THE PROTECTION OF INFANTS AGAINST TUBERCULOSIS*

BY

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During the past five years we have vaccinated 7,115 people. This may seem a very inadequate number on which to base any firm conclusions, but all the newborn infants (5,215) have been seen personally by Dr. Margaret Griffiths or myself and, so far as is possible with a changing population, followed up yearly, so that many infants have already had their fourth annual check-up and tuberculin test as well as repeated chest x-ray examinations. What we primarily tried to achieve was the eradication of progressive (and fatal) disease in the first few years of life.

Between 1949 and 1954 there were 50 deaths from tuberculosis in Manchester in children under the age

FIG. 1.—X-ray film of chest of child with primary tuberculosis.

of 5 years, of whom 12 were under 1 year old. There may well have been others, not certified as due to tuberculosis. No deaths from tuberculosis have occurred in our 5,215 vaccinated newborn babies—and 537 (just over 10%) of them were known contact cases: in addition, there were another 250 known contacts between the ages of 1 month and 2½ years and more than 100 over that age—nearly 1,000 in all. There were also 28 mothers who developed tuberculosis (or it became clinically evident) after their infants had been vaccinated, yet, despite their not having been segregated, none of these infants developed tuberculosis. Furthermore, no radiological lesions of tuberculosis have been seen in any vaccinated children from tuberculous homes during the four-year follow-up, whereas there have been

FIG. 2.—X-ray film of child in Fig. 1 five years later.

13 infants born at St. Mary's Hospital or on the district during the same time who developed primary tuberculosis; none of these had been vaccinated. In our contact families almost exactly half of the patients were suffering from active tuberculosis and in half the disease was quiescent. The percentage of parents accepting vaccination for their newborn infants has been approximately 40%; the remainder serve as unwitting controls, and it was from among these that the 13 tuberculous cases came.

Even in older children primary infection cannot always be regarded lightly, for the lesion may be long-lasting, as shown by the two x-ray films (Figs. 1 and 2), taken five years apart (with intervening ones unchanged), and such children are at risk all this time, particularly from such infections as measles and whooping-cough and also from any debilitating condition. In addition, this type of case provides a large proportion of the cases of bronchiectasis seen in later childhood. It is problems such as these that make a consideration of the advisability of using isoniazid germane.

Contacts

Fig. 3 brings to light another problem. Although we had nearly a thousand known contact cases it is impossible

FIG. 3.—Primary focus discovered at pre-vaccination x-ray examination.

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to estimate the number of unknown contacts. This is the picture found in a child aged 17 months, who was the sister of one of our vaccinated infants. She attended with her sister, who was due for a follow-up tuberculin test, and was tested at the same time because the mother wished her to be vaccinated also; but she was found to be Mantoux positive. An x-ray film was then taken (Fig. 3). The mother gave us no history of contact, but in the light of this film the tuberculosis authorities were informed and replied promptly that the father was known to them as a phthisical patient who had taken his discharge from a sanatorium against advice. The vaccinated infant, happily, remained well.

Children with home contacts are undoubtedly at greater risk. Bentley *et al.* (1954) estimated that 5.3% of all children in London lived in tuberculous households. Dr. M. J. Greenberg kindly gave me the comparable figure for Manchester—it was 5.6%. In Birmingham conditions would appear to be a little better. Dr. V. H. Springett estimates the figure at 4%, and I am indebted to him for his assessment, and also for pointing out that this type of calculation can clearly provide only a very rough estimate, because of the difference between the age-sex distribution of the family contacts and that of the population in general, and because it applies to all children under the age of 16 years and not to the restricted period of infancy which I am discussing. With regard to Birmingham, Dr. Springett further pointed out that there may well be differences in the distribution of family sizes between the city and the region as a whole.

Nevertheless it is interesting how closely the figures agree; they at least give some indication of the extent of the risk of the child population in general in England's three most important cities.

Jachnis (1947) recorded a mortality of 9.5% from tuberculosis among 378 infants and children under the age of 4 years who came from tuberculous households. It is fair, therefore, to assume that there should certainly have been some deaths from tuberculosis by now among our vaccinated contact infants if the vaccination had not been effective.

