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PART III. CLINICAL TRIAL IN BRITISH CHILDREN

BY

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The studies of measles vaccine in the United States reported by Katz *et al.* (1960a, 1960b) included children living in institutions. Vaccination against measles is likely to have a special application in these circumstances, where measles may be associated with serious morbidity and a high mortality.

In this investigation the clinical and antibody response to three vaccines has been studied among mentally deficient children at the Fountain Hospital, Tooting, London, and at Queen Mary's Hospital, Carshalton, Surrey. These hospitals together provide accommodation for 600 severely subnormal children in the imbecile and idiot range. They were especially suitable for the study since close medical supervision was possible throughout.

Procedure

In December, 1960, samples of serum were taken from 107 children and examined for measles neutralizing antibodies. Eighty-five children were found to be non-immune and eligible for participation in the investigation; parental consent for the vaccination of these children was obtained. Eight of these children were subsequently excluded either because of intercurrent illness or because they had been exposed to chicken-pox between the time of allocation and vaccination. The remaining 77 children took part*; almost all were between 3 and 11 years of age (Table VIII).

TABLE VIII.—*Age of Children*

Vaccine	No. of Children	Age Range (Years)						Average Age (Years)
		Under 3	3–5	5–7	7–9	9–11	Over 11	
3C	19	0	7	6	4	2	0	5 10·12
4A	18	0	5	6	4	3	0	6 6·12
8	19	1	4	7	6	1	0	6 3·12
Controls	20	0	7	4	4	4	1	7 2·12
Total	76	1	23	23	18	10	1	

Three vaccines were used: vaccine 3C (dried, low-temperature type), vaccine 4A (dried, Enders type), and vaccine 8 (dried Parke, Davis type). All were given by subcutaneous injection. Details of these vaccines are given in Part I.

The children lived in self-contained wards each housing between 20 and 50. There was considerable inter-ward contact at the Fountain Hospital by virtue of attendance at the hospital school. To facilitate observation of vaccination reactions the children were vaccinated in groups at fortnightly intervals; at the Fountain Hospital 28 children were vaccinated on January 9, 1961, and 19 on January 23; at Queen Mary's Hospital all were vaccinated on February 6. The children were allocated to the vaccination groups independently by the Statistical Unit of the Wellcome Research Laboratories, as follows. The children were ranked by age in each ward and adjacent children in ranks were allocated randomly to one of three vaccination groups or to the unvaccinated control group. This procedure produced four groups of similar size and age composition (Table VIII). Each vaccine was used at each session.

Both vaccinated and unvaccinated children were closely observed for 21 days. Each child had an examination at least once a day by a physician kept unaware of the group to which the child had been allocated. The examination included an axillary temperature recording made in the late afternoon or evening and an examination for rash. On the twenty-first day a post-vaccination blood sample was taken. Thereafter, although the daily examinations were discontinued, the children were kept under observation within the hospital.

Results

The commonest symptoms observed during the follow-up were pyrexia, rash, and fretfulness.

Pyrexia

One child had a temperature of 100.4° F. (38° C.) on the day of vaccination, associated with a running nose and mild conjunctivitis. The remainder had temperatures of 98.6° F. (37° C.) or less (Table IX).

TABLE IX.—*Post-vaccination Daily Axillary Temperatures (°F.)*

Vaccine	Mean Temperature before Vaccination	No. in Group	No. with No Pyrexia	No. with Pyrexia (99°+)	99–99·9°	100–101·9°	102–103·9°	>104°
3C	97·7°	19	4	15	0	8	6	1
4A	97·3°	18	3	15	6	6	3	0
8	97·6°	19	3	16	3	9	4	0
All measles vaccinated		56	10	46	9	23	13	1
Controls	97·5°	20	16	4	2	2	0	0

Of the 56 vaccinated children, 10 (18%) had no appreciable rise in temperature throughout the follow-up period, and in a further nine the fever was slight. In the remaining 37 (66%) pyrexia was higher, and in one child reached 104.2° F. (40.1° C.). A similar degree of fever was found with all three vaccines. Pyrexia

*One child died during the follow-up period (see below) and has been excluded from the Tables.

persisted from one to six days, with an average of two days. In contrast, only 4 of the 20 unvaccinated children had any fever.

