Behavioral Ecology Vol. 12 No. 2: 140–149

Evidence for MHC-correlated perfume preferences in humans

Manfred Milinski and Claus Wedekind
Abteilung Verhaltensökologie, Universität Bern, Wohlenstrasse 50a,
CH-3032 Hinterkappelen, Switzerland

Fragrances have been used since at least 5000 years ago and all traditional scents are found in modern perfumes. Although perfumes are obviously involved in sexual communication, the significance of great individual differences in preference for fragrances is an evolutionary puzzle. The major histocompatibility complex (MHC) is a highly polymorphic and conserved set of genes that plays an important role in immune function in vertebrates. Both mice and humans have been shown to prefer the body odor of potential partners that have a dissimilar MHC genotype, which would result in heterozygous offspring. We tested whether individual preferences for perfume ingredients correlate with a person's MHC genotype. The human MHC is called HLA (human leukocyte antigen). A total of 137 male and female students who had been typed for their MHC (HLA-A, -B, -DR) scored 36 scents in a first test for use on self (''Would you like to smell like that yourself?'') and a subset of 18 scents 2 years later either for use on self or for a potential partner (''Would you like your partner to smell like that?''). An overall analysis showed a significant correlation between the MHC and the scorings of the scents ''for self'' in both tests. In a detailed analysis we found a significant interaction of the two most common HLAs with the rating of the 36 scents in the first study as well as with the 18 scents in the second study when evaluated for self. This result suggests that persons who share, for example, HLA-A2, have a similar preference for any of the perfume ingredients. The significant repeatability of these preferences in the two tests showed that the volunteers that had either HLA-A1 or HLA-A2 were significantly consistent in their preferences for the perfume ingredients offered. Hardly any significant correlation between MHC genotype and ratings of the scents ''for partner'' were found. This agrees with the hypothesis that perfumes are selected ''for self'' to amplify in some way body odors that reveal a person's immunogenetics. *Key words:* HLA type, immunogenetics, major histocompatibility complex (MHC), perfume, scent preference, sexual communication. *[Behav Ecol 12:140–149 (2001)]*

Many women and men seem to boost their sexual attractiveness by using expensive perfumes, which is apparent from the advertising campaigns that usually accompany the marketing strategies of the perfume industry and which is also testified by the Bible (Song of Songs 1, 3): ''fragrant is the scent of your anointing oils, and your name is like those oils poured out; that is why maidens love you.'' ''All cultures are known to place great importance on artificial body odour, suggesting a deep-seated psychological awareness that human bodies should smell . . . and perfumes have been used since the earliest times of recorded history . . .'' (Stoddart, 1986). Perfumery is one of the earliest crafts, and the basic techniques of today's perfumers are essentially the same as those of their Egyptian predecessors 4000 years ago (Dodd, 1991). Many of today's perfume ingredients such as cassia, cinnamon, sandalwood, styrax, benzoin, jasmine, rose, and so on were used for incense by ancient Chinese, Indian or Egyptian cultures already 5000 years ago (Stoddart, 1991). Also the bible describes detailed incense and perfume recipes, for example, myrrh, labdanum, galbanum, and olibanum in specified quantities (Exodus 30:34–36), which are contained, for example, in ''Insensé'' by Givenchy, from 1993, and ''Henry M. Betrix'' from 1980 (Glöss, 1995). Fashion does not appear to be very important for human perfume preferences: many of today's well selling brands are older than 50 years, for example, ''Mitsouko'' (Guerlain) from 1919, ''Chanel No.5'' from 1921, ''L'Air du Temps'' (Ricci) from 1948, and many of the new perfumes are similar to established ones (Glöss, 1995). Thus, there has been a long history of humans selecting and using artificial scents.

Although olfactory communication is natural in humans (reviews; Doty, 1981; Stoddart, 1990), perfumologists are undecided about the biological significance of perfume use and of the observed great individual differences in preference for fragrances that underlies the broad spectrum of perfumes on offer everywhere in the world (Van Toller and Dodd, 1991). Daly and White (1930) noted that the functional significance of perfume may not be for the purposes of disguising or masking natural body odor, as other authors assume (e.g., Stoddart, 1986), but to heighten and fortify natural odor. As Pratt (1942) put it, perfumes ''unconsciously reveal what consciously they aim to hide.'' Supporting this hypothesis Jellinek (1951) found with methods of professional perfumers that several incense ingredients resemble scents of the human body. However, this does not explain the existence of individual differences in preferences for perfumes.

