaccination, had smaller scars than the others. The first observation suggests, that if at the time of vaccination two or more insertions are made close enough together, they will mutually inhibit each other's full development—a phenomenon noticeable in other skin infections. The second observation indicates that the subject, who gave a more severe reaction than usual to vaccinia virus in infancy, as indicated by the large resulting scars, probably had a special inherent skin allergy, or susceptibility to the virus, which made

Table III. *Revaccination at 12 years. Type of reaction, with area and number of old scars.*

1 scar			2 or 3 scars			4 scars			Total boys				
Area (sq. cm.)	Reaction		Area (sq. cm.)	Reaction		Area (sq. cm.)	Reaction		Area (sq. cm.)	Reactions			% I
	I	A		I	A		I	A		I	A	Total	
-2	3	9	-4	4	4	-6	14	5	-4	12	25	37	32
2-4	5	12	4-6	6	6	6-9	12	8	4-6	23	23	46	50
4+	3	12	6+	5	6	9+	8	6	6+	25	20	45	56
Total	11	33	—	15	16	—	34	19	—	60	68	128	47
% I	25		—	52		—	64		—	47			—
<i>Average area of a single scar in sq. cm.</i>													
—	3.1	3.9	—	2.1	2.2	—	1.7	1.9	—	1.9	2.4	2.1	—
I = maximum areola within 3 days A = „ „ after 3rd day													

him more prone again to give a more intense and delayed reaction than the average on revaccination. In fact boys, who had the smaller old scars than the mean, were in general born with a higher degree of “natural” immunity to vaccinia than those with the larger marks, which *natural* immunity they retained irrespective of any subsequent gain or loss in *acquired* immunity. Thus as a rule the extent of a primary vaccinia lesion probably depends more on the nature of the host than on variation in the parasitic virus.

The data in Tables II and III show that in this sample the frequency of immediate reactions in a group was more closely associated with the number than the total area of old scars, and was inversely associated with the area of scar tissue when the number of scars was held constant.

V. ON THE DISABILITY CAUSED BY VACCINIA.

The carefully kept sick books of Greenwich Hospital School enabled some reliable statistics on the amount of disability caused by vaccinia to be abstracted (see Table IV). The same clinician (P. M. M.) treated all these samples and decided which vaccinated boys should stand off duty, and how long they should remain on the sick list. The personal equation of the observer was therefore the same for all the groups represented in Table IV. The groups

vaccinated with two or three scarifications will be called "old"; those who received one insertion of lymph by "multiple pressure" (Leake's technique), will be referred to as "new." Before comparing these groups, it may be noted that about three-quarters of the morbidity from vaccinia was caused by the primary vaccinations. As judged by this series of revaccinations, one insertion at the age of 12 rarely caused a reaction severe enough to interfere with a boy's normal work or recreation. Other factors being equal, the proportion of primary vaccination in these groups did not vary sufficiently to affect the relative incidence of sickness appreciably.

In the "old" group the year 1924 was included because at that time three insertions of lymph was the rule, after which two became the routine. The average duration of illness was greater in the sub-groups which received three insertions, but there is little significant difference in the proportion of boys who

Table IV. *Disability caused by vaccinia.*

Tech- nique	No. in- sertions	Date of vaccination	No. of vaccina- tions	% primary vaccina- tions	No. sick with vaccinia	% sick with vaccinia	Days sickness per vac- cination	Average no. days sick per case
Old	3	1924	320	21	50	15.6	1.83	11.8
	2	1927	334	22	43	12.7	0.90	6.9
	2	1928 Jan.- Sept.	169	20	33	19.4	1.91	9.8
	3 & 2	Total "old"	823	21	126	15.3	1.47	9.6
New	1	1928 Sept.- Dec.	124	24	7	5.6	0.68	12.0
	1	1929	346	22	17	4.9	0.78	15.4
	1	1930	357	28	23	6.5	0.80	12.4
	1	Total "new"	827	24	47	5.7	0.77	13.4

Total no. days sickness by "old" technique 1209
 " " " " "new" technique 632

were stood off duty in the "old" sub-groups. Comparing the total "old" with the total "new" group, it is seen that 15.3 per cent. of the former and only 5.7 of the latter were placed on the sick list—the morbidity was therefore 2.7 times higher with the old than with the new technique. The days lost per vaccination were, however, only twice as many with the old technique, because the average time (each vaccinated boy who "went sick" was on the list) was proportionately greater among the "new" groups. This was an unexpected observation, but when the sick records are examined in detail, one of the reasons for the apparently more protracted illness caused by the single lesion than the multiple becomes clear. The new entrants to the school are more susceptible to all common infections than other boys. The morbidity from conditions other than vaccinia is not affected by the vaccination technique. In the sick records there were many entries such as "vaccinia and tonsilitis," "vaccinia and boils," etc. All such cases were included in making Table IV, since it was impossible always to decide whether a vaccinated boy would have

been stood off duty at all but for a coincident disease. In such double infections it was rarely certain whether the vaccinia or the accompanying disease was responsible for the length of time the patient remained on the sick list. Thus to some extent the number and duration of the entries of "vaccinia" in the sick records depended on the prevalence of other infections. As all recruits were vaccinated, the above effect on duration of illness was more marked, the lower the proportion of new entrants whose arms were sufficiently bad to necessitate their "going sick." This is the main reason why an *apparently* more protracted illness was caused by a less damaging technique. There is also a possible secondary cause, accelerated reactions generally run a shorter course than primary reactions. It is therefore not unlikely that, in the "old" group, the multiple scarifications caused the ratio, of sickness among revaccinated boys to sickness among primary vaccinated boys, to be higher in the "old" than in the "new" series. Such an increase in the relative proportion of accelerated reactions, bad enough to cause "sickness," would tend to make the mean duration of total illness from vaccinia less in the "old" than in the "new" group. There was little obvious difference in the time taken to heal by the uncomplicated but severe primary vaccinia which were produced by the old and new technique. All things considered, it is probable that the number of vaccinated boys to be placed on the sick list, rather than the number of days' sickness reported, is the better indication of the relative amount of disability which was directly due to the virus of vaccinia.