Rash

Of the 56 vaccinated children, 48 (86%) had a morbilliform rash (Table X). The rash was pink, fading to brown before clearing. It consisted of macular and occasionally papular elements, usually discrete but in more severe cases coalescent. It occurred behind the ears, on the face, neck, thorax, and abdomen, and in a few cases it spread to the limbs. The extent of the rash varied greatly, but it was unusual for all these areas to be involved in a single case. In most instances the rash was much less pronounced and extensive than that found in measles. In six children fleeting macular or erythematous rashes appeared and faded a few days before the onset of the main response. The main rash appeared at an average of 11 days after vaccination, with a range of 9 to 14 days. In some children the rash persisted for one day only; in others the fading rash was visible for as long as 10 days. The average period during which any element of the rash was visible was four to five days.

TABLE X.—*Onset and Duration of Pyrexia and Rash*

Vaccine	No. of Children	Pyrexia of 100° F. (37·8° C.) or More					Rash				
		No.	Onset (Days after Vaccination)		Duration (Days)		No.	Onset (Days after Vaccination)		Duration (Days)	
			Range	Mean	Range	Mean		Range	Mean	Range	Mean
3C	19	15*	5–10	8	1–6	3	16	9–14	11	2–9	5
4A	18	9	6–11	8	1–3	2	14	9–12	11	2–10	5
8	19	13	7–10	8	1–4	2	18	9–14	11	1–8	4
Controls	20										

* Including one child with pyrexia on admission.
In several children an occasional pyrexia of less than 100° F. (37·8° C.) occurred, apart from the main pyrexial response.

Other Clinical Findings

Many of the vaccinated children were miserable or fretful during the period of rash and pyrexia, and this was common to all three vaccines (Table XI). Acute tonsillar enlargement with exudate indistinguishable from follicular tonsillitis occurred among five children given vaccine 3C; *Streptococcus β-haemolyticus* was isolated from one and *Staphylococcus aureus* from another. The remaining three cultures were negative for pathogenic bacteria.

TABLE XI.—*Clinical Findings*

Vaccine	No. of Children	Clinical Findings	Systemic Reactions*			
			Marked	Moderate	Slight	Negligible
3C	19	Fretful during rash and pyrexia 13; Tonsillitis .. 5; Vomiting .. 1	4	10	4	1
4A	18	Fretful during rash and pyrexia 9; Vomiting .. 1; Bronchitis .. 1	2	5	8	3
8	19	Fretful during rash and pyrexia 11; Broncho-pneumonia .. 1	3	7	9	0
All measles vaccinated	56		9	22	21	4
Controls	20	Epileptic fit .. 2; Fretful .. 1	0	0	2	18

* For definitions, see text.

A case of bronchopneumonia occurred in one of the children given vaccine 8. The diagnosis was made on the twelfth day after vaccination; the child was given intramuscular penicillin, and recovered by the fifteenth day. Acute bronchitis was recorded in one child receiving vaccine 4A who had a history of this condition. One child in the unvaccinated group had three major epileptiform seizures on the fourth, twelfth, and thirteenth days of the follow-up, requiring oxygen and tracheal aspiration, and another had two major epileptic attacks on the thirteenth day of the follow-up.

On the twenty-first day after vaccination the physician responsible for the follow-up assessed the reactions as marked, moderate, slight, or negligible (Table XI). This assessment took into account, in each case, the presence and severity of rash, pyrexia, toxicity, and the presence and nature of any complication.

In 9 of the 56 children the reactions were described as marked—six had an illness similar to natural measles, one of which was associated with bronchopneumonia; one appeared toxic with photophobia immediately before the onset of the rash, one had bronchitis, and the remaining child had tonsillitis.