It is an accepted fact that the younger the child the greater the mortality; the zenith is reached in congenital tuberculosis, and more than one-fifth of all deaths from non-respiratory tuberculosis occur in the pre-school years. Mitchell and Willis (1944) reported in a series of 243 children under their care in a Detroit sanatorium that there were 29% of deaths in the infants under 19 months of age as compared with 10.5% between that age and 3 years. Jorup (1946), in Sweden, recorded a 60% mortality in those infected in the first three months of life, and this is not an exaggerated figure, taking the literature throughout, although to-day's mortality is undoubtedly lower, following the introduction of isoniazid.

What is even more serious is that in Stockholm, which is renowned for its tuberculosis services, Söderling (1939) found that the infants under 2 years of age who were infected owed this to previously undiscovered tuberculous adults. This is the risk which is ever present—one simply cannot exclude the casual contact with an unsuspected adult with open tuberculosis.

"It is paradoxical that where the tuberculosis services are best the risk to infants is greatest because it almost certainly comes from an unexpected, and unsuspected, source—whereas appropriate arrangements for segrega-

tion and a high standard of hygiene are likely in most of the families known to the tuberculosis authorities" (Hewell and McClellan, 1954).

Development of Immunity

In the newborn period—with which, as I said, we have been particularly concerned in our studies in Manchester—the development of immunity and the placentally transmitted immunity and the possibility of the absorption and utilization of antibodies by the ingestion of colostrum have been extensively studied. It is generally agreed that there can be some degree of immunity placentally transmitted against certain infections, such as poliomyelitis and measles. It is also the consensus of opinion that colostrum is practically valueless as a source of immune bodies in infancy. The great protective value of breast-feeding is in eliminating the risk of bovine infection from unclean or infected cows' milk, and this, of course, applies to tuberculous as well as other milk-borne infections.

The powers of independent immunity development in the newborn are generally thought to be very poor. For this reason diphtheria prophylaxis and other like measures are usually postponed till the age of 4 to 6 months. In the case of diphtheria it is well known that if the mother is Schick-negative the development of immunity in the infant following toxoid is inhibited for some weeks by the passively transmitted antitoxin.

Rollof and his associates (1954) have suggested that a similar mechanism exists in tuberculosis, for they found that newborn infants of tuberculous mothers were slow to respond to B.C.G. vaccination and that they reverted more readily. By serological studies, using the Middlebrook-Dubos haemagglutination titres, they showed that the antibody did not pass across the placenta, but thought the delayed response was due to passively transferred immunity in some other way. It is interesting to note that Ström, in his studies on radioactive B.C.G., showed that newborn infants vaccinated with B.C.G. possessed the ability to localize the organisms at the site of vaccination to some extent even before Mantoux conversion, and this supports the opinion that there may be some passively transferred immunity already existing at birth. Antibodies are certainly present in the liquor, and the foetus drinks this in abundance from about the fourth month onwards; he therefore has ample opportunity to acquire some immunity before birth. Hagberg (1954), in investigating contact newborn infants, reported, like Rollof, that their conversion rate was much slower than in non-contact infants. Our figures have been quite contrary, for 97% of our contact infants had converted by four weeks compared with 81% in the non-contact cases.

In considering the suggestion of delayed conversion in general in the newborn, Hewell and McClellan (1954) reported findings identical with ours—that their highest conversion rate occurred in this age group, and, furthermore, that the least change in sensitivity with the passage of time was in this group; with this we also agree.

Duration of Tuberculin Sensitivity

The actual duration of sensitivity we do not yet know. After four years our number of reversions is still extremely small. The latest report from Sweden, a careful seven-year study by Enell (1955), showed that, of infants vaccinated at birth with the attenuated Swedish vaccine, 85% were still positive after seven years. For schoolchildren whose average age at vaccination was 7½ years the figure was 91% at the end of the ninth school year, but for schoolchildren the chances of exogenous superinfection and consequent allergy boost are of course greater than in infants.

We have used in general 100 T.U.—that is, 1/100 O.T.—in our Mantoux tests to reach our conversion figures of 100%, and this draws attention to the work of Palmer

et al. (1954) on non-specific tuberculin sensitivity. They maintain that only reactions to 5 T.U. can be regarded as specific. However, in our series, although more of the initial post-vaccination Mantoux tests have been with 100 T.U., we have repeatedly found positives with 10 T.U., and those reacting to 100 T.U. very strongly, as many have, rapidly show an equally good response to 10 T.U. These non-specific reactions are much less likely to be significant in newborn infants than in adults or even older children.