Major histocompatibility complex (MHC)-correlated odor preferences in mice and humans might be regarded as biological analogues of preferences for artificial scents in humans (Vollrath and Milinski, 1995). Mice prefer potential mates that have an MHC that differs from their own (Egid and Brown, 1989; Penn and Potts, 1998a; Potts et al., 1991, 1994; Yamazaki et al., 1976, 1978, 1983, 1994). Evidence also exists for MHC dissassortative odor (Wedekind & Füri, 1997; Wedekind et al., 1995) and mating preferences in humans (Ober et al., 1997). Wedekind et al. (1995) found in a double-blind study that women (not using the contraceptive pill) prefer the odor of t-shirts worn by MHC-dissimilar men to those with more similar MHC-

Address correspondence to M. Milinski, who is now at the Max Planck Institute for Limnology, Department of Evolutionary Ecology, August-Thienemann-Strasse 2, D-24306 Ploen, Germany. E-mail: milinski@mpil-ploen.mpg.de. C. Wedekind is now at the Institute of Cell, Animal and Population Biology, University of Edinburgh, West Mains Road, Edinburgh EH9 3JT, Scotland, UK.

Received 30 January 2000; revised 15 May 2000; accepted 2 June 2000.

© 2001 International Society for Behavioral Ecology

genotype. The preference was reversed in women who took oral contraceptives. Moreover, odors of MHC-dissimilar men reminded the women significantly more often of their own mates. These results have been replicated and extended to men whose preference was similar to that of women not taking contraceptives, although the reversed preference in women taking oral contraceptives was replicated only as non-significant trend (Wedekind and Füri, 1997). Numerous studies have shown that MHC genes correlate with individual odors (review in Penn and Potts, 1998b). How do MHC genes influence odor preferences? A set of olfactory receptor-like genes have been found to be located in the human MHC although it is unknown if they are involved in MHC-mediated odor preferences (Fan et al., 1995; see Penn and Potts, 1998b, and Ziegler et al., 2000 for further discussion).

The MHC is a large chromosomal region that contains several closely linked highly polymorphic genes that play a central role in controlling immunological self and non-self recognition (Penn and Potts, 1999). Many polymorphic sequence motifs are shared among different contemporary species, suggesting conservation over millions of years of evolution (Erlich et al., 1996). MHC diversity may be maintained by pathogen interactions and inbreeding avoidance mechanisms (e.g., Apanius et al., 1997; Brown and Eklund, 1994; Penn and Potts, 1999).

Why do mice and humans prefer to mate with MHC-dissimilar individuals? The preference will increase the MHC heterozygosity of an individual's progeny (Brown, 1997). MHC heterozygotes could be resistant to infections of multiple parasites; they might provide a moving target to rapidly evolving pathogens; they might reduce inbreeding by increasing overall genetic heterozygosity, which is likely to increase disease resistance (reviews in Apanius et al., 1997; Penn and Potts, 1998b, 1999).

The aim of Test 1 of the present study was to test whether individual preferences for specific perfume ingredients to be used on self correlate with the person's MHC genotype in both females and males (null hypothesis: no correlation). Such a correlation would be compatible with either of the following hypotheses:

(1) Since the human MHC is highly polymorphic, resulting in great individual differences, and since humans have MHC-disassortative mating preferences based on body odor, they might select their perfumes according to their individual preferences (''sensory bias'') (Ryan et al., 1990) for body odors. According to this hypothesis people would prefer for themselves simply what they would like as odor of potential partners.

(2) If perfume preferences are self-selected to reveal or enhance one's own body odors, more than a preference that is based on a ''sensory bias'' is required. One needs to like on oneself what one would dislike on others. A mechanism for such a switch of preference in one choosing one's perfume might have been evolved, or it could have been borrowed from another context (e.g., ''phenotype-matching'' [Blaustein, 1983]) that may be used for kin recognition).

According to hypothesis (2) we expect a significant correlation only between MHC type and preference for perfume ingredients to be used on oneself. No pronounced correlation is predicted between own MHC type and preference for perfume ingredients to be used by potential partners: for MHC-disassortative mating preferences any other allele which is different from one's own alleles would do (Wedekind and Füri, 1997), and individuals with the same MHC type might randomly prefer one or several of those. However, a perfume for use on self would be expected to be specific to reveal one's own MHC alleles. As Stoddart (1990: 163) put it: ''for a perfume to fulfil its function to the maximum extent it is important that it is tailored to the wearer's natural odour signature.'' To test this second hypothesis we asked the volunteers in Test 2 to evaluate the perfume ingredients both for use on themselves and for use on potential partners. To expect that the same scent is scored differently for self than for partner seems reasonable, because the context in which an odorant is perceived can determine whether it gives a positive or negative response, for example, methyl mecapten is scored negative in axillary odor but positive in cheese (Kirk-Smith and Booth, 1987; Labows and Wysocki, 1984). Since oral contraceptives appear to interact with the scoring of body odors (Doty, 1981; Wedekind and Füri, 1997; Wedekind et al., 1995), we test for a potential interaction with the appreciation of perfumes.

METHODS

A total of 137 male and female students and lab assistants from the University of Bern took part in this study (63 women [23 used oral contraceptives], 74 men). All participants were informed about the aims of the study, that is, a test for a potential correlation between MHC and perfume preferences, and they gave their consent after the theoretical background of the study had been explained. Their HLA-A, -B, -DR had been typed in the course of the studies by Wedekind et al. (1995) and Wedekind and Füri (1997), and most of them had participated in one of these former studies. The privacy of their personal data was assured by C. Wedekind.

