BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 5 1955

THE PROTECTION OF INFANTS AGAINST TUBERCULOSIS*

BY

WILFRID GAISFORD, M.D., M.Sc., F.R.C.P.

*Professor of Child Health and Paediatrics, University of Manchester; Hon. Physician,
Royal Manchester Children's Hospital; Hon. Paediatrician, St. Mary's
Maternity Hospital, Manchester*

[The lecturer began with a tribute to Sir Leonard Parsons, saying: "He was as humble as he was great, and was always willing to discuss problems, even with those many years his junior—treating them as equals and giving them that vital encouragement that means so much. As a clinician, a writer, a lecturer, a research worker, or an administrator he was equally outstanding, and as a friend he is unforgettable. In honouring, or perhaps revering is a better word, his memory to-day this University is paying just homage to one who served her more than well and enhanced her reputation in the paediatric centres of the world, and I am quite sure that this concerned him much more than his own reputation ever did. He was particularly interested in the problems of tuberculosis in childhood, and would therefore, I believe, approve the title of this lecture and would also forgive—as was ever his wont—the many imperfections in the presentation of the subject, appreciating only that it is offered as a tribute to him and an acknowledgment of the great debt I personally owed to him for so many years of kindness, encouragement, active help, and friendship."]

I propose first to discuss the various measures available to protect infants from tuberculosis and then to describe the work we have done in Manchester in this connexion with various vaccines.

The term "infancy" is an elastic one, usually limited to the first year of life, but, for the purposes of a discussion about tuberculosis, it may properly be extended to the end of the second year. This is because it is in the first two years of life that resistance to tuberculosis seems to be particularly lacking—and therefore it is the most important and worth-while time to ensure all possible protection, taking every step to prevent exposure and also providing all such active procedures as will enhance resistance.

Proneness to Tuberculous Infection

Why are infants so prone to tuberculous infection? Clearly, the first and most obvious reason is because when very young they are at the mercy of any tuberculous adult who happens to come near them. Secondly, because it is customary among relatives and friends to pick up, and probably kiss, any new arrival as soon as he or she is "on show," and this continues until the infant is able to exercise his active resentment in one way or another. Thirdly, because, as soon as they can crawl, infants are exposed to the dust and dirt on the floor or ground where they are crawling, and may either inhale—or more likely ingest if they are at the "oral phase," as the psychiatrists would term it—any bacilli lying around, as a result of sucking their fists. And tubercle bacilli can, of course, live for many weeks in dry dust, particularly when protected from sunlight.

This proneness is largely incidental. Is there any other cause affecting their resistance which, for example, renders them more prone to progressive lesions than children over 2 years of age? For it is clearly evident from universal experience that after the period of infancy children enter a phase of relative immunity—that is, of being able to deal effectively with any save the most virulent tuberculous infections—a state which persists until the early teens, despite the greatly increased incidence of tuberculous infection during this time. Also during this period they make their first contact with "mass humanity" in the shape of school and classmates and have their general resistance lowered by repeated upper respiratory infections and a succession of exanthemata. By the age of 14 years, approximately 40% of children in most large cities in Great Britain have had their primary infection, acquired, luckily, after the period of infancy, and in the majority of cases have successfully overcome it—often without appreciable (or appreciated) symptoms. Clearly, then, there must be some special circumstances at work in the first two years of life.

Are the body's powers of resistance inadequate generally during this time? It would seem rather unusual that Nature should play such a prank; or is it that there is a specific lowering of resistance to tuberculosis?

Meningitis is a devastating disease, and meningococcal, influenzal, and pneumococcal meningitis are most frequent in infancy, yet to-day the mortality from all three can be almost negligible. In the last seven years, of such types of meningitis under my care at the Royal Manchester Children's Hospital, there have been admitted 19 infants under 2 years of age and there has not been a single death. It is true that the onset is often so dramatic that intensive treatment can be undertaken promptly, but that there is a resistance to the infection is clear, for all these infants were treated by a "therapia sterilisans magna"—that is, a single massive chemotherapeutic dose—intravenously and orally combined, and repeated if and when necessary; the dose given being sufficient to inhibit the multiplication of the organisms, and the infants then being allowed to develop and exercise their own defence mechanisms, which have proved to be eminently efficient. Infants with fibrocystic disease of the pancreas are liable to repeated and severe respiratory infections and can now successfully overcome these for years with the aid of antibiotics. Yet meningitis of all sorts used to be fatal in a high percentage of cases, and fibrocystic disease invariably so. Can we look for a comparable antituberculous chemotherapeutic which will similarly alter the prognosis in the tuberculous infection of infancy?

