Symposium on Recent Advances in Tuberculin and BCG—continued

VAGARIES OF BCG-INDUCED TUBERCULIN ALLERGY

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I INTEND to speak mainly on the results of the Dublin City Scheme. Dublin has a population of over half-a-million and our scheme was commenced at the end of October 1948. At that time Dublin had a major childhood tuberculosis problem and there were approximately 140 childhood tuberculosis deaths per year, 81 were due to meningitis—two-thirds of these occurred in the 0 to 5 years age group. In 1949 the National BCG Committee was set up to cover the rest of the country. Up to the present date three-quarters of a million vaccinations have been made—a high number in a country with a population of less than three millions.

Detailed records have been kept so it has been possible to check the mortality and morbidity of the vaccinated. No case of tuberculous meningitis and no death from tuberculosis has occurred in any of those vaccinated under our Dublin Scheme.

Since 1958 the Dublin childhood tuberculous deaths have varied from three to one per year, and these few have been in unvaccinated children. The high priority given to BCG work in Dublin was intensified by the knowledge that when the scheme began, the need was great—now after 14 years we are pleased with the results.

Naturally, we wanted to know how long the protection of the vaccine could be expected to last. Study of the literature on the subject of duration of BCG—invoked tuberculin allergy yielded such diverse results that one could only assume that allergy fluctuates as the wind blows. Most studies on BCG material are confined to the incidence of morbidity and mortality occurring in the vaccinated and controlled groups. When tuberculin allergy figures are stated, they vary in each report. We decided to study our accumulated records to find the duration of allergy and look for an explanation of the variance in figures.

For the purpose of this study we read allergy as the retention of BCG-induced tuberculin sensitivity. Although it is probable that immunity persists after response to the tuberculin tests has

faded, we assess the duration of post-BCG tuberculin allergy on the response to the tuberculin tests.

The retention of allergy must be influenced by the potency of the particular vaccine and so the selected vaccine is of vital importance. A recent editorial in the *British Medical Journal* (1961) has called for standardization of the vaccine, but despite that advice BCG workers have personal, and often prejudiced opinions about their selection. In Ireland we use four different vaccines. This indicates the search for a vaccine sufficiently potent to give a satisfactory conversion rate, and which will reduce to the minimum the number of revaccinations as they appear more subject to complications than primary vaccinations.

It is now generally recognized that the potency of a vaccine affects the duration of invoked tuberculin sensitivity, and that change in the strength of the vaccine is reflected in the results. In Dublin we have used Danish liquid vaccine since 1948. You will recall that this vaccine was reduced to half-strength (from 0.75 mg./ml. to 0.375 mg./ml.) in 1955, but even this reduced strength has proved sufficiently potent to ensure a satisfactory conversion rate. We have had less severe reactions and less glandular complications with the half-strength vaccine. In the last year or so we have used some Glaxo freeze-dried, but our assessment of allergy duration was made on vaccinations with Danish liquid vaccine. The scheme which covers the rest of Ireland uses Glaxo freeze-dried, Swedish freeze-dried and Swedish liquid and Danish liquid vaccines. You will agree that one of the causes of variation in allergy duration reports is the use of different vaccines.

The next point to be considered is the prevention of vaccine deterioration. It may be presumed that the care taken in regard to exposure to heat and light, proper storage and time interval between manufacture and use does not vary much from one BCG centre to another, but variation in technique may occur and affect conversion and reversion

rates. In Ireland we use the intradermal technique, as we consider it gives the more exact dosage.

We have carefully studied the part played by super-imposed natural infection on the retention of BCG-induced tuberculin sensitivity and we believe that the duration of such sensitivity varies directly with the local infection rate.

The assessment of local infection may be made from estimates of the mortality and morbidity rates, but neither of these methods is very satisfactory today.

Nowadays, the mortality figure, owing to better therapy, is not a true index. Morbidity notifications are notoriously inaccurate. However, we know that our mortality is now one-fifth of what it was ten years ago (0.15/1,000) and that the number of primary cases under treatment at our Primary Clinics has dropped from 1,279 to 110 over the same period. The most reliable and sensitive index is got from tuberculin surveys and from these we know that the degree of infection varies from country to country, and within a country from urban to rural area.

In Dublin City the percentage of positive reactors in the 10 to 14 years age-group is dropping quickly—in the last four years it has fallen 15%, but in comparison with British cities it is still relatively high. The percentage of positive reactors in Britain at 13 years of age is reported as 16%—in Dublin the corresponding figure at the end of 1961 was 32%. These figures indicate that we have still a high rate of infection in Dublin and so our vaccinated groups are exposed to superinfection. We believe that this superinfection maintains vaccination allergy.

The picture of infection in our rural areas is in marked contrast with that of Dublin. Along the western seaboard infection is very low—under 1% tuberculin reactors have been found in school children in some isolated areas. These young people, especially those from the western seaboard, being tuberculin negative and so unprotected when they leave their rural homes, form a weak point in our defences against tuberculosis. Young adults are difficult to advise, and their generation are not familiar with the havoc wrought by tuberculosis. Unfortunately a high percentage of these young people emigrate without availing themselves of BCG vaccination.

The relative lack of infection in our rural areas and the presence of superinfection in Dublin is reflected in the different duration of vaccination allergy, Dublin showing a low reversion rate in comparison with rural Ireland.

