THE OPTIMUM AGE FOR MASS B.C.G. VACCINATION IN ENGLAND AND WALES*

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Three years have passed since B.C.G. vaccination of 13-year-old schoolchildren was first authorized in England and Wales, and, although this is not a long period in the epidemiology of tuberculosis, further information now available about vaccination, as well as the probable reduction in the risk of tuberculous infection since 1953, makes it of interest to inquire whether 13 years is the most suitable age at which to give the first, and in most cases the only, anti-tuberculosis vaccination under present conditions. To make an assessment of this kind, the current proportion of children infected with tubercle bacilli by the age of 13, the results of tuberculous infection acquired before that age, the risks of infection at puberty and adolescence, the duration of protection conferred by vaccination, and some other factors all need to be considered.

Frequency of Tuberculin Sensitivity in 13-year-old Children

During 1955 the adoptive scheme for the B.C.G. vaccination of 13-year-old schoolchildren (Ministry of Health, 1953) was being undertaken by more than half of the 145 local health authorities in England and Wales. Seventy-three of

TABLE I.—*Tuberculin Sensitivity in 13-year-old Schoolchildren, 1955 (Summary of Results of Skin-testing by 73 Local Authorities in England and Wales*)*

Method of Skin Testing	Smallest and Largest No. of Children Tested by Each Method	No. of Authorities			
		Total Using Each Method†	According to the Proportion of Children found to be Tuberculin-positive		
			11–20%	21–30%	31–40%
Mantoux 10 T.U.‡ old tuberculin	100–2,459	8	3	1	4
Mantoux 10 T.U. purified protein derivative	94–11,287	38	15	18	5
Mantoux 100 T.U. old tuberculin as final test	388 and 657	2	0	0	2
Heaf multiple puncture (2 mg. purified protein derivative per ml.)	320–4,315	15	8	7	0
Heaf multiple puncture (undiluted old tuberculin)	88–3,152	6	1	3	2
Mantoux 10 T.U. and Heaf multiple puncture at different times	1,287–8,481	4	1	2	1
Total	..	73	28	31	14

* In one further area the results for 1955 were unaccountably high (77%). This area is not included.

† Four authorities used two different tests and reported the results separately. The lower proportion only is given in the Table.

‡ T.U. = tuberculin units.

the local authorities known to have begun the scheme have supplied details of the tuberculin tests employed and of the proportion of children found to be tuberculin positive immediately before vaccination in 1955. These results are summarized in Table I.

When the results of all tests are compared they show a wide variation, the range in the proportions with positive

*Based on a paper read in the Section of Diseases of the Chest at the Annual Meeting of the British Medical Association, Brighton, 1956.

reactions being from 11% to 40%. This is partly the result of the diversity of tests, but there are sufficient differences among areas using the same test to suggest that the frequency of infection with tubercle bacilli varies considerably in different areas. None the less, it is evident that in England and Wales at the present time substantial proportions of children have been infected with tubercle bacilli by the age of 13, and cannot benefit from a vaccination scheme at that age. The morbidity which results from childhood infection is thus of special relevance. An indication of the extent of this morbidity may be obtained from the new notifications of tuberculosis in the age group 0–14 years, but cases which are never notified and those which arise later in life have also to be taken into account.

Morbidity from Tuberculous Infection Received Before the Age of 14

Notified Cases in the Age Group 0–14 Years

In 1955 the notifications of new cases in the 0–14-year group in England and Wales were: respiratory, 3,614; meningeal, 337; other organs, 1,171; total 5,122 (Registrar-General, 1956).

A case of notifiable tuberculosis is defined as one which "because of tuberculous infection may infect others: or a person who is suffering from an active tuberculous lesion which calls for medical treatment or for some modification of the patient's normal course of living" (Ministry of Health, 1951). The above notifications thus represent cases of various grades of severity and are difficult to assess in medical and social terms.

The serious nature of most non-respiratory disease in childhood is self-evident; so also is "adult type" pulmonary disease at this period of life. However, most respiratory tuberculosis notified in the 0–14-year group is probably associated with primary disease—considered for the present purpose to be those lesions in which a primary complex is visible radiographically. Reports of the course of primary lesions show great variation, depending on the ages of the patients and whether the cases studied were those admitted to hospital or attending out-patient clinics.