The 22 children with moderate reactions were sufficiently unwell in most cases to be confined to bed for two days.

Twenty-one had slight reactions exhibiting fever or rash but appearing well throughout, with little or no toxicity. In the remaining four children given measles vaccine no reactions were observed.

Among the 20 unvaccinated children in the control group, two were unwell during the follow-up and were classified as having a slight reaction. The remaining 18 cases were classed as having no reaction.

One death occurred in the study population during the investigation. The child was severely mentally retarded and had a history of epilepsy. After vaccination (vaccine 8) he was well, without pyrexia or other symptoms. On the seventh day he developed status epilepticus and died next day. At necropsy he was found to have had bronchopneumonia; there were no lesions characteristic of measles in the lungs, although typical measles giant cells were present in the appendix.

Pneumonia is a common cause of death in severely subnormal children, often associated with epilepsy and unconnected with specific infection (Hilliard and Kirman, 1957). In this case there was no evidence relating the pneumonia to the vaccine, and we believe the death to have been coincidental.

Immunity

Antibody Production.—The sera taken 21 days after vaccination were titrated for measles antibody simultaneously with sera taken during the initial pre-vaccination screening (Fig. 3). All the vaccinated children showed a rise in measles neutralizing antibody after vaccination. In contrast, none of the unvaccinated control group had antibodies to measles. The antibody levels were similar with all three vaccines.

Protective Effect.—An outbreak of measles which occurred at the Fountain Hospital provided an opportunity of observing protection conferred by the vaccines. The first case was diagnosed on March 12, 1961, 48 days after the last vaccination; a total of 30 cases were recorded during the nine-week period up to and including May 16. The distribution of measles throughout

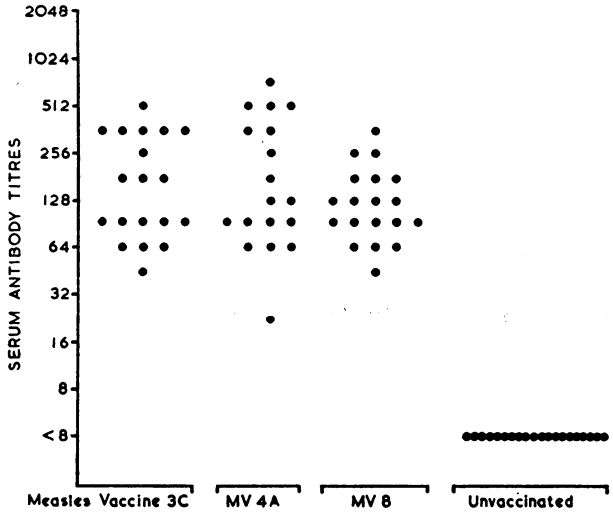

FIG. 3.—Individual antibody titres.

the hospital was not uniform, there being a complete absence of cases in certain wards (Table XII). In those wards where certain exposure took place, eight out of eight unvaccinated controls developed measles while none of the 23 vaccinated children contracted the disease. Table XIII gives the incidence of measles in

TABLE XII.—*Exposure to and Incidence of Measles in Vaccinated and Unvaccinated Children (Fountain Hospital)*

Wards	Vaccinated Children		Unvaccinated Children	
	No. in Wards	No. Developing Measles	No. in Wards	No. Developing Measles
3, 5, 8, 14 ..	11	0	5	0
1, 4, 6, 9, 16 ..	23	0	8	8
Total ..	34	0	13	8

TABLE XIII.—*Incidence of Measles in Ward One (Fountain Hospital) According to Antibody Status*

Antibody	No. of Children	No. of Measles Cases
Present—naturally acquired ..	4	0
,, —vaccinated	8	0
Absent—unvaccinated	3	3
Unknown	25	9
Total	40	12

a ward of 40 children, all mongols, of whom 15 had been examined for antibodies. No case of measles occurred among the four naturally immune or eight vaccinated children; the three unvaccinated controls, all without antibody, developed measles. Altogether 12 children out of 40 in the ward contracted the disease in two waves of infection between March 25 and April 10. Eleven children in wards showing cases of measles had been excluded from the investigation because of the presence of antibody at the pre-vaccination screening. None of these developed measles, although five of them showed only low-level antibody titres (16–32).