Follow-up tests are part of our routine work and many thousands of tests have been made. To simplify our task of assessing allergy-duration we

TABLE 1
DUBLIN CITY
NO. TESTED AND NO. REVACCINATED 1958/61
SURVEYS

Time after Vacc.	No. Tested	No. Revacc.	Reversion
2 years	1,985	34	1.71
3 "	2,650	43	1.62
4 "	1,584	20	1.26
5 "	2,104	37	1.76
6 "	1,941	48	2.47
7 "	1,536	27	1.76
8 "	940	21	2.23
9 "	732	23	3.14
10 "	342	19	5.56
11 "	124	10	8.06
12 "	7	1	Not cal.
	13,945	283	2.03

TABLE 2
IRELAND (MAINLY RURAL)
NO. TESTED AND NO. REVACCINATED 1957/60
SURVEYS

Time after Vacc.	No. Tested	No. Revacc.	Reversion
2 years	2,116	206	9.74
3 "	6,641	744	11.20
4 "	12,450	1,877	15.08
5 "	6,384	1,030	16.11
6 "	10,268	1,547	15.07
7 "	6,912	1,030	14.90
8 "	3,361	489	14.55
9 "	1,019	116	11.38
10 "	178	25	14.04
	49,329	7,064	14.32

Figures supplied by National BCG Committee.

analysed the number of tests made in each of the four years 1958-61 in Dublin, and subdivided the material according to the number of years which elapsed since vaccination in each case.

In the four-year period 13,945 tests were made and the number of reverters was 283 i.e., approximately 2%. There was practically no difference in the percentage of reverters up to eight years after vaccination, but in the 9th and 10th year this had increased. From ten years up, there is a definite increase, but the numbers tested in these years are small due to the fact that most of the children who had been vaccinated ten years earlier had left school (Table 1).

Table 2 shows the reversion rate for the rest of Ireland outside Dublin and is compiled from the records of the National BCG Committee. These are not my own personal work and the figures have been compiled from the various Local Authorities throughout the country. It will be understood that many different doctors have read these tests

so that uniformity is difficult to assess, especially when different vaccines have been used.

Undoubtedly, the table shows a marked difference in the reversion rate compared with Dublin City and supports our view that superinfection plays an important part in maintaining allergy.

The increased percentage of revertors at the 10th year in Dublin (5.56%) serves as a pointer to us to retest children vaccinated in infancy at the 10th year, rather than at school entry. In Dublin we have the unique opportunity for the BCG protection of the new born as we have three large maternity hospitals where most of the births occur. The response is excellent, and in the Rotunda Hospital the acceptance rate is almost 90%. This section of our scheme commenced in 1950 when it was confined to contacts. It was not until 1954 that the scheme was extended to all new-borns so that assessment of duration of allergy in this age group is not due until 1964.

Our Dublin reversion figures agree with those reported by Ellman and Andrews (1959) who found only 2% reversion five to eight years after vaccination. Irvine (1959) reported approximately the same figures when the tuberculin positivity rate of his school leaver group was 21%—a figure almost the same as our present Dublin rate in the 10 to 14 years age group.

We consider that any report on the duration of allergy would be more valuable if accompanied by a statement regarding the local tuberculin positivity rate. It is apparent from our experience in Ireland that this duration varies with the infection rate and so the reversion rate could serve as an indicator of the infection rate in a given area.

It would be of interest if we could get the comparative figures from this country—it is possible that the reversion rates of rural parts of Scotland are much higher than those of Glasgow.

In Dublin when the stimulus of re-infection abates it is expected that the duration of BCG-induced allergy will decrease, and so we expect there will be a rise in our reversion rate sometime in the future.

I would like to turn now to consider another factor which has an influence on prolonging allergy i.e., the age group of the vaccinated. If there is a preponderance of older children in the groups under review the allergy produced by BCG will be maintained by the booster effect of superimposed natural infection—the longer period for which they have been exposed will tend to prevent reversion of allergy.

It is well known that the appearance of the follow-up tuberculin test alters with the advent of superinfection, and instead of the flat, bluish appearance there is a definite increase in induration and intensity. A clue to superinfection may be had from increase in measurements of the tuberculin reaction.

That immunity persists after disappearance of tuberculin sensitivity appears to be evident in our material as all of the children, including revertors, vaccinated under our scheme have remained free of tuberculous meningitis, and none has died from tuberculosis. The 17 cases of tertiary tuberculosis which occurred in our vaccinated groups have been mild in character and these, with the cases of pleural effusion and primary tuberculosis, have all recovered.

Some cases of sarcoidosis were referred to us for BCG vaccination and the noted feature in these cases was the continued negative tuberculin reaction. We have seen cases of sarcoidosis in our previously vaccinated personnel, all of whom were vaccinated as ordinary tuberculin negative reactors, so it is possible that sarcoidosis was present at the time of BCG vaccination.

We vaccinate young adult groups and it is in these groups that we have found the continued negative reactor.

Today we are not entering into the old question 'mystic sarcoidosis what kin to tuberculosis.' I mention it only as a vagary of tuberculin sensitivity which illustrates the negative reactor who may not be made positive by BCG vaccination.

Calculation of the length of time for which BCG protects has many difficulties. Owing to the movements of population much material is lost. This particularly applies to school-leaver groups, who may be impossible to locate after ten years. The agreement in Britain to use one vaccine only may solve a part of the problem which arises from the use of different vaccines. It is difficult to get uniformity of results when various tuberculin tests are employed and different techniques used. The literature on the value of BCG vaccination abounds in observations and the reports on duration show much discrepancy. Perhaps no other vaccine has caused so much debate or illustrates so well the whims and prejudices of those who study it.

In Ireland we have spent millions in fighting tuberculosis. Our work has passed from control of the disease to the study of its final eradication.

It is my pleasure to report from Ireland that BCG vaccination has helped in this success.

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