Thomas and his colleagues (1954) followed up cases of primary disease which appear to be representative of those notified. Their study was of 298 cases of primary tuberculosis, each with a radiographically evident pulmonary complex, attending Swansea Chest Clinic. Most would be notifiable as cases of respiratory disease, and the majority were under 13 years of age. Seventy-three per cent. were treated at home under supervision and the remainder were admitted to hospital. The majority required bed rest for four months, were not allowed to attend school for six to nine months, and were subsequently supervised for three years. Sixteen per cent. of the total cases developed serious complications. Although there may be variation in the practice of chest clinics in different parts of the country, this experience suggests that the notified cases in the 0–14-year group may represent serious morbidity, having regard to the interruption of normal activities and the medical care required in childhood. Moreover, primary lesions which appear to have healed in childhood sometimes precede further morbidity in later life.

Unnotified Cases in the 0–14-year Age Group

Evidence of the frequency of unsuspected tuberculosis among children about to pass out of the age group 0–14 years was observed in the Medical Research Council's (1956) clinical trial of tuberculosis vaccines. In that investigation, in which 14-year-old entrants had a chest radiograph, 134 previously unsuspected cases of tuberculosis requiring close observation or active treatment were found on entry among approximately 56,000 participants. Almost all of these cases were of pulmonary tuberculosis. The fact that primary infection in childhood may result in lesions of clinical importance which escape notification is also emphasized in the notable study from High Wood Hospital (Bentley *et al.*, 1954). Some

cases of non-respiratory tuberculosis may also remain unnotified in childhood (Wallis, 1955).

A primary tuberculous lesion causing minor or no symptoms and remaining undiagnosed and unnotified in childhood may produce morbidity later, not only through tuberculosis but also as a result of non-specific structural damage—for example, segmental or lobar collapse with subsequent bronchiectasis—or infertility due to pelvic changes.

Bronchiectasis.—Collapse of a pulmonary lobe or segment results not infrequently from primary tuberculous infection. Bentley *et al.* (1954) estimated that segmental lesions often associated with collapse occurred in 5–10% of all primary infections. About 6% of segmental lesions studied in the High Wood survey were found to result in bronchiectasis of a sufficient degree to come to notice; the incidence was much higher than this in lesions of the middle and lower lobes. The frequency with which bronchiectasis occurs among primary pulmonary lesions which are discovered suggests that it may also occur, though perhaps less commonly, among primary pulmonary lesions which remain undetected. Bronchiectasis from primary infections may give rise to serious morbidity much later in life (Brock, 1950).

Infertility.—Pelvic tuberculosis has been reported (Sutherland, 1956) to be the cause of infertility in more than 5% of patients attending a fertility clinic. The serious nature of morbidity of this type is not always generally appreciated, but should not be underestimated; infection at puberty is especially dangerous in this respect (Barns, 1955). In most cases a manifest extragenital lesion precedes the discovery of genital tuberculosis, but in some the initial lesion gives rise to few symptoms and is unlikely to be notified before the age of 14.

Respiratory Tuberculosis and Tuberculosis of Other Organs in Later Life

The frequency with which tuberculous infection in childhood produces tuberculous disease manifest only in later life is not known. In the M.R.C. trial (see above) a relatively high incidence of tuberculosis (1.45 per 1,000 annually), including pulmonary lesions and tuberculosis of other organs, was found during a two-and-a-half-year follow-up among those who were tuberculin-positive on entry at the age of 14 but with no radiological evidence of disease at that time. The incidence was higher among those who were tuberculin-sensitive to 3 T.U. (1.75 per 1,000 annually) than among those who were tuberculin-negative to 3 T.U. but positive to 100 T.U. (0.74 per 1,000). Such a high incidence may not continue in later life, but the possibility requires serious consideration.