Test 1

In February 1996 each person was sent a package with 36 number-coded glass vials each of which contained a 3.5 cm long smelling strip (as used in perfumology) that was fixed to the plug. We had supplied each strip with two drops of a common perfume ingredient (Essencia AG, Winterthur). Except for four synthetic ingredients (cariophyllen, heliotrope, leather, lilac), the remaining 32 fragrants were natural products of highest quality (see Figure 1 for details). Since some ingredients (e.g., castoreum and zibet) are used in much lower concentrations in perfumes (e.g., Jellinek, 1951) and since intensity and pleasantness of odors are inversely related (e.g., Doty, 1981; Engen and McBurney, 1964), absolute scorings of the 36 ingredients are of limited value; however, we are interested in relative scorings dependent on the MHC type of the smeller. The strip could be removed with the plug from the vial untouched by the smeller. We used smelling strips to avoid that the skin changes perfume qualitatively, although the opportunities for this are limited (Behan et al., 1996). The package contained a questionnaire with a line-scale between ''unpleasant'' and ''pleasant'' (as in Wedekind et al., 1995) for each of the 36 scents. The test persons were asked (in German) ''As how pleasant do you perceive this scent as a potential ingredient of a perfume/aftershave that you would like to use for yourself? (mark between unpleasant and pleasant).''

Test 2

In May 1998 each person was sent again a package with 36 coded glass vials, this time two sets of 18 vials each, each set containing the same 18 perfume ingredients. We had selected 18 of the 36 original scents using the following criteria in the order: natural ingredient; good representation of products from animals, flowers, wood, and so on (see Figure 1); furthermore we thought that it would not make sense to keep ingredients for which preferences did not vary very much among individuals. The test persons were told that the numbers of the scents were not identical to those of the first study. They were not told that the sets were subsets of the 36 scents from the first study.

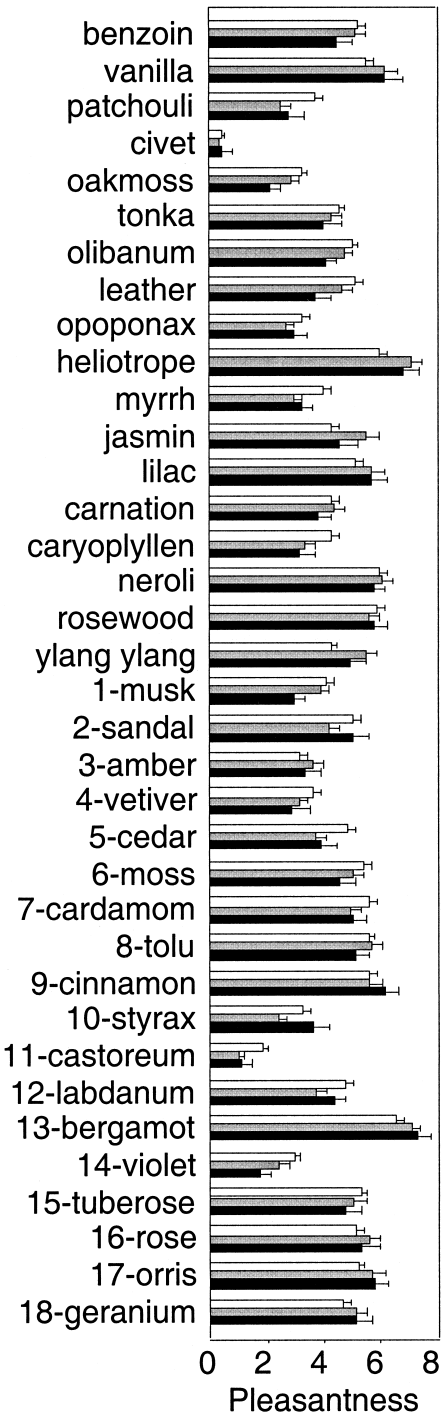

Figure 1
Pleasantness of 36 scents presented in the first study. The figure shows the mean (± SE) scorings per group of smeller (white bars: men, grey bars: non-pill using women, black bars: pill using women). The lower 18 scents were selected for the second study. The numbers correspond with the numbers in Figure 3.

