Summary

A method is described for producing uterine haemostasis by P^{32} without damaging the ovaries.

A surface burn by P^{32} is quickly healed and regeneration of endometrium follows.

Preliminary animal experiments were followed by a clinical trial on 16 patients, 11 of whom were allowed three months between irradiation and hysterectomy. Seven cases were cured, two were somewhat improved, and two, with unsuspected fibroids, were failures.

We wish to thank Dr. A. G. Glucksmann, of the Strangeways Laboratories, Cambridge, who initiated and took part in this study, and Dr. C. W. Taylor, Director of Pathology at the Birmingham and Midland Hospital for Women, who advised us on the histology. We are also grateful to our colleagues Miss M. Neville and Mr. L. M. Park, Selly Oak Hospital, who operated on one of the patients and sent us the clinical notes and pathological material to complete this report. Finally, we wish to thank Miss M. E. Attwood and Mr. D. H. S. Boyd for technical assistance.

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VARIATION IN TECHNIQUE OF INTRACUTANEOUS B.C.G. VACCINATION

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The technique for giving an intracutaneous injection is ordinarily set forth very clearly: 0.1 ml. of fluid is to be injected as superficially as possible into the skin. Yet when even such a simple procedure becomes a commonplace in the everyday work of a great number of persons, as is the case in the large public health programmes of to-day, individually insignificant errors and deviations from the prescribed technique may, when taken collectively, amount to considerable variations, and thereby create problems of unexpected magnitude. The full impact of this situation—and its possible consequences—was probably not really felt until intracutaneous injections of B.C.G. vaccine were being given to literally millions of persons in the international mass vaccination campaigns. The present paper gives the results of several studies designed to provide preliminary information on the immediate measurable results of B.C.G. vaccination in schoolchildren when the technique of intracutaneous injection of vaccine was deliberately varied within the limits likely to occur under ordinary field conditions.

There are two principal ways in which an intracutaneous injection may deviate from the recommended technique. First, more or less than the specified volume of 0.1 ml. may be given; and, secondly, the fluid may not be injected superficially into the skin. Theoretically, these two kinds of deviation ought not to be correlated: variation in volume should be independent of variation in depth.

So long as B.C.G. vaccination remained mostly in the hands of a few interested people, the technique of injection was probably more of an art than a science. Each worker undoubtedly developed his own method of gauging the volume and depth of his injections. With the start of mass vaccination, however, hundreds of new workers had to be instructed in the technique, which could no longer be left to the whim of each worker; some uniformity and standardization was essential. In mass vaccination campaigns it would be difficult, or even impossible, to enforce a standard procedure for measuring the volume from the graduated marking on the syringe, because most syringes—even new syringes—soon begin to leak badly. Experience had already shown, however, that the size of the wheal—the white, rounded elevation of the skin caused by the injection—corresponded at least roughly with the volume of fluid injected; and this method was adopted for gauging the dose. There seems, however, to be little agreement on the size of the wheal representing the standard (0.1 ml.) dose of vaccine.

The first edition of *B.C.G. Vaccination against Tuberculosis* (Holm, 1948), issued by the International Tuberculosis Campaign, contained the following instructions for making intracutaneous B.C.G. vaccination: "By the intracutaneous vaccination, 1/10 c.cm. of the vaccine is injected as superficially as possible into the skin. . . . If the injection is given correctly, a wheal will appear, in which the follicles of the hair are easily visible. The wheal must have a diameter of about 10 mm." Two years later, in the *Second Annual Report of the International Tuberculosis Campaign* (1949–50) the instructions for vaccination were revised to read: "(*a*) The injection should be made as superficially as possible, and very slowly. (*b*) The dose should be as accurate as possible —0.1 c.cm. If judged by the size of the wheal, *the diameter of the wheal must be 8 mm.*" An account of the B.C.G. vaccination programme in Finland (Savonen, 1949) did not specify the volume of vaccine or depth of injection, but simply stated that "so much vaccine is used that the anaemic wheal appearing on the skin has a diameter of 10–12 mm."

The British Ministry of Health (1950) issued the following instructions for B.C.G. vaccination programmes: "0.1 c.cm. (ml.) of the vaccine is then injected *strictly* intradermally without loss due to leakage from the needle track. A satisfactory vaccination should produce a white wheal 5 mm. in diameter." A brochure from the Bureau of Tuberculosis Control (1952), Commonwealth of Pennsylvania and the Henry Phipps Institute in the United States, does not mention the size of the wheal but merely states: ". . . 0.1 c.cm. is injected intracutaneously as superficially as possible into the skin."