Isoniazid has already transformed the picture of progressive tuberculosis in children, but in the treatment of the primary as opposed to the post-primary progressive lesions (like miliary and meningeal infection) has proved singularly ineffective to date. Yet, if given at the same time as B.C.G. vaccine, isoniazid has been found to prevent the development of the vaccination in guinea-pigs (Djourichitch *et al.*, 1953), as judged by inability to secure tuberculin conversion, and to prevent immunity development in mice (Dubos *et al.*,

*The first of the 1954-5 Leonard Parsons Memorial Lectures, delivered to the Faculty of Medicine, Birmingham University, on May 11, 1955.

1953), as judged by survival time and by the difference in the number of living organisms recovered from the spleen and lungs of vaccinated animals untreated with isoniazid, compared with those given the drug. The effects of isoniazid depend chiefly on the time of starting treatment after the challenge infection and on the length of time during which treatment is continued, and vary between complete immunity, as judged by persistently negative Mantoux reaction and absence of any evidence of tuberculous infection at necropsy when the animals are sacrificed, and increased resistance—that is, prolongation of survival time. Thus, if we could only know with certainty the time of an infant's primary contact with *Mycobacterium tuberculosis*, or tubercle bacillus, it might be possible by the immediate administration of isoniazid to prevent the development of the primary infection—and this might be repeated as necessary, until the "danger period" had passed and the child could acquire an adequate resistance after an unprevented primary infection in due course. This is naturally impracticable for several reasons, but chiefly because, although in earliest infancy the contact is usually known, it is often only discovered later as a result of the development of the infection in the infant. Secondly, there is unfortunately no certainty that adequate resistance will be developed after a primary infection at any age in any given child, or that, if adequate resistance does develop, it may not wane from time to time to inadequate levels; therefore, benign as tuberculosis usually is in childhood, unprotected exposure still provides an appreciable source of morbidity and, to a lesser degree, of mortality.

Individual Resistance

In addition to these considerations there is the problem of the individual resistance of any given infant, and this may involve hereditary factors which may in some cases explain the proneness of exposed infants to progressive disease. In answer to the pertinent question, "Why do only some of the enormous number of infected persons develop progressive disease?", Rich (1951) answers that it depends largely on individual native resistance, which may be both racial and individual. He defines this native resistance as "the relative ability to destroy or prevent the progressive growth of a micro-organism on first contact with it." He clearly differentiates between this native (or natural) resistance and heredity, and remarks on the difficulty in determining the relative importance of each. This same difficulty exists in rheumatism, but the most recent work of Wilson and Schweitzer (1954) strongly supports the suggestion that rheumatism is inherited. That heredity is important in tuberculosis also is probable. Studies with twins have supported this. For example, concordance occurred in 65% of 80 pairs of infected identical twins and in only 25% of 125 pairs of non-identical twins in a series reported by von Verschuer (1950). In a 22-year study Zeidberg and his co-workers (1954) found that in children with a parent with a positive sputum the attack rate was almost twice as high as in those whose parents were sputum-negative, although there were other sputum-positive but less-nearly related members of the family in the same household, and therefore the contact was equally intimate in the two groups. This they consider is most likely explained on the basis of a hereditary constitutional factor. An interesting finding in this study was that the highest attack rate was in the under-5-year-olds in the "parental positive" group, and not till early adult life in the "parental negative" group. These authors observed further that the risk of the children's developing tuberculosis *after removal* from the household was still significant—a matter of some practical importance.

Meyer and Palmer (1954), on the basis of tuberculin allergy following B.C.G. vaccination, similarly concluded that the results depended on the family membership of the child. By the analysis of variance they showed that both the tuberculin reactions and the local lesions after B.C.G. vaccination were more uniform in size among children of the same family than in children from different families, some families showing strong tuberculin allergy and others

weak. Their results, which showed that lower death rates were found in the families with rapidly developing local lesions, suggest that this rate of development may be useful as an index of the hereditary resistance to tuberculosis.

Vaccination against tuberculosis has been widely practised as an active protective measure, and I shall deal with this in more detail later. Wallgren, the greatest protagonist of B.C.G., the most extensively used vaccine, has repeatedly stressed, however, that vaccination is only one aspect of the attack on tuberculosis, and Heaf (1955) pointed out in his Litchfield Lecture at Oxford last year that its biggest disadvantage is the unwarranted confidence that it has inspired amongst laymen, many of whom believe that it affords complete protection, thereby leading to the neglect of the other essential measures of eliminating the predisposing causes and the spread of infection.

