a refractory state. This failure of adequate response is not only seen with low dosage but may develop in spite of continued high initial dosage, usually appearing after four to eight weeks of treatment.

Attempts to explain these failures have so far been unsuccessful. The following possibilities have been excluded by special study: masked corticogenic hypothyroidism; diminished response of the peripheral target-organs; vitamin C deficiency; and decreased activity of the pituitary hormone preparations.

Investigations into the possible development of neutralizing antibodies or a shift in the hormone production of the adrenals appear to be indicated.

The administration of A.C.T.H. in cases of rheumatoid arthritis should still be regarded as worthy of investigation.

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B.C.G. VACCINATION IN THE NEWBORN

PRELIMINARY REPORT

BY

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AND

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No one can rest satisfied with the results of treating tuberculous meningitis with streptomycin. Even the best figures so far reported show a mortality of some 40–50% (Debré *et al.*, 1949; Smith and Vollum, 1950). The residua, too, in the recovered cases are by no means negligible.

Tuberculous meningitis takes its heaviest toll in the early months of life—that is, in the first two years, when the chances of close contact with heavy and often continual exposure are maximal and the source of such contact is all too often undiagnosed till it is too late to save the infant.

Because of the enormous number of people with active tuberculosis at large—140,000 in England and Wales, according to a recent report (Heaf, 1950)—the risk of infants' being exposed and contracting the disease is a very real one. Indeed, guaranteed freedom from exposure is virtually impossible, and it would seem, therefore, that active immunization offers the greatest hope of success in abolishing tuberculous meningitis in infancy. Such an immunization would protect simultaneously against bovine tuberculosis, and thus the risk of infection from imperfectly treated milk would also be removed.

It has for long been held that newborn infants do not react to immunization, or do so most inadequately; and on these grounds active immunization procedures have commonly been delayed till the fourth month of life or later, and a similar recommendation might be expected to apply to vaccination against tuberculosis.

Early Immunization

If any proposed immunization programme is to be fully satisfactory it must start as soon after birth as possible, so that protection may be given against the earliest exposure. There is no placentally transferred immunity to tuberculosis as there is, or may be, to diphtheria in the early months of life.

It is now known that newborn infants can and do respond reasonably well to immunization, though in general their powers of antibody production are probably less than they are at six months of age and thereafter. Wallgren (1950) has commented on the remarkable insensitivity of newborn infants to B.C.G., and has recommended that for their vaccination larger doses should be given (twice the adult dose) and that the development of tuberculin sensitivity should not be expected till a longer time afterwards (10–12 weeks, as against 4–6 weeks in childhood).

Where segregation of the infant is necessary because of a tuberculous *milieu* in the home to which he would return, it is obviously desirable for administrative reasons, if for no other, that the period of segregation should be as short as possible. Any place of isolation, whether it be a cubicle in a hospital, a residential nursery, or a foster-home, should be free from the risk of exposure of the infant to any cross-infection, for manifestly it would militate against the success of any immunization regime if, in the process of protection against tuberculosis, death were to result from some intercurrent infection. The minimal period of isolation is therefore a matter of some practical importance.

Procedure

As part of the child health programme it was decided to immunize infants born in St. Mary's Maternity Hospital, Manchester, with B.C.G. during the first week of life. All parents are invited to have their infants thus immunized; approximately 50% avail themselves of the offer. The aim of this project is the abolition of tuberculous meningitis in infancy, and this paper is therefore obviously only a preliminary report of what will be, in the first place, a five-year follow-up study.

Attached to the department of child health is a welfare centre, open daily, to which any mother delivered at St. Mary's Hospital, or on the district, may bring her infant. It is thus hoped to be able to follow closely and at frequent and regular intervals the progress of immunized infants.

The immediate questions to which answers were desired were: (*a*) What dose of B.C.G. is necessary for effective vaccination in the newborn? (*b*) What is the minimal time in which conversion can occur? (*c*) What are the dangers of overdosage if it be found that the answer to (*b*) varies with the dose of vaccine given? (*d*) In the event of complications, what is the best treatment for them?