In this country 100 T.U. is the generally accepted strength for pre-vaccination testing, and if greater dilutions are used and a negative reaction is accepted as indicating freedom from past infection, a number of Koch phenomena may occur after vaccination, suggesting that the individuals so reacting had, in fact, already been infected.

Heaf (1955) drew attention to the high reversion figures he obtained, and suggested that this might be explained on the basis of local desensitization of the skin to tuberculo-protein following a previous Mantoux test; but we have not experienced this phenomenon, having seen only 14 reversions (and 6 of these were with freeze-dried vaccine, which is notable for its varying antigenicity) among all our newborns. Reversion is commoner after scarification and multiple puncture techniques, and the fewer complications after such vaccinations are undoubtedly due to the smaller quantity of vaccine absorbed, with diminished multiplication of the bacilli *in vivo*, lower allergy, and lower immunity. One must always pay more for the best—and the price of intradermal vaccination, at least in the newborn with a potent vaccine, is an increase in scars, though this is now reduced to a reasonable proportion and depends almost entirely on the individual susceptibility of the infant concerned. Biering-Sorensen (1953) reported an excessive number of abscesses following vaccination in the newborn in a maternity hospital in Copenhagen, and questioned whether this incidence of complications was sufficient to discountenance vaccination at this age or whether scarification should replace the intradermal route.

The number of complications reported to the Ministry of Health, showing this marked preponderance of these complications in the newborn, may be explained, at least in part, by the fact that these reports, which are from many thousands of vaccinations, nearly all occurred in the early days of B.C.G. in this country, and the thigh was used regularly initially until it was realized to be unwise, and the dose used at that time was much more than that which we now know to be necessary to ensure conversion.

Vaccine Dosage in the Newborn

We have stressed before (Gaisford and Griffiths, 1954) that newborn infants do not require twice as much as older children or adults, and that this is a dangerous recommendation when a potent vaccine is used. It is based on Wallgren's work, which referred directly to the Swedish vaccine—a much more attenuated one than the Danish. Half the adult dose is all that is required in the ordinary newborn infant, so that almost all these cases reported to the Ministry were likely to have received four times the optimal dose, and this with a highly antigenic vaccine—the Danish B.C.G. The only occasions when we vary our dose are when known contact infants are to be vaccinated, and even then only half the Ministry-recommended dose is given; we are now inclined to believe that this is not really necessary, for the immunity may well depend on the active multiplication of the organisms rather than on their initial numbers. With a really potent live vaccine a very few organisms may rapidly multiply *in vivo* and produce a better and longer-lasting effect than two hundred or more times the initial number of more attenuated bacilli.

Although scarification produces fewer complications it is completely inaccurate regarding the dose absorbed, and does not compare with the intradermal route for controlled trials.

The same applies to vaccination by aerosol, which has been used in France by Maclouf and Fichez (1952), who found that five minutes' inhalation of B.C.G. produced conversion regularly, and to oral vaccination, which, despite the "hit and miss" effect of this method, is followed routinely, and compulsorily, in Russia, where every newborn infant is so treated, and in Brazil, where Rosenberg (1954) reported that there had been no cases of tuberculosis among 401 newborn infants given six doses of B.C.G. by mouth at monthly intervals. These infants all lived in a tuberculous environment in Rio de Janeiro and São Paulo (cities with very heavy tuberculosis morbidity rates). It may be recalled that, when first used for the vaccination of infants by Weill-Hallé as long ago as 1921, the B.C.G. was given by mouth.

Complications

With regard to complications, I have nothing much to add to our previous publications on this aspect except to say that they are now rare (0.3%) and that we have seen no other untoward effect than local or nodal sinus formation.

FIG. 4.—Pyrexia observed at time of Mantoux conversion.

Included in our series were 40 pairs of twins. It was interesting that in "like" twins the size of the local reaction and the area of induration of the post-vaccination Mantoux test were identical and that when one twin developed a regional adenitis the other one showed corresponding enlargement of similar nodes.