Protective Measures

What other methods of protection are there available in early infancy? Firstly, there is the arranging for segregation of all infants who are to be born into families or homes where there is known tuberculosis.

In the ordinary domiciliary midwifery practice, both by practitioners and by midwives, there is as yet no systematic arrangement whereby, in such households, whether the infected person is either of the parents or a relative or lodger, the infant is removed from contact. This naturally will require some considerable organization, for, even if vaccination is to be done, adequate segregation should be provided for at least four weeks—and preferably longer—to allow of increasing the resistance afforded by vaccination, which undoubtedly does not reach its peak until some weeks later. Although tuberculin conversion may be obtained within two weeks, strict protection from contact is desirable for a further period; but if this can be achieved in the home the duration of segregation in an institution or preventorium may not need to exceed two to four weeks. If relatives, or foster-parents, can take the infant, they too will require careful investigation and must submit to having their, and their household's, chests radiographed. If the infant is to be admitted to an institution it must be ascertained that adequate nursing staff is available, for to save an infant from tuberculosis and then to lose him from gastro-enteritis contracted in an understaffed nursery or ward is a sad and profitless exchange. Nevertheless it is a very real possibility, and the matter requires constant thought and supervision.

A further factor in the infection of infants is the returning father or relative who has taken his own discharge from a sanatorium, or who comes home to visit at week-ends—or just to see the new baby—or who is discharged from a sanatorium being sputum-negative as a result of treatment with isoniazid and streptomycin and who subsequently excretes bacilli for some time before it is realized that he is again infectious. These considerations cannot be ignored. Undoubtedly the whole major problem of segregation is bound up with the need for better housing and will not be solved except on a national basis.

Antenatal X-ray Films

A second protective measure would be the routine taking of chest x-ray pictures of all pregnant women. This is most important. Every year a number of cases of active tuberculosis—and more of quiescent tuberculosis which may become active during pregnancy or shortly after delivery—will be detected, having been previously unsuspected. This will allow of appropriate obstetric dispositions then being made and arrangements put in hand for the segregation of the infant from the mother immediately after birth, for the suppression of lactation, and for the vaccination of the infant as soon as possible. It is heartening to know that the Joint Tuberculosis Council has just appointed a committee to investigate the range of antenatal and post-natal radiological services throughout the country.

Genital tuberculosis should also be observed carefully during pregnancy, for infection of the newborn infant from infected liquor amnii or by ingestion or inhalation of bacilli during the birth process is possible. Congenital tuberculosis is comparatively rare, and up to date has been almost uniformly fatal, but perinatal infection (as from infected liquor) can be treated successfully by prompt administration of isoniazid and streptomycin. Reports are now appearing in the literature of recoveries in such cases (Lesné *et al.*, 1949; Hesselman, 1951; Kringelbach, 1954).

Early Segregation

Thirdly, it would be advantageous if there were more special units for the delivery of tuberculous pregnant women; maternity hospitals in general are not suitable for such cases. Arrangements for the segregation of the infant immediately after birth—and the absolute breaking of contact with the mother—are essential, as in domiciliary practice. This involves having a nursery (using this in the sense of a room for newborn infants) preferably in a separate building, whereby the temptation to let the mother have “just a peep” at her baby (and it may be a fatal peep at that) can be overcome.

Is segregation sufficient without any such added protection as vaccination? The experience at Papworth—gained before B.C.G. was generally available—would lead one to believe that it was; but it must be remembered that the almost ideal conditions prevailing in that village settlement, with constant attention to health education and hygiene, are unlikely to be encountered in the population at large; and at Papworth to-day it is significant that infants born into the colony are all vaccinated, and this has been practised since 1950 (Trail, R. R., 1955).

Diet

Fourthly, can diet help in protection? The effect of diet on increasing the resistance to tuberculosis follows the accepted principles—namely, providing an optimal quantity of good protein and vitamins. There is no particular evidence that extra protein or vitamins, for example, will help, or that extra fat is valuable. Although in the prophylaxis of rheumatism there is evidence that increase in the protein and diminution in the carbohydrate intake will lessen recurrence, this has not been observed especially in tuberculosis. As the diet of infants, at least in the first four months of life, is almost entirely limited to milk, it would be difficult to modify the constituents to any great extent without taxing the infant's digestive powers. Breast-feeding undoubtedly produces the greatest general resistance to infection of all sorts in infancy, but it must be denied to the infants of tuberculous mothers, and I doubt whether breast milk given by bottle (from a breast-milk bank or elsewhere) has any special merits over a suitably modified dried cows' milk preparation. Although great care is necessary in the preparation of a cows' milk formula, both in regard to its constitution and its cleanliness, equal care is necessary to prevent bottle-given breast milk from becoming contaminated.