A volume of 0.1 ml. is almost always specified, yet the wheal expected to result from this volume varies in diameter from 5 to 12 mm. There must therefore be considerable variation in interpreting what is meant by a very superficial injection, for about the only way the size of the wheal could differ and still represent a constant volume of vaccine would be by variation in the depth of injection.

Thus one may be justified in thinking that intracutaneous injections of B.C.G. vaccine, and of tuberculin as well, must have varied widely in mass campaigns.

Many vaccinators began working in the campaigns after only the most cursory instruction and little

practice in giving injections. Often lacking critical supervision, they naturally developed their own habits for estimating the size of the wheal and the depth of the injections. A consistent error of only a few millimetres in estimating the size of the wheal from a deep intracutaneous technique could, as we shall show, result in their giving much more than the recommended dose. Moreover, large doses could easily pass unnoticed, because a leaking syringe makes it difficult for anyone to estimate the volume injected. On the other hand, it can be assumed that no vaccinator (even with a badly leaking syringe) would refill her syringe before completing at least one vaccination, so the maximum volume injected is not likely to have exceeded 0.6 or 0.7 ml.

Independently of technique, the volume of vaccine given has probably also been influenced by the attitude of the vaccinator (and the supervisor) towards the work: a strong conviction that a larger dose assures greater protection, coupled with an equally strong belief in the harmlessness of B.C.G., is known to have accounted for many conscientious vaccinators routinely and deliberately giving each person "a *good* vaccination." On the other hand, some vaccinators, fearing complications from too much vaccine, especially in younger children, have undoubtedly overestimated the size of the wheal and given only a fraction of 0.1 ml. Precise information on this subject is unobtainable; but from what is known of variations between vaccinators, both in their technical performance and in their attitude to the work, it is reasonable to conclude that the average volume of vaccine routinely given by some vaccinators has been at least four or five times that given by others. Furthermore, taking into account the range of variation for each individual vaccinator, it is quite possible that some vaccinated persons received eight or ten times as much vaccine as others.

Material

The data in this paper are derived from an extensive series of field studies on B.C.G. vaccine and vaccination, carried out during the past three years by the Tuberculosis Research Office of the World Health Organization, Copenhagen, in co-operation with the Danish Statens Seruminstitut and the International Tuberculosis Campaign. In general, the work was done among Danish schoolchildren, in groups large enough to provide reliable results. Each study was carefully planned and supervised to ensure that the observations were, so far as possible, objective and free of personal bias. Children were selected for vaccination on the basis of their reactions to a Mantoux test with 10 units of purified protein derivative (P.P.D.*); those in whom the indurated area was less than 6 mm. in diameter were vaccinated. Post-vaccination tests were made with the same dose and batch of tuberculin, and all observations were made according to a standard procedure by the same team of highly trained field personnel.

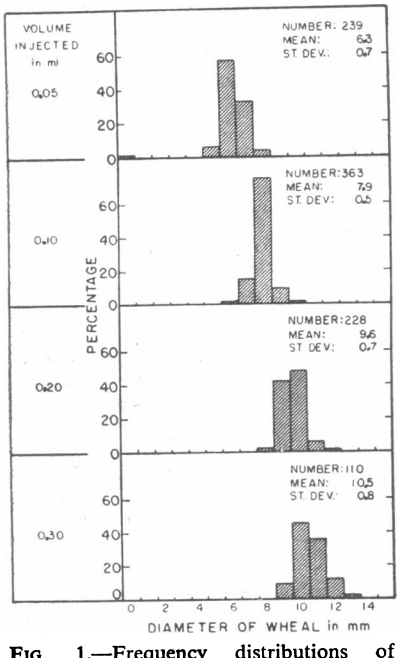

FIG. 1.—Frequency distributions of diameter of wheals according to volume of B.C.G. vaccine injected very superficially into the skin.