Intermediate problems to be studied are the duration of tuberculin sensitivity in infants vaccinated at birth; whether this varies with the type of vaccine used or with the dose injected; the number of revaccinations that will be required; and the proportion of immunized infants known to be in contact with open tuberculosis: these infants will of course receive close attention, as they comprise the group for which this study is basically aimed—the group from which our cases of tuberculous meningitis would otherwise have come.

A further study is concerned with the value of B.C.G. tuberculin for conversion testing. Magnusson and Lithander (1949) have shown that the reaction with this tuberculin may become positive some days before the old-tuberculin Mantoux test will. In all cases in which the B.C.G. tuberculin test is positive the O.T. test will also become positive; it may therefore be assumed that the homospecific allergy develops earlier. If the development of this allergy coincides with an increase in resistance to infection by human tubercle bacilli the use of B.C.G. tuberculin may prove of great value in further lessening the period of segregation necessary.

The Vaccine

Two forms of vaccine were used. One was the standard Ministry of Health vaccine delivered weekly from Copenhagen, and the other was a freeze-dried preparation made at the Pasteur Institute in Paris. The obvious advantage of the freeze-dried preparation (apart from its keeping properties) is that its strength may be altered at will by varying the volume of water in which it is dissolved without increasing the total amount injected.

All vaccinations were done intradermally, and in newborn infants 0.2 ml. is about the maximal amount that can be given in a single injection by this route. Initially we followed Wallgren's recommended dose and injected 0.2 ml. into the outer aspect of the thigh. Later we gave the injection in divided doses of 0.1 ml. about ¼ in. (0.6 cm.) apart from one another or used both thighs, giving 0.1 ml. into each. After encountering some complications we changed the site of inoculation and used the skin over the deltoid, giving 0.2 ml. as a single injection or as two injections of 0.1 ml. close to one another or one on each arm. Still later we found that 0.15 ml. was adequate to produce conversion, and finally that 0.1 ml.—the ordinary adult dose—was equally effective.

With the freeze-dried preparation the maximal dose given was 0.375 mg. in 0.2 ml., the standard strength recommended being 0.1 mg. in 0.1 ml.; but we now recommend 0.2 mg. in 0.1 ml. as the routine dose.

Results

Of the 1,461 newborn infants vaccinated to date 1,015 have completed their course and undergone Mantoux conversion. The shortest conversion time has been 16 days. All those tested have been converted within 10 weeks. In a few instances return for Mantoux testing has been delayed—in one for as long as 31 weeks. All such cases were found to be positive. With the freeze-dried vaccine the earliest conversion was on the 17th day, and the longest conversion period was 17 weeks.

For post-vaccination tests the strength of tuberculin used never exceeded 0.1 ml. of 1/100 O.T., and a large number of infants reacted to 1/1,000. The strength used varied according to the extent of the reaction at the vaccination site. Infants showing pustule formation generally react to 1/1,000; if only a small papule is evident at the primary site 1/100 dilution will probably be necessary to evoke a positive response.

There is little doubt that the time taken for allergy to develop (conversion time) does vary with the dose given. If, therefore, early conversion is imperative, larger doses must be used.

Reactions and Complications

As it is impossible to tell beforehand what sort of reaction any infant will have to the vaccine it is impracticable to vary each individual dose. Some will react more violently than others, and such reactions may be focal (that is, at the site of injection) or regional (that is, in the gland draining the area of injection). No specific systemic reactions of any kind have been encountered.

Ulceration, often very slight, has occurred at the focal site in a great many cases, but this has depended not on the size of the dose alone but also on the individual sensitivity of the infant. The reaction appears to be unrelated to the site of injection, for where the arm has been used (as is our present practice exclusively) focal reactions are just as frequent as in the thigh.

With regard to regional gland involvement, this is at first sight a more disturbing problem, particularly when fluctuation is present. It should be understood that the glands are "physiologically" enlarged in every case of B.C.G. inoculation, as they are in natural tuberculous infection, and that in infancy, and throughout childhood generally, the lymphatic involvement is always more marked than the reaction at the primary focus. Careful search, therefore, will reveal palpable enlargement in a great many cases. In the present series small glands 1–5 mm. in diameter were found in the axilla in about half the cases inoculated in the arm, and a similar enlargement was almost universally present in the inguinal glands in the cases inoculated in the thigh.

