Case 3

A 29-year-old housewife had been suffering from bilateral galactorrhoea and mammary discomfort for the past six years since the birth of her only child. During this time she had been evaluated psychiatrically because of a hyperventilation syndrome associated with perioral and localized acral paraesthesia, muscular cramps, and occasional fainting spells. No other abnormalities were noted. Physical examination on 17 November 1970 showed nothing other than galactorrhoea. X-ray appearances of the sella turcica were normal.

From 19 to 28 December the patient took daily a single 3-mg capsule of CB 154 by mouth before breakfast. While she experienced slight nausea, her galactorrhoea and mammary discomfort greatly diminished, the latter disappearing entirely. Increasing the dose to 3 mg twice daily on 29 December resulted by 1 January in regular vomiting soon after taking the drug, and it was therefore withdrawn. Physical examination on 6 January showed a milky discharge from both breasts of similar magnitude to that present before CB 154 administration.

Evaluation of Results

In Case 1 the gradual disappearance of galactorrhoea after persisting nearly five years (possibly associated with a pituitary tumour) and the recurrence after stopping CB 154 wholly justifies linking the response with the action of the drug.

In Case 2, as in the first, a gradual disappearance of galactorrhoea was noted, beginning with the first week of therapy. In this instance, however, the condition was acute and a therapeutic response was interrupted by the patient having initially to reduce and eventually withhold the drug entirely because of dizziness. The ensuing acute mammary engorgement on withdrawal and its disappearance after reinstituting CB 154 assured the observers and the patient of the drug's therapeutic effect.

The situation in Case 3 was less decisive but nevertheless suggestive. Here a therapeutic response was short-lived by the occurrence of side effects. Unfortunately, at the time a 3-mg capsule formulation was all that was available. When the more flexible dosage form of 1 mg again becomes obtainable another therapeutic regimen will be tried.

Discussion

Management of non-puerperal galactorrhoea has centered chiefly on the use of various oral contraceptives or oestrogens (Williams, 1968). While some have claimed that oral contraceptives are therapeutically effective, others have implicated them as causative (Gregg, 1966). The clinician confronted by a patient with non-puerperal galactorrhoea, in whom a pituitary lesion is suspected (as suggested by our Case 1), believes that he is dealing with an organic abnormality which is interfering with the normal inhibitory control mechanism of prolactin secretion. On the other hand, when an aetiological factor is not evident the galactorrhoea is probably regarded as attributable to an ill-defined hypothalamic dysfunction associated with an inadequate production of prolactin inhibitory factor or interference with its action (analogous to our Case 2).

A series of animal pharmacology experiments using various species in Sandoz's Laboratories suggested that CB 154 interfered specifically with pituitary prolactin (Billeter and Flückiger, 1971; Wagner *et al.*, 1971).

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MEDICAL MEMORANDA

Pulmonary Tuberculosis Due to B.C.G.

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British Medical Journal, 1971, **3**, 229-230

Cases of individuals who lack the capacity to resist mycobacteria and suffer a progressive and fatal infection when vaccinated with B.C.G. despite the organism's low virulence are rare. Mande (1968) reviewed 13 such patients but noted only 20 further cases of "metastatic" lesions due to B.C.G. He

considers, therefore, that susceptible people of this type represent a distinct class and not the tail end of a distribution curve of innate immunity. In the fatal cases at least other immunity defects were usually evident also.

Fatal infections with B.C.G. are generalized and the lungs are affected like other organs. Nevertheless, there appears to have been no previous record of a case of metastatic B.C.G. infection presenting as pulmonary tuberculosis. Such a case is reported here.

Case History

The patient, a girl born in 1950, developed juvenile rheumatoid arthritis in 1955 but had never been treated with corticosteroids. Vaccination with B.C.G. in 1964 was a routine measure without a subsequent tuberculin test for conversion. Her arm was uncomfortable and the lesion discharged for six weeks but no other local reaction was seen. In 1967 Crohn's disease was diagnosed and a hemicolectomy was performed; non-caseating granulomata considered typical of the condition were found on section. A further operation was necessary a year later for relieving intestinal obstruction. Urine and faeces were not cultured for mycobacteria during these illnesses.