Vitamin D has long been used in the treatment of tuberculosis—especially in the large-dose technique for scrofula—but prophylactically its chief value in infancy is probably to be found in the prevention of rickets and the associated generally diminished resistance which inevitably accompanies this condition. Adequate vitamin D supplements are given to and taken by nearly all infants in Great Britain to-day, and there would seem to be no indication for exceeding the accepted 750 I.U. daily to give added protection against tuberculosis. Indeed, there is now a suggestion that excessive amounts are being taken, and that with fortified dried milks and cereals, together with the daily dose of cod-liver oil, susceptible infants may develop hypercalcaemia.

Education in Hygiene

Fifthly, raising the general standard of hygiene and of education in matters of hygiene is important, particularly that of tuberculous patients, and Wandelt (1954) has recom-

mended that for all such patients there should be a planned co-ordinated education programme. In an interesting paper recording the results of a questionnaire, answered by each patient in two separate sanatoria, about the protection of others, she found that less than 40% gave correct answers to all the questions and one out of every eight would have failed ignominiously with a mark of only 10%; so that unless all adult tuberculous patients are told specifically of the danger they can be to infants and small children they are unlikely to take the precautions necessary to prevent such risks. It was obvious in this inquiry that the educational teaching had varied considerably in the two sanatoria, and doubtless there are similar variations in this country.

In the recently published report of the Joint Tuberculosis Council (1955) occur the following sentences: “The actual risk of infection is occasioned by chance factors which may determine the transference of organisms from one person to another. The habit of spitting has largely disappeared, but there has been little reduction in the practice of indiscriminate coughing and sneezing. Certainly the sanatorium-treated patient is usually well trained, but this does not apply to the unknown sputum-positive patient. Although mortality is declining, if patients with active disease are not effectively ‘neutralized’ in respect of their infectious potential, either by sputum conversion, stabilization of disease, or training in precautionary techniques, and so rehabilitated by adequate standards of living that relapse is unlikely, the declining mortality may prove to be the forerunner of an increasing number of secondary cases.” This is a timely warning.

General Prophylactic Measures

Protection of infants from the effects of tuberculosis should not be limited entirely to specific prophylaxis. In those who have already been infected (as judged by a positive tuberculin test) special care should be taken when they are suffering from or exposed to measles and whooping-cough.

Although statistical proof is uncertain, most paediatricians and practitioners can recall cases where rapid dissemination of a tuberculous process has followed one or other of these infections. Any infant, therefore, who is known to have had primary tuberculosis should be protected so far as possible from exposure to measles and whooping-cough. Where contact with measles has occurred, gamma globulin, if available, should be given. As there is no immediate prophylaxis for pertussis, but protection during the dangerous period of infancy can be extremely satisfactory following adequate immunization—that is, by the use of a really efficient vaccine—it would be logical to immunize all infants having primary tuberculosis with pertussis vaccine (if they have not been immunized already) and to give them a booster dose immediately after any known contact.

Whether protection—in the form of active chemotherapy—should be given to infants with primary infection is debatable. Long-continued prophylaxis with penicillin or sulphonamide has been proved beneficial in preventing recurrence of rheumatic fever in children. Lincoln (1954) has recently recommended that infants with a positive Mantoux reaction (without demonstrable clinical or radiological lesions) should be treated for a year with isoniazid. This may seem rather drastic, but it must be remembered that isoniazid is quite different in its action from streptomycin, for example.

Isoniazid is singularly non-toxic in the majority of infants, and can be given for long periods with safety; Marquézy *et al.* (1953) gave up to 20 mg./lb./day to children for as long as six months and found this non-toxic. Lincoln's suggestion, if carried out on a large scale, might prove valuable, but it must be remembered, in discussing prophylactic possibilities, that isoniazid is only really effective when the bacilli are in large numbers and actively multiplying.

