B.C.G. VACCINATION AFTER REPLACEMENT BLOOD TRANSFUSION

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B.C.G. vaccination has been performed for a number of years in many maternity hospitals in this country and Gaisford (1955) has suggested that it might with advantage become an accepted part of the care of the "new-born" in such hospitals. In spite of the number of publications on the subject we have not seen direct mention of B.C.G. having been given to a baby within a short time of its receiving replacement transfusion.

Case Report

A baby suffering from haemolytic disease was born in a Glasgow maternity hospital on March 24, 1955, and a replacement blood transfusion was carried out the same day. B.C.G. vaccination was given on March 28. One week later the reaction had so far progressed that there was an indurated area 8 mm. in diameter, with a small ulcer crater in the centre from which there was watery discharge. During the next two weeks the ulcer became slightly larger and there was slight discharge of yellowish pus. The ulcer crusted frequently, only to break down again, but it healed finally at about three months. A few weeks later the mother noticed a small lump in the axilla. This was ignored until the middle of October, when it was felt to be larger. At that time it was a rubbery swelling 19 by 15 mm., with no definite fluctuation, though the skin over it was rather telangiectatic. The child's general condition was excellent and x-ray examination of his chest showed no evidence of past or present pulmonary tuberculosis. The Mantoux test, using 1/1,000 dilution, gave a strong positive reaction. There was an area of erythema extending to 38 mm. diameter with a central induration of 21 mm. diameter.

The swelling was kept under observation, and by November 11 it had increased to 25 by 18 mm. Definite fluctuation was now present and the pus was aspirated, with streptomycin replacement. The pathological report on the pus was: "Exceedingly scanty acid- and alcohol-fast bacilli present; no growth obtained on culture."

The x-ray film of the mother's chest showed no evidence of pulmonary tuberculosis and her Mantoux (1/1,000) reaction was negative.

At the replacement transfusion 540 ml. of blood was withdrawn from the baby and 600 ml. administered. Of the latter, 540 ml. was received from donor A and 60 ml. from donor B. In each case the blood had been donated on March 22. The donors have subsequently been examined. Their x-ray films show no abnormality. Donor A proved negative to a 1/10,000 dilution tuberculin test, but developed positive induration of 20 mm. diameter with the 1/1,000 strength. Donor B gave a positive result with induration of 7 mm. diameter with the 1/10,000 and of 10 mm. with the 1/1,000 dilution.

Discussion

The following is an extract from Irvine (1954): "When introduced into the skin of a tuberculin-negative person in a suitable dose, nothing appears to the naked eye for two to three weeks. . . . At the end of this time a small area of induration may be felt at the site of the vaccination which gradually increases to a lump or papule, usually about the

size of a split pea. Between the fourth and sixth weeks a bleb appears on top of this papule in the majority of cases." Another baby from our area was vaccinated in the same hospital on the same day and with the same batch of B.C.G. In this case the papule began to appear on the fourteenth day and pursued the usual course.

The following factors are worthy of consideration.

(a) *Secondary Infection.*—The rapidity with which the ulcer formed must suggest the possibility of secondary infection at the time of vaccination. However, the whole course of eruption was normal, apart from the unusually short time taken to reach this stage. Further, the subsequent glandular enlargement and the pus therefrom were identical with those of B.C.G. adenitis.

(b) *Rate of Evolution of Lesion Altered by Maternal Influences.*—There is at present a diversity of opinions whether or not children born to tuberculous mothers respond more quickly or more slowly to B.C.G. than is normally the case. Gaisford (1955) found that 97% of contact infants had converted by four weeks, compared with 81% in the non-contact cases. Hewell and McClellan (1954) reported similar findings. However, Hagberg (1954) reported that the conversion rate was much slower than in the non-contact group. Roloff and his co-workers (1954) are in agreement with this latter view, believing that there is passively transferred antibody, but that this does not pass across the placenta. Ström (1950) has shown that even the newborn possess the ability to localize the B.C.G. organisms to some extent at the site of the inoculation. This supports the view that there may be some passively transferred immunity. The baby under consideration here has shown no evidence of congenital tuberculosis and was breast-fed for the first six weeks. The x-ray film of the mother's chest showed no abnormality and her Mantoux reaction was negative. These factors indicate that the baby could not have been "tuberculin positive" at birth and was unlikely to have received any passive immunity from the mother.

(c) *Rate of Evolution of Lesion Altered by Blood Received from a Tuberculin-positive Donor.*—When B.C.G. inoculation of a tuberculin-positive person occurs, a Koch phenomenon and possible local glandular reaction are to be expected. Zammit-Tabona (1952) reported that the commonest finding in the Koch phenomenon was a darkish circular ulceration, with a tendency to sloughing at the vaccination site three to six days after inoculation. His other findings sometimes included concurrent enlargement of lymph nodes in the axilla on the side of vaccination. There is no doubt that a circulating antibody exists which may give passive immunity, but there are conflicting opinions concerning the allergic state. Harries and Mitman (1947) state: "Like immunity, hypersensitivity may be induced actively or passively. Almost all clinical examples of hypersensitivity are active. Passive sensitivity follows the injection of serum from a sensitized animal. The state develops more rapidly and passes off quickly."

Hadfield and Garrod (1947) state: "The serum of a sensitized animal will render a normal animal anaphylactic—whereas no amount of serum from an allergic animal will confer on a normal animal the capacity to react allergically. Anaphylaxis thus depends on the presence of circulating antibody, and allergy does not." However, they go on to quote Rich and Lewis (1932), who claim to have proved that the change is in the cells themselves. Tissue cultures were prepared from the leucocytes and spleen of guinea-pigs sensitized by an injection of avirulent tubercle bacilli. To these cultures were applied various dilutions of tuberculin, which were found to kill the cells while they had no effect on the cells of similar cultures prepared from a normal animal.