The subsequent incidence of tuberculosis in the tuberculin-positive groups aged 13 years in the current B.C.G. vaccination scheme for schoolchildren might be less than among those found to be tuberculin-positive at 14 in the M.R.C. trial, since a higher proportion in the latter inquiry would have been infected during the susceptible period of adolescence. On the other hand, most of the tuberculin tests preparatory to the vaccination of 13-year-old schoolchildren are performed with doses of tuberculin less than the final test of 100 T.U. used in the M.R.C. trial (Table I). The tuberculin-positive groups determined by such tests will therefore contain a higher proportion of the more highly sensitive and vulnerable individuals than the tuberculin-positive group in the M.R.C. trial: this would tend to result in a higher future incidence among the positive group in the current vaccination scheme than in the M.R.C. investigation.

From all the above considerations there is no doubt that the morbidity arising from infection received before the age of 13 is still a serious matter—indeed, more than would appear from the notifications in the 0–14-year group. This suggests that B.C.G. should be given before 13 years of age. On the other hand, doubts about the duration of protection conferred by vaccination make it desirable that the vaccine should be given shortly before a period of increased risk from tuberculous infection begins, if the period of risk is likely to extend over several years.

Risks from Infection at Puberty and Adolescence

It is generally accepted that between 5 and 10 years of age the immediate dangers of a primary tuberculous infection are less than at other periods of life, while at puberty and adolescence morbidity resulting from primary infection increases. By 14 years, for example, an appreciable prevalence of tuberculosis was found among entrants to the M.R.C. trial. It would be reasonable to try to forestall the effects of natural infection at this period by vaccination at, say, 10 years. Vaccination at this age has been advocated by Griffiths and Gaisford (1956).

However, a single vaccination at 10 years instead of 13 might reduce the benefit to those infected after 13 years of age if protection from the vaccine lasted only a very few years, since exposure to tuberculosis might be more frequent at work during late adolescence after the protection conferred by vaccination had declined, than between the ages of 10 and 13 during school life. Much thus depends upon how long protection from vaccination may be expected to last.

Duration of Protection Afforded by B.C.G. Vaccination

The period of protection conferred by B.C.G. vaccine under present conditions in Britain will not be known until the M.R.C. trial has continued for some further years. There was no evidence of a decline in protection in that investigation four years after the vaccine was given. In a clinical trial among American Indians of various ages by Aronson and Aronson (1952), protection lasted for 10 years, although there was a suggestion that it might wane thereafter. Hyge (1956) has reported the result of a follow-up of schoolchildren infected in a tuberculosis epidemic in a school, first reported in 1941. In this instance B.C.G. was shown to confer considerable protection against the development of post-primary tuberculosis for at least 12 years after exposure to a natural infection sustained shortly after vaccination.

Whatever the final outcome of these investigations, it should be borne in mind that B.C.G. might not confer the same duration of protection at all ages or in all types of community. If protection in Britain lasts for a decade or more, vaccination at 10 instead of 13 years of age would appear to offer definite advantages. But even if protection should last for a shorter period vaccination at 10 years might still be a sound policy, since tuberculous infection appears to be declining; the current 10–13-year group may be at greater risk from disease now than by the time they reach late adolescence.

Thus an assessment of the information at present available suggests that the advantages of vaccination at 10 years are likely to outweigh the risk of a relatively early fading in protection. If vaccination much earlier in life—for example, in infancy—were thought to be desirable revaccination at 10 years would have to be considered.

Vaccination in Infancy

Although there is general agreement in Britain about the need for mass vaccination in adolescence and also for the vaccination of infants in known contact with the disease, there are widespread doubts about the desirability of vaccinating infants who are not contacts. The main issue is whether tuberculosis is frequent enough in early childhood to justify the vaccination of approximately half a million infants each year. This consideration is, however, sometimes obscured by doubts about the number and severity of the complications after infant vaccination. There is also the fear that the loss of the tuberculin test in infancy might seriously impede the control of tuberculosis at the present time.

Complications of Infant Vaccination.—The frequency and severity of the complications due to infant vaccination in Britain have been reported by Gaisford and Griffiths (1954) and by Purser (1954). These studies suggest that, provided due attention is paid to technique and dose, the frequency of significant complications and their severity are not greater

than in older children. Complications were later shown by Gaisford (1955) to be greatly reduced when half the adult dose of vaccine was given; such a dose produced no constitutional upset in premature infants.

Loss of the Tuberculin Test

Vaccination in infancy would certainly entail the loss of the tuberculin test, and so, by interference with case-finding and epidemiological investigation, affect the control of tuberculosis.

