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).

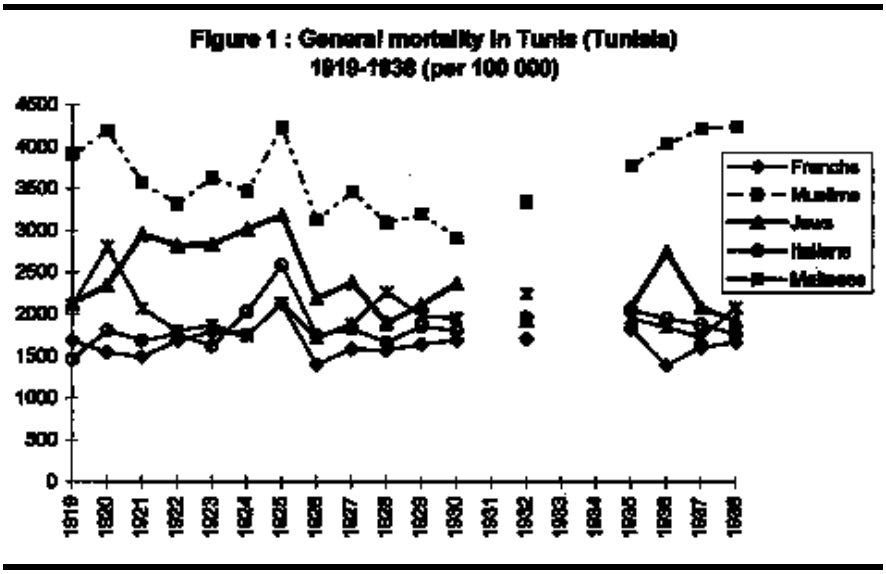
Resistance to tuberculosis and low mortality from tuberculosis remain a good hypothesis for MEFV gene mutation carriers. To the indirect arguments given by S. Özen *et al*. we can add that Ethiopian and Yemeni Jews do not have FMF or MEFV mutations (4, 5) and experienced in the 1950s very frequent, severe and lethal pulmonary and extra-pulmonary tuberculosis (6, 7).

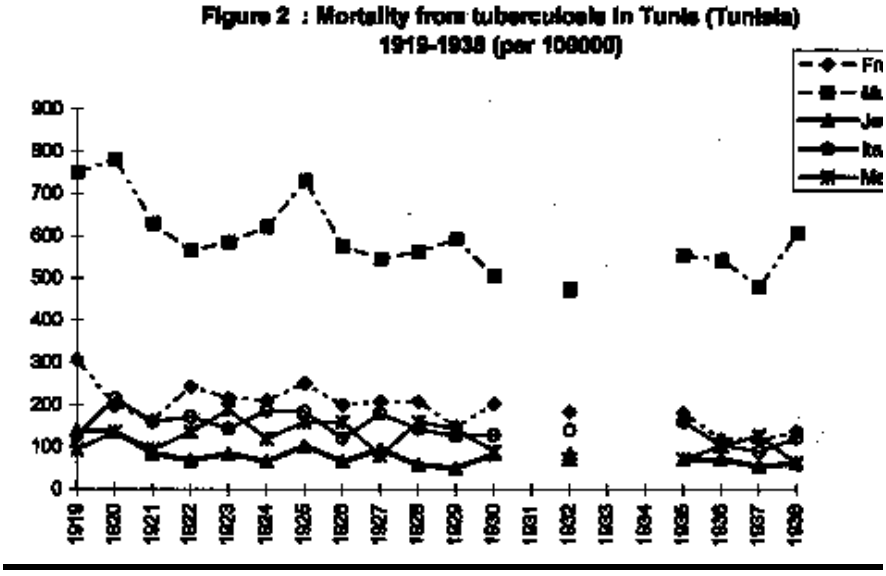
The study of mortality from tuberculosis in FMF patients is,of course, difficult because treatment against tuberculosis appeared when FMF had been completely described (8). Nevertheless an approach to this problem can be given by the study of mortality from tuberculosis in populations known to have a 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





Malteses living in Tunis was significantly lower than the mortality from tuberculosis in Muslims and French, and significantly higher than the mortality from tuberculosis in Jews.

The reasons for the very low mortality from tuberculosis in Jews in Tunis are not known. From numerous data, we know that the prevalence of tuberculosis was higher in Jews than in Muslims and in French (11). The low mortality in Jews cannot be explained by differences in socio-economic status among studied groups: indeed the standard of living of Jews and Muslims did not differ, and was much lower than that of Europeans. Jews were living as an "isolate" in a ghetto (La Hara) inside the arabian Medina whereas Europeans were living in the modern city. The relationship between the Infant Mortality Rate (IMR) (deaths under one year of age per 1,000 live births) and socioeconomic status is well known; in Tunis (1909-1948) the mortality rate (per 100,000) from tuberculosis was correlated with IMR in the French and the Muslim populations but not in the Jewish one (data not shown, to be published).

The explanations advanced for the low mortality from tuberculosis in Jews were: wet rather than dry sweeping, strict control of meat, and low milk consumption. However, these explanations are not satisfying since they do not explain the discrepancy between morbidity and mortality.

Has the Koch bacillus in the past been one of the possible triggers of FMF rich in polymorpho-nuclear-rich serositis attacks?

Have M694V and E148Q MEFV gene mutations in Sephardic Jews, other mutations in Ashkenazi Jews and an increased acute phase inflammatory response (12) been selective advantages in homozygotes and heterozygotes against tuberculosis?

It will be interesting to confirm in Muslims living in Tunis the low prevalence of MEFV mutations observed in North African Muslims living in France, to confirm the high prevalence of MEFV mutation in the south of Italy and Sicily (13), and to know the prevalence of MEFV mutations in Malta [perhaps as high as in Cyprus (14)], another Mediterranean island.

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Reply: Do mutations in the gene for FMF favor a better survival in tuberculosis?

Sir,

We have read Dr Cattan's letter (1) suggesting a low mortality from tuberculosis in familial Mediterranean fever (FMF) patients, with interest. We had also thought that tuberculosis could have been a disease to exert selective pressure in favor of mutation(s) that conferred protection against it. It was not just because the disease was so frequent in the past, but also because of certain characteristics of the microbe touched upon in our paper (2). However, in our study we were not able to show that mutations in the gene causing FMF (the MEFV gene) protect against tuberculosis (2)

However, our study was not designed to analyze whether a mutated MEFV gene protected against mortality. The historic data presented by Dr Cattan suggests that this fact may be true (1). It will be very hard to test this hypothesis since the treatment of tuberculosis has substantially improved. One approach may be to extract DNA from patients who had died of tuberculosis, which would include a number of ethical and technical problems. Indeed progress in medicine and changes in our lifestyle affect the demographics of the population and environment which in turn hinders population studies. And we may never find the selective microbe with the selective potential for MEFV mutations – if it ever existed – as is the case with malaria in the sickle cell trait.

Another question that remains would be the pathogenesis of the lower mortality and the better defense against the microbe in this selected group. It may simply be because of the increased acute phase response, as suggested by us and others (3). The FMF patients and carriers of MEFV gene mutations have a higher baseline level of CRP and other acute phase reactants. It is tempting to speculate that innate immunity may be more primed in these individuals. We may need to search for more specific pathways. Underhill *et al.* (5) have suggested that a certain Toll-like receptor is essential for the induction of a protective immune response to mycobacteria. One interesting issue would be to assess the possible associations between pyrin and these receptors. The function of pyrin and why a mutated protein has been favored with such a high selection remains a hot topic of research.

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