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EDITORIAL

HIV-related tuberculosis due to *Mycobacterium bovis*

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The bovine tuberculosis eradication programmes in many of the industrially developed countries have been amongst the most effective control measures ever mounted against any bacterial disease. In Great Britain, for example, the percentage of cattle infected with the bovine tubercle bacillus, *Mycobacterium bovis*, dropped from around 18% in 1945 to 0.06% in 1965. The impact of such control measures on human tuberculosis of bovine origin appeared to be equally dramatic, so that many now regard this disease as a historical curiosity. In fact, the decline was not as steep as it appeared to be, owing to the failure of many laboratories to distinguish between the human and bovine tubercle bacilli, and a reluctance to notify the latter as this sometimes led to official enquiries which caused problems of patient confidentiality [1].

Although uncommon, cases of human tuberculosis due to *M. bovis* continue to be detected in the developed countries, but the majority of these appear to be due to reactivation of infection acquired in the days before the completion of the bovine tuberculosis eradication programmes. Thus, in South East England, very few patients of indigenous origin seen in the last 10 yrs were born after 1960, the date of completion of the eradication programme; and it is possible that the very few younger patients acquired their infection abroad [2, 3]. It therefore seemed likely that this form of human tuberculosis would become increasingly rare. With the advent of the human immunodeficiency virus (HIV) pandemic, however, this trend could be reversed.

In order to comment on the possible effects of HIV infection on disease in humans due to *M. bovis*, it is first necessary to consider the similarities and differences between this form of tuberculosis and that caused by *M. tuberculosis*.

Both types of tuberculosis have primary and postprimary forms, and the sites of disease reflect the route of infection. Thus, *M. tuberculosis* is usually inhaled and leads to primary pulmonary lesions, with occasional extrapulmonary lesions due to lymphatic and haematogenous dissemination; whilst *M. bovis*, which is usually acquired by consuming contaminated milk, is more likely to cause nonpulmonary lesions. Farm workers are, however, prone to primary pulmonary tuberculosis due to inhalation of infective droplets from diseased cattle. Thus, the incidence of pulmonary, relative to nonpulmonary, tuberculosis of bovine origin is higher in rural than in urban regions [4].

Reactivation of disease due to *M. tuberculosis*, after a period of dormancy, usually occurs in the lung where it often leads to open, smear-positive, infectious disease. There has been much argument as to whether reactivation of disease due to *M. bovis* occurs with the same frequency as that due to *M. tuberculosis*. This question is not easily resolved, as it is very difficult to determine whether a covert primary infection manifesting as tuberculin conversion is of human or bovine origin. Despite this difficulty, MAGNUS [5] used a mathematical model to demonstrate that the risk of developing late pulmonary tuberculosis following primary infection by *M. tuberculosis* was between two and ten times greater than that following infection by *M. bovis*.

Nevertheless, reactivation disease due to *M. bovis* is encountered in regions where cattle tuberculosis is well-controlled, and a high proportion of such cases involve the lung. Thus, in South East England between 1977 and 1990 a total of 232 cases were diagnosed and 94 (41%) involved the lung [3]. The next most common site was the genitourinary tract (53 cases; 23%), followed by lymph node disease (39 cases; 17%).

The existence of such postprimary pulmonary tuberculosis raises the question of infectivity. Human-to-cow transmission of infection has been well-documented [6]. (Although most of this transmission is by air borne infection, cattle in several herds have been infected as a result of farmers with genitourinary tuberculosis urinating on hay in the cowsheds [7]). The evidence for human-to-human transmission is less firm, and is largely anecdotal. A major problem in proving such transmission in humans is that bacteriologically positive tuberculosis only occurs in a minority of those infected, and often not until many years after infection.

Thus, although many questions remain, it appears that *M. bovis* is less virulent than *M. tuberculosis* in humans, and, as a result, is less likely to proceed to postprimary infectious disease, and that human-to-human transmission leading to overt disease is a very uncommon event. If the apparent differences in virulence are the result of differing susceptibility to the host defence mechanisms, the immunosuppression induced by HIV infection could well annul these differences.

The serious impact of HIV infection on human tuberculosis due to *M. tuberculosis* has been well-documented [8, 9]. The chance of a person infected with both pathogens of developing active tuberculosis rises from less

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than 1% to 8–10% annually, and such disease often develops early in the course of the HIV infection [9].

The first reports of HIV-related tuberculosis due to *M. bovis* were from France, where it was the cause of 2 out of 123 cases of tuberculosis in HIV-positive patients [10], and in South East England, where it was responsible for 2 out of 167 such cases diagnosed between 1984 and 1992 [11]. In the English series, one patient was a 32 year old female with pulmonary tuberculosis and the other was a 49 year old male with lymph node disease.