Reports by MacDougall, Mikhail, and Tattershall (1953), Cuthbert and Randall (1954), Ritchie, Calwell, and Barr (1955), and Davies (1955) illustrate the value of the tuberculin test as a case-finding measure. The cases discovered, however, represent the final result of much tuberculin-testing and follow-up work. It is doubtful whether this way of finding sources of tuberculosis can be widely and consistently put into practice in many areas at the present time, because the numbers of tuberculin-positive children are still high enough to make the follow-up of the potential sources of their infection a considerable undertaking. There are obvious future possibilities, however, of increasing the use of the tuberculin test as a case-finding measure when the frequency of infection has declined further.

It is not easy to assess the extent to which the loss of the tuberculin test would obstruct the control of tuberculosis if a long-term view is taken of the practical value of the information obtained. It should, however, be remembered that, so far as tuberculin surveys are concerned, the findings are generally of most value when the results from different surveys can be usefully compared. In practice, variation in the tests used limits the conclusions which can be drawn from such comparisons. The control of tuberculosis is certainly assisted if regular and accurate estimates of the decline in tuberculous infection can be made; for this purpose mass radiography surveys of some social groups, carried out intensively at intervals of a few years, might be used as a substitute for tuberculin surveys. A comparison of the prevalence of radiographically evident pulmonary tuberculosis would enable an estimate of the decline in tuberculous infection to be made. Such an estimate would probably be sufficient for practical purposes, although less sensitive than the findings of co-ordinated tuberculin surveys. The number of radiographic examinations required would not materially increase the annual number of radiographic examinations undertaken throughout the country.

If the above considerations are taken into account it appears probable that at the present time the control of tuberculosis in England and Wales would not be seriously impeded if the tuberculin test was no longer available, although this might not be true in future.

Frequency of Tuberculous Infection in Infancy

The most important objection to infant vaccination is that the frequency of natural tuberculous infection in infancy may be insufficient to warrant vaccination of non-contacts.

Tuberculin-testing of infants of 5 years and less has not been done on a scale approaching the 13-year-old group; knowledge of the frequency of infection in infancy is in consequence very incomplete. In a few local tuberculin surveys in this country between 1950 and 1954 it was found in the main that between 3 and 5% of children of 5 years of age were tuberculin-positive (Coles, 1952; Palmer *et al.*, 1954; Carstairs, 1955; Jarman, 1955). It seems likely that in many areas the proportion will now be less than this.

TABLE II.—*Tuberculosis (All Forms): Notification Rates Per 100,000 Living, Age Group 0-5 Years, 1950-5. England and Wales*

Year	Males	Females	Year	Males	Females
1950 ..	86	72	1953 ..	72	66
1951 ..	81	78	1954 ..	57	53
1952 ..	79	74	1955 ..	49	48

The rate at which tuberculous infection is declining is not known, but a general indication can be obtained from a study of the tuberculosis notification rates for recent years. These rates for the age group 0-5 years from 1950 to 1955 are shown in Table II. During the last few years a decline in the rates is evident, and it seems not unlikely that this decline will be sustained and may become accelerated.

The numbers of new cases notified in the age group 0-5 years in 1955 were: respiratory, 1,165; meningeal, 155; tuberculosis of other organs, 295. The new notifications for all ages were: respiratory, 34,192; meningeal, 532; other forms, 4,151 (Registrar-General, 1956). Thus pulmonary notifications in the 0-5-year group represent a rather small proportion of the notifications for all ages; and, although notifications of meningitis in infancy constitute more than a quarter of the meningitis for all ages, the total number judged on a national scale is small; the latter consideration also applies to the notifications of other non-respiratory tuberculosis.

These figures, of course, leave out of account the cases of tuberculosis which are not notified; also the serious nature of tuberculous infection in infancy should be borne in mind. But despite these considerations it is doubtful whether the amount of disease consequent upon infection in infancy justifies widespread vaccination at this age in the present circumstances. Similar observations have influenced opinion in Scandinavia, where the wisdom of continuing to vaccinate infants who are not contacts has been questioned (Wallgren, 1956).

