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SMALLPOX VACCINATION BY THE MULTIPLE-PRESSURE METHOD

BY

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During the smallpox epidemic in Scotland in 1942 (MacGregor and Peters, 1942; Sutherland, 1943) some members of the staff of the Wellcome Laboratories asked to be vaccinated as a precautionary measure in case the epidemic should spread south. It was decided to offer to the whole staff vaccination by the multiple-pressure or multiple-puncture method. This is the technique of choice in the U.S.A., but has never been adopted in Great Britain; a perusal of the literature has revealed no completely satisfactory explanation for the differences in procedure in these two countries.

Technique

Multiple-pressure Method (see Leake, 1930a, 1930b; Kolmer and Tuft, 1941).—The site chosen was usually the left upper arm over the deltoid muscle, but a few women elected to be vaccinated on the lower thigh. The skin was swabbed gently with acetone, following American practice, care being taken not to rub so vigorously as to damage the epidermis and thus encourage the development of secondary vaccinal vesicles. A very small drop of lymph was placed on the cleansed area with a glass rod, and "pressures" were applied to the skin through the drop with the side of the point of a Hagedorn needle. The needle was moved rapidly up and down with enough force to demonstrate the elasticity of the skin but not so vigorously as to draw blood. (A few hours after the operation there was no visible lesion.) In accordance with American writers' recommendation for the vaccination of adults, 6 to 10 pressures were used for primary vaccinations and 30 pressures for secondary vaccinations; 30 pressures are recommended for primary vaccinations of young babies because they are less prone to reaction than adults. The area covered by the pressures was only 1/8 in. in diameter. After vaccination any excess of lymph was removed gently with a pledget of cotton-wool. No dressing was applied.

Scratch Method.—This technique is only referred to briefly by way of contrast with the multiple-pressure method. The usual recommendation in this country is a superficial scratch, 1/8 in. in length. Parallel scratches are regarded as unnecessary by American workers (Kolmer and Tuft, 1941); nevertheless, the public health authorities of Glasgow, in their anxiety for efficient vaccination during the large epidemic of smallpox in 1942, advised three parallel scratches, 3/8 in. long and 1/8 in. apart (MacGregor and Peters, 1942). The usual method in Great Britain was formerly "cross-hatching" (scratches crossing one another), but reactions tended to be unduly severe, and it was given up. It is legally prohibited in Germany.

Intradermal Method.—Since it is obviously undesirable to inject intradermally any contaminated fluid, this method is unsuitable for ordinary glycerin-cured lymph, which does unfortunately contain living bacteria. (The Therapeutic Substances Orders, dated Oct. 21, 1942, and Feb. 11, 1944, permit the issue of vaccine lymph containing not more than 20,000 living bacteria and other visible micro-organisms in each c.cm., provided tests for *Cl. tetani* and beta haemolytic streptococci are negative. Glycerin is added to vaccine lymph in normal times in this country to keep down the bacterial content; in the U.S.A.

brilliant green is added in addition.) The intradermal route should be very satisfactory, however, for culture virus, since an exact volume of virus suspension, without extraneous bacteria, would be injected into each patient. The multiple-pressure method appears to be preferred in America, since it is claimed that the percentage of "takes" is just as high, additional advantages being simplicity and painlessness during performance.

Advantages of the Multiple-pressure Method

The multiple-pressure method is regarded as better than the scratch method for the following reasons: (1) Reactions are less severe and less painful. Scars are smaller. (American authorities are at variance with the Report of the Ministry of Health (1928), for they place little reliance on the area of scar formation as an indication of the degree of immunity. They claim that there is no evidence that the duration of immunity is less with the multiple-pressure method than with other methods.) (2) The technique is more rapid, the whole operation taking about 10 seconds; this assertion of greater speed is doubted, however, by experts in the scratch method. (3) The epidermis is left nearly intact and there is no bleeding—in contrast with the general "messiness" of the scratch method, especially when the latter is inexpertly performed. The risk of septic infection is thus eliminated. (4) The multiple-pressure method obviates the use of any control site for estimating the degree of trauma in the so-called "immune" reaction (immediate reaction). This is a doubtful advantage, since many experts, including Marsden (personal communication), never use any form of control as part of the scratch technique; if no specific reaction is obtained the subject is not regarded as immune until the inoculation has been repeated with lymph of proved potency and the same result obtained. (5) Since excess vaccine lymph is wiped off gently and there is minimal trauma, the immediate application of a dressing is unnecessary (Leake, 1930a, 1930b). I am inclined to doubt this assertion, however, because some patients in my series infected their fingers by touching the primary lesion and developed secondary lesions at other sites; a protective dressing would have prevented this accident. The case for and against a dressing is well discussed by Stimson (1936). Marsden (1942), who uses the scratch method, recommends a simple dry dressing fixed by strips of elastoplast.

