Tay–Sachs carriers and tuberculosis resistance

SIR—Rotter and Diamond[1] discuss the causes of high allelic frequencies of certain genetic diseases in specific human populations. Unfortunately, they perpetuate the myth that carriers of the Tay–Sachs (TS) allele have an increased resistance to tuberculosis (TB).

Three papers are cited[2-4] in support of this claim. The first is an entire book in which only three articles mention the possibility of TB resistance in Tay Sachs carriers. None of these articles supports the hypothesis of heterozygote advantage: "...number of observations (of increased fitness of TS carriers) was insufficient to guarantee statistical significance." (ref. 2, p. 100). "In the case of TS [disease], it is difficult to visualize a genetic interaction that converts half-levels of hex-A into a selective advantage." (p. 287). "The biological resistance of Jews to tuberculosis, if it exists, is only relative and can be overcome by external environmental deprivations." (p. 306).

The other articles quoted[3,4] by Rotter and Diamond contain data that allow the calculation of TS allelic frequencies only and present no direct data linking TS carriers with tuberculosis. On the basis of these two papers, therefore, no valid statement can be made about the relationship between the TS allele and TB resistance.

To date, the only direct study supporting the heterozygote advantage hypothesis is that of Myrianthopoulos and Aronson[5] who compared TB deaths of TS carriers versus non-carriers. However, these authors point out that their correlations between TS and TB resistance are two small to be significant and only suggest trends". We have presented[6] an independent data set that shows no statistically significant difference in the incidence of TB between the TS and control group. Thus, there is no known selective advantage in being a carrier for the Tay–Sachs allele.

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DIAMOND REPLIES—Spyropoulos misstates the evidence that Tay–Sachs (TS) carriers must have some selective advantage; and also that resistance to tuberculosis probably contributes to that advantage. The evidence is as follows.

The TS heterozygote frequency in Ashkenazi Jews is 0.03–0.11, far higher than could be maintained by mutation[4]. As drift or the founder effects are unlikely explanations[4,7], and as TS homozygotes all die before reproducing, heterozygotes must have some balancing advantage. The advantage probably resides in lipid storage, because Ashkenazi Jews also have high frequencies of two other, unrelated, autosomal recessive diseases of lipid storage besides Tay–Sachs: Niemann–Pick disease and adult-type Gaucher's disease.

Half of the grandparents of TS homozygotes must be TS heterozygotes. The grandparents show the expected selective advantage, in the form of a greater completed family size resulting from greater survival of their children to adulthood[7,8].

Death rates from tuberculosis were much lower for those grandparents who were TS heterozygotes[4] (1 in 254) than for those who were not TS carriers[6] (10 in 356); the difference is significant ($P < 0.05$). Spyropoulos failed to observe this difference in her independent Toronto data set because she examined grandparents not of homozygotes but of heterozygotes[6]: only one-quarter of the Toronto grandparents would themselves have been heterozygotes.

The frequencies of TS heterozygotes and of grandparental tuberculosis deaths among US Ashkenazi Jews vary in parallel with their geographical origin: both are highest for Jews from Austria, Hungary and Czechoslovakia[4]. A similar distribution of TS is also evident in the Toronto sample that Spyropoulos analysed[4]. Thus, TS distribution matches that of the putative selective factor, tuberculosis, as is also true for sickle-cell haemoglobin distribution and falciparum malaria. Why should tuberculosis have selected for TS among Ashkenazi Jews but not among other European peoples? Because Jews, being confined to the tubercular urban areas, were under extreme selective pressure to evolve resistance, whereas urban populations of other ethnic groups were continually maintained by immigration from rural areas.

It remains to be discovered whether Niemann–Pick and Gaucher's disease heterozygotes also are resistant to tuberculosis, and how lipid storage produces that resistance.

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Cometary organics

SIR—In a recent letter, Greenberg and Zhao[1] write: "No published laboratory residue spectrum provides a perfect fit to the Halley dust emission, although that of Chyba and Sagan is closer than that of Hoyle and Wickramasinghe". The figure shows both published flux curves[2,3], from which the reader can judge the validity or otherwise of the above statement. Anyone having the patience to make measurements from the two panels could further verify that the mean square departures from all the observational points for the Chyba–Sagan curve is somewhat more than 2.5 times the corresponding value computed for our model.

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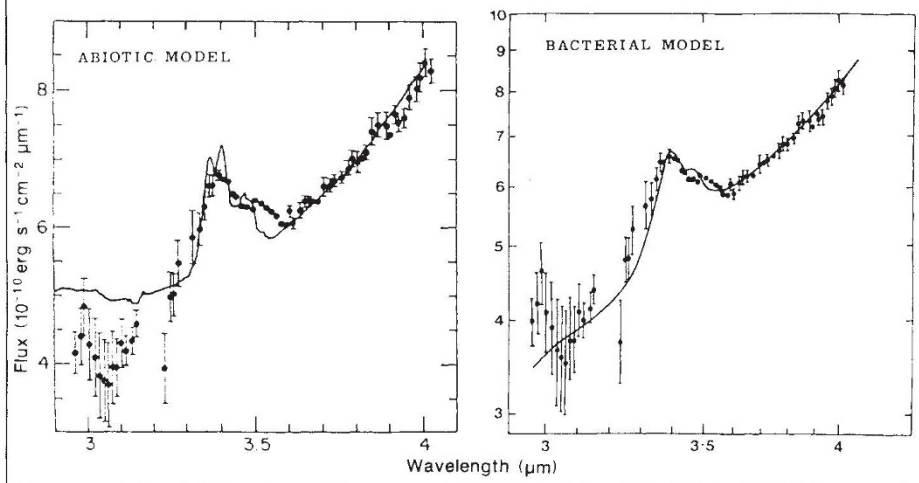

The curve in the right-hand panel shows our original bacterial model with $T = 320$ K; the curve in the left-hand panel is the multi-component abiotic model of Chyba and Sagan. Points, data for comet Halley on 31 March 1986. (Note that the ordinate scales are different in the two panels.)