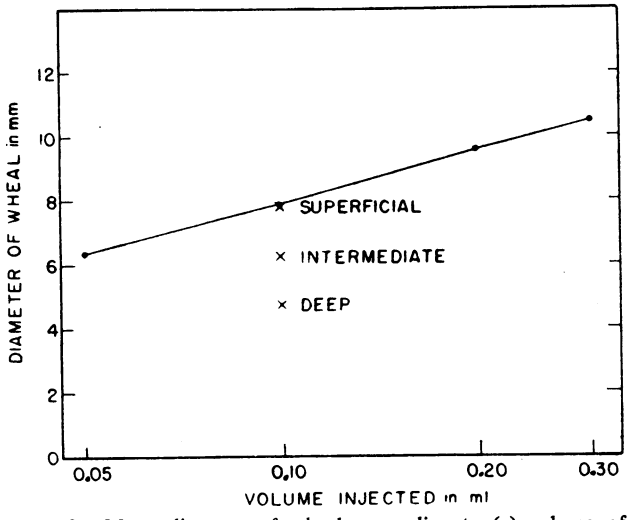

FIG. 2.—Mean diameter of wheals according to (*a*) volume of B.C.G. vaccine injected very superficially, and (*b*) depth of injection of 0.1 ml. of B.C.G. vaccine.

Results

Wheal Size with Variation in Volume and Depth of Injection

Before investigating the relation between the size of wheal and the volume and depth of vaccine injected the personnel chosen for this work had to be specially trained. Varying the volume presented no problem: with carefully selected non-leaking syringes, different volumes could be measured quite accurately by reading from the graduations on the barrel of the syringe. But after having become skilled in giving injections very superficially for other studies the vaccinators needed practice in order to become proficient in varying the depth of their injections. For this purpose members of the office staff volunteered as subjects on whom one of the vaccinators practised with saline until she could inject, at will, into different layers of the skin and could classify her injections according to depth.

Two studies were then made in groups of Danish schoolchildren totalling nearly 1,400. In the first study only volume, not depth, was varied: each child was given 0.05, 0.1, 0.2, or 0.3 ml. of vaccine, always injected very superficially. In the second study depth was varied but volume kept constant: 0.1 ml. was given at one of four different skin levels, graded as superficial, intermediate, and deep intracutaneous, and just below the skin into the subcutaneous tissue. A regular sequence was followed in both studies: the different volumes

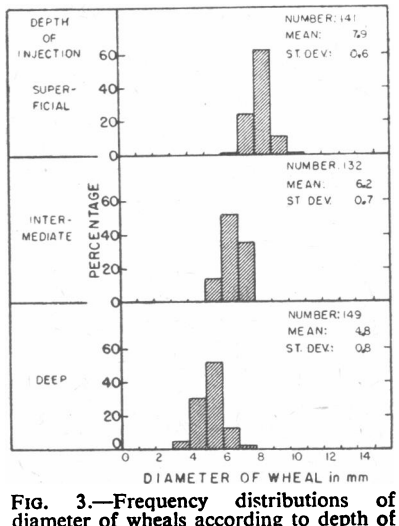

FIG. 3.—Frequency distributions of diameter of wheals according to depth of injection of 0.1 ml. of B.C.G. vaccine.

*RT XIX-XX-XXI from Statens Seruminstitut, Copenhagen.

or depths were given in rotation as children came in line for vaccination. In this work, the vaccinator herself measured the diameter of the wheal immediately after each injection; the measurements therefore may not be entirely free of bias. The vaccinator also classified each injection according to its actual rather than intended depth, since she did not always strike the depth aimed for. Her classification of depth was used for analysing the material. (Wheals produced by subcutaneous injections are not included in the results, because often no wheal appeared, and when it did it was very small with indistinct margins, and it rapidly disappeared.)

The histograms in Fig. 1 show that the usual amount of 0.1 ml. of vaccine, given superficially, very often produced a wheal 8 mm. in diameter; and almost all of the wheals which were not 8 mm. in diameter measured either 7 or 9 mm. Larger and smaller volumes caused a corresponding change in the size of wheals, associated with slightly greater variations in the distribution around the central value. The average size had a linear relation to the logarithm of the volume injected, as shown by the line in Fig. 2. Doubling or halving the dose made a difference of about 1.5 mm. in the average size of the wheals; a sixfold increase (from 0.05 to 0.3 ml.) made a difference of about 4 mm.

The mean size of the wheals resulting from injection of 0.1 ml. at different depths is also shown in Fig. 2, and the corresponding histograms in Fig. 3. The size of the wheal clearly decreased with increasing depth of injection: the difference in average size between wheals produced by superficial and by deep intracutaneous injection was 3.1 mm., a difference as great as that produced by a fourfold difference in volume of vaccine given superficially.