While it cannot be regarded as a complication, or even untoward, an interesting occurrence was observed occasionally. During their in-patient stay for segregation, contact-vaccinated newborn infants were subject to the same routine as other infants, and this included temperature recording. It was noted that for no apparent reason some of them became mildly

FIG. 5.—Weight gain in vaccinated and control infants.

pyrexial for a few days—without signs of any sort—and this may well have been due to the mild febricula of initial B.C.G. infection, which passes unnoticed in the home. The fever coincided with the change-over to a positive tuberculin reaction (Fig. 4).

It has been stated that a slowing of weight gain occurs in vaccinated infants. In a series in which we investigated this we found no such effect (Fig. 5).

In view of the experimental suppression of vaccination in animals by the concurrent administration of isoniazid it has been interesting to observe those infants who, at or about the time of vaccination, were given streptomycin because of some neonatal infection. No suppressive effect was evident, which might be considered as evidence in favour of the superiority of isoniazid over streptomycin, but most likely it was that the streptomycin, being given for a relatively short time, could hardly have been expected to affect the action of the B.C.G.

After a well-marked adenitis, calcification in the axillary region is commonplace, but in our serial follow-ups we have seen no intrathoracic calcification, although when we used the thigh for the injections originally, and inguinal calcification was frequent, we occasionally saw calcification extending to the deep iliac glands.

Calcification lasts for a long time, though there is a tendency to gradual diminution in size. Where the glands are much enlarged calcification later is the rule. Where the glands break down and discharge calcification is subsequently much less evident. Calcification was present in all the glands of long standing (Fig. 6).

FIG. 6.—Incidence of calcification.

I would again draw attention to the importance of the site of vaccination on the arm—at any age—because if the injection be given much above the insertion of the deltoid there is an increased risk of supraclavicular adenitis and a commensurate possibility of breaking-down in this region because of its association with the cervical glands and their involvement in repeated upper respiratory infections.

There is no need to stress these complications, because we know they are all minor in character and will heal spontaneously in time. Nevertheless, they can be worrying to parents and disfiguring to the infant, even if this be only temporary. Any treatment, therefore, which will accelerate healing is worth undertaking. Local surgical treatment, excision or incision, is rarely necessary. Aspiration is often helpful, with isoniazid, streptomycin, or P.A.S. replacement. Ultra-violet light locally is also of value in accelerating healing. Exposure to fresh air and sunlight is probably the best treatment of all. It has been very striking how secondary infection has been absent, even in the longest-continuing sinuses.

Early Vaccination and Immunization

It is, then, well established now that newborn infants can react satisfactorily, and we have vaccinated them on the first day of life; this applies to even the less immature premature

infants, for we have vaccinated a number of premature infants to determine this fact and found that they reacted well and converted promptly with the same dose as full-term infants. The smallest infant weighed 3 lb. 15 oz. (1.8 kg.), and with only 0.05 ml. of vaccine—that is, 0.0375 mg.—converted after eight weeks. There were no adverse systemic effects in any of the premature infants, but an increased incidence of adenitis makes us consider it advisable to postpone vaccination till maturity is reached, although most premature infants could safely be vaccinated and be allowed to convert before leaving the nursery—that is, at 5 lb. (2.3 kg.) or thereabouts—and in contact cases this would obviate the need for subsequent segregation.

Immunization at birth against diphtheria, whooping-cough, and tetanus, singly or combined, is being practised effectively in many centres. In my department, Dr. G. V. Feldman has, concurrently with our own studies, immunized some 1,500 newborn infants against these infections and found that an adequate response, both serologically and clinically, can be obtained, and that, in the main, when failure occurs it is more likely to be attributable to the vaccine than to the infant.

It has been suggested that in the administration of combined antigens there is likely to be dominance of one, to the possible detriment of another, and his experience has borne this out. The same may consequently apply to different antigens given within a short time; an interval of at least four weeks should therefore elapse between two different vaccinations, such as tuberculosis and smallpox, if the optimal effect of each is to be obtained with certainty.

It is true that there are certain differences of reaction in the newborn, particularly regarding speed and intensity, but these differences cannot, we feel, be considered sufficient to justify postponement of active prophylaxis where this is indicated (Figs. 7 and 8).