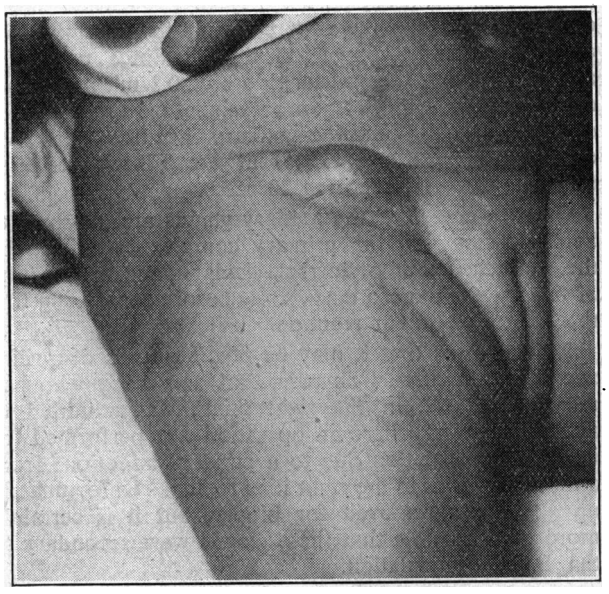

FIG. 1.—Marked inguinal adenitis with fluctuations following vaccination in right thigh—0.2 ml.—three months previously. Gland aspirated subsequently, with rapid recovery.

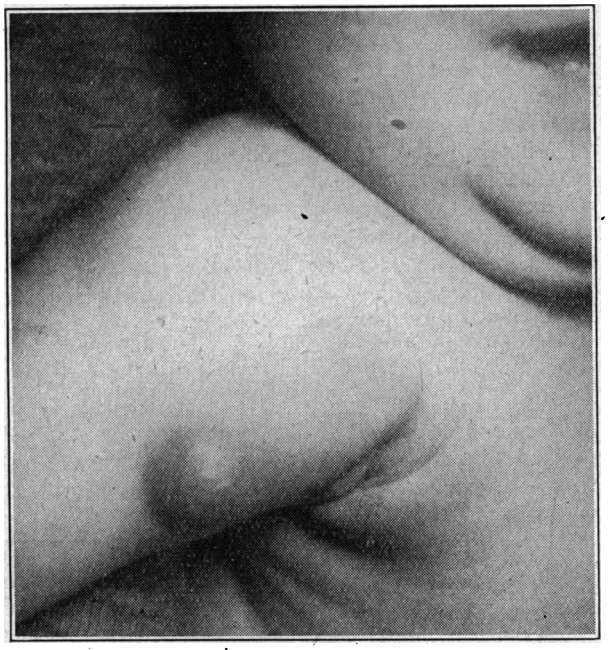

FIG. 2.—Abscess at site of primary inoculation in right arm. Aspirated once, with streptomycin replacement. Subsequently healed rapidly—no axillary adenitis.

Fluctuation or actual breaking-down of a gland has been seen 50 times—47 times in the inguinal region and three times in the axilla. All these cases had received 0.2 ml. at a single site. Because of the frequency of this complication the thigh injections were abandoned. The probable explanation is that in infancy the inguinal glands are more active than the axillary, having continually to cope with the prepuce, vulva, and napkin areas, and that the sudden influx of a number of tubercle bacilli causes them to " blow up," whereas the comparatively quiescent axillary glands can cope successfully with the new invasion.

The high incidence of this complication which we encountered was undoubtedly due in the main to the large doses we used, particularly in the earliest stages of this study, when we were trying to determine the quickest possible conversion time. Since using the arms and giving the standard dose of 0.1 ml. no further cases have occurred, but an occasional case may still be expected, as suppurative axillary adenitis has been observed by Rekling (1945) at the Finsen Institute, Copenhagen. He reported 20 cases.

On rare occasions the axillary glands are, or seem to be, by-passed and the primary complex completed by the supraclavicular or infraclavicular gland. Palpation of this area is therefore advisable before concluding that there is no glandular reaction.