One set was to be scored as perfume ingredient used by self (numbers 1–18 in red for female, in blue for male smellers), the other set to be used by potential partner (letters A–S in blue for female, in red for male smellers). The order was the same in each set, but we cannot exclude that the smellers, for example, picked a glass vial from the plastic bag and then looked it up in the list to make the mark. This potential variation should have conservative effects on the results, because the volunteers were double-blind. We had four different letters with rules (for female starting with set for self or for partner, for male starting with set for self or for partner) to randomize potential sequence effects. Each smeller received one letter (in German), for example, a female smeller starting with the set for potential partner: ''Please assess the scents marked blue (A–S) as potential ingredients of a perfume that your partner uses. Would you like your partner to smell like that?''—''Please send your first set of assessments within the first envelope and wait at least for two days until you begin assessing the second set.''—''Then please assess the scents marked red (1–18) as potential ingredients of a perfume that you would use yourself. Would you like to smell like that yourself?''—''Please send your second set of assessments within the second envelope.'' Each smeller received two questionnaires, each with the rule for one set and lines between ''unpleasant'' and ''pleasant'' for each of the 18 scents (A–S or 1–18) and a sentence in bold type either ''Would you like your partner to smell like that?'' or ''Would you like to smell like that yourself?'' However, we cannot be sure that the volunteers were paying attention continuously to one or the other purpose. A partial failure to achieve this would have made the results of the two sets more similar, which, if it were the case, would have a conservative influence on our analyses. Much more care should be taken in follow-up studies to provide the volunteers better with the respective imagination while smelling.

As in Test 1 we did not want to restrict, for example, smelling times, or prevent re-evaluations. Only the order of evaluation ''for self'' and ''for partner'' was strictly alternated between individuals within both male and female smellers. If procedural aspects were not handled in the same way by the smellers, the variance of the results would be increased, which would again have a conservative effect on the analyses. The students were double blind: they did not know their MHC type and they could not predict the result. The effect that we found might become stronger if the students would evaluate the scents under better defined conditions.

A total of 113 students (82.5% of Test 1) sent their assessments (51 women [12 used the contraceptive pill], 62 men). Three women sent only one questionnaire (one ''self,'' two ''partner''); their second assessments are missing in the analysis. The proportion of male and female participants and females using the pill did not differ significantly between Test 1 and Test 2 ($\chi^2 = 2.282$, $p = .32$). Questionnaires of 58 smellers in Test 1 and of 23 smellers (eight for ''self,'' 15 for ''partner'') in Test 2 had missing or double assessments (double assessments consisted of two marks in the same line with no hint of which should be taken. There was the risk that the volunteer had mixed up two lines, especially when a mark was missing from another line). These missing data points make up 2.7% of the total in Test 1 and 0.67% in Test 2. In order to perform repeated measurements ANOVA, the missing data are substituted by the average from the test from the respective category (self or partner) from the respective group of smellers (male, female, female using pill) for the respective scent.

RESULTS

There are 15 different antigens on HLA-A, 31 on HLA-B (only 30 in the sample of the second study) and 13 on HLA-DR in our study population. Two potential positive linkage disequilibria exist: A1B8 (first study, $n = 25$; second study, $n = 22$) and A3B7DR15 (first study, $n = 11$; second study, $n = 9$) (2×2 χ^2 test of independence for the combinations A1B8, A3B7, B7DR15, A3DR15 in both studies, p always $\leq .001$) (see also Bender, 1991). In a linkage disequilibrium alleles from

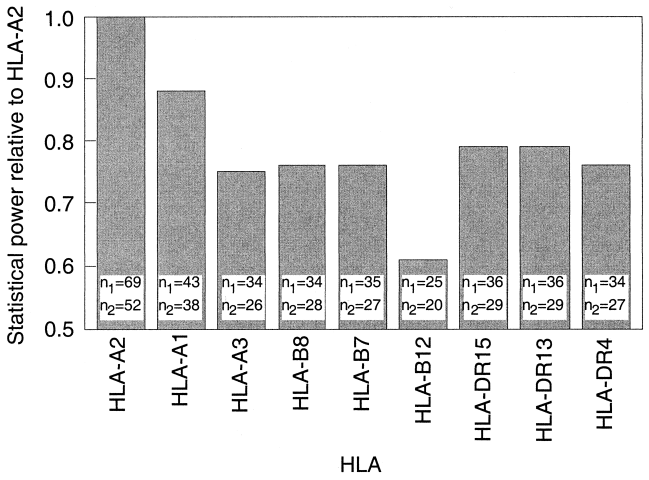

Figure 2
Estimation of the statistical power (= the chance of finding an effect of it exist) for the three most common antigens each per HLA-A, -B and -DR. An estimation of the power of *t* -tests for independent samples (and of other comparable but more complex ANOVAs) depends on both the overall sample size (i.e., the total number of replicates) and the sample sizes of the two groups that are to be compared. The overall sample sizes are constant within each of our two studies, but the sample sizes of the two groups that are to be compared differ for the nine HLAs according to how often each can be found in our study population. The figure gives the statistical power (mean of both studies) per HLA relative to the power achieved with the most common HLA, A2, calculated for *t* tests for independent samples (Cohen, 1988) using the formula $n' = 2 \cdot n_1 \cdot n_2 / (n_1 + n_2)$ (Cohen, 1988). The number of persons that possessed a given antigen in the studies one and two are given within the boxes.

different loci occur in gametes non-independently (e.g., Maynard Smith, 1989). HLA-A2 is the most common antigen here. It has a prevalence of 50.4% in the first study and 46.9% in the second study. The other antigens are less common and, as a consequence, offer less statistical power in *t*- or *F*-statistics. We restricted the analyses a priori on the three most common antigens each per HLA-A, -B, and -DR found in our study population. Figure 2 shows an estimation of the relative statistical power of analyses based on these nine antigens. This power estimation assumes that, in the context of our study, the class I antigens HLA-A and -B are comparable to each other and to the class II antigen HLA-DR with respect to a correlation with scent perception.

