Am. J. Hum. Genet. 61:494–496, 1997

INVITED EDITORIAL
HLA and Mate Selection in Humans: Commentary

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Lewis Thomas (1974) was the first to suggest a relationship among human reproductive biology, pheromones, individual odor, and MHC (major histocompatibility complex—called HLA in humans) types. In postulating that the genetically based body odor of a person might be coded by MHC genes, he speculated that "Man's best friend might be used to sniff out histocompatibility donors" (p. 19). Since this initial suggestion, a large number of studies, mainly on inbred mice and rats, have demonstrated that MHC genes do indeed influence body odor (reviewed by Boyse et al. 1991). Most striking, from the perspective of evolutionary biology, has been the finding in some inbred mouse strains (Yamazaki et al. 1976, 1978; Egid and Brown 1989) and in semioutbred mice (Potts et al. 1991) that there is a tendency for individuals to choose to mate with mice different from themselves at MHC loci, presumably based on odor differences coded by the MHC genes. That is, there is a tendency for negative assortative mating according to MHC type. Such negative assortative mating could, in part, account for the maintenance of extensive heterozygosity at the MHC and/or assist in the avoidance of inbreeding in many species in addition to the mouse (Beauchamp et al. 1985; Brown and Eklund 1994; Potts et al. 1993).

Ober et al. (1997[in this issue]) and Hedrick and Black (1997 [in this issue]) have now addressed the hypothesis that HLA haplotype affects the choice of mates in human populations. Hedrick and Black examined 194 couples selected from 11 South Amerindian tribes and found no evidence for negative assortative mate choice. In stark contrast, Ober et al. found evidence for negative assortative mate choice according to HLA type. Taking a somewhat similar approach to that of Hedrick and Black, Ober and colleagues evaluated 411 Hutterite couples (Hutterites are a North American, reproductively isolated, cultural and religious group of European ancestry) and found fewer matches of HLA haplotypes between spouses than were expected.

What could account for the different results obtained in these two studies? First, as both sets of authors note, selection favoring coupling between individuals of dissimilar HLA types may be fairly weak and thus easily overwhelmed by other biological or cultural factors. The larger number of couples studied by Ober et al. combined with the special characteristics of the Hutterites (see below) may have made this group particularly felicitous for finding a small but real effect.

Second, all laboratory studies of mating preferences in mice have observed mating itself—that is, copulation between male and female mice. Neither of the human studies actually observed matings; they both (reasonably) assumed that pairing or marriage is a good surrogate. This seems particularly valid for the Hutterite group, since mating outside of marriage is probably very rare, on the basis of descriptions of the Hutterites by Ober et al. Whether this assumption is as valid for the Amerindians studied is not as evident.

Third, even among inbred mice, a tendency to mate with nonself MHC types has not been evident in all cases. For example, in the original study (Yamazaki et al. 1976), four of six strains preferred to mate with nonself MHC types, whereas one of six preferred to mate with MHC-identical females. The reasons for differences among strains are not known, but it is clear that even mouse strains differ in their tendency toward negative assortative matings. Moreover, as noted by Hedrick and Black, it is not known what genes or gene classes within the MHC mediate mating preferences.

Fourth, at least in male mice, mating choice is strongly influenced by early experience with parents or surrogate parents. Yamazaki et al. (1988), reported that males of one strain of mice (C57 BL/6 [B6]) and males of their MHC congenic partner strain (C57BL/6-H-2^k [B6-H-2^k]) preferred to mate with a female that is different than the male's parental MHC type. That is, the mating preference of a male was determined by its rearing history: B6 males fostered into B6-H-2^k families preferred to mate with B6 females, and vice versa. Is it possible that, for the Hutterites, care of infants involves more direct and exclusive contact with biological parents than is the case for the

Received June 20, 1997; accepted for publication July 7, 1997.

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This article represents the opinion of the authors and has not been peer reviewed.

0002-9297/97/6103-0006$02.00

Amerindians? Studies of mate preference and MHC that focus on child-rearing patterns and history of adoption should be illuminating. More studies on female choice and early social experience are also warranted (Beauchamp et al. 1988; Eklund et al. 1991).

From the perspective of those who study MHC, odors, and behavior in mice, what are we to conclude from the contradictory human mate choice studies reported by Ober et al. (1997) and Hedrick and Black (1997)? Most important, there is some positive evidence in human populations for negative assortative pairing (and likely mating) according to HLA type as predicted from the mouse studies. Although there is no particular reason to assume that this selection is odor based as Thomas (1974) might have predicted, it certainly could be. But, as Ober et al. indicate, other sensory attributes could be influenced by HLA (Boyse et al. 1983). In spite of the positive evidence from Ober et al., the data of Hedrick and Black, as well as a few earlier studies (Pollack et al. 1982; Rosenberg et al. 1983; Jin et al. 1995), caution that this may not be a very easily observed phenomenon and it is possible that in most human societies cultural and biological factors overwhelm it. Nevertheless, it has recently been shown that women single out body odors from alternative sensory attributes as the most important variable for mate choice (Herz and Cahill 1997). It is interesting to speculate whether negative assortative mating according to MHC type might have played a larger role earlier in human or primate evolution, perhaps when female choice, unencumbered by many cultural factors, was more easily expressed. Data such as those of Ober et al. surely provide impetus to examine MHC and mate choice and mating frequency in other primate species. This could provide clues as to how differences in social structure may effect the relative importance of MHC genes in mate choice.

Some recent evidence suggests that the MHC influences human odor, as originally postulated by Thomas (1974). One study indicated that trained rats can discriminate human body odor according to HLA type (Ferstl et al. 1992) and a second demonstrated that, under certain circumstances, human females choose the odor of T-shirts worn by HLA-different male donors in choice tests (Wedekind et al. 1995). If MHC-determined odors exist in humans, their importance may also extend beyond mate choice. For example, we have found that mouse pups are attracted to mothers and offspring with MHC-similar odors and, correspondingly, mouse mothers preferentially retrieve pups of the same MHC type as their offspring (Yamazaki et al. 1996). We have also found that the MHC odor type of a pregnant mouse is a combination of the adult female's odor and her fetuses' odors (Beauchamp et al. 1994). A similar effect was found for humans, although no particular set of genes was identified (Beauchamp et al. 1995). Perhaps in humans the ability of mothers and infants to recognize each other and to bond, even prior to birth, depends in part on HLA-determined odor.

In summary, the results of Ober et al. are exciting, since they implicate MHC type in human mate choice. Hedrick and Black's failure to reach a similar conclusion cautions that many other factors, some of which we have suggested above, may obscure such a tendency in various human populations. Continued study in this area is clearly warranted on the basis of both the theoretical and the practical importance of understanding factors maintaining MHC diversity in many mammalian populations.

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