Analysis of the influence of age and sex on the size of the wheal showed that older children had slightly larger wheals than younger ones, but the difference was too small to be important. These studies were carried out in healthy, well-nourished white children. We believe, from what field workers from different parts of the world have told us, that skin qualities may differ appreciably in different races and perhaps also with different nutritional conditions. These factors may influence the size of the wheal, although we have no definite data on this subject.

Unfortunately we have no information about the variation in size of wheal for volumes other than 0.1 ml. given by intermediate and deep intracutaneous injection. But if we assume that the size of wheal and volume of vaccine injected have the same linear relation (and slope) for the deeper as for the superficial injections, then small differences in size of wheal may represent very large differences in volume. For example, it appears that a wheal of 5 mm. may be produced by hardly more than one-quarter of the usual (0.1 ml.) dose given very superficially, whereas a wheal of 6 mm.—only 1 mm. larger—could result from a dose nearly twice the regular dose if injected deeply into the cutaneous tissue. If, in addition, the vaccinator underestimates the size of the wheal, the dose may be three or four times the recommended 0.1 ml.

Effect of Variations in Volume of Vaccine on Post-vaccination Response

Many workers favour the intracutaneous method of giving B.C.G. vaccine primarily because they assume that with it the amount of vaccine injected can be measured. But, as we have already explained, in practice the amount given is probably far from constant. It is important to know whether, and how much, the observable consequences of vaccination are affected by failure to give a constant dose of B.C.G. Information on post-vaccination allergy and size of local lesions is available from the studies in which volume and depth were deliberately varied. One restriction on this work was that the total amount of B.C.G. given to any child could not exceed the Danish standard dose (0.075 mg. of organisms), so dilutions of a regular batch of vaccine were prepared and used in various volumes.

TABLE I.—*Mean Diameter of Mantoux Reactions to 10 T.U. and of Vaccination Lesions According to Strength and Volume of Vaccine Injected*

10½ Weeks after Vaccination

Strength of Vaccine as Fraction of Standard	Mean Diameter of Induration of Mantoux Reactions to 10 T.U. (mm.) — Volume Injected (ml.) 0·05	0·1	0·2	0·3	mg. B.C.G. Injected	Mean Diameter of Induration of Vaccination Lesions (mm.) — Volume Injected (ml.) 0·05	0·1	0·2	0·3	mg. B.C.G. Injected
1/2	17·8	17·6				7·1	8·6			
1/4	16·9	17·8	17·6			6·5	7·3	8·1		
1/8		16·8	17·3		0·0375		5·3	6·7		0·0375
1/12				16·5	0·0188				5·5	0·0188
					0·0094					0·0094

One Year After Vaccination

Strength of Vaccine as Fraction of Standard	Mean Diameter of Induration of Mantoux Reactions to 10 T.U. (mm.) — Volume Injected (ml.) 0·05	0·1	0·2	0·3	mg. B.C.G. Injected	Mean Diameter of Vaccination Scar (mm.) — Volume Injected (ml.) 0·05	0·1	0·2	0·3	mg. B.C.G. Injected
1/2	18·2	19·3				5·8	6·6			
1/4	18·2	18·8	19·6			5·2	5·8	6·6		
1/8		18·0	18·3		0·0375		4·5	5·5		0·0375
1/12				17·6	0·0188				4·6	0·0188
					0·0094					0·0094

The results (Table I) are from the study designed to determine the effect of varying the volume alone and both volume and strength of vaccine simultaneously. Altogether 951 children were vaccinated. They were divided into eight subgroups, each receiving one of the various volume–dose combinations. The horizontal rows in Table I show the average size of the tuberculin reactions (left) and local lesions (right) for the groups given different volumes (0.05 to 0.3 ml.) of the same dilution of vaccine (1/2 to 1/12 standard strength). The vertical columns furnish similar data for groups given different dilutions but the same volume. From the diagonal rows one can compare the results when different volumes and dilutions were combined so that the groups got the same total milligram dose of B.C.G. organisms.

The figures in the left-hand section of the table may surprise many B.C.G. workers : over quite a broad range neither volume nor strength of vaccine had much, if any, effect on the average size of the tuberculin reactions either 10½ weeks or one year after vaccination. For example, 0.05 ml. of 1/4 strength vaccine (0.0094 mg. B.C.G.) gave reactions whose diameter averaged 16.9 mm. at 10½ weeks, compared with 17.6 mm. from 0.2 ml. of the same dilution (0.0375 mg. B.C.G.): a fourfold difference in volume (and in milligram dose of B.C.G.) made a difference of less than 1 mm. in the size of the tuberculin reactions.