Potency of Vaccine Lymph

Only if the potency of the lymph is suspect or if there has been exposure to smallpox do the Americans deviate from the above simple technique. Multiple vaccinations—30 pressures at more than one site—are then advised in order to obtain more "takes." (It will be remembered that the practice during the recent Glasgow outbreak was also modified to obtain more "takes"—viz., vaccination by multiple scratches instead of the usual single-scratch technique.)

The Regulations for the potency of vaccine lymph laid down under the Therapeutic Substances Act may require revision in the light of further advances in our knowledge and

experience. The use of a standard lymph, preferably a dried preparation, would be advantageous, and it might also be feasible to stipulate an upper limit of potency in addition to the lower limit now enforced. The issue of a more stable product is desirable. So long as wet lymph is issued, undesirable and rapid deterioration is inevitable unless the tubes are kept continuously at a temperature below 0° C. The practitioner often keeps vaccine lymph in a drawer at room temperature, and as time elapses his proportion of "failures" may be unduly high. This may explain the official preference in this country for the scratch method, which may be more "drastic," as generally performed, than the American multiple-pressure method. Evidence should be collected to settle this point. (It may also explain the experience of Goodall (1942) of a somewhat higher successful reaction rate among those cases in which blood was drawn than among those in which bleeding did not occur. Immediately after this statement in the abstract of Goodall's paper in the *Bulletin of Hygiene* was the reviewer's comment: "It should be realized, however, that the latter group would include any cases in which the incision was too superficial for success—a not uncommon cause of failure." Both the above statements seem strangely at variance with American experience with the multiple-pressure method, where damage to the skin is trivial.) The findings of Rivers, Ward, and Baird (1939) clearly show that the potency of a vaccine lymph used for revaccination makes a decided difference to the numbers of persons who show incomplete protection against smallpox. A highly potent lymph at the time of use is of primary importance whatever technique is adopted.

Reactions of some severity are to be expected in association with successful first vaccinations, more particularly in adults.

Reactions correlated with Degree of Immunity

Reactions may conveniently be classified in three categories which represent for practical purposes three grades of immunity. (1) If the patient has no immunity, or very little, he will develop a "typical" reaction, the so-called primary "take" or vaccinia. This is represented by a papule developing in 3 to 4 days, followed by a vesicle which is at its maximum in 9 to 10 days, followed in turn by a pustule and a scab which separates about the 31st day. Occasionally, in persons with no immunity, the reaction is more severe and of longer duration. In all cases there is some degree of associated adenitis. Constitutional upset with rise of temperature is invariable, and sometimes necessitates absence from work and rest in bed. (2) When there is partial immunity an accelerated or vaccinoid reaction may be expected, sometimes referred to as secondary vaccinia. Here the reaction is less severe, all the changes being speeded up and the maximum vesicle formation occurring in 4 to 7 days. Finally, (3) the typical response in a person who is highly immune is an immune or immediate reaction, characterized by papule formation reaching its maximum in 8 to 72 hours and seldom going on to vesiculation. The American writers state that if no reaction occurs the lymph should be regarded as suspect and the test repeated; in the present series it was found that some of the "no reactions" reported were really "immune reactions" which the patient had failed to observe or had ignored on account of their triviality and short duration. An additional control of the potency of the vaccine lymph used for such patients, if this were needed, was furnished by the numerous relatively severe reactions observed after vaccinations which were performed at the same time with the same batch of lymph. American authors also mention that a rough criterion of a fully potent lymph is that it should give more than 50% of vaccinoid reactions in a group of persons vaccinated more than 10 years previously; this percentage figure was exceeded by a considerable margin in our group.