VI. DISCUSSION.

The frequency of immediate reactions to vaccine lymph in any group depends on many variables, among which may be potency, dose, and strain of the virus, time elapsing between two vaccinations, the number of revaccinations, the age and skin sensitiveness of the subject, and the personal equation of the observer. In consequence it is not surprising that the reported frequencies of immediate reactions show considerable variation. In one American sample Thomas (1926) found 57 per cent., while Force (1917) in another sample obtained 48 per cent. of immunes. These frequencies are considerably higher than the 37 per cent. recorded at Greenwich, though the average time elapsing since the previous vaccination was greater in the American groups. Neither Thomas nor Force, however, mention the age of their subjects or state if they had had more than one vaccination prior to the time when the immediate reactions were recorded. Mackenzie (1928) revaccinated 85 British army recruits, aged 18 to 21 years, who had only been previously vaccinated in infancy. This group produced only 18 per cent. of immediate reactions. Among another small group of 20 recruits who had been primarily vaccinated or revaccinated since infancy, 18 (90 per cent.) were "immunes." The first group of soldiers was comparable with the Greenwich new entrants, except that the mean interval between the vaccinations was 20 instead of 12 years. The lower percentage of "immunes" among the soldiers

could be attributed therefore to loss of immunity during the extra lapse of time. The excessive difference in the immunity of the two groups of soldiers, examined by the same technique and observer, is very suggestive that, although the time between two vaccinations may be equal, yet, if the first vaccination is also a revaccination, the probability that the second reaction will be immediate is increased. Hence the greater frequency of immune reactions in Force and Thomas' groups than among Greenwich schoolboys, if not due to the use of a less potent virus, could be attributed to the exclusion of subjects who had been vaccinated more than once from the Greenwich group.

With regard to the use of old vaccination marks as an index of immunity Leake and Thomas (1926) say: "Judging by the immunity reaction the smallest scars indicated the best... and the largest scars the poorest protection." No mention is made of the number of marks in this paper. On the other hand, Mackenzie (1928) found that in his group the greater the total area of scar tissue, when the number of marks was ignored, the greater the persistence of immunity to vaccinia. The observations at Greenwich confirmed the conclusion of Leake and Thomas, *provided the number of scars was held constant*, and were consistent with Mackenzie's results when the number of scars was not taken into account—because, irrespective of the size of the scar, the probability of obtaining an immediate reaction was greater at Greenwich in subjects possessing two or more old vaccination marks than those with only one. This last conclusion has an interesting analogy in the association of the small-pox mortality among vaccinated patients with the number and area of their scars. In the Ministry of Health, *Report on Vaccination, 1928* (p. 60), from an analysis of Cameron's statistics on this subject, Greenwood concludes "that for a given area there is rather more probability of death with only one or two scars than with four."

At Greenwich the substitution of one insertion of lymph with a minimum of trauma for two or three scarifications halved the days lost from vaccinia. The data are not good enough to decide what fraction of the saved time was due to the single insertion and what to the minimal trauma. But, from our experience, provided scarification is limited to an area of skin no larger than a normal vaccine vesicle, the lesion which results in *primary* vaccinations is not appreciably more severe than that produced by "multiple pressure" or "the eighth of an inch linear scratch." This impression receives some support from an experiment described in the above-mentioned report (*loc. cit.* p. 70), where six 6 mm. scratches produced more local and constitutional disturbance than two 18 mm. linear insertions of vaccine lymph. It would therefore appear that the reduction in the number of insertions, rather than the change in the technique of insertion, was the factor chiefly responsible for the fall in the morbidity from vaccinia at Greenwich Hospital School.

The practical lesson of this work is that where a community is under a discipline which permits the enforcement of revaccination every five years, the saving in disability (caused by the use of single instead of multiple insertions)

is well worth while—even if multiple insertions convey a more durable protection. In the civil population, where the compulsory revaccination at such short intervals is not practicable, the question of using multiple insertions still remains debatable. Finally, Force (1927) maintains that the subject of an immediate reaction has his immunity to variola raised to the same level as the subject of a typical vesicular vaccinia, provided both have been vaccinated with the same batch of lymph. We think it safe to act on this hypothesis, if the lymph is known to produce over 90 per cent. of primary reactions to primary vaccinations; and that, therefore, a technique which allows the reading of immediate reactions should always be used, and such reactions should be recorded as successful “takes” on official vaccination returns.

VII. SUMMARY.

1. In a group of boys, revaccinated 12 years after primary vaccination in infancy, 37 per cent. gave “immune” reactions to vaccine virus.
2. Immune reactions were more than twice as common in those boys with two or more old vaccination scars than those with one.
3. When the number of scars was held constant there was no tendency for groups with large scars to be more immune than those with small scars.
4. The average area of a single old scar was smaller in the “immunes” than in the rest of the group.
5. The substitution of a vaccination technique consisting of one insertion of lymph with a minimum of trauma, for two or three insertions by “cross-hatched” scarifications was followed by nearly a threefold fall in the recorded vaccinia morbidity, and a halving of the number of days’ sickness attributed to vaccinia.

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