By contrast, the figures on the right of Table I show that varying the volume or varying the strength of vaccine has a slight but consistent effect on the average size of the local lesions at 10½ weeks, and of the resulting scars at one year. An increase in dose (either by increasing the volume or the strength of the vaccine) is associated with larger lesions. This observation is confirmed by an earlier study (Edwards and Gelting, 1950), in which 0.1-ml. volumes of standard strength and of four-times standard strength vaccines were compared. The average size of post-vaccination tuberculin reactions differed by only 1 mm., but with the stronger vaccine the local lesions were on average 2.3 mm. larger.

An additional point, perhaps of more theoretical than practical interest, is shown by the diagonal rows in Table I. Apparently increasing the quantity of diluent for a constant dose of B.C.G. is associated with a very slight tendency for the post-vaccination tuberculin reactions to decrease in size. This may reflect a true relation between dose and volume, or it may depend on some systematic error associated with the injection of different volumes. (Vaccine may tend to ooze from the larger wheals resulting from the superficial injection of large volumes; or possibly the vaccinator tended to inject a little more than she should when giving small volumes and a little less when giving large ones.)

Effect of Variations in Depth of Injection on Post-vaccination Response

Studies of the effect of varying the depth at which vaccine was injected gave striking results, shown in Tables II and III. In the first study 188 children were alternately given a superficial and a deep injection of 0.1 ml. of vaccine ; and each injection was classified by the vaccinator as superficial, intermediate, or deep intracutaneous, or subcutaneous. The same procedure was followed in the second study, on about 500 children ; but here both standard strength and 1/100 standard strength vaccine were used. As the children came in line to the vaccinator, the first was given a superficial, the second an intermediate, and the third a deep intracutaneous injection. When this sequence had been completed three times the next child was given an injection just below the skin into the subcutaneous tissues. Thus, 1 out of every 10 injections was subcutaneous (given only to boys). The same rotation system was followed for both strengths of vaccine.

It is evident from both studies that the average sizes of the tuberculin reactions were not appreciably affected by the depth at which standard strength vaccine had been injected. For the 1/100 strength vaccine, however, the

TABLE II.—*Mean Diameter of Mantoux Reactions to 10 T.U. and of Vaccination Lesions According to Depth of Vaccine Injection*

10½ Weeks after Vaccination

Strength of Vaccine	Depth of Injection	Mean Diameter of Induration of Mantoux Reactions to 10 T.U. (mm.)	Vaccination Lesions: Mean Diameter of Induration (mm.)	Vaccination Lesions: % with Local Abscess
Standard (0·75 mg. per ml.)	Intracutaneous superficial	18·8	8·1	1·2
	Intracutaneous intermediate	17·6	9·0	0·0
	Intracutaneous deep	18·2	13·5	11·7
	Subcutaneous	18·5	15·1	28·6

One Year after Vaccination

Strength of Vaccine	Depth of Injection	Mean Diameter of Induration of Mantoux Reactions to 10 T.U. (mm.)	Vaccination Lesions: Mean Diameter of Superficial Scar (mm.)	Vaccination Lesions: % with Abnormal Scarring*
Standard (0·75 mg. per ml.)	Intracutaneous superficial	22·1	7·3	0·0
	Intracutaneous intermediate	21·6	7·1	4·3
	Intracutaneous deep	21·9	8·1	30·2
	Subcutaneous	21·8	6·8	40·0

* Scar surrounded by zone of discoloration, irregular and often retracted, adherent to underlying tissues.

TABLE III.—*Mean Diameter of Mantoux Reactions to 10 T.U. and of Vaccination Lesions According to Depth of Vaccine Injection*

10½ Weeks After Vaccination

Strength of Vaccine	Depth of Injection	Mean Diameter of Induration of Mantoux Reactions to 10 T.U. (mm.)	Vaccination Lesions: Mean Diameter of Induration (mm.)	Vaccination Lesions: % with Local Abscess
Standard (0·75 mg. per ml.)	Intracutaneous superficial	19·9	8·2	0·0
	Intracutaneous intermediate	20·0	10·7	4·7
	Intracutaneous deep	19·3	13·7	13·4
	Subcutaneous	19·3	16·6	30·4
1/100 standard (0·0075 mg. per ml.)	Intracutaneous superficial	14·6	2·7	0·0
	Intracutaneous intermediate	13·3	4·0	0·0
	Intracutaneous deep	13·2	4·1	0·0
	Subcutaneous	12·9	3·8	0·0