The results in Table I suggest that the frequency of tuberculous infection before 5 years may be unduly high in some areas. Thus, although a national scheme for infant non-contacts is not indicated, the results of tuberculous infection in early childhood are serious enough to encourage tuberculin surveys of school entrants, aged 5, in any area where the frequency of tuberculous infection may be much higher than the national average. Local authorities might then decide whether an adoptive scheme for infant non-contacts was justified in the particular area concerned.

Conclusions

During 1955 a substantial proportion of school-children in England and Wales had already been infected with tubercle bacilli by the age of 13.

The morbidity arising from infection received before the age of 13 is considerable, and is greater than appears from tuberculosis notification rates.

Puberty and adolescence is a relatively dangerous period to sustain a first tuberculous infection, and it is desirable that children should be protected by vaccination before entering this period.

The available evidence suggests that protection from B.C.G. vaccine may last for a considerable period. Thus vaccination at 10 years of age may make a greater contribution to the prevention of tuberculosis in England and Wales than vaccination at 13 years.

Widespread vaccination of infant non-contacts does not appear to be justified on a national scale. The indications for local schemes deserve investigation.

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REFERENCES

- Aronson, J. D., and Aronson, C. F. (1952). *J. Amer. med. Ass.*, 149, 334.
- Barns, T. (1955). *J. Obstet. Gynaec. Brit. Emp.*, 62, 162.
- Bentley, F. J., Grzybowski, S., and Benjamin, B. (1954). *Tuberculosis in Childhood and Adolescence*. N.A.P.T., London.
- Brock, R. C. (1950). *Thorax*, 5, 5.
- Carstairs, L. W. (1955). *Tubercle (Lond.)*, 36, 34.
- Coles, H. M. T. (1952). *Lancet*, 2, 927.

- Cuthbert, J., and Randall, G. H. (1954). *Med. Offr.*, 92, 239.
 Davies, J. V. (1955). *Tubercle (Lond.)*, 36, 69.
 Gaisford, W. (1955). *British Medical Journal*, 2, 1101.
 — and Griffiths, M. I. (1954). *Tubercle (Lond.)*, 35, 7.
 Griffiths, M. I., and Gaisford, W. (1956). *British Medical Journal*, 2, 565.
 Hyge, T. V. (1956). *Acta tuberc. scand.*, 32, 89.
 Jarman, T. F. (1955). *British Medical Journal*, 2, 1235.
 MacDougall, I. A., Mikhail, J. R., and Tattershall, W. H. (1953). *Ibid.*, 1, 64.
 Medical Research Council (1956). *Ibid.*, 1, 413.
 Ministry of Health (1951). Circular 33/51.
 — (1953). Circular 22/53.
 Palmer, C. E., Nash, F. A., and Nyboe, J. (1954). *Lancet*, 2, 1274.
 Purser, H. M. (1954). *British Medical Journal*, 1, 368.
 Registrar-General (1956). *Statistical Review for 1955*, Part 1. London.
 Ritchie, J., Calwell, H. G., and Barr, A. (1955). *Tubercle (Lond.)*, 36, 301.
 Sutherland, A. M. (1956). *J. Obstet. Gynaec. Brit. Emp.*, 63, 161.
 Thomas, J. H., Morgan, D. B., and Davies, T. W. (1954). *British Medical Journal*, 2, 1325.
 Wallgren, A. (1956). *Nord. Med.*, 55, 21.
 Wallis, H. R. E. (1955). *British Medical Journal*, 1, 128.

FIRST FIELD TRIAL OF 377 C 54, A NEW ANTIMALARIAL COMPOUND

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The action of modern antimalarials is such that they provide a reasonably satisfactory range of chemotherapeutic weapons at the disposal of the clinician. The public health worker in endemic malarious areas is less fortunate.

Difficulties encountered in many parts of Tropical Africa in achieving malaria eradication have renewed the interest in possibilities of mass chemotherapy, and several recent W.H.O. malaria conferences recommended that drugs be used in conjunction with residual insecticides wherever this combined attack may lead to the rapid elimination of malaria.

