BCG OVERDOSAGE TREATED WITH ISONIAZID

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ISONIAZID is used for the treatment or prevention of tuberculosis under three different conditions, namely, when clinical manifestations of active disease are present, when infected individuals are considered to have active but not radiographically demonstrable lesions and when uninfected persons are likely to be exposed to virulent infection. The efficacy of isoniazid treatment of disease has already been well established, but there is no general agreement on its role as a prophylactic agent. The main objection to its use in the prevention of clinical disease is that the vast majority of those treated with the drug over the necessary period of several months would not have developed the disease anyway. There can hardly be any doubt, however, that under certain conditions isoniazid therapy prevents the development of progressive disease.

Isoniazid therapy has been shown to be effective in preventing progressive disease in laboratory animals if treatment is started before or immediately after infection with virulent organisms has occurred (Rich, 1950; Barnett, Bushby and Mitchison, 1953; Pasquier and Mauro, 1960; Tai, Jen, Chu and Han, 1961). Animals infected with virulent organisms and treated with isoniazid resisted re-infection well, even when no longer under drug treatment (Ferebee and Palmer, 1956; Tai and others, 1961), but it is uncertain how long this state of immunity persists after the administration of the isoniazid has been discontinued.

The efficiency of isoniazid prevention depends, however, on the size of the infecting dose. It is less effective against large-dose infections than against small doses (Peizer, Chaves and Widelock, 1957). Infection with very low doses of virulent tubercle bacilli, which would otherwise produce immunity in animals, has no immunizing effect if they are treated with isoniazid (Dubos and Schaefer, 1956). Thus, isoniazid will completely suppress an infection with a small number of tubercle bacilli, so that the animal remains as if it had not been infected. Larger infections with virulent organisms are controlled by the drug and

a state of immunity comparable to that found in the BCG-vaccinated is produced. When the infecting dose is increased further, the efficiency of isoniazid in preventing progressive disease deteriorates correspondingly. It may be, however, that the efficiency of isoniazid in suppressing or controlling tuberculous infection is more closely related to the number of isoniazid-resistant organisms in the infection rather than to the total number of organisms.

The development of immunity following vaccination with attenuated organisms was, at first, considered to be adversely affected by isoniazid treatment (Dubos, Pierce and Schaefer, 1956), but evidence to the contrary was presented later (Bloch and Segal, 1955). Indeed, BCG-vaccinated animals treated with isoniazid were found to possess a greater degree of immunity to virulent infection than vaccinated but untreated animals (Mauro and Pasquier, 1961). When only small doses of BCG were used for vaccinating animals, treatment with isoniazid prevented the development of post-vaccination immunity (Dubos and Pierce, 1956). It appears, therefore, that isoniazid therapy has a similar effect on all tubercle bacilli infections, whether they are BCG or virulent organisms, suppressing completely small dose infections and controlling larger dose infections without preventing the development of immunity. The effect on an infection with either BCG or virulent organisms is as if all or a large proportion of the infecting isoniazid-sensitive bacilli are destroyed immediately, thus reducing correspondingly the effective size of the infection.

It is not surprising, therefore, that the degree of post-vaccinal tuberculin sensitivity found in BCG-vaccinated guinea pigs, which had been treated with isoniazid immediately after vaccination, was less than in vaccinated animals which had not been treated (Jankov, 1959). In guinea pigs which had been infected with virulent organisms and treated with isoniazid, 14% were tuberculin negative 36 weeks later (Peizer, Chaves and Middlebrook, 1957). Isoniazid therapy increases

TABLE I
DIAMETERS OF VACCINATION SCARS AND MANTOUX REACTIONS IN TEN CHILDREN
GIVEN HIGH DOSES OF BCG AND TREATED WITH ISONIAZID

Age of Child	Prescribed daily dose isoniazid (mg.)	% Prescribed tablets recovered later unconsumed	Diameter (mm.) of			
			ant. and post. BCG scars after		Mantoux reactions after	
			9 weeks	36 weeks	9 weeks	36 weeks
3	100	37	5 — 5	7 — 7	5	10
8	200	Nil	0 — 0	0 — 0	6	3
13	300	48	12 — 6	10 — 5	12	11
13	300	43	5 — 4	4 — 3		6
13	300	14	7 — 0	7 — 0	3	11
13	300	11	5 — 5	6 — 6	2	5
13	300	10	10 — 7	10 — 5	10	11
13	300	Nil	7 — 6	9 — 9		11
13	300	Nil	5 — 6	7 — 7	0	11
13	300	Nil	2 — 0	2 — 0	0	2

the tuberculin reversion rate also in tuberculin-positive infants (Robinson, Meyer and Middlebrook, 1955) and children (Dahlstrom, Wilson and Sedlacek, 1960). Even in patients suffering from active tuberculosis there was a reduction in tuberculin allergy following antibiotic treatment (Collas, Appeau, Dhenin, Gelain and Pelletier, 1960). In the United States Public Health Service study, however, only small decreases occurred in the tuberculin sensitivity of children with primary tuberculosis treated with isoniazid (Ferebee, Mount and Anastasiades, 1957).