One Year After Vaccination

Strength of Vaccine	Depth of Injection	Mean Diameter of Induration of Mantoux Reactions to 10 T.U. (mm.)	Vaccination Lesions: Mean Diameter of Superficial Scar (mm.)	Vaccination Lesions: % with Abnormal Scarring*
Standard (0·75 mg. per ml.)	Intracutaneous superficial	21·2	7·5	3·2
	Intracutaneous intermediate	20·4	7·5	5·5
	Intracutaneous deep	20·5	8·0	32·3
	Subcutaneous	20·2	9·1	52·0
1/100 standard (0·0075 mg. per ml.)	Intracutaneous superficial	14·0	1·2	0·0
	Intracutaneous intermediate	13·1	1·4	0·0
	Intracutaneous deep	12·2	1·3	0·0
	Subcutaneous	11·7	0·8	3·8

* Scar surrounded by zone of discoloration, irregular and often retracted adherent to underlying tissues.

more superficial injections gave a higher level of allergy : the most superficial gave an average at 10½ weeks of 14.6 mm., compared with 12.9 mm. for the subcutaneous, while at one year the averages were 14.0 and 11.7 mm. respectively.

The average size of local lesions 10½ weeks after vaccination showed a systematic and pronounced difference with the depth of injection. In both studies the lesions averaged about 8 mm. for the superficial technique and increased with depth of injection to become twice as large (15–16 mm.) for subcutaneous injections. Of even more practical importance, the frequency of local subcutaneous abscesses also increased with deeper injection technique.* Superficial injection of standard strength vaccine led to an abscess in less than 1% of cases, but the frequency of abscesses increased substantially with increasing depth, and nearly one-third of the children given vaccine subcutaneously developed a local abscess. (The subcutaneous injections, it may be recalled, were given not deeply into the subcutaneous tissues, but just under the skin.)

A further interesting point is brought out by Table III. With the 1/100 strength vaccine the depth of injection had much less, though probably still some, effect on the size of the local lesions, and there were no local abscesses. It is also noteworthy that the measured size of superficial scars at one year for the standard vaccines in both studies (Tables II and III) increased only slightly with increasing depth of injection. There was, however, a pronounced difference in the scars after deep injection : they were commonly surrounded by a zone of discoloration ; they were irregular in shape, and often retracted and adherent to the underlying tissues.

Fig. 4 gives histograms of the local lesions at 10½ weeks and resulting scars at one year for the four different depths of injection for the two studies combined ; the frequency of local abscesses and abnormal scars is shown by the darker shading. With increasing depth the whole distribution moved towards the right on the scale and local abscesses became more frequent with increase in the proportion of lesions over 14 mm. in diameter. None of the smaller lesions were associated with an abscess ; but an abscess was associated with 30% of the lesions over 14 mm. in diameter, and with more than half of the lesions over 20 mm. in diameter.

Discussion

The widespread adoption of the intracutaneous method of giving B.C.G. vaccine in mass campaigns has been explained in several ways: (*a*) it is regarded as more exact than other methods because a measured amount of vaccine can be injected ; (*b*) the technique is believed to be fairly easy to learn and to apply rapidly in mass vaccinations ; and (*c*) results, in terms of post-vaccination tuberculin sensitivity, are thought to be better than with other methods.

Practical problems have, however, arisen. At least one problem can be inferred from the inconsistencies, almost amounting to contradictions, in the instructions for making intracutaneous injections. Nearly all of these instructions specify that 0.1 ml. of vaccine should be injected very superficially. But the size of the resulting wheal is usually also specified, testifying to the fact that the volume of vaccine is not expected to be measured by the graduations on the barrel of the syringe. The reason for this cannot be doubted : the syringes often leak so badly that some other way had to be found to gauge the volume injected. Even if syringes did not leak it would be questionable whether the graduated markings could be used for vaccinations done at the speed expected in mass campaigns. In practice, therefore, volume is commonly gauged by the size of the wheal, and this is usually *estimated* rather than measured. Some vaccinators are told to try to make wheals 5 mm. in diameter, and others wheals 10–12 mm. in diameter, but at the same time all are told to inject 0.1 ml. very superficially.