First study

We constructed an overall analysis to test whether there is any correlation between the nine selected HLAs and the scorings of the scents: for each group of smellers ($n = 3$), each antigen ($n = 9$) and each scent ($n = 36$) we calculated a *t* test for separated variances between the scorings of those subjects that possessed a given antigen and those who did not. This ended up in 972 ($= 3 \times 9 \times 36$) *t* tests and corresponding *p*-values of which on average 1.35 ($= .05 \times 27$) per scent are expected to be below .05 under the null hypothesis of no association between the MHC and scent preferences. We found, however, on average 1.92 *p*-values to be below .05 (Wilcoxon signed rank test, $p < .05$). For a control of this unusual statistical procedure, we performed it again with nine "dummy" alleles that were randomly assigned to the test subjects and that had the frequencies of the nine selected HLAs. We both repeated this random assignment and calculated the Wilcoxon signed rank test 200 times. We found on average only 1.45 *p*-values to be below .05, which is, as expected, not significantly different from the null hypothesis (Wilcoxon signed rank test, $p \gg .05$).

Again under the null hypothesis of no MHC effect we would expect the minimal *p*-values of the 27 *t* tests per scent to be in half of the cases below .037 (= 1/27). We observed, however, 26 of the 36 minimal *p*-values to be below this value ($Z = 2.67$, $p = .008$). This suggests that there is a connection between the MHC and the scorings of the scents. When we performed this latter test after randomly re-assigning the scorings of the scents to the HLA genotypes, and repeating the re-assigning and the test 200 times, we found on average 12.9 minimal *p*-values to be below .037. This is, again as expected, not significantly different from the null hypothesis ($Z = 1.70$, $p \gg .05$, directed).

To study this statistical relationship between the MHC and the scorings of the scents in more detail, we performed full factorial MANOVAs calculated separately for each of these nine antigens, each with two grouping factors (group of smeller and whether or not a person possessed a given HLA) and one trial factor (i.e., repeated measures, here 36 scents) (see Table 1). We found that the mean scoring of the 36 scents was not significantly different between the three groups of

Table 1
First study: MANOVAs on the pleasantness of 36 scents, with three groups of smellers (men, women not on the pill, and women on the pill), analyzed for the three most common antigens each per HLA-A, -B, and -DR found in our study population

		Antigen: HLA-								
Source of variation	df	A2 *F*	A1 *F*	A3 *F*	B8 *F*	B7 *F*	B12 *F*	DR15 *F*	DR13 *F*	DR4 *F*
Between subjects										
Group of smeller	2	1.3	1.6	1.5	1.0	2.8	1.1	1.0	0.4	1.7
HLA	1	0.1	0.5	0.5	0.3	1.5	<0.1	1.6	<0.1	0.7
Group of smeller × HLA	2	0.4	0.6	0.5	<0.1	1.8	0.4	0.4	0.6	0.7
Error	131									
Within subjects (36 scents evaluated)										
Scent	35	47.7***	31.3***	33.4***	31.8***	35.0***	32.4***	28.6***	37.8***	36.2***
Scent × group of smeller	70	2.0***	1.4*	1.5**	1.1	1.7***	1.7**	1.6**	2.1***	1.7**
Scent × HLA	35	2.7***	1.7*	1.1	1.0	0.9	0.8	1.3	1.1	1.0
Scent × group of smeller × HLA	70	1.4*	1.0	1.5*	1.0	0.9	1.1	1.7**	1.0	1.3
Error	4585									

*** $p \leq .001$; ** $p \leq .01$; * $p \leq .05$; all other *F*-values are not significant (Huynh-Feldt corrected).

Table 2

First study: MANOVAs that are calculated analogously to the MANOVA in Table 1, but separately for (A) men only, (B) non-pill using women only, (C) pill-users only, (D) pill-users excluded, and (E) men excluded

Interaction term (within subject)	df	Antigen: HLA- A2 *F*	A3 *F*	DR15 *F*
(A) Men only (n = 74)				
Scent × HLA	35	2.2***	1.0	0.8
(B) Non-pill using women only (n = 40)				
Scent × HLA	35	0.8	0.7	0.8
(C) Pill-users only (n = 23)				
Scent × HLA	35	2.0**	1.7*	2.1**
(D) Pill-users excluded (n = 114)				
Scent × gender	35	2.6***	2.0**	2.2***
Scent × HLA	35	1.2	0.7	0.8
Scent × gender × HLA	35	1.3	0.9	1.0
(E) Men excluded (n = 63)				
Scent × pill	35	0.7	1.1	1.1
Scent × HLA	35	2.0**	1.4	1.5
Scent × pill × HLA	35	1.3	1.4	1.6*

Shown are only the interaction terms of the within-subject analyses for HLA-A2, -A3, and -DR 15, for which at least one of the interaction terms in Table 1 was significant. None of the main effects (between-subjects analyses) was significant, while the effect of scent only in the within-subject analyses was in all comparisons highly significant ($p < .001$) as in Table 1.