As I said earlier, reports to date have suggested that isoniazid is ineffective in primary tuberculosis—that is, in

children with a positive Mantoux reaction and x-ray evidence of parenchymal or hilar involvement. Todd (1955), in a careful eighteen-months study of 50 children with primary tuberculosis (25 treated with isoniazid for three months and 25 controls), considered that the results were better than with streptomycin or P.A.S. in similar previous trials, and that the isoniazid-treated children showed a better clinical response. Only 10 of these 50 children, however, were less than 2 years of age, and one to three years later there was no difference in the clinical and radiological signs between the isoniazid-treated children and the controls. Todd concluded with only "an impression" that isoniazid was of value, and said that further studies on a larger scale would be necessary before the impression could be converted into fact.

Lincoln's latest idea is more in parallel with the continued prophylaxis successfully applied to childhood rheumatism. Care must be exercised, however, and long-continued treatment would be essential, for Fisher (1954) has shown that isoniazid is at best only bacteriostatic—tubercle bacilli kept for five weeks in a medium containing isoniazid could be revived subsequently—and Dubos and his colleagues, in their experiments with mice given B.C.G. and isoniazid concurrently, found that on withdrawal of the drug bacterial multiplication was resumed in those animals in which treatment with isoniazid had been delayed even for six days after they had received their B.C.G. infection.

B.C.G. Vaccination

Let us now consider vaccination in greater detail—particularly the use of B.C.G. I will not weary you with its history and its changing fortunes since it was introduced by Calmette and Guérin. Since those days it has been given to millions of children all over the world.

There is general agreement that a successfully overcome primary infection gives generous support to the resistance to any subsequent exogenous infection. What one cannot control in such cases is the flare-up of the original infection—that is, an endogenous reinfection—at any time for an indefinite number of years, although Marfan's law, which dates back to 1886 and states that a tuberculous cervical adenitis that is healed before puberty protects against phthisis, is still, in the main, true. The principle of B.C.G. vaccination is simple—to provide the successfully overcome primary infection without the risk of subsequent endogenous reactivation and in the hope and belief that similar resistance (though probably less in degree) to exogenous human or bovine infection will result.

The primary infection in cutaneous vaccination is in the skin—which is a good antibody promoter—and the systemic reaction provoked by B.C.G. is non-progressive.

Is there any real evidence that B.C.G. has diminished the incidence or lessened the severity of tuberculosis? This is a question that is still being asked. The answer must surely be "yes." Even taking into consideration the improved hygienic conditions and education that have come to exist in many countries coincidentally with the use of B.C.G., and the general decline in mortality from tuberculosis, there are clear proofs of the efficacy of the vaccine—and even more clear proof in countries where mass B.C.G. inoculation has been the only step taken to combat the infection among a population. One of the best-known studies is that of Aronson and Aronson (1952), started in 1936 and ending in 1951, in which 1,551 Indians in the United States and Alaska were vaccinated, and 1,457 were taken as controls, a work involving a total of 42,000 person-years. The deaths from tuberculosis were only 12 among the vaccinated, as compared with 65 in the controls during the 15 years. Subsequently Stein and Aronson (1953) reported on the radiological changes after annual x-ray examination for eleven years. The incidence of tuberculous lesions was 4.1% in the vaccinated and 16.4% in the controls—that is, the deaths were more than five times greater in the unvaccinated cases

and the radiological lesions four times as great. With regard to children, in the most recent study of school-children from Sweden, by Enell (1955), it was found that the percentage of clinical cases of tuberculosis among children who were tuberculin-negative on starting school was 0.12 in those vaccinated on entry and 6.53 in those who remained unvaccinated—that is, 64 times as great in the controls—over a period of more than 1,200 person-years.

The effects of B.C.G. have been thoroughly studied, both in experimental animals and in humans, particularly since the introduction of radioactive B.C.G., and the course of the induced infection is quite clear. Ström (1950) has shown that B.C.G. tagged with radioactive phosphorus, when injected intradermally into human beings, passes rapidly along the lymphatics draining that particular area of skin into the regional lymph node, where the bacilli appear in large numbers within 10 to 15 minutes. The spread and distribution of the B.C.G. are identical with those of virulent bacilli similarly injected. If the vaccine is live and the dose adequate, multiplication of the bacilli occurs in the node, and undoubtedly there is a spill-over into the general circulation and a bacillaemia results. Being incapable of causing a progressive disease because of the induced attenuation of the organism, the bacillary foci lie dormant for an indefinite time—probably years in some cases—as in a naturally acquired infection, and finally die. The bulk of the bacilli, however, are immobilized in the lymph node and are subsequently destroyed by phagocytosis in the mononuclear cells. Lurie (1942) showed that tuberculous infection confers on these cells an increase of bacteriostatic properties independent of immune body fluids, and Suter (1953) found that vaccination resulted in the inhibition of the multiplication of virulent bacilli in animals and that this inhibition occurred from the eighth day after their vaccination.