Quantitative data from the studies described in this paper show that the diameter of the wheal is directly related to the volume as well as to the depth of the injection ; the largest wheals are produced by the largest volumes given most superficially ; the smallest wheals by the smallest volumes given most deeply. A wheal 8 mm. in diameter, for example, was usually found to represent 0.1 ml. of vaccine injected superficially, but a wheal of this size could probably represent 0.4 ml. or more given in the deeper layers of the skin. On the other hand, only one-quarter of the recommended dose, given very superficially, can give rise to a wheal 5 mm. in diameter. The results indicate that there must be enormous differences in the volume of B.C.G. given in mass campaigns—the differences between vaccinators alone amounting to four or five times, and probably still greater variations in the amount given to individual persons.

This investigation has shown that tuberculin allergy, measured by the size of tuberculin reactions at different intervals after vaccination, is practically unaffected by variations of technique within the likely range in mass campaigns. The size of the local responses at the vaccination site, on the other hand, depends to a large extent on the depth of injection and to a less extent on the volume of vaccine injected. A given volume injected subcutaneously produces lesions twice as large as those resulting from the same

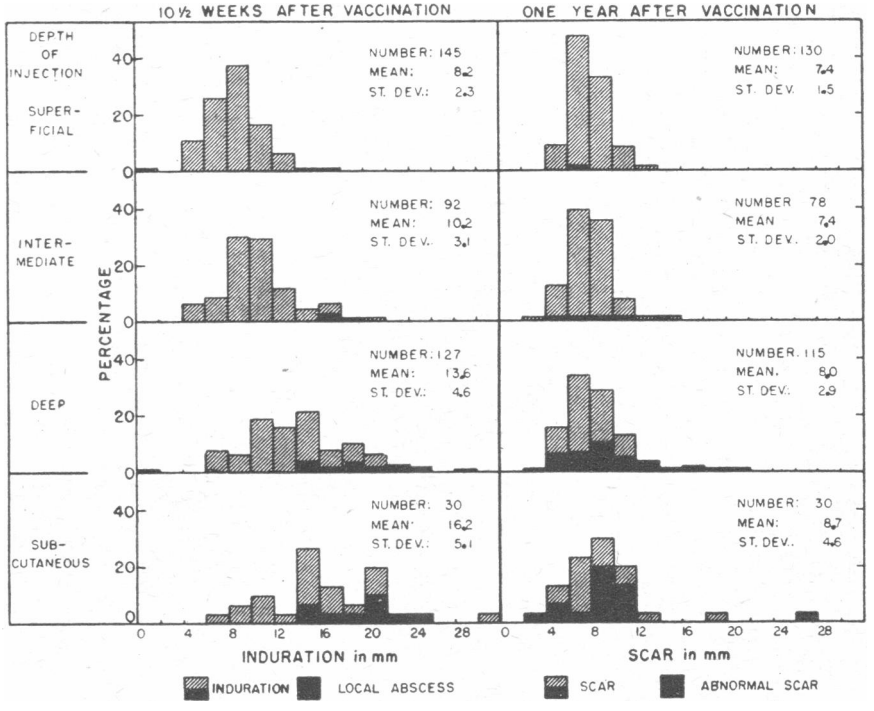

FIG. 4.—Frequency distributions of diameter of local vaccination lesions, and frequency of local abscesses and abnormal scars, according to depth of injection of 0.1 ml. of B.C.G. vaccine.

*The term " abscess " is used to denote a collection of fluid *beneath* the corium, as opposed to the normal ulceration *in* the corium, which, when covered, is covered by epidermis and crust only.

volume injected superficially. Moreover, abscesses at the site of the local lesion are rare after superficial injections, but increase progressively in frequency with increasing depth of injection; and in this investigation nearly one-third of the children had associated subcutaneous abscesses when the vaccine was injected just below the skin into the subcutaneous tissues.

These findings bear directly on the question whether laymen should be employed as vaccinators for mass B.C.G. campaigns in countries with few professional personnel. So far as post-vaccination allergy is concerned, variations in the technique of giving intradermal injections apparently make so little difference that lay vaccinators could probably be employed with impunity. If, however, the success of a campaign depends on keeping to a minimum the frequency of large vaccination lesions and of complications, then all vaccinators must be intensively trained to inject the vaccine into the most superficial layers of the skin.