Marsden (personal communication) does not accept the immediate or immune reaction, which he regards as a misnomer; it does not indicate immunity, he believes, but merely sensitization to lymph. To quote his paper (Marsden, 1942): "Nothing less than a red deep-seated indurated swelling beneath the seat of inoculation, developing about the third day and subsiding gradually, should be accepted as a specific reaction; and when the revaccination has been performed in the face of smallpox infection, or if the interval since the primary

vaccination has been considerable, the process should be repeated at least once. Under similar circumstances, if no specific reaction be obtained the subject should not be regarded as immune until the inoculation has been twice repeated with lymph whose potency is proved by its effect on other patients."

Henderson and McClean (1939) produced evidence that, in a susceptible person, vesiculation must occur before vaccination can be regarded as successful. They inoculated volunteers intradermally and subcutaneously with a specially purified vaccine lymph, and found that immunity to subsequent vaccination by scarification was obtained with certainty only if there was vesiculation at the site of the primary vaccination.

Results of Vaccination on 214 Persons

The results obtained with the laboratory staff were analysed with reference to the type of reaction which developed and the history of previous vaccinations (Table I).

TABLE I.—Vaccination of 214 Adults

Previous Vaccinations*	Reactions					Total
	N°1	Immune or Immediate	Accelerated or Vaccinoid	Typical or "Primary"		
				Moderate	Severe	
None	0	1	13	33	15	62
One	11	6	70	23	4	114
More than on.	2	15	16	3	2	38
Total ..	13	22	99	59	21	214

* Based on patients' histories, which were supplemented in most instances by direct evidence from scars.

The information about previous vaccination depended mainly on the patients' statements, which could not always be confirmed by inspection of scar sites; the original notes had sometimes to be revised, therefore, after further discussion. Again, the severity of reactions observed in the present investigation did not always fit precisely under any of the headings in the table. The 13 reactions which are listed as accelerated or vaccinoid, in the group of patients who stated they had never been vaccinated previously, could almost all have been classified, in retrospect, as moderate "typical" or "primary" and transferred to the next column in the table; the majority of these reactions were intermediate between "accelerated" and "typical." Intermediate grades are to be expected in any study of biological reactions, but a more elaborate and cumbersome classification appeared inadvisable. At all events, the figures in the table give a reasonably accurate analysis of the available data.

The main feature of the table is the decreasing severity of reactions, depending on the frequency of previous vaccination. There were many more severe reactions in persons vaccinated for the first time than in the other two groups. The majority of persons who had never been vaccinated before gave moderate or severe "typical" or "primary" reactions, and persons who had been vaccinated more than once before gave "immune" and "accelerated" reactions in approximately equal proportions. One person who had never been vaccinated before gave an "immune" reaction on repeating the inoculation; there is no obvious explanation of this unexpected result.

In a further analysis it was seen that sex (79 males and 135 females) had apparently no influence *per se* on the grading of the reactions observed. Stout persons tended to have more severe reactions than thin.

The degree of reaction in relation to one or more previous vaccinations was further analysed with regard to the time which had elapsed since the last "successful" vaccination (Table II). Fewer persons gave "immune" reactions when the interval which had elapsed was long. In the "over 30 years" group there were many "typical" or "primary" reactions, mostly of moderate severity. It is noteworthy, too, that two persons who had been vaccinated 10 to 20 years previously gave reactions classified as severe; these were women who elected to be vaccinated on the thigh and reacted so severely that they had to be off work for some weeks. More severe reactions appear to be associated with thigh than with arm vaccinations (Buchanan and Laidlaw, 1942), and we agree with certain other workers that the thigh is an unsuitable site and should rarely

be employed. At the foot of Table II are given for comparison the data of reactions occurring among persons with no previous vaccination.

