happened in several other countries. This striking reduction apparently resulted from actions such as the removal of phenacetin from analgesic mixtures by both voluntary and legislative means; there is no evidence that it is associated with an overall decrease in analgesic use. The use of the chemically related acetaminophen continues, but rarely is this agent combined with ASA, and this seems to be of great importance.

We must, however, recognize that this form of serious renal disease will continue to appear at a low frequency. Clinicians will have to maintain their awareness of analgesic nephropathy, an uncommon but still largely preventable disease.

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Disseminated tuberculoid lesions in infants following BCG vaccination

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The records of 830 consecutive autopsies at Children's Hospital, Winnipeg revealed that 26 of the 36 infants (34 Canadian Indian, 1 Inuit and 1 Caucasian) given BCG vaccine shortly after birth had tuberculoid granulomas in various sites, including the vaccination site, regional lymph nodes, liver, spleen, lung, bone marrow and salivary gland. *Mycobacterium bovis*, BCG type, was identified in three of the four cases in which isolation was attempted. The principal causes of death had been sudden infant death syndrome and respiratory tract infections. None of the infants had histologic evidence of an immune deficiency. However, it is possible that in two cases the dissemination of BCG was enhanced by a temporary immunologic defect induced by malnutrition.

Les dossiers de 830 autopsies consécutives pratiquées à l'hôpital pour enfants de Winnipeg ont révélé que 26 enfants sur 36 (34 Amérindiens canadiens, 1 Inuit et 1 Caucasien) à qui on avait donné le vaccin BCG peu après la naissance avaient des granulomes tuberculeux en diverses localisations, dont le point de vaccination, les ganglions lymphatiques régionaux, le foie, la rate, les poumons, la moëlle osseuse et les glandes salivaires. Du *Mycobactérium bovis* de type BCG fut identifié dans trois des quatre cas ou l'isolation fut tentée. Les principales cause de décès avaient été le syndrome de mort soudaine du nourrisson et les infections des voies respiratoires. Aucun des bébés ne présentaient de signes histologiques d'un déficit immunitaire. Toutefois, il est possible que dans deux cas la dissémination du BCG ait été favorisée par une anomalie immunologique temporaire provoquée par la malnutrition.

Although BCG (bacille Calmette–Guérin) vaccination is widely used around the world to protect against tuberculosis, particularly in newborn infants in high-risk populations, recent reviews have questioned its efficacy.[1,2] The occurrence of local complications in normal patients and fatal dissemination of the bacillus in immunodeficient individuals is well known. It is not widely appreciated, however, that nonfatal dissemination after BCG vaccination of infants may occur in the presence of an apparently intact immune system,[3,4] as the following study showed.

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Patients and methods

We reviewed the records of 830 consecutive autopsies performed at Children's Hospital in Winnipeg over a 4-year period (January 1977 to December 1980). In the age range of 1 month to 1 year, 36 of the infants (34 Canadian Indian, 1 Caucasian and 1 Inuit) had been vaccinated with BCG shortly after birth. Tissue specimens from these cases were examined microscopically and were stained for acid-fast bacilli whenever granulomas were found.

Results

In 26 of the 36 vaccinated infants (72%) tuberculoid granulomas were found. The lesions were confined to the site of the BCG vaccination (Fig. 1) and ipsilateral axillary or cervical lymph nodes in 12 infants; the involved nodes were usually enlarged and caseous, and acid-fast bacilli were frequently seen within the caseous foci.

The remaining 14 infants all had granulomas in the liver lobules and portal tracts. These granulomas were composed predominantly of epithelioid cells, although occasional multinucleated giant cells were noted (Fig. 2). Typically, an infiltrate of lymphocytes encircled the granuloma, but no caseation was seen in any of those in the liver, nor could acid-fast bacilli be identified there. Organs other than the liver were less commonly involved, the spleen being the site of granuloma formation in only four cases. The involvement there was often extensive, with large areas of caseation, but again no acid-fast bacilli could be seen. Isolated granulomas were noted in the lung in four, in bone marrow in two and in salivary gland in two cases. None was seen in the meninges.