The conclusions drawn from these studies indicate that the efficacy of isoniazid treatment against simultaneous infection with isoniazid-sensitive organisms in man could be assessed by starting isoniazid treatment immediately after BCG vaccination and determining its effect on the development of post-vaccinal tuberculin sensitivity.

An accident necessitating this treatment occurred at a BCG clinic in Cardiff during 1962, when ten children were vaccinated with a BCG suspension which had a viability count of 93 million/ml. instead of the usual count of between 5 and 9 million/ml. (Griffith, 1963). Eight of the ten children were 13-year-old girls and the other two were boys, a diabetic aged 10 and a 3-year-old. Each child received two inoculations of 0.05 ml. each of this concentrated suspension, into the skin over the anterior and posterior border of the insertion of the left deltoid. They thus received a total of 9.3 million viable units of BCG instead of the usual dose of between 0.5 and 0.9 million viable units, that is, between ten and 20 times the normal dose.

Three days after vaccination the children were given exactly 30 days' supply of isoniazid; the 13-year-old girls were to receive 300 mg. daily, the 10-year-old boy 200 mg. and the 3-year-old

100 mg. After 28 days they were given another 30 days' supply. On the 63rd day an attempt was made to recover all unconsumed isoniazid tablets, but it is suspected that some parents claimed that all had been consumed when, in fact, this was not the case. A Mantoux test, 5 T.U. O.T., was also carried out on the 63rd day on nine of the children and the diameter of the BCG lesions measured. The Mantoux reaction in eight of the children was read on the third day. After 36 weeks another 5 T.U. O.T. Mantoux test was carried out on the ten children and again the diameter of the BCG lesions measured (Table 1).

None of the children had local abscesses or discharging sinuses when seen after vaccination, the axillary lymph glands were not palpable and the chest radiographs showed no abnormalities. The diabetic 10-year-old boy had no visible BCG lesions at any time and one girl had only one scar, with a diameter of only 2 mm. The BCG scars measured from 0 to 12 mm. in the other children. Four of the eight children had tuberculin reactions of less than 5 mm. diameter after nine weeks, but only two of the ten were tuberculin negative after 36 weeks. Those with the smallest BCG scars had the least Mantoux reactions 36 weeks after vaccination.

At the time that this accident occurred a study to compare the efficiency of intradermal and multiple-puncture BCG was in progress in Cardiff (Griffith, Kinsley and Anderson, 1963). The intradermally vaccinated participants in that study also received two inoculations of 0.05 ml. BCG suspension, each child receiving a combined total dose of 0.71 million viable units. Twelve weeks after vaccination they had BCG lesions of an average diameter of 4.9 mm. per lesion, compared with an average diameter of 4.9 mm. at nine weeks and 5.2 mm. at 36 weeks in the ten isoniazid-treated children. Although the average size of the BCG

lesions was similar in the two groups, the average Mantoux reaction in untreated children who had a normal dose of BCG was 11.1 mm. after 12 weeks, compared with average diameters of 4.7 mm. at nine weeks and 8.1 mm. at 36 weeks in the BCG-overdosed, isoniazid-treated children. This suggests that isoniazid treatment, although not completely suppressing the initial high dose BCG infection, reduced the level of tuberculin allergy produced during the period of treatment and that, although the allergy increased after the two months' treatment was completed, it did not reach the level found at 12 weeks in children vaccinated in the normal manner. Unfortunately, however, the Mantoux reactions at nine weeks were

measured by a different practitioner from the reader at 36 weeks.

As the efficiency of isoniazid treatment in animals is dependent on the size of the infecting dose, it may be presumed from this study that normal human dose of BCG or a small dose of virulent infection could be completely suppressed if isoniazid treatment were started immediately after infection had occurred. This investigation contradicts the suggestion made (Lambert, 1959) that preventive isoniazid treatment started immediately after accidental laboratory inoculation with virulent tubercle bacilli may be ineffective and would merely prolong the incubation period.

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