In 1968 small lesions were found radiologically in the lower zones of both lungs (see Fig.), which had been clear in 1967. The lesions could not be traced to acute infection. A Mantoux test was negative with 100 tuberculin units and no tubercle bacilli were seen in sputum films, but the cultures proved positive. Treatment was therefore undertaken with streptomycin 1 g daily by intramuscular injection

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together with sodium para-aminosalicylic acid 12 g and isoniazid 300 mg daily from the beginning of September until November. The streptomycin was then discontinued and she was discharged on the latter two drugs. These produced a certain amount of gastric intolerance, however, and in January 1969 a change was made to streptomycin 750 mg and isoniazid 500 mg twice weekly. By the end of the second month of treatment sputum culture had become negative, while the radiological opacities had completely disappeared by the end of a year. The total treatment extended over two years. At the time of writing her condition was satisfactory, though she was still suffering from rheumatoid disease.

Lesions in lower zones of both lungs ascribable to B.C.G. infection.

BACTERIOLOGICAL FINDINGS

Nine specimens of sputum were positive on culture for tubercle bacilli over a period of two months. The strain was sensitive to major and minor antituberculosis drugs except for resistance to pyrazinamide and a borderline response to cycloserine and thiacetazone. These findings, which were confirmed on a separate isolate, prompted detailed examination of the organism, which otherwise would have been passed as an ordinary tubercle bacillus.

DIAGNOSIS OF B.C.G.

The identification "consistent with B.C.G." is made in the Tuberculosis Reference Laboratory when an organism (1) passes the screening test for tubercle bacilli (mammalian)—that is, fails to grow at 25° or 42°C or on *p*-nitrobenzoic acid (500 µg/ml) or thiacetazone (10 µg/ml) in egg medium—has an acceptable morphology, including cord formation in suitable medium, and produces no pigment when grown in light; (2) gives a negative test for niacin production; (3) exhibits resistance to pyrazinamide, with uniquely eugonic growth on the acid egg medium; (4) does not prefer pyruvic acid to glycerol in egg

medium; (5) grows superficially in semisolid agar medium; and (6) has negligible pathogenicity for the guinea-pig.

The present organism had all these properties, but because of the special interest of the case it was sent to the Tuberculosis Department of the State Serum Institute, Copenhagen, for an independent diagnosis. No intimation was given of the Cardiff findings or diagnosis. The report was that the organism "cannot be distinguished from B.C.G." Additional tests made at Copenhagen were as follows. The organism was sensitive to furfuroyl hydrazine, nitrate reduction was negative, catalase was weakly positive, Tween degradation was negative, and amidase was positive with carbamide but negative with nicotinamide, pyrazinamide, and the Bönicke amide series. Two guinea-pigs were inoculated intraperitoneally and two intravenously with 1 mg of culture, rabbits and hens intravenously with 1 mg and 5 mg, and white mice intraperitoneally with 10 mg. All the animals survived, and when killed no evidence was found of progressive infection having been established.

Comment

The pulmonary infection with B.C.G. in the present case clearly indicates a defect in immunity. Antibody production has often been imperfect in fatal cases but the course of this patient's smallpox vaccination in childhood was normal, she had no history of recurrent infections, and plasma cells were plentiful in the appendix, excised at the time of hemicolectomy. Her juvenile rheumatoid arthritis, however, may have been connected with the impaired immunity, and this and allied diseases might suggest caution when live vaccines are considered for use. Furthermore, it seems desirable to add B.C.G. to the official list of vaccines contraindicated by immunity defects and also by immunosuppression therapy, the hazard of which is known—for example, in relation to *Pneumocystis carinii* infection. It is possible that the enteritis diagnosed as Crohn's disease was due to B.C.G.

The histology did not suggest tuberculosis, and the routine culture of excised material for mycobacteria, especially lymph nodes, seems advisable in Crohn's disease to investigate the possibility of aberrant response to mycobacteria. In the present case, as in all examples of generalized B.C.G. infection investigated, the tuberculin reaction was negative, suggesting an incapacity to develop or display the delayed type of hypersensitivity. The same phenomenon is often observed in sarcoidosis, which in the present case was excluded by the positive cultures, but may also perhaps represent an aberrant response to infection. Finally, the chance finding of resistance to pyrazinamide led to the diagnosis of B.C.G. infection. It is necessary for recent B.C.G. vaccination to be mentioned to the laboratory in cases investigated for tuberculosis because B.C.G. will in most cases be mistaken for *Mycobacterium tuberculosis* if tests are not specifically made to identify it.

Reference

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