TABLE II.—*Degree of Reaction in Relation to One or More Previous Vaccinations (Males and Females)*

Years Since Last "Successful" Vaccination	Reactions					Total
	Nil	Immune or Immediate	Accelerated or Vaccinoid	Typical or "Primary" Moderate	Severe	
Less than 5 ..		1				1
5-10 ..	2	2		1		6
10-20 ..	6	13	41	4	2*	66
20-30 ..	3	4	24	6	1	38
More than 30 ..	2	1	20	15	3	41
Total ..	13 (8.6%)	21 (13.8%)	86 (56.6%)	26 (17.1%)	6 (3.9%)	152
Cf. No Previous Vaccination:						
Total ..	0	1 (1.6%)	13 (21.0%)	33 (53.2%)	15 (24.2%)	62

* Women with thigh vaccinations.

Abnormal Reactions, Complications, etc.

(a) In two cases the reaction did not appear till the 10th and 12th days respectively after vaccination. The patients believed they were immune, but they did in fact develop a moderate and a severe reaction respectively. It is not known why there should have been an unusually long delay in the incubation period of these persons who had little or no immunity. (The statement has been made that "if a reaction is not found on the second or sixth day the vaccination must be repeated, as *either the virus was impotent or the technique was at fault*" (Gloyne, 1943). Apparently the reasons given for repetition do not invariably hold, as is shown by our experience, and also since, on occasion, primary and "repeat" vaccinations have both shown typical "takes" developing possibly after different time intervals (Anderson, personal communication).)

(b) In seven subjects "supernumerary" vesicles developed around the vaccination site.

(c) Three persons developed so-called "vaccinal rashes," which were papular and pustular and of scanty distribution, and not to be confused with generalized vaccinia—a much more serious condition (Jubb, 1943). In our series there were no cases of generalized vaccinia and no encephalomyelitis.

(d) There were four cases of auto-inoculation or auto-vaccination. The first patient had complained of a "stiff neck," which was explained by a typical lesion of the scalp with an associated adenitis at the back of the neck. The second patient had single lesions of neck, finger, buttock, and thigh; the third, two lesions of the cheeks and one of the left arm; and the fourth, single lesions of elbow and leg and three lesions on the body. The somewhat high incidence of subsidiary lesions in this series may possibly be explained by the natural interest of laboratory workers in a new method and their desire to follow carefully all stages in the development of their vaccinia. The lesions, as a rule, were not protected by any form of dressing, and were certainly palpated by some persons.

(e) A patient who had been vaccinated on the thigh and developed a severe reaction infected her daughter, aged 19. The daughter developed a typical primary lesion of the thigh, with associated adenitis. Mother and daughter had had baths on successive nights and used the same bath towel. It was a family joke that the daughter always used a scrubbing-brush in her bath and rubbed herself down so vigorously afterwards that her skin was reddened; this may serve to explain her vaccination via the bath towel! (A local medical practitioner who heard of this accident told me that his father had infected his own nose after vaccinating a child and had to be away from his practice for several weeks.)

(f) Two patients developed boils and had successive crops for many weeks, and one patient had a neuritis of forearm and hand which lasted about 48 hours and cleared spontaneously. Both conditions were probably coincidental, although the patients tended to blame the vaccination.

Discussion

The multiple-pressure method of vaccination is an innovation in this country, and aroused considerable interest among the staff, who were impressed by its apparent simplicity and painlessness at the time of performance. There was therefore no difficulty in obtaining volunteers, although some persons may have regretted their enthusiasm when severe reactions developed. It is fortunate, perhaps, that the multiple-pressure method was used, as even more severe vaccinal reactions might have followed scratch methods, with the added possibility of septic infection. A factor in the severity may have been "green lymph"—i.e., lymph issued and used soon after preparation, and kept, as in our experiment, in cold storage until required for use. The worst sufferers were certain persons who were being vaccinated for the first time in adult life or revaccinated after the lapse of many years. The remedy is therefore primary vaccination in infancy, followed by periodic revaccination throughout life. A sore arm and disturbance of health necessitating absence from work are thus obviated. (American practice is to carry out primary vaccination in the first year of life, and revaccination at 5 or 6 years and again when puberty is reached. In the American Services further vaccinations are performed yearly; there is little trouble from reactions.)