Although the numbers in these two reports were small, it was postulated that they might represent the beginning of a major health problem worldwide, and that more epidemiological information on the incidence and distribution of infection and disease due to *M. bovis* in the human and animal population was urgently needed [12].

Confirmation of these fears was not long in coming [13]. A study of tuberculosis due to *M. bovis* in San Diego, California, USA, mostly in patients of Hispanic ethnic origin, showed that 1/24 adult patients with respiratory disease and 11/24 adult patients with nonrespiratory disease were HIV-positive. The latter group included 3 patients with mesenteric lymphadenitis and 8 with disseminated disease, being of miliary appearance on radiology in 4 of these cases. One of 25 children, a boy aged 16 yrs with abdominal tuberculosis, was HIV-positive.

The occurrence of human-to-human spread of disease was unequivocally demonstrated by a nosocomial outbreak in a hospital in Paris [14]. Infection by the source case, an HIV-positive patient with pulmonary tuberculosis due to a multi-drug resistant strain of *M. bovis*, led to five cases of active disease 3–10 months from the time of contact. This outbreak demonstrates three worrying features of HIV-related tuberculosis due to *M. bovis*. Firstly, human-to-human transmission leading to overt disease definitely occurs. Secondly, the interval between infection and overt disease is short. Thirdly, multi-drug resistant disease may be generated and disseminated.

These reports, though few in number, raise serious implications for the global control of tuberculosis. In the developing nations, many communities are economically dependent upon cattle and are in frequent close contact with them. There is a lack of detailed information on the extent and distribution of cattle tuberculosis, but it has been reported in 94/136 tropical countries [15]. Likewise, the prevalence of human tuberculosis of bovine origin is largely undocumented, and, as a result, there is little direct information on the extent of human disease due to *M. bovis* in relation to the prevalence in cattle. A study in Tanzania, however, revealed a positive correlation between the number of cattle per human population and the prevalence of nonpulmonary tuberculosis in the latter [12, 16]; and in Ethiopia the prevalence of tuberculosis was over five times higher in pastoralist than in nonpastoralist tribes [17]. In a recent (unpublished) study in Tanzania, biopsies from 4/11 patients with cervical lymphadenitis yielded *M. bovis* on culture. Thus, it is highly likely that cattle-to-human transmission of *M. bovis* regularly occurs. Many such transmissions may lead to self-limiting lesions and, possibly, induction of protective immunity against further infection. Any such protective immunity would be suppressed by HIV infection, and many more infections would lead to overt and progressive disease. Thus, in regions with a high prevalence of HIV positivity, a cycle of cattle-to-human, human-to-human and human-to-cattle transmission of disease could be established.

A wide range of domestic and wild animals other than cattle are susceptible to disease due to *M. bovis*. There have been cases of human infection, but not overt tuberculosis, due to exposure to diseased elk and a rhinoceros [18, 19]. An HIV-positive person would be at risk of infection proceeding to overt disease from such a source, and, whatever the source of infection, could then infect a range of domestic or farm animals in addition to other human beings.

For these reasons, more information on the occurrence and distribution of tuberculosis in cattle and other animals worldwide, and on the occurrence, extent and mode of interspecies transmission of disease in pastoralist communities with a high prevalence of HIV infection, is needed. This will require more laboratory facilities, a greater degree of co-operation between veterinary and medical microbiological services and more funding for fieldwork. These points and other research priorities concerning zoonotic tuberculosis have recently been stressed by the Veterinary Public Health Unit of the World Health Organization [20].

Accumulation of data would, however, be valueless unless it led to practical control measures. A better understanding of the epidemiology of *M. bovis* infection and disease in developing countries could lead to the design and adoption of area-specific public health measures. The eradication of cattle tuberculosis, so successful in several developed countries, by the test and slaughter policy would be prohibitively expensive in most developing nations. In some countries, such as India, religious beliefs would prevent the slaughter of cattle. Thus, protection of cattle and other farm animals from tuberculosis by vaccination would, if effective, be an appropriate alternative. This approach fell into general disfavour following the apparent failure of a large BCG vaccination trial of cattle in Malawi [21], and because such vaccination leads to tuberculin conversion, thereby compromising the key diagnostic skin test. Nevertheless, the advent of more effective vaccines [22], possibly including those that confer protection without inducing tuberculin positivity, could lead to a radically new approach to this additional threat to human health.

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