No death occurred among the eight control children who developed measles, but there were three deaths among the 22 children not in the investigation who contracted measles during the outbreak.

Discussion

The investigation described here is the first account of the use of measles vaccine in Britain. The vaccine was given to mentally deficient children, among whom measles constitutes a serious risk. The design of the trial permitted a valid comparison of the vaccination reactions and antibody titres between three groups of children given different batches of measles vaccine and an unvaccinated control group. None of the children had antibodies to measles before vaccination.

The results show that every child developed measles antibody after vaccination. The adequacy of the protective effect indicated by the antibody levels was substantiated by the findings on exposure to measles. An epidemic of measles occurred in one of the hospitals concerned in the months subsequent to vaccination. None of the vaccinated children developed measles. In contrast, all of the eight children in the unvaccinated control group who were intimately exposed contracted the disease. The findings therefore indicate that measles vaccine confers substantial protection. This is in keeping with those described elsewhere (Krugman *et al.*, 1960).

The main features of the vaccination reaction were pyrexia, which occurred in 82% of the children, and rash, which occurred in 86%. A high incidence of rash and pyrexia has previously been reported after measles vaccination. More than half the children were distinctly unwell during the vaccination reaction. There were five cases of tonsillitis and one case of bronchopneumonia in vaccinated children during the follow-up. These findings differed from those recorded by Krugman *et al.* (1960), who observed little systemic upset during the period of pyrexia and rash in a similar group of vaccinated children. The differences in clinical reaction reported from the two studies may have been due to unknown differences in the population groups or to variations in the batches of vaccine employed; differences in observation and assessment in the two studies may have been a contributory factor.

A comparison of the three batches of vaccine employed did not indicate any difference in their capacity to produce antibody. Reactions were most common after 3C and least after 4A. In Nigeria (Part II), where both vaccine 3C and 4A were used, no difference in the incidence of the reactions after vaccination was observed. There was no evidence that the extra passages undergone by vaccines 3C and 8 had resulted in increased attenuation.

These results suggest that the use of measles vaccine under close medical supervision may be a preventive measure of value in groups where natural infection is associated with a high mortality. The reactions after vaccination, however, indicate that further attenuation of the measles virus is desirable.

Summary

A clinical trial of attenuated measles vaccine in British children is described. Fifty-six severely mentally subnormal children living in an institution were vaccinated with one or other of three vaccines. The clinical reaction, antibody response, and protective effect were compared with an unvaccinated control group. All vaccines produced an adequate antibody response and protective effect. Over half the children had a moderate or marked systemic reaction. A morbilliform rash occurred in 48 vaccinated cases and pyrexia above 102° F. (38.9° C.) in 14.

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MAGNESIUM METABOLISM IN PARATHYROID DISEASE

BY

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A number of reports suggest that the parathyroid glands may influence magnesium as well as calcium metabolism. Greenwald and Cross (1925) claimed that prolonged administration of parathyroid extract increased the faecal excretion of magnesium. Greenberg and Mackey (1932) observed an elevation of serum magnesium in dogs receiving injections of parathyroid extract. The first account in man is that of Bulger and Gausmann (1933). They described a case of hyperparathyroidism in which a negative pre-operative balance of both calcium and magnesium became positive after operation. Bassett and Van Alstine (1935) found a small change in magnesium balance after parathyroidectomy, and Tibbetts and Aub (1937) and Barnes, Krane, and Cope (1957) confirmed the findings of Bulger and Gausmann. Potts and Roberts (1958) have drawn attention to the dangers of hypomagnesaemia occurring after parathyroidectomy. We here present pre-operative and post-operative data obtained on the last seven cases of parathyroidectomy performed in the Hammersmith Hospital.