Rich (1951) states: "In contrast to the anaphylactic type, the tuberculin type of hypersensitivity cannot be transferred to a normal individual by an injection of the serum of a hypersensitive one. The reported exceptions to this rule are so rare and irregular that it is evident that in this type of

hypersensitivity the serum rarely contains sensitizing antibody in amount sufficient to sensitize the previously normal body." He further quotes the work of Chase (1945), who reported that guinea-pigs injected with a leucocytic peritoneal exudate derived from tuberculous hypersensitive guinea-pigs acquired, within one to three days, the capacity to react to tuberculin. This reactive capacity was of brief duration, and, curiously, could be conferred only by living cells. Freezing the cells of the exudate, or heating them to 48° C. for fifteen minutes, destroyed their sensitizing power.

The prompt reaction to the B.C.G. with local tissue destruction in our patient, who received *whole blood*, was identical with the Koch reaction, which is usually ascribed to a state of hypersensitivity (Rich and McCordock, 1929; Rich, 1930). Clawson (1933) found that the lesions produced by intravenous B.C.G. were more extensive and severe in previously sensitized rabbits than in the control animal.

Apart from the speeding up of the appearance and stages of the local reaction which we describe, there is no definite evidence that the B.C.G. vaccination was more pathogenic than usual. The subsequent gland abscess could fairly be regarded as a typical accepted complication. However, the extent of the induration (21 mm. diameter) resulting from 1/1,000 tuberculin is much in excess of the average seen after B.C.G. conversion. The glandular complication was not prevented by passive immunity, though the local fixation effect of agglutinating antibody received from the donors might have waned before a natural cellular reaction had time to develop.

Conclusion

In a case such as we have described one has to decide which of the following factors played a part: allergy and/or immunity; if allergy, from the cells and/or serum of a tuberculin-positive donor; if immunity, from a passive humoral agglutinating antibody reaction, with or without a cellular reaction.

Having regard to the opinions quoted above and to our investigations, the reaction appears to have been an immediate allergic phenomenon without obvious evidence of immunity, and was probably induced by the cells in the 600 ml. of refrigerated, but not frozen, blood received from the tuberculin-positive donors.

When, as at present, the study of allergy is of such general interest and importance, and when, in addition, immunization as a preventive measure on the one hand and desensitization as a therapeutic measure on the other are being advocated, this case, though a single one, seems to be worthy of record and consideration.

It is hoped that parallel findings by others will also be reported.

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Medical Memoranda

Herpes Zoster

Between October 1, 1948, and October 1, 1954, I attended 72 patients with herpes zoster (41 females, 31 males). Their ages ranged from 13 to 88 years, and more of these patients were over than under 50 (Table I).

TABLE I.—Ages in Decades

	1-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
No. of cases	0	4	5	2	5	15	20	16	5

The distribution of the rashes was as follows: trigeminal first division, 7 cases; second division, 2; third division, 3; cervical roots, 16; dorsal roots, 35; lumbar roots, 3; sacral roots, 6. There was some overlapping, as adjacent roots were often affected, and in one third-division trigeminal case the second cervical root was also involved.

Pre-herpetic pain varied from nil to severe, and was variously described as itching, irritation, "like a needle," neuralgia, burning, soreness, shooting, crushing bones, stomach-ache. Pre-herpetic symptoms were absent or negligible in 44 cases, slight or moderate in 21, and severe in 7. The longest period of pain before the onset of the rash was 10 days, the usual being two to three days (Table II).

TABLE II.—Pre-herpetic Pain in Days Before the Onset of the Rash

Days	Nil	1	2	3	4	5	6	7	8	9	10	Total
No. of cases	44	1	12	9	1	1	0	3	0	0	1	72

Pain during the stage of eruption varied from slight discomfort to severe pain, and the same descriptions were applied as for pre-herpetic pain where it had occurred. Eruptive pain was experienced by some patients who had had no pre-herpetic pain, and vice versa. The amount of rash varied within wide limits, but no relation was noticed between the extent of rash and the degree of pain. One man aged 26, with left intercostal (D 5) herpes, was dyspnoeic on exertion during the eruptive stage. Eruptive pain usually corresponded with the distribution of the rash, but in two supra-orbital cases the main pain was in the mastoid region. Two males with S4/5 involved had painful and difficult micturition during the eruptive stage.

Treatment was mainly symptomatic with powder, calamine lotion, or collodion, and aspirin, aspirin compounds, or "nepenthe" as required. Four cases received ultra-violet rays, three systemic penicillin (two oral and one parenteral), and one chloramphenicol at the onset of the rash. The reasons for giving these additional treatments were more experimental than clinical. In no case was the course of the disease apparently altered thereby, but it is interesting to note (see below) that two cases treated with ultra-violet rays developed post-herpetic pain and two did not, and the one case treated with parenteral penicillin developed post-herpetic pain, as did also the one treated with chloramphenicol.

The vesicles dried into scabs which separated in from five days to six weeks. Although the cases often appeared in batches of two, three, or four, with intervals of up to six months without a single case, no association was established with known chicken-pox epidemics.

Pain lasting more than six weeks from the onset of the rash, and severe enough to require advice or treatment, occurred in five cases—that is, one in 14. Three were males and two females. In each case this post-herpetic pain was a continuation of the eruptive pain and was of the same nature. In these five cases the ages and situation of the rashes were: aged 73, maxillary; aged 70, supraorbital; aged 70, occipital; aged 68, intercostal; aged 56, intercostal.