*** $p \leq .001$; ** $p \leq .01$; * $p \leq .05$; all other *F*-values are not significant (Huynh-Feldt corrected).

smellers, and there was no significant correlation between any HLA and the mean scoring of the 36 scents (see between subjects analyses). A significant term would mean that these groups of smellers had a general tendency to use the preference scores differently, for example, if men scored all the scents on average more pleasant than women did.

However, the 36 scents were rated differently (effect of scent in the within subject analysis in Table 1). In most comparisons the groups of smellers differed in their ratings of the 36 scents (first interaction in the within subject analyses in Table 1). The two most common HLAs, HLA-A2 and -A1, interacted significantly with the ratings of the 36 scents (second interaction term in the within subject analyses in Table 1). Furthermore, it depended on the group of smellers whether the antigens HLA-A2, -A3 and -DR15 interacted significantly with the ratings of the 36 scents (third interaction term in the within subject analyses in Table 1). An analogous MANOVA calculated with ''dummy'' alleles that were randomly assigned to the test subjects and that had the frequencies of the nine selected HLAs did not result in any significant interaction term that involves one of these ''dummy'' alleles.

When the analogous MANOVAs were calculated for men only, non-pill using women only, and pill users only, we found again in all comparisons that the mean scorings of the 36 scents did not correlate significantly with the MHC, but the scents were always scored differently. Table 2 (A–C) shows the interaction terms in the within subject analyses of these MANOVAs. Only the most common antigen, HLA-A2, correlated significantly with the men's scorings of the 36 scents. In non-pill using women, there was no significant correlation between the MHC and the scorings of the scents, but in pill using women, there were significant correlations with HLA-A2, -A3, and the most common class II antigen, HLA-DR15. Although the sample size here was nearly half the sample size of the non-pill using women, which reduces the statistical power, the correlations with the MHC appeared to be stronger in the pill-using group. This may indicate that pill users were more sensitive with respect to MHC-correlated perception of scents.

When the pill-users were excluded from the analyses, we found a significant gender effect for the scorings of the 36 scents (Table 2D, first interactions), but we could not find any significant correlations to the MHC (Table 2D, second and third interaction terms). Among women, we could not find a significant effect of the pill on the scorings of the 36 scents (Table 2E, first interactions), but the scorings correlated to the HLA-A2 and -A1 in this subsample (Table 2D, second interaction terms). Moreover, there appeared to be a significant pill effect in interaction with the most common class II antigen HLA-DR15 (Table 2D, third interaction term). This is the first (weak) indication of a MHC-correlated reversal of scent perception that is correlated to the pill.

When testing for possible interactions of the two potential haplotypes (suggested by the positive linkage disequilibria) with the ratings of the scents we excluded the pill-using women because only three of them possessed the antigen combination A1B8, and only one possessed the antigen combination A3B7DR15. The Appendix shows that there are no significant effects of these antigen combinations on the ratings of the 36 scents.

Second study

In the second study 18 scents were rated twice, once for ''self'' and once for a potential ''mate.'' Since only 12 pill-using women participated in the second study (compared to 23 in the first study), we excluded them in our overall analysis in which we tested whether there is any correlation between the nine selected HLAs and the scorings of the scents. Analogous to the first study, for each group of smellers (n = 2), each antigen (n = 9), each scent (n = 18), and whether the scent is evaluated for ''self'' or for ''mate'' (n = 2) we calculated a t-test for separated variances between the scorings of those subjects that possessed a given antigen and those who did not. This ended up in 648 (= 2 × 9 × 18 × 2) p-values of which on average .9 (= .05 × 18) per scent and per evaluating for ''self'' or for ''mate'' are expected to be below .05 under the null hypotheses. We found on average 1.2 p-values to be below .05 when rated for ''self,'' and .7 p-values to be below .05 when rated for ''mate'' (Wilcoxon signed rank tests, always $p > .05$). Under the null hypotheses of no MHC effect we would expect the minimal p-values of the 18 t tests per scent and per evaluating for ''self'' or for ''mate'' to be in half of the cases below .056 (= 1/18). This was actually observed when the scents were rated for ''mate'' (nine of 18 cases), however, when rated for ''self'' 14 of the 18 minimal p-values were below the null expectancy ($Z = 2.36$, $p = .02$). This suggests that there is again a connection between the MHC and the scorings of the scents as observed in the first study. The difference between ''self'' and ''mate'' was not significant ($\chi^2 = 3.01$, $p = .08$, two-tailed).

