

Familial Mediterranean fever: Is low mortality from tuberculosis a specific advantage for MEFV mutations carriers? Mortality from tuberculosis among Muslims, Jewish, French, Italian and Maltese patients in Tunis (Tunisia) in the first half of the 20th century

Sirs,
 S. Özen *et al.* (1) analysed in a Turkish population whether carriers of the MEFV gene mutations which underlie Familial Mediterranean Fever (FMF) had increased resistance to the development of tuberculosis. The carrier frequency among tuberculosis patients was almost 1/6. The difference with healthy controls was not significant. The determination of what is and what was the selective advantage of the heterozygotes in early historical periods that caused the abundance of FMF carriers in the Middle East and North Africa is an extremely interesting question (2). The fact that not only one or two mutations appeared and expanded in these regions suggests that the large numbers of the carriers were not the result of a founder effect, but that a very important advantage had helped them to survive better than the non-carrier of the MEFV gene (2). On the other hand, the role of natural selection by infectious diseases in shaping human evolution is a subject of considerable importance and growing interest (3). Such a major cause of mortality as tuberculosis had certainly in the past considerable potential to exert selective pressure in favor of human genes that confer protection against it. Within populations, variations in susceptibility to tuberculosis have been associated with polymorphisms in a number of genes (3).

Resistance to tuberculosis and low mortality from tuberculosis remain a good hypothesis for MEFV gene mutation carriers. To the indirect arguments given by S. Özen *et al.* we can add that Ethiopian and Yemeni Jews do not have FMF or MEFV mutations (4, 5) and experienced in the 1950s very frequent, severe and lethal pulmonary and extra-pulmonary tuberculosis (6, 7). The study of mortality from tuberculosis in FMF patients is, of course, difficult because treatment against tuberculosis appeared when FMF had been completely described (8). Nevertheless an approach to this problem can be given by the study of mortality from tuberculosis in populations known to have a high rate of MEFV mutations. According to 24 studies collected by Arnould (9) and by Rakower (7), the mortality but not the morbidity from tuberculosis in Jews living in various cities in eastern

and western Europe, North America and the Maghrib appeared to be lower than in other groups from the same cities regardless of their economic status. Specific genetic advantages were invoked, for instance heterozygosity for Tay Sachs and Gaucher diseases in Ashkenazy Jews. Heterozygosity for the M694V (MEFV gene mutation) is very frequent in the North African Jewish population (1/5) (10).

The data collected in the "Statistiques Sanitaires et Démographiques; Régence de Tunis; Protectorat Français" and "Annuaire statistique de la Tunisie" allow us to study the causes of mortality in different communities – Muslim, European and Jewish – from 1909 to 1956 in the city of Tunis (Tunisia). It was well known in Tunis among epidemiologists, historians, and military and civilian physicians that the mortality from tuberculosis was lower in Jews than in Muslims and Europeans (11). In Tunis the general mortality per 1000 (mean;

range) from 1909 to 1956 was 33.02 (19.1 – 47.7) for Muslims, 15.4 (8.6 – 18.8) for Europeans and 20.1 (9.6 – 29.8) for Jews. The mortality from tuberculosis per 100,000 in the same populations was 506 (160-785), 133.4 (13 – 184) and 76.4 (25 – 109), respectively. The number of deaths from tuberculosis per 100 deaths in the same groups was 13.6 (7.3 – 10.2), 7.21 (1.3 – 11) and 4.3 (2.2 – 8.3), respectively. The contribution of pulmonary tuberculosis to the overall mortality from tuberculosis (pulmonary and extra-pulmonary) was 83.8% (75.6 – 88.2) in Muslims, 78.3% (71.4 – 81.2) in Europeans and 77.3% (57 – 79.3) in Jews. All of these differences were statistically highly significant.

For the period 1919–1938 (except for 1931, 1933 and 1934) data for French, Italians, Maltese are available (Figs. 1, 2). The mortality from tuberculosis in Italians living in Tunis (Italians who had emigrated from the south of Italy [Calabria] and Sicily and

Figure 1 : General mortality in Tunis (Tunisia) 1919-1938 (per 100 000)

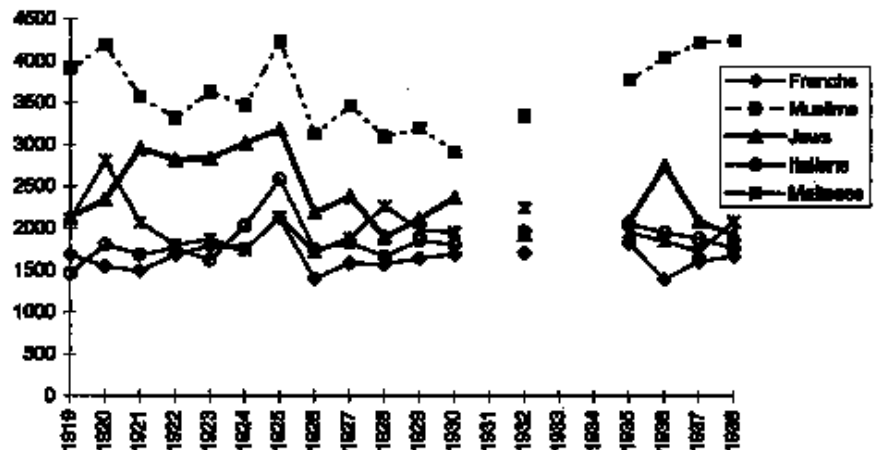


Figure 2 : Mortality from tuberculosis in Tunis (Tunisia) 1919-1938 (per 100000)