It also seems that it may be possible for a deep iliac adenitis to occur. One case, that of a baby who had received 0.2 ml. in the right thigh, was admitted to another hospital where an operation was performed for intestinal obstruction due to a band of adhesions from a mass of glands in the right iliac region. Unfortunately no gland was removed for biopsy, but it is certainly more than possible that these glands were secondary to the B.C.G. inoculation.

A case of pyloric stenosis has been reported following oral vaccination, in which pressure from mesenteric glands led to narrowing of the pyloric lumen (Ustvedt, 1951). Iliac and mesenteric glands may, however, be inflamed from other causes, and it is impossible to state dogmatically that these cases were solely B.C.G. reactions even though it is highly probable. Similarly, enlarged hilar glands may be found to follow B.C.G. inoculations in the arm, but their exact relationship to the inoculation remains unproved. None of the infants with abscesses were upset systemically ; fever, anorexia, and weight loss (or failure to gain) were not noted, and secondary infection did not occur in any case.

In answer to the question which parents often ask—" Is this vaccination harmless to newborn infants ? "—the answer is that, generally speaking, it is harmless, but the case of intestinal obstruction shows that there may on very rare occasions be complications of a harmful nature.

The fact which emerges is that it is possible, using large doses, to immunize a newborn infant in less than three weeks. This may be a matter of some importance in the case, for example, of an infant with a mother suffering from active tuberculosis or where there is great pressure on " preventorial " accommodation.

The fact that large doses, certainly if injected at a single site, add to the risk of complications has suggested that where early conversion is important the dose should be given in small quantities at different sites. The problem to be studied is whether the adenitis is related to the total number of organisms draining into a particular gland or group of glands or whether the bacillaemia which follows inoculation is also a factor in determining the localization of the adenitis.

Treatment of Complications

In dealing with the complications it should be borne in mind that they are without systemic danger and will heal spontaneously in time (weeks or months) even without treatment, and they have by no means the same significance as the cold abscesses of ordinarily acquired tuberculosis. Heroic measures, therefore, are not called for in dealing with these " Calmette abscesses."

Local application of a sulphathiazole powder containing 10% of streptomycin is of value, and, in the case of a fluctuant swelling, aspiration and replacement with 10,000 to 20,000 units of streptomycin may considerably expedite the subsidence. We have given P.A.S. for short periods to infants with marked glandular involvement, but do not feel that systemic streptomycin is indicated.

It must be remembered that as the adenitis may not become evident for some weeks after the post-vaccination Mantoux test has been done regular follow-up is necessary. It has happened on a few occasions that an infant has been taken to another hospital and fomentations or penicillin injections, or even surgical intervention undertaken. In an endeavour to prevent the repetition of this every mother is given a card after the successful vaccination of her infant and instructed to show it to her doctor, who may be made aware of the preceding vaccination and of the resulting positive tuberculin test.

Summary

It is both possible and practicable to immunize newborn infants with B.C.G.

They react to 0.1 ml. of vaccine as do older children and adults. For routine immunization larger doses are unnecessary, and are apt to produce complications.

The time taken for allergy to develop may be appreciably diminished by increasing the dose used.

Although complications are not generally harmful they are nevertheless undesirable, and the effort to secure a minimal conversion time should be restricted to selected infants for whose special circumstances the time factor is of great importance.

It is suggested that in such circumstances complications may be prevented or minimized by giving the injections in divided doses at different sites.

We are indebted to Professor F. R. G. Heaf for his help in arranging for our supplies of vaccine; to Dr. van Diense and Colonel Bensted for the freeze-dried vaccine ; to Professor Arvid Wallgren and Dr. J. H. Magnusson for generous gifts of B.C.G. tuberculin; and to our obstetric colleagues at St. Mary's Hospital for their willing co-operation.

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PETHIDINE AS AN ADJUVANT TO NITROUS OXIDE AND OXYGEN ANAESTHESIA

BY

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The scope of thiopentone in general anaesthesia, first popularized by Lundy in 1934, was enormously extended by the introduction of D-tubocurarine in 1942 by Griffith and Johnson. Administered by continuous intravenous drip or repeated fractional doses in combination with nitrous oxide and oxygen and, where indicated, a muscle relaxant, it has proved generally satisfactory in experienced hands.