Isolation of the organism from the axillary lymph nodes was successful in three of four cases, and *Mycobacterium bovis*, BCG strain, was recovered. In the fourth case acid-fast organisms were readily seen in smears but could not be cultured.

There were no granulomas in 10 of the 36 vaccinated infants. Four of these, aged 2, 4, 6 and 8 months, had a small dermal scar, and in the other six the site of vaccination and the regional lymph nodes were not examined microscopically.

Sections from the thymus and lymph nodes of the 26 infants with granulomas, who ranged in age from 2 to 7 months, showed no features of an underlying immunodeficiency. Most of the infants had been well and had died suddenly at home or after very brief illnesses in hospital. The causes of death in the group were varied and included sudden infant death syndrome (in 11 infants), pneumonia (in 3), and meningitis, laryngotracheitis, pertussis, aspiration, anoxic brain damage, heart failure, necrotizing enterocolitis and gastroenteritis (in 1 or 2 each). The most extensive organ involvement had

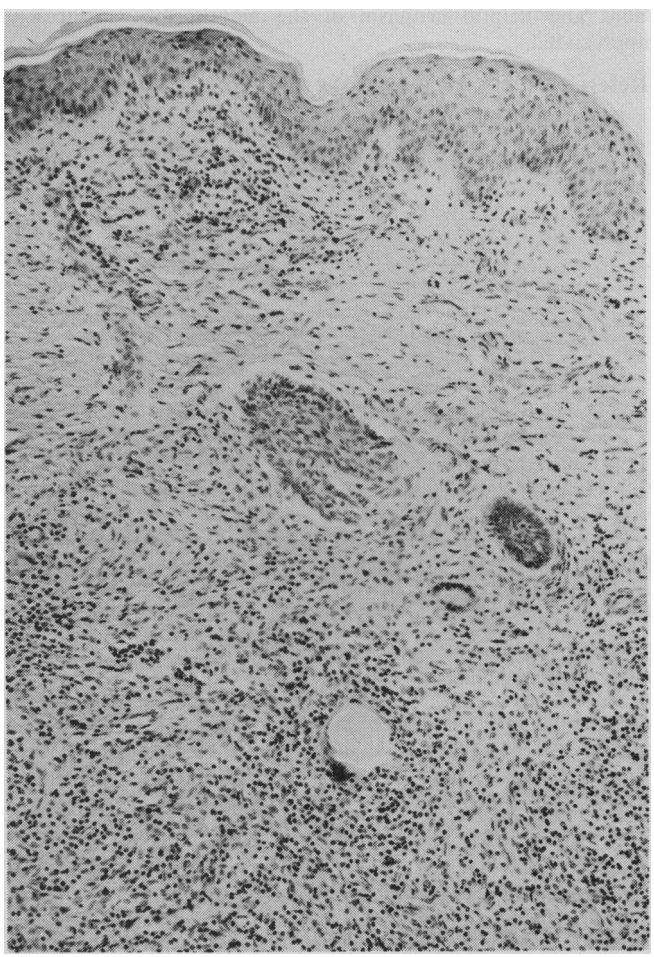

FIG. 1—Site of BCG vaccination in 4-month-old infant, showing granulomatous reaction, including giant-cell formation (hematoxylin–eosin [H–E]; original magnification ×128).