What bearing do these findings have on the search for more fundamental knowledge on the problem of tuberculosis immunization? We cannot answer this question, yet it may be permissible to speculate on certain possibilities. To regard a large, ugly vaccination lesion as a promise of strong and long-lasting immunity is, if not an obvious inference, at least a tempting idea to the vaccinator, and a consoling idea to the person vaccinated. But our findings provide little support for such an inference. Certainly a weak vaccine (such as the 1/100 dilution of standard strength used here) gave rise to extremely small lesions and rather weak allergy; but when standard strength vaccine was injected at different depths in the skin very considerable differences in the size of the lesions were not associated with differences in allergy. The inconstant correlation between the local reaction and the allergic response to B.C.G. does not justify the belief that both can be used as a true guide to immunity. A strong or a weak local reaction—a good or fair "take"—may reflect properties associated with immunization we do not know; yet from these studies it seems to depend to such an extent on the way the vaccinator did her work that size of the local lesion may well reflect factors that have nothing whatever to do with immunity.

Summary

An intracutaneous injection of B.C.G. vaccine may deviate from the recommended technique in two principal ways: more or less than 0.1 ml. may be given, and the vaccine may not be injected superficially into the skin. This paper reports the results of several studies, altogether comprising about 1,400 schoolchildren, in which volume and depth of injection of B.C.G. vaccine were deliberately varied within the limits likely to occur in ordinary mass vaccination campaigns, and the effect of such variations on the resulting post-vaccination tuberculin allergy and the local reactions at the site of vaccination.

Because of the fact that most syringes leak, the volume of vaccine injected is commonly gauged by estimating the size of the wheal formed on the skin rather than by reading from the graduated markings on the barrel of the syringe. In a study of about 950 children when different volumes of B.C.G. vaccine were injected very superficially into the skin, 0.1 ml. of vaccine produced wheals averaging 8 mm. in diameter. Doubling or halving the volume caused a difference averaging 1.5 mm.: a sixfold increase (from 0.05 to 0.3 ml.) caused a 4 mm. increase in the diameter. In a second study of over 400 children, depth of injection was varied but volume was kept constant: deep intracutaneous injection of 0.1 ml. gave wheals averaging 3.1 mm. smaller than the same volume injected superficially—a decrease as great as that from a fourfold reduction in volume given superficially.

Tuberculin allergy in schoolchildren, measured by the tuberculin reaction at intervals after vaccination, was practically unaffected by variations in intracutaneous technique likely to occur in the field. Volumes of 0·05–0.3 ml. of vaccine injected at depths ranging from very superficial in the skin to subcutaneous all gave about the same mean level of post-vaccination allergy.

A given volume of vaccine injected just beneath the skin into the subcutaneous tissue produced local lesions twice as large as those from the same volume injected superficially. The frequency of local subcutaneous abscesses increased with increasing depth of injection.

These studies show that the size of the reaction at the site of vaccination is influenced by the depth of injection of vaccine, but the level of B.C.G.-induced tuberculin allergy is not. If, therefore, post-vaccination allergy is to be taken as an index of immunity, the local vaccination reaction does not necessarily measure the same thing.

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MEASUREMENT OF LEAKAGE OF TUBERCULIN SYRINGES

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Many of the syringes used for intracutaneous injections tend to leak between plunger and barrel, often to such an extent that reading from the graduated scale may be grossly misleading. In practice the quantity of liquid actually injected is therefore usually estimated by measuring the size of the wheal produced at the site of injection. For scientific work, however, where accurately measured dosage is required, unsatisfactory syringes must be detected and eliminated before use.

A simple and easily constructed apparatus for accurate and quantitative measurement of leakage in syringes is

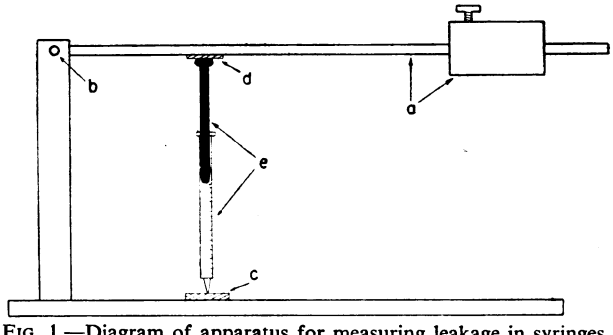

FIG. 1.—Diagram of apparatus for measuring leakage in syringes. a = lever with adjustable weight; b = joint for vertical rotation of lever; c and d = rubber disks; e = tuberculin syringe.