In regard to tuberculosis particularly, it is impossible to protect an infant too early. Although, as I have said, the immediate contacts can be found in a great many cases of infection in children—and the

FIG. 7.—Histogram showing delayed response in newborn.

FIG. 8.—Histogram showing that response at 1 year is as good in infants vaccinated at birth as in those vaccinated after the newborn period.

younger the infant, the greater the number—in a recent study Walker (1955) found that even under 3 years of age the contact was unknown in 33% of 194 children, so that family freedom is not by any means indicative of immunity of any infant from infection. Bentley found that more than 30% of the tuberculous meningitis in his children at High Wood originated in the first two years of life, and, what is particularly striking, in 16 of the 41 infants so affected no contact could be traced.

An infant may be exposed to infection at birth or at any time thereafter, and whatever method of vaccination is used a certain minimal amount of time must elapse before any protection can be afforded. The shorter this minimal period is after birth, the greater are the chances of preventing tuberculosis. Another point in favour of vaccination in the newborn period is the ease of access to the infant while he is still immobilized, either at home or in hospital, and this is of great practical importance. If prophylactic immunization is undertaken the vaccine is brought to him: he is not dependent on his mother's taking him to the doctor or to a clinic. Another minor but not entirely irrelevant point is that at this age no pre-vaccination tuberculin test is necessary.

It may well be asked, "Will vaccination serve to provide protection in the first six months of life?" The theoretical answer should be, "No—it takes some time for the vaccine to exert its influence." Yet practical experience shows that

there may after all be some value even in the early days after vaccination, for the protection should not be, and, indeed, experimentally has been shown not to be, dependent on tuberculin conversion, which is only an expression of allergy. Protection may start before conversion, and persist after reversion. The truth of this early protection is borne out by the very few infants vaccinated at birth who have contracted tuberculosis in the first six months of life. Gyllenswärd (1949) has pointed this out in Swedish infants in whom—with the more attenuated vaccine in use in that country, often not giving conversion for ten to twelve weeks—there has nevertheless been a negligible mortality in these first six months.

We have used a variety of vaccines, but chiefly Danish, French, vole, and Swedish. Fig. 9 shows the relative numbers of each.

Vole Vaccine

With regard to the vole vaccine, Dr. Wells has supplied us fortnightly with this vaccine, of constant antigenicity, all from one strain, and it has the great advantage of being prepared with a definite number of bacilli per ml. instead of by weight. Using the intradermal method of vaccination, as we have throughout, this means that we have been able to control to a reasonable degree of accuracy the actual number of bacilli injected—and they have been almost 100% live bacilli. The practice hitherto has been to vaccinate by multiple puncture when using vole vaccine, but we determined to continue with our existing intradermal routine.

We started tentatively, at Dr. Wells's suggestion, with a dose of 50,000 bacilli and were more than agreeably surprised to obtain a conversion with 100 T.U. after as short an interval as eight days. And this, for newborn infants, is something worth achieving, particularly from the practical point of view in relation to segregation. Subsequently we found the Danish vaccine did just as well with regard to the rapidity of conversion.

However, some three to six months later it became evident that this dose of vole vaccine must be reduced, because,

although the local lesion was not excessive—indeed, no more than B.C.G. produced—and there were no systemic upsets, the axillary glands overflowed in too many.

Reduction of dose proceeded by gradation until we reached the phenomenally low figure of 1,250 bacilli, with which a higher proportion of non-conversions at four weeks became evident than in B.C.G. vaccinations (41% positive with vole against 97% with B.C.G.), though of course they all converted later (Figs. 10 and 11).

There has been only one case with an axillary abscess at the low dosage, but even this one shows that the margin between minimal effective dose and that producing undesirable side-effects is narrow. However, as Wells and Wylie (1954) had recorded that 1,000 times the optimal dose of vole vaccine has been given intradermally to several people without any harm, save the unpleasantness of excess local reaction, we did not anticipate any systemic disturbances, and, indeed, none were encountered. So far, in the yearly follow-up there have been no reversions after vole vaccination with doses of 25,000 bacilli or more; indeed, the tuberculin response with 1 T.U. has been better than with B.C.G., and this may prove to be an important factor (Fig. 12).