Material and Methods

Six cases of primary hyperparathyroidism and one case of pluriglandular syndrome are presented. The former were found at operation to have enlargement of one parathyroid gland, and in all but Case 5 the histological appearance of the gland was that of a chief-cell adenoma. In Case 5 the cells were mostly oxyphil. The case of pluriglandular syndrome (No. 3) had, in contrast, enlargement of all parathyroid glands. Three of these were removed and part of the fourth was excised. Previously he had undergone subtotal adrenalectomy for Cushing's syndrome, and because of enlargement of the pituitary fossa he was on large doses of dexamethasone. He was also hypertensive and was receiving treatment with chlorothiazide and mecamylamine throughout. Biochemical details of the seven cases are given in Table I.

TABLE I.—*Biochemical Data in the Seven Cases*

Case	Sex and Age	Serum Ca (mEq/l.)	Serum Mg (mEq/l.)	Serum Inorganic P (mg./100 ml.)	Serum Alk. Phosphatase (K.-A. Units/100 ml.)	Blood Urea (mg./100 ml.)
1	F 61	7·0	1·5	2·3	74	75
2	F 58	7·8	1·9	2·2	135	55
3	M 33	6·5	1·6	2·1	11	74
4	F 72	9·0	1·7	3·8	21	72
5	F 32	9·0	0·5	2·0	54	40
6	F 52	6·6	1·7	2·1	78	38
7	F 40	7·7	1·4	2·4	10	63

The balance techniques and methods of analysis have been described (Hanna *et al.*, 1960). Muscle biopsy specimens from Cases 1, 2, and 7 were analysed for their magnesium and calcium content by the method described by MacIntyre and Davidsson (1958).

Illustrative Cases

Three cases are described in some detail to illustrate the evolution of changes after parathyroidectomy. The first of these received no magnesium supplements, the second required acute magnesium therapy, while the third was maintained on oral magnesium post-operatively.

Case 4.—A woman aged 72 complained of pain and swelling in her knees for seven months. She had suffered from thirst, with polyuria and constipation, for one year. A nodule was palpable in the right lobe of the thyroid, and effusions were present in both knees. *X*-ray examination

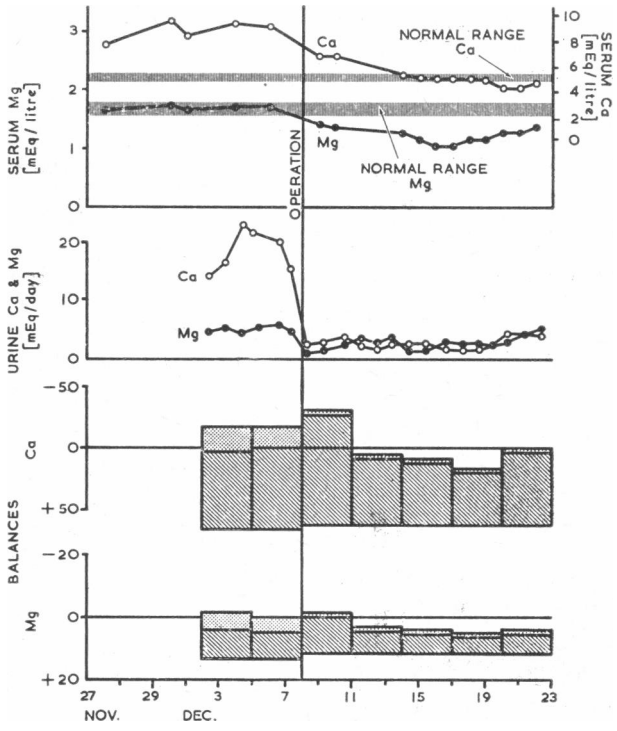

FIG. 1.—Calcium and magnesium metabolic data in Case 4. In the balance studies in Figs. 1-3 stipling=urinary output and hatching=faecal output.