Mass chemotherapy of malaria with drugs available at the present time has two disappointing features. One is the possibility of development of resistant strains to otherwise excellent protective drugs such as proguanil and pyrimethamine. The other is the fact that all available antimalarials are excreted relatively rapidly and have a short "carry over" value. Thus any "mass treatment" of malaria aimed at elimination of the infection in the community and consequent interruption of transmission must be based on giving the drug at intervals of one to four weeks but not greater than one month (Bruce-Chwatt, 1956).

The more frequent the regimen the greater the chances of its irregularity, also the greater the difficulties and the higher the costs of correct administration over large areas with a low population density, poor communications, primitive educational level, and inadequate rural health service organization. The length of action of the drug required for mass chemotherapy of malaria should be at least equal to the "carry over" period of pentamidine, which when administered in a dose of 200–250 mg. will protect an individual from trypanosomiasis for three to six months.

The ideal antimalarial combining the virtues of causal prophylaxis, suppression, rapid and complete curative action, sporontocidal effect and inability to create parasite resistance, absence of toxic effects, slow excretion, palatability, and (last but not least) low cost is still wait-

ing to be discovered. Any new advances of synthetic chemistry applicable to chemotherapy of malaria are therefore of considerable practical importance.

The finding of Rollo and Duffin (1957) that the compound known under a code number, 377 C 54, belonging to a series of hydroxynaphthalenes, has a pronounced action against malaria parasites is of particular interest. It introduces an entirely new group of drugs and opens for the synthetic chemist the possibility of many variations on the main theme in the hope of producing, if not an ideal antimalarial, an improvement on present drugs.

Characteristics of 377 C 54

Coatney and his associates (1952), who tested nearly 4,000 chemical compounds for antimalarial activity, reported that naphthalene derivatives had some effect on the experimental infection of chickens with *P. gallinaceum*. Nevertheless in the final table of tested products with a significant therapeutic index, the halogenated naphthalene amino-alcohols occupied only a modest place in the middle of the range of just over 200 chemical compounds.

377 C 54, a new compound, synthesized recently in the laboratories of the Wellcome Foundation in London, is 2:5-bis(cyclo-hexylaminomethyl)naphthalene-1:6-diol dihydrochloride. It belongs to a series of mono- and dihydroxynaphthalenes which were first tested for antimalarial activity against *P. gallinaceum* infections in young chicks and *P. berghei* in mice (Rollo and Duffin, 1957). In further trials use was made of *P. cathemerium* in canaries and *P. knowlesi* in a rhesus monkey.

Screening tests showed that the activity of 377 C 54 against the two avian plasmodia was of a high order. In *P. gallinaceum* infections the median effective dose was about twice that of chloroquine. The therapeutic index of the new compound, calculated according to the method used by Coatney *et al.* (1952), is of the order of 60–70, and thus in the first third of the American table of compounds with a significant plasmodicidal activity. In single-dose experiments the speed of action of the new compound was of the same order as that of chloroquine. Its action on a virulent strain of *P. knowlesi* in the rhesus monkey was fast and complete.

The early pharmacological tests of 377 C 54 on chicks and man showed that the drug is rapidly absorbed; it appeared that its excretion is slow owing to retention in the liver and lungs. Its toxicity in laboratory animals and in man seemed to be low.

Method of Field Trial

Prior to the large-scale field trial of the new drug it was taken by each of us for seven days at the daily dose of 600 mg. This high dosage having produced only nausea and fatigue, it was decided to use the drug for a field trial.

The method of the trial was that used for the past five years for several similar investigations (Bruce-Chwatt, 1951; Archibald, 1951; Bruce-Chwatt and Archibald, 1953; Charles and Bruce-Chwatt, unpublished). It was based on a selection of two or more volunteer groups of African schoolchildren naturally infected with malaria. Preliminary screening was followed by the administration to each group of a suitable therapeutic dose of the tested drug. The speed of disappearance of parasitaemia in each group was used as an indication of the respective activity of the tested drug and its dosage. It is fully realized that this method has its disadvantages. It cannot serve as a substitute for a well-controlled laboratory experiment in which all the variables of the infection are well assessed and the toxicity of the drug can be gauged during the investigation. Nor can this trial claim to give more information than a true therapeutic trial on non-immune patients with acute clinical malaria.

The method adopted by us stands half-way between the two mentioned above. It provides rapidly a good deal of