After discussion with Dr. Wells and Dr. Vollum we then decided to try the effect of a preliminary injection of dead bacilli followed after a week by the live vaccine to see whether this would diminish the number and size of the glandular reactions without affecting conversion. Practical difficulties, however, led to the abandoning of this technique; firstly because some of the mothers did not return with their infants after the initial injection of dead bacilli only, and, despite having been told that a second injection was necessary before the vaccination

FIG. 9.—Numbers injected with the various vaccines. Danish, 5,991; French freeze-dried, 569; vole, 516; Swedish, 39.

FIG. 10.—Reaction to 100 T.U. at four weeks. (Conversion.)

FIG. 11.—Reaction to 100 T.U. at four weeks. (Induration.)

FIG. 12.—Reaction to 1 T.U. one year after vaccination.

could be considered complete, may well have considered their infants protected and consequently relaxed essential hygienic precautions. Secondly, this method obviously involved an increase in the time elapsing before adequate protection could be given.

We next mixed live and killed bacilli in known proportions—1,250 live and 12,500 killed—at a single injection to confirm or refute Palmer's suggestion that a mixture of live and dead bacilli was better than 100% live bacilli. We found that conversion was better with the mixture, thus agreeing with Palmer, and opening the way for further interesting study of varying combinations (Fig. 13).

This 1,250 bacilli level is a remarkable reduction from the accepted figure for B.C.G., and this is directly due to the greatly increased potency of vole vaccine. It is quite conceivable that we shall find that even half this dose will suffice.

Wells and Wylie recorded lupoid reactions at the vaccination site in 3.3% of their cases. We have had no such cases so far. They found, however, as compensation, that the incidence of tuberculosis in 2,500 vaccinated persons

was 0.085% compared with 2.35% in their controls. Only seven cases of lupus following B.C.G. have been recorded so far; we have seen none. Frew and his colleagues (1955) reported that the lupoid reactions after vole vaccination healed well.

Wells also found a higher and longer-lasting sensitivity than that

FIG. 13.—Results with mixed live and killed bacilli compared with those from 100% live bacilli.

produced by B.C.G., and, experimentally, he found a greater resistance to challenge infection in guinea-pigs—and this resistance outlasted the tuberculin sensitivity.

At present it is too early to define clearly the future position of vole vaccine in infants. It has certain advantages—uniformity, viability, and known number of organisms—and certain disadvantages resulting from its highly antigenic properties, which make the margin between complication-producing dose and minimal effective dose rather narrow. With minimal doses the conversion time is prolonged, and this is certainly a disadvantage in contact infants requiring segregation.

A possibility to be considered is the deliberate attenuation of the bacilli, as in the case of B.C.G., by growing them on bile-salt media as has been suggested by Cronin (1954); but this would relegate vole vaccine to a mere alternative to B.C.G. without any of the advantages which it may well finally prove to have, unless it is possible to produce a limited degree of attenuation, approximately half-way between its present potency and that of B.C.G.

We are following up closely those infants whom we have vaccinated with vole bacilli, and if, with the low dose we have used most recently, or an even lower one, complications are few and allergy reasonably maintained for as long as or longer than that following B.C.G. we shall certainly consider recommending its further use.

Results from Various Vaccines

The differing antigenicity of various vaccines has produced a striking difference in the results (Fig. 14). Stein and Aronson (1953) noted this, for they found that their 4% of vaccinated subjects who had radiological evidence of pulmonary tuberculosis had been those vaccinated with a low-antigenicity vaccine. Rosenthal (1952) found that he had to wait 58 days to get conversion with a freeze-dried

vaccine, as compared with 28 days when fresh B.C.G. was used; this is a significant time difference if segregation is considered.

This variation in vaccines may depend on the parent strain, cultural differences (including date of collection), and the percentage of live to dead organisms. Also, of course, on the method of keeping (length of time, temperature, and exposure to light), which will affect the percentage of living organisms. Birkhaug investigated the effect of time and temperature on B.C.G. and found that the vaccine lost 50% of its living population in one week at 20° C. and nearly 100% in three weeks, and nearly 100% after one week at 37.5° C.; these findings were confirmed by the diminishing vaccination lesions and post-vaccination Mantoux reactions and by reduced resistance to challenge infection in guinea-pigs.