Figure 3 shows the differences in the scorings of scent pleasantness (mean scoring of persons that possessed a given HLA or antigen combination minus mean scoring of persons that did not possess the HLA or antigen combination), that is, positive values for a given scent indicate a preference for the scent by those that possess a given MHC specifity relative to those who do not possess it, while negative values indicate the contrary. The figure shows that the mean effects of two most common HLAs and of the potential haplotype A3B7DR15 were significantly correlated between the first study and the

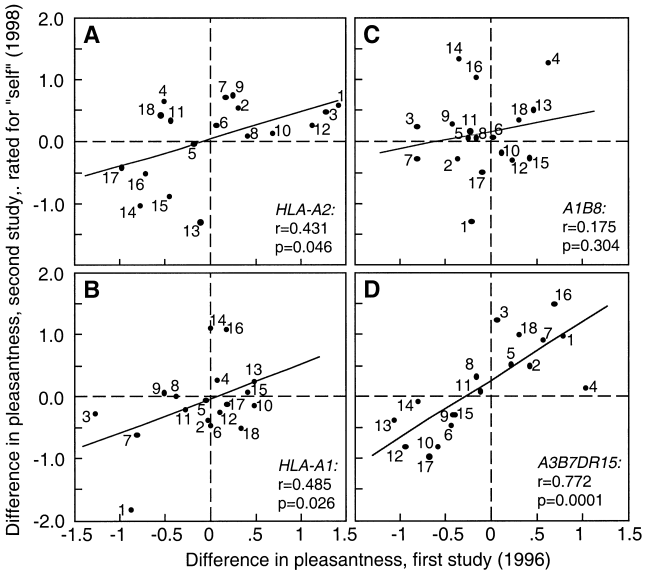

Figure 3
Comparison of the effects the MHC appeared to have on the scorings of 18 scents that were presented in both studies, shown for the two most common HLAs A2 (A) and A1 (B), and for the two potential haplotypes A1B8 (C) and A3B7DR15 (D). The figure shows the differences in the scorings of scent pleasantness (mean scoring of persons that possessed a given HLA or antigen combination minus mean scoring of persons that did not possess the HLA or antigen combination), that is, positive values for a given scent indicate a preference for the scent by those that possess a given MHC specifity relative to those who do not possess it, while negative values indicate the contrary. The figures also give the regression lines, the Pearson's *r*s and the corresponding directed *p*-values; we use directed instead of one-tailed tests to avoid inflation of the alpha value (Rice and Gaines, 1994). See Table 1 for more information about the 18 scents.

ratings for "self" in the second study. However, the mean effects of the other potential haplotype A1B8 did not significantly correlate between the first study and the ratings for "self" in the second study, nor did the effect of any antigen or possible haplotype correlate between the first study and the ratings for "mate" in the second study (data not shown). We also excluded the pill-using women from the MANOVAs, because in all comparisons except for HLA-A2, only 0–3 women of this group would have possessed the respective antigens.

Table 3 shows the MANOVAs on evaluations for "self" and for "mate," calculated separately for each of the nine antigens, each with two grouping factors (gender and HLA) and one trial factor (18 scents). Analogously to the first study, we found that the 18 scents were, in general, rated differently. When rating for "self," the genders differed in the scorings of the 18 scents (Table 3a, first interaction terms in the within subject analyses), while gender did not play a significant role when the scents were rated for a potential mate (Table 3b, first interaction terms in the within subject analyses). The two most common class I HLAs A2 and A1 interacted significantly with the ratings of the scents, but only when evaluated for "self" (Table 3a,b, second interaction terms in the within subject analyses). (Any significant interaction term involving the grouping factor "HLA," e.g., "scent × HLA" or "scent × group of smeller × HLA" points towards a correlation between MHC and scent perception.) There was no significant gender-specific correlation between the MHC and the rating of the scents, except a weak one for the most common class II antigen HLA-DR15 (Table 3a,b, third interaction terms in the within subject analyses).

We could include the pill-using women only in a MANOVA with the most common HLA-A2, because six pill-users possessed this antigen and six did not (Table 4). The results were analogous to Table 3, that is, when rating for "self," the group of smeller differed in the scorings of the 18 scents, while it did not play a significant role when the scents were rated for a potential mate. HLA-A2 correlated again with the rating of the scents and only when evaluated for "self." This correlation appeared to be much stronger when the 12 pill users were included (total $n = 113$, Table 4) than when they were excluded (total $n = 101$, Table 3), which again suggests that pill users were more sensitive with respect to MHC-correlated perception of scents.

When analyzing the two potential haplotypes with the ratings of the scents we had to exclude the pill-using women because none of them possessed any of the antigen combinations. Table 5 shows the MANOVAs for the two antigen combinations. The evaluations for "self" and "mate" were included as the second trial factor (i.e., as repeated measures). It turned out that the potential haplotypes have a significant effect on the ratings of the scents, but only in interaction with gender and whether the subjects evaluated for "self" or for "mate" (see last two interaction terms in Table 4). When analyzed separately for "self" and "mate" (analogous to Table 3, *F*-values not shown), none of the interactions with the potential haplotypes remains significant except for A3B7DR15 when rating for "mate" ($p = .05$).