In a naturally acquired primary infection, with numerous or virulent organisms or a low-resistant host (hereditarily or after debility), bacterial multiplication may be so great that multiple metastatic spread occurs, and this may progress rapidly to cause death from generalized tuberculosis, or, if the acute infection be successfully overcome, organisms may live in the foci forming as a result of the metastases and flare into activity, as has been said, many years later. No one knows how long tubercle bacilli may live in the body—even in seemingly impenetrable calcified shells, and yet break through and produce evidence of clinical activity years after the primary infection. Dubos (1953) has said "... No technique is as yet available to bring about with certainty a complete eradication of the bacilli from infected tissues. After antimicrobial drugs have ceased to exert their restraining influence . . . only the resistance of the host can act as a brake on reactivation of the disease caused by the bacilli surviving here and there." In vaccinated animals Ström and Widström (1951) found that radioactive virulent organisms subsequently injected intradermally did not trek to the lymph node but remained at the site of inoculation for quite an appreciable time—even up to 24 hours, as compared with minutes in the unvaccinated animal—and many were destroyed *in situ*.

There is no doubt that the clearing capacity—that is, the ability to accelerate the removal of bacilli from the blood stream—is greater in vaccinated people. This has been known for many years, for as long ago as 1921 Debré and Paraf reported this increased capacity in guinea-pigs. Recently, Ström found that when radioactive B.C.G. was injected into non-infected guinea-pigs the bacilli were subsequently maximal in the lymph nodes, but when the labelled bacilli were given intravenously to previously infected animals they were taken up chiefly by the liver and spleen, not in the lungs. As Rich has demonstrated, the liver and spleen have the greatest macrophage content and can most effectively destroy the bacilli and prevent metastatic dissemination. Nègre (1954) studied the influence of B.C.G. on the subsequent course of experimental superinfection in

guinea-pigs and rabbits as judged by the bacillary content of the organs. In vaccinated animals the virulent bacilli (injected one to three months after vaccination) did not appear in the organs for a month; in the unvaccinated controls they appeared much earlier—towards the end of the second week—and were ten times as numerous. He concluded that the two important factors in determining resistance following vaccination are, therefore, a retardation of dissemination of the virulent organisms and a diminution in their number. Siebenmann (1951) similarly showed that, in mice, multiplication of virulent organisms in the lungs, liver, and spleen was much reduced in B.C.G.-vaccinated animals compared with controls, and this has been confirmed by Dubos and his co-workers.

The first fear about B.C.G. was that, despite the claims of Calmette, the vaccine might vary and some batches prove more virulent, even if the bacilli were grown strictly under the customary careful conditions. The second fear was that the vaccine might become contaminated—either by virulent tubercle bacilli as happened at Lübeck, or by some other pathogenic organism. Neither of these fears has been fulfilled. Since the Lübeck disaster scrupulous care has been taken to prevent human bacilli being anywhere in the vicinity of the laboratory preparing the B.C.G., so that no repetition is likely as long as the present strict control is exercised. This same careful control—at all stages of the preparation of the vaccine—will similarly prevent contamination with other pathogens. In fact, the greater fear to-day is that the attenuation of the organism may progress too far and the vaccine may become antigenically inadequate. There is already a marked variation in strength between different vaccines being used—not so much a variation from batch to batch from any given laboratory as from the different countries manufacturing B.C.G.—and account must be taken of this in comparing results.

Are There Any Disadvantages of Vaccination?

Tuberculin surveys are accepted by most authorities as being the most sensitive means available for obtaining an index of tuberculous infection in a community—and widespread vaccination would invalidate any such future surveys. This must be accepted as a disadvantage, particularly where the infection rate is low, but Heaf suggests that if the tuberculin reaction is positive in 10% of the under 5-year-olds mass vaccination should be undertaken, as the loss would then be of secondary importance. He says it is obviously unwise to vaccinate 99.5% of infants (where the percentage of positives is 0.5) when the risk of infection is so small.

Is this reasonable? If we compare tuberculosis with smallpox and tetanus we find that very few children in this country die of either of these last two infections—but is it not a fact that in the case of smallpox this is directly due to the efforts of the vaccination enthusiasts of the past?; and that with the low vaccination figures to-day (less than 40% of infants being vaccinated) the risk of a scourge of smallpox is increasing? The tetanus-immunization antagonists say that tetanus is so rare that it would be wasteful to immunize thousands of infants to save dozens—or perhaps only half-dozens—from dying. Yet if it were one's own child who was infected and died, how remorseful would one be that such a simple and efficient prophylactic remedy as toxoid had not been applied in infancy. And in early infancy tuberculosis is as deadly as tetanus.