Edwards and Gelting (1950) on the other hand, found little alteration in allergy after nine weeks at temperatures up to 20° C. and at room temperature after a month, which shows the greater importance of challenge infections than allergy and establishes a correlation between the percentage of living organisms and protection, which was stressed by Dubos and his colleagues, who concluded from their studies that the effect of the vaccine was dependent on the multiplication of the organisms *in vivo* and that live bacilli were therefore essential. Edwards and Gelting, however, wisely made two reservations in drawing their conclusions. Firstly, that they had used a potent vaccine—and their results

FIG. 14.—Reaction to 100 T.U. after various vaccines.

could hold good only for similar vaccines; and, secondly, that their post-vaccination tuberculin reactions were at ten weeks, and subsequent testing might disclose major differences (Figs. 15, 16, and 17).

Anyone working with such a variable as a tuberculosis vaccine can draw conclusions on the efficacy only of the particular vaccine he is using, and the variations encountered are responsible for the sometimes widely different results published from different centres. For example, Dubos claims that *in vivo* multiplication of the organisms is an important part of the total reaction. Bloch (1954), on the other hand, holds that so long as there are live organisms their multiplication is not essential, and that even resting bacilli can elaborate the products necessary for immunization; the Italians hold that live organisms are not necessary at all.

For the past year we have used a special half-strength vaccine (0.375 mg./ml.) which Professor Heaf kindly arranged to be sent to us from Copenhagen. This allows of more accurate dosage. It will be seen from the mean of the responses that there is virtually no significant difference between any of them, but technically the third is the easiest and most accurate. It is not easy to give 0.05 ml. accurately to an active newborn infant (Fig. 18).

We have used O.T. and not P.P.D., and have used comparable batches of O.T. in the same way that we have with the vaccines.

After the work of Magnusson and Lithander (1949) with B.C.G. tuberculin, in which they reported that the Mantoux conversion occurred appreciably earlier in newborn vaccinated infants with this tuberculin than with ordinary old tuberculin, we tried it for a short time. Magnusson kindly sent us a supply from Stockholm, but we could obtain no

quicker conversions than with O.T., and this, I think, was probably due to the fact that his tuberculin was made from Swedish B.C.G. and therefore, although comparatively weak, was homologous with the vaccine he used, whereas we were using Danish B.C.G. I think there might well be a difference

Fig. 15.—Histogram showing effect of storage (refrigerated).

Fig. 16.—Effect of temperature.

Fig. 17.—Reaction to jelly test one year after vaccination. (Danish, 0.0375 mg.)

if we could use vole tuberculin, which would undoubtedly be more potent, but there are technical difficulties in its preparation.

Palmer and Edwards (1955) showed that homologous tuberculin produces a larger reaction than heterologous and that this might be useful in differentiating between specific and non-specific reactions; for example, if the reaction to avian tuberculin was as great as that to human O.T. a non-specific reaction would be the likely explanation.

Freeze-dried Vaccines

Freeze-dried vaccine offers so many possible practical advantages that its use must be seriously considered. The longevity of the vaccine, the ease of transport, and the freedom from temperature control are all in its favour. Its disadvantages at present are the varying quantity of living organisms, its generally more marked attenuation, and the difficulty of overcoming the clumping which occurs: even

solutions which are clear to the naked eye will be found to show marked clumping under the microscope, so that accurate dose estimation is almost impossible. Such vaccines will certainly provide adequate local lesions and lead to Mantoux conversions—though on an attenuated scale—and the tendency to reversion is greater than with fresh vaccine. By way of increasing the difficulty, the complications, which might be expected to be fewer, are not; for some infants get too many, some too few, bacilli, owing to the clumping. When the clumping problem is overcome there will be a much wider scope for freeze-dried preparations.

We have used the dried vaccine prepared at the Pasteur Institute, and, most recently, a product made in this country which is suspended in dextran before

freeze-drying. Our results with the French vaccine have been comparable with those we obtained with the fresh Swedish vaccine—that is to say, slower conversions and lower allergy—which are both disadvantages in the newborn period. On the British preparation it is too early yet to make any pronouncement, but our results so far show it to be comparable with Danish B.C.G.—at least so far as the speed and intensity of allergy development and the appearance of the local lesion—but we do not yet know how long its effects will last or whether it will enable us to reduce still further the incidence of glandular reaction. It certainly promises well.