Some of the instances of spread from the original site to other parts of the body, and in one instance to another individual, would seem to indicate that warning should be given to the patient and his relatives of the highly infectious nature of vaccine lymph. The usual American procedure is to dispense with any form of protective dressing, but the wisdom of this recommendation is questionable. The risk of autovaccination is by no means negligible, and subsidiary lesions may lead to permanent disfigurement. These risks apply to vaccination by any method and not by the multiple-pressure method alone.

I have also been informed of doctors developing lesions from applying their lips to vaccine capillary tubes to blow out the lymph. Here again a word of warning is necessary, and some other method of expelling the lymph—e.g., the use of a special rubber teat—is essential.

It is disturbing that a significant number of soldiers in this war who have been vaccinated at home and found to be negative have developed typical "takes" when revaccinated over-seas. The explanation may be poor-quality lymph at the first vaccination or bad technique, or both. Although the scratch method was implicated in these observations, at least an equal number of "discrepancies" might be expected with the multiple-pressure method. Whatever method of vaccination is adopted the only safe working rule is to disregard all histories of previous vaccination that are not supported by direct evidence. As already quoted, Marsden (1942) stresses the necessity for a sceptical attitude towards a negative or an "immune" reaction in the face of a smallpox epidemic or if a considerable interval has elapsed since the primary vaccination. Two repeat vaccinations may be indicated with lymph which is of assured potency on the basis of tests on other patients.

The difficulty of obtaining an accurate record of previous vaccinations has already been mentioned. In cross-examination it was ascertained that some persons had obviously confused vaccination against smallpox with inoculations of diphtheria prophylactic. It would be extremely useful if some form of health record could be devised which would accompany each patient and give accurate information of all inoculations (date, preparations, and batch number, dose, degree of reaction, etc.) and of infectious diseases and other illnesses. "One more card to be lost!" was the abrupt comment of one well-known fever hospital superintendent when this idea was discussed; but if this serious defect in the scheme could be circumvented more reliable vaccination histories would be obtainable for consideration alongside the direct visual evidence provided by scars.

Summary

The multiple-pressure method was used for vaccinating 214 members of the laboratory staff.

The advantages of this method, which is in common use in the U.S.A., are discussed.

The potency of calf lymph before issue is controlled by official regulations, but storage under suitable conditions is requisite if

results are to be satisfactory. Whatever method of vaccination is adopted, lymph must be highly potent *at the time of use*.

The necessity for obtaining direct evidence of a successful "take" is stressed. Unless only a short interval has elapsed since a satisfactory primary vaccination, a negative or "immune" reaction on revaccination should be distrusted until confirmed. Two reinoculations with lymph of proved potency may be necessary before this finding is accepted.

There is insufficient appreciation of the highly infectious nature of vaccine lymph. A dressing should always be applied immediately to the site of vaccination to reduce risks of auto-inoculation.

Severe reactions necessitating absence from work would be obviated if vaccination in infancy and periodic revaccination were the general rule.

Some system of permanent health records which would accompany each patient is desirable. Full details of vaccinations and other inoculations, including reactions, would be entered and would supplement the direct evidence presented by vaccinal scars.

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A TWO-STAGE METHOD OF TREATMENT IN DIABETES

BY

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This communication describes a simple method of carrying out adjustments of insulin dosage or diet (or both) in those diabetics for whom a change of some sort is obviously necessary. It is particularly applicable to the patient who is ambulant or under treatment in his own home.

It is described as a two-stage method of treatment because its first object is the restoration of the patient to vigorous health by insulin without any restriction in diet other than the close spacing of meals which prevents hypoglycaemic attacks. During this stage no attempt is made to maintain normal levels of blood sugar or a sugar-free urine, and the dose of insulin is controlled by daily observation of the patient's body weight and the record of the volume of urine passed. When normal weight has been reached and maintained for some time on a constant dose of insulin, then the secondary object of diabetic treatment—namely, the lowering of the blood-sugar levels to near normal—can be tackled (if it is thought well to do so), and the effect of carbohydrate restriction observed.

The method may be summarized in a few words: the patient is restored rapidly to health and vigour by insulin on a diet which is more than adequate, the question of blood-sugar levels being left over to a later date; diet charts and blood-sugar estimations are not needed for the first stage, though they are necessary for the second.