Has anyone dared to suggest that diphtheria immunization should be discontinued now that diphtheria has virtually disappeared? To-day, an infant's chances of being infected with tuberculosis are greater than his chances of contracting diphtheria.

It is true that tuberculosis vaccination will not guarantee such certain protection as cowpox vaccination or tetanus or diphtheria toxoid, but it possibly offers the best protection at our disposal to-day, and must therefore surely be seriously considered.

With regard to the contention that the value of the diagnostic tuberculin test is lost, this is more worthy of consideration, for in the past twenty-five years the Mantoux test has come to be the most valuable single diagnostic test in paediatrics, and it is true that infants and children successfully vaccinated with B.C.G. will lose the benefit of this test. On the other hand, if those of us who hold that vaccination is a real protection against tuberculosis are right, the need for considering tuberculosis in the differential diagnosis in any vaccinated child should be slight indeed—there are other methods available, although not so easy and quick as the tuberculin test.

Although it is generally conceded that, to put it at its lowest value, vaccination in some form offers a practical means of increasing resistance to tuberculosis in infancy, it is well to recall the dictum stressed by that great American paediatrician Joseph Brenneman, *Primum non nocere*, and to remember that this is as applicable in prophylactic therapy as it is in active treatment. Encephalitis and convulsions following pertussis immunization, eczema vaccinatum following smallpox vaccination, and fatal anaphylaxis following antitetanic serum (another potent argument in favour of immunization with toxoid, by the way) are as important to the unfortunate patient as aplastic anaemia following chloramphenicol or deafness following dihydrostreptomycin treatment. The risk of complications following vaccination against tuberculosis must therefore be weighed carefully against the risks of non-vaccination.

The two most important complications of vaccination would be the development of a progressive tuberculous disease due to the vaccine itself—that is, a return of virulence of the organism—and a systemic upset following vaccination, leading to an easy succumbing to any intercurrent infection. In infancy these two complications would be particularly serious. So far, out of more than 100 million vaccinated subjects only three cases of progressive B.C.G. tuberculosis have been recorded, and only one of these three was an infant. These have recently been referred to in annotations in both the *Lancet* (1955) and the *British Medical Journal* (1955).

A number of deaths after B.C.G. in other series have been attributed to vaccination, but closer scrutiny has absolved the vaccine from blame; most of them were due to human infection which had preceded or followed immediately after vaccination and segregation had not been provided. Considering the number of vaccinations, the fatalities have in fact been fewer than in any other form of prophylactic inoculation.

There has been no evidence of any systemic upset lowering the general resistance to other infections. On the contrary, a paraspecific immunity against such infections has been claimed, as it has with some other inoculations, but this is difficult of convincing proof.

Another consideration to offset against the possible risks of vaccination is—it being agreed that no vaccination is likely to give as adequate an immunity as a successfully overcome naturally acquired infection—that with the falling incidence, both of morbidity and of mortality, in most cultured communities, and with the advent of isoniazid and the probability of other similar and, one hopes, even better drugs, the prognosis of previously fatal complications like miliary dissemination, bronchogenic spread, and meningitis has improved immeasurably, and many of these are now eminently curable or at least not fatal. Further, advances in the technique of thoracic surgery have led to successful surgical intervention in bronchostenosis and consequent pulmonary collapse due to hilar gland enlargement—both by extirpation of the affected nodes and by removal of a severely involved segment or lobe of lung.

A few years ago an infant with tuberculous meningitis might have been considered fortunate if he died untreated, for the horrible repeated intrathecal, as well as intramuscular, injections to which he was subjected for months on end—only to emerge, in a proportion of cases, with

mental and physical disabilities rendering future life high unbearable—were a nightmare to all who had the misfortune to participate in this phase of the management of tuberculous meningitis. Happily we are now rapidly passing to a more rational and infinitely more kindly treatment and are getting better results, as was shown by Smellie (1954). Yet some infants must inevitably succumb if they are involved in a progressive infection, whatever treatment they have, and vaccination might well save these.

What Alternatives Are There to B.C.G.?