There is certainly a decline in mortality from tuberculosis. Fig. 19 shows that the mortality in infants under 1 year has not fallen a great deal. However, the interesting

Fig. 18.—Mantoux 100 T.U. Newborn (Danish 0.0375 mg.)

Fig. 19.—Deaths from tuberculosis under the age of 5 years. (England and Wales.)

fact is that the incidence remains high, and though the death rate (overall) dropped by 59% between 1948 and 1953 the notifications fell by only 7%. The risk of exposure therefore persists.

Certain practical problems have arisen and must be dealt with carefully if the principle of early vaccination is not to fall into disrepute.

Precautionary Measures

After successful vaccination a card should always be given to the mother stating that the infant has been vaccinated and that the Mantoux test was positive in 10 or 100 T.U., as the case might be, on the date given. This card should always accompany the infant (and, later, the child) to hospital. Surgeons are apt to be misled by swellings in the axillae or groins, particularly as by the time these appear the vaccination

has been forgotten if the infants have not been attending a follow-up clinic. Physicians too, viewing shadows and opacities in the thorax or investigating a child with a cough, should know of a preceding vaccination, for such shadows will surely be non-tuberculous, but B.C.G. will not prevent a child from having a cough.

Furthermore, the family doctor and welfare clinic should always be informed of the vaccination, so that due care may be exercised when other prophylactic immunizations are undertaken; for the arm used for B.C.G. should be "rested" for at least six months, whereafter lighting up of the vaccination site or regional nodes is unlikely. We have for some time now used the right arm routinely for our vaccinations, except in those contact infants in whom we divided the dose and gave half into each arm. We have thus left one arm free for any other prophylactic or therapeutic procedure. Personally, even if a double dose is to be given, I prefer to give it at a single site even if that should increase the risk of adenitis, for this allows one arm to be completely free.

Conclusions

Finally, what conclusions can we draw from our studies? They are:

That infants are at risk and that this cannot be prevented. That vaccination at birth is safe, practicable, and effective, though it does not obviate the need for segregation and for general hygiene and education in hygiene. That it would appear that vaccination is effective in protecting throughout the danger period of infancy, though we do not know whether revaccination may not be necessary at 10-12 years; this may well depend on any exposures in the intervening years. That, of all the vaccines we have used, quickest conversion is afforded by the standard Danish B.C.G. That a half-strength vaccine—that is, 0.375 mg. per ml.—is preferable for this work in infants, as it allows of more accurate dosage. That the complications are mainly directly proportional to the antigenic potency of the vaccine and to the dose given. That until the tuberculous antigen is isolated, vaccination with live attenuated bacilli offers a sound means of protection, and, because of the urgent need of this protection from the earliest possible moment, vaccination may most profitably be undertaken in the newborn period despite the slightly increased risk of glandular complication at this age, provided the vaccine is given in accurate dosage, by an experienced person.

That when potent freeze-dried vaccine is available generally the problem of "shortevity" and temperature control will no longer cause difficulty in distribution. A freeze-dried vaccine, free from clumping when dissolved, and containing a known number of evenly distributed and living bacilli, allowing of accurate controlled dosage, will be a great step forward.

That in view of the need for careful follow-up and the difficulty of getting sufficient trained personnel it would not be practicable to carry out mass vaccination in the newborn at present even if that were desirable. Nevertheless, where facilities exist—that is, in maternity hospitals and where there is experienced paediatric supervision—we believe that vaccination in the newborn period offers a very real contribution to the protection of infants against tuberculosis, and we consider that it might with advantage become an accepted part of the "care of the newborn" in maternity hospitals. But, apart from such hospitals, we think that it should at present be reserved for infants who are known to come from, or be going to, tuberculous households, and in these it should be a routine procedure as soon after

birth as possible—that is, during the first week of life. Many such infants are, of course, born at home or in district maternity homes, and not every district has a paediatrician, but there are maternity and child welfare doctors in all areas, and one or more of these from each area could be trained to undertake this special work without its adding greatly to his or her existing clinical commitments, and so all infants at known risk could in fact be satisfactorily vaccinated.

I would conclude with the warning that with the changing pattern of tuberculosis and the rapidity of introduction of new antituberculous chemotherapeutics our future programme may well differ significantly from that which I have outlined.

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