Advantages of the Two-stage Method

A two-stage method of treatment (though applicable to hospital work, and in fact used in my own hospital practice) is not needed by the experienced diabetic specialist, who has his patient in hospital, who can have frequent blood-sugar estimations carried out, and who can make certain that the patient takes a prescribed diet. For it is possible for a physician so placed to roll both stages into one, and combine his most important duty (the discovery of how much insulin is needed, and how often) with the much less important one of controlling hyperglycaemia by a rationed diet. But it offers very definite advantages to physicians who have to carry out adjustments for the already instructed diabetic outside hospital. For them it is a "safety play" which enables them to restore

a slightly maladjusted diabetic to effective health as rapidly as possible, leaving to a later date the question of exact dietetic control. It enables them to use insulin freely without fear of hypoglycaemic attacks. If at a later stage they decide to tackle the question of dietetic restriction, they will then be in the happy position of knowing that if these restrictions bring about hypoglycaemia the fault lies with the diet being too low, and not with the insulin dosage being too high.

Not the least of the advantages of the two-stage method is that the patient himself becomes correctly oriented towards his disease. He learns that his restored health is due to injecting insulin, and not to abstaining from carbohydrate. He learns that loss of weight, thirst, and polyuria (the cardinal symptoms of diabetes) are signs of underdosage with insulin and must be noted and reported whenever they occur. Too many diabetics imagine that the only yardstick whereby they can measure their health is a sugar test on the urine, and fail to learn the far more important lesson that the adequately treated diabetic should so live that he is free from all the symptoms of his disease.

The First Stage

During this stage the physician's only concern is to restore the patient to full health. He allows the patient to satisfy his appetite so that wasted tissues may be built up and hypoglycaemia avoided; he gives enough insulin often enough to keep the urinary output as near normal as possible and to produce a steady daily gain in weight. If he fears hypoglycaemia—for example, at night—he does not let that stop him from increasing the dose of insulin, but he takes the precaution of ordering glucose at the appropriate periods. The rationale is the same as that of most specific replacement therapies: make sure that enough is given. Prophylactic glucose enables this to be done without risk.

Insulin.—Unmodified (soluble) insulin should always be used in even minor diabetic relapses. Except in cases of coma and threatened coma (which should be rushed into hospital), doses of about 30 units twice daily, with a small evening dose, will be adequate in many instances and entail little risk of hypoglycaemia during the first few days, but there is of course no general rule. If a marked improvement does not set in on a dosage not very much higher than the patient's usual maintenance dose, the physician should suspect that coma may be nearer than he at first thought.

Diet.—The two essentials are that it shall be adequate and contain small meals interpolated between the chief meals of the day, with additional glucose whenever a hypoglycaemic attack is to be feared. Occasionally an overconscientious diabetic who has relapsed through cutting down his total intake to near the point of undernutrition will be afraid to increase his diet, but such patients will usually take glucose without any dark suspicions about their doctor's intelligence. It must never be forgotten that the diabetic who cannot eat or who vomits is a candidate for coma, and therefore a case for hospital.

Weighing.—Daily weighing of the patient is essential, and home treatment must not be undertaken without scales in the house. If diet is more than adequate and the weight does not rise, then insulin dosage is too low, and a polyuria will indicate the period or periods of the day at which it is inadequate. If the weight refuses to rise, and the diet is adequate and there is no polyuria, then the cause of the loss of weight is not simply diabetes; there must be some concomitant disease—for example, tuberculosis or gall-bladder disease.

Urine Measurement.—The patient should record the time and approximate volume whenever he passes urine. Measurement need not be done with great accuracy (a half-pint milk-bottle marked with stamp-paper may be used), and the ambulant patient can make a rough guess if he passes water away from home. There is no constant figure for all diabetics, but, apart from a few puzzling exceptions, the 24-hour output can usually quickly be reduced to within or about 50 oz. Adequate insulin dosage in a previously inadequately treated patient will always markedly lower the urinary output. If the urinary output during the night is relatively high, that points to the need for a bedtime dose of insulin.

Testing for Sugar.—Testing the urine for sugar should be done during the first stage only with the object of avoiding hypoglycaemia.