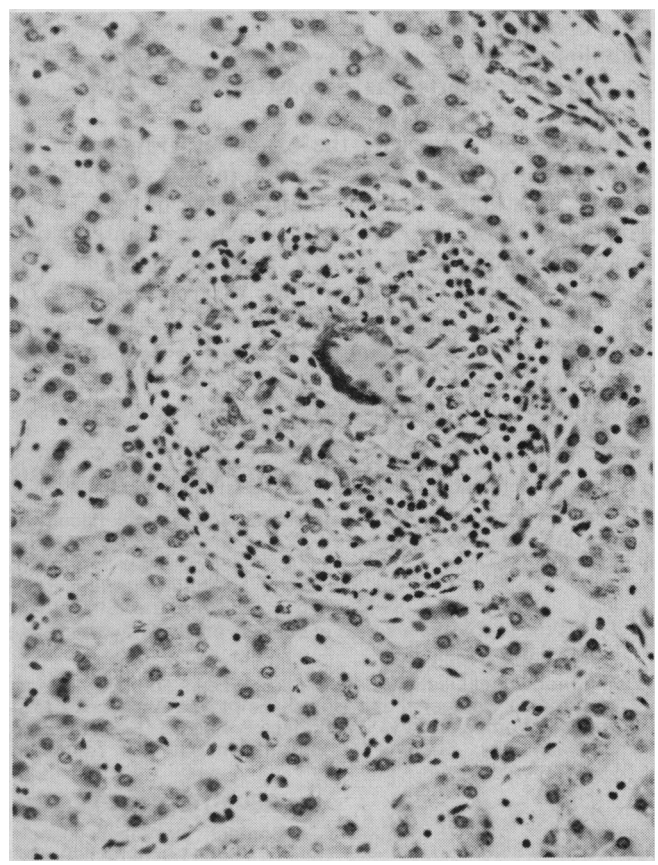

FIG. 2—Section of liver from 4-month-old infant, showing granuloma encircled by lymphocytes (H–E; original magnification ×320).

occurred in the two infants with severe diarrhea and dehydration secondary to gastroenteritis.

Discussion

Gormsen,[3] in 1956, was the first to suggest that bacterial invasion of the bloodstream is a natural sequel of BCG vaccination in humans. He had examined autopsy tissues from 25 individuals from 6 weeks to 12 years after vaccination, and in 13 of them he found granulomas in various organs, including the liver, lungs, spleen and kidneys. Usually these lesions were few and scattered, but in two malnourished infants, aged 4 and 5 months, they were more numerous. At that time it was known that subcutaneous or intracutaneous injection of BCG into experimental animals was promptly followed by spread to the bloodstream, and it was presumed that any resulting disease was related to individual immunity. In Gormsen's study the granulomas were most frequently found within 2 or 3 months of vaccination and tended to regress after that.

Support for the relatively benign nature of this hematogenous dissemination appeared in 1969, when Freundlich and Suprun[4] reported two cases of marked axillary lymphadenopathy in apparently healthy infants 1 to 3 months after BCG vaccination. Liver biopsies showed granulomas in both cases, but the infants were clinically well and recovered uneventfully.

Since the late 1950s, concern over BCG osteomyelitis has been increasing,[5-7] particularly in Sweden, where in 1972 its frequency was about 1 in 5000 vaccinations. Two of our Manitoba infants showed bone marrow granulomas. Such lesions may partly explain the distant osteomyelitis reported as a consequence of BCG vaccination.

We do not know why the extent of granulomatous involvement should vary so much in infants of comparable age. It is highly unlikely that the dose of the vaccine would be responsible. All the vaccinated infants in our series received 0.05 ml of BCG vaccine, half the dose given in previous years. The route of administration of the vaccine, however, might influence dissemination. Although we cannot confirm whether the injections were intradermal, as recommended, or subcutaneous instead, we found no differences in the depth and extent of inflammation at the site of vaccination between the infants with disseminated granulomas and those without.

Our observations suggest that the incidence of BCG dissemination may also be fairly high in infants that survive. Those we examined at autopsy seemed to have been generally well, with the possible exception of two infants. These two, who died of severe dehydration, showed the most extensive organ involvement of our series. Gormsen[3] made a similar observation regarding two underweight and presumably malnourished infants. Severe malnutrition in infants can impair cellular immunity to much the same extent as is seen in primary cellular immunodeficiency states.[8] In a malnourished patient, then, BCG vaccine might well be expected to disseminate widely before an adequate immunologic response occurred. Although the severe dehydration alone would have been sufficient to account for the deaths of these two infants, we cannot rule out BCG dissemination as the cause of their malnutrition.

Our data, the first reported from a North American series, confirm the findings in Scandinavian countries.[2,3,5-7] Although we doubt that the dissemination of the bacteria was associated with any significant disease, the clinical implications, particularly in malnourished infants, remain to be determined.

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