The first alternative that comes to mind is the vole bacillus vaccine (Wells, 1937). With the great practical help of Dr. Wells—the original finder of the vole mycobacterium in 1936, and the first to see the possibilities of a vaccine, and indeed the first actually to prepare a vaccine for clinical use in 1942—we have been able to use his vaccine for the immunization of newborn infants for the first time, and, though so far we have vaccinated only 516 infants, the results present some interesting facts and problems, as I shall show in my second lecture.

The vole vaccine differs from B.C.G. chiefly in being made from living bacilli directly—that is, without having their virulence in any way attenuated by growth on, or passage through, any particular media—and it is not only antigenically potent but also of constant strength when it is grown on Dorset egg medium for a maximum of ten passages.

The use of isoniazid-resistant bacilli (Bloch *et al.*, 1953) has been suggested, as they are less virulent and still antigenic, and experimentally have been found to cause regression of tuberculous lesions in guinea-pigs (Karlson and Ikemi, 1954), but in view of the risks inherent in such a vaccine it is unlikely to be acceptable clinically. Tuberculin, both prophylactically and therapeutically, was tried extensively some thirty or more years ago and found to be valueless. The use of dead bacilli was a logical extension of this trial and has been practised for a number of years.

We have had no experience with the use of such killed vaccines, but it has been shown that dead tubercle bacilli contain an immunizing substance; therefore the use of vaccines made from dead bacilli (which would be even less dangerous than live vaccines) must be considered among the potential protective measures available, but on general principles they are less likely to provide as prolonged protection as live vaccines.

Among the killed vaccines are Iland's (1953) urea-treated killed virulent bacilli, which he claims produce greater allergy than B.C.G., Petragani's anatuberculin, and Salvioli's "V.D.S.," diffusing vaccine (vaccino diffondente), which has hyaluronidase added to the heat-killed mixed human and bovine organisms. These are used extensively in Italy. Salvioli (1953) states that the addition of hyaluronidase produces in the dead bacilli a migratory property characteristic of living organisms—and indeed also produces lesions in the regional lymph nodes that are not seen when dead bacilli are used alone. He considers that V.D.S. has all the advantages of a live vaccine, without the disadvantages. The risks of adding hyaluronidase to a live vaccine, however, are considerable, and Birkhaug (1953) has recorded protracted ulcerative skin lesions and occasionally generalized tuberculous infection in guinea-pigs following its use: this warning is timely, for hyaluronidase has already been given to children at the same time as their B.C.G., and the combination has been found to produce quicker conversion and increased skin allergy and therefore might appear tempting. There is no evidence that any risk occurs with killed vaccine, but it might be dangerous with a mixed one.

It is evident, therefore, that, though one has come to think in terms of "B.C.G." when talking of protective vaccination against tuberculosis, this is certainly not necessarily the last word in protection, and the future may see other and better alternatives coming into practical use.

[The second lecture, together with a list of references, will appear in our next issue.]

MALIGNANT CHANGE ARISING IN TISSUES AFFECTED BY HERPES

BY

R. WYBURN-MASON, M.D.

Late Gordon Jacob Research Fellow, Royal Marsden Hospital, London

The skin lesions of herpes zoster lie in the sensory dermatomes. Lewis (1927) showed that "herpetic and herpetiform eruptions occur as sequels to lesions of the sensory nerve tracts; not only do they follow irritative lesions of the [root] ganglion, but they are produced also by lesions of those tracts distal to the ganglia themselves." He also demonstrated that irritation of sensory nerve roots or fibres releases a vasodilator substance (H-substance), probably histamine, in the skin. He further showed that the phenomena of herpes zoster result from a release of the same substance in the affected tissues. The posterior nerve root vasodilator fibres are unmyelinated and supply not only the skin but also the deep tissues and viscera.

In cases of herpes zoster typical inflammatory changes are found in the affected tissues. The skin becomes red and swollen. In the papillae there is a heavy infiltration with polymorphs and lymphocytes. The subcutaneous vessels are dilated, and their walls are markedly infiltrated with a cellular mantle and show changes, such as swelling of the media and infiltration of the intima, which may be so great as to block the lumina. Thrombi

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1.—Basal-cell carcinoma developing directly out of lesions of herpes zoster (Case 2). FIG. 2.—Basal-cell carcinoma developing directly out of lesions of ophthalmic herpes (Case 3). FIG. 3.—Basal-cell carcinoma developing one year after an attack of herpes zoster in the same site (Case 4). FIG. 4.—Basal-cell carcinoma of skin of abdomen with numerous small pigmented papillomata and melanomata developing in the site of an old herpes zoster (Case 5).