This type of anaesthesia, however, is not without its disadvantages. Thiopentone is a powerful respiratory depressant with a weak analgesic action. Used with a gas-and-oxygen mixture, rich enough in oxygen to prevent anoxia, the amount required to obtund pain may cause undesirable respiratory depression, which, in long procedures requiring a relatively high total dose, may be prolonged into the post-operative period. Moreover, its powerful hypnotic but weak analgesic action is a cause of post-operative restlessness. The parasympathetic effect of thiopentone is, in theory at any rate, undesirable, especially when combined with a muscle relaxant, which, itself a potential liberator of histamine, may initiate bronchial constriction and spasm.

The search for a suitable adjuvant to nitrous oxide and oxygen anaesthesia led to the introduction into clinical anaesthesia of pethidine hydrochloride by Neff *et al.* (1947) in America, and by Mushin and Rendell-Baker (1949) in England.

First synthesized by Eisleb and Schaumann in 1939, pethidine is widely used in surgery and obstetrics for the relief of pain. Many other piperidine derivatives related to it have since been synthesized, and the properties of two of these—bemidone " 10446 " and keto-bemidone " 10720 "—have been described by Thompson and Neff (1950). They found the keto-compound " 10720 " to be fifteen to twenty times more powerful than pethidine, with which it compared favourably as an adjuvant to nitrous oxide and oxygen anaesthesia in dogs and human beings.

Unlike morphine, pethidine produces a high degree of analgesia without undue effect on the respirations and the blood pressure. It exerts a weak narcotic effect, thus allowing, in contradistinction to thiopentone, a rapid return to consciousness with delayed post-operative pain. It possesses, in addition, other properties, which have perhaps not been stressed enough by anaesthetists.

Professor J. H. Burn (1948) has drawn attention to the common action of a wide group of substances used medicinally. This group includes procaine, quinidine, atropine, the antihistamines, and pethidine. All have in greater or lesser degree a local anaesthetic action, the power to relax smooth muscle and to lengthen the refractory period of the heart, an analgesic and an antihistamine effect. Thus pethidine, in addition to its powerful analgesic action, has 80% of the activity of quinidine on the auricle, is similar in potency to procaine as a local anaesthetic, and has an antihistamine effect which is considerable. Burn (1950) suggested that intravenous pethidine would be more effective than procaine for the release of bronchial spasm in man. That it has a selective action on the laryngeal reflex has been shown by Ruben and Andreassen (1951), who, using intravenous pethidine alone, have intubated a series of 25 cases without eliciting laryngeal spasm.

The action of pethidine on the heart has been noted by Mushin and Rendell-Baker (1950), who, in over 100 thoracic operations, were particularly impressed by the absence of pulse irregularities when using gas and oxygen, gallamine triethiodide, and pethidine, and who suggest that this combination of drugs is especially suitable for operations on the heart.

Morphine is known to cause spasm of the lower end of the common bile duct near the sphincter of Oddi, yet it still continues to be used by anaesthetists and surgeons before and after operations on the biliary passages. Pethidine, because of its spasmolytic effect, is the drug of choice. Similarly, pethidine exerts a spasmolytic effect on the distal colon and rectum, and Griffiths (1950) has noted its value in combination with gas and oxygen in such operations as haemorrhoidectomy and posterior colporrhaphy.

The theoretical advantages of pethidine as a substitute for thiopentone in the maintenance of nitrous oxide and oxygen anaesthesia led me to try it in a large number of cases. In an attempt to arrive at a satisfactory standard technique use was made of wide variations in premedication, induction, and the dose and concentration of pethidine employed for maintenance. Premedication was with morphine and atropine, " omnopon " and scopolamine, pethidine and scopolamine, or pethidine and atropine in appropriate doses. In most cases thiopentone was used for induction, but some were induced with nitrous oxide and oxygen and others with cyclopropane. Intubation was performed under thiopentone and a muscle relaxant, thiopentone and cyclopropane, or a combination of all three. Maintenance was with nitrous oxide and oxygen, using a circle absorber or the semi-closed