Figure 3 indicates which scents may interact most with the HLAs A2 and A1, or the potential haplotypes A1B8 and A3B7DR15 in the two studies. Overall, the perception of scents such as musk, rose or cardamone appear to be correlated with the MHC, while the perception of scents such as castoreum or cedar does not appear to be correlated much with these most common antigens or antigen combinations.

For analyzing the results of this study we chose a method that we consider very powerful in telling us whether there is any hint for an association between MHC and scent preference, that is, whether the null hypothesis that the MHC and scent preference are not correlated can be rejected. A drawback of this statistical method and our study design is that we cannot really say which odors are in what way related to the MHC. However, our study and the first hints we got about which scent may be associated with which MHC allele (see Figure 3) provides the necessary basis for studies that would test such associations in more detail. The level of independence of the single tests is very difficult to judge. The puristic approach that avoids any such conflict may be to use each person only once in a global analysis. This would mean to restrict the whole analysis to, for example, the most common antigen HLA-A2 only. If we would do that, the chapter "results" would look much "nicer," with many significant interaction terms and few non-significant ones. We had decided to include more than one MHC allele to provide more information about our data.

DISCUSSION

Humans can recognize at least 10,000 different odors (Prasad and Reed, 1999). It is therefore not surprising that chemosensation is involved also in human sexual communication both with body odors (Doty et al., 1975; Wedekind & Füri 1997; Wedekind et al., 1995) and with perfumes (Van Toller and Dodd, 1991). Individual differences exist in the perception of both body odors (Wedekind and Füri, 1997; Wedekind et al., 1995) and perfumes (e.g., Gilbert and Kemp, 1996; Labows and Wysocki, 1984; O'Connell et al., 1989). Since perfumes have been used for more than 5000 years, we investigated whether individual preferences for perfume ingredients

Table 3

Second study: MANOVAs on the pleasantness of 18 scents evaluated (a) for "self" and (b) for "mate," with two groups of smellers, analyzed for the three most common antigens each per HLA-A, -B, and -DR found in our study population

		Antigen: HLA-								
Source of variation	df	A2 *F*	A1 *F*	A3 *F*	B8 *F*	B7 *F*	B12 *F*	DR15 *F*	DR13 *F*	DR4 *F*
(a) Evaluated for "self"										
Between subjects										
Gender	1	1.0	1.4	<0.1	1.5	<0.1	0.2	4.3*	0.2	0.4
HLA	1	0.4	0.5	<0.1	0.6	0.3	3.7	0.3	0.2	<0.1
Gender × HLA	1	0.1	1.1	1.3	1.6	1.1	<0.1	5.9*	6.1*	0.1
Error	96									
Within subjects (18 scents evaluated)										
Scent	17	34.7***	33.0***	27.9***	29.6***	21.2***	22.4***	20.8***	27.6***	27.2***
Scent × gender	17	3.3***	3.6***	3.4***	3.5***	2.4**	2.8***	3.1***	2.6***	2.3**
Scent × HLA	17	1.7*	1.7*	0.8	1.0	0.7	1.4	0.7	0.6	0.8
Scent × gender × HLA	17	0.6	1.0	1.1	1.0	1.4	0.5	1.9*	0.6	1.4
Error	1632									
(b) Evaluated for "mate"										
Between subjects										
Gender	1	3.8	3.1	4.1*	2.9	3.0	1.6	2.1	5.8	1.5
HLA	1	1.3	1.3	0.2	1.3	<0.1	<0.1	1.4	<0.1	0.5
Gender × HLA	1	0.5	<0.1	1.0	<0.1	0.5	<0.1	0.1	3.0	0.4
Error	94									
Within subjects (18 scents evaluated)										
Scent	17	29.1***	27.9***	23.7***	25.2***	18.1***	17.3***	17.8***	24.1***	20.8***
Scent × gender	17	1.0	0.9	1.0	1.0	1.4	0.9	1.8*	0.6	0.9
Scent × HLA	17	0.8	1.1	0.8	0.5	0.6	1.5	1.0	0.9	0.7
Scent × gender × HLA	17	0.7	0.8	0.6	0.6	1.5	1.2	1.7*	0.8	0.9
Error	1598									

Women not on the pill and men were included; women on the pill were not included in this analysis. ***$p \leq .001$; **$p \leq .01$; *$p \leq .05$; all other *F*-values are not significant (Huynh-Feldt corrected).

(scents) could have a biological significance in that they correlate with an individual's MHC (HLA) that has been shown to correlate with natural human body odors (Wedekind and Füri, 1997; Wedekind et al., 1995) and mate choice (Ober et al., 1997).

Our test persons who had been typed for two class I (A, B) and one class II (DR) HLAs scored 36 perfume ingredients in the first test and a subset of 18 in the second test 2 years later for potential use on self. An overall analysis depicted a significant association between the MHC and scent preferences in both studies. We can thus reject the null hypothesis which states that no correlation exists between the smeller's MHC type and her/his preference for perfume ingredients. Tests 1 and 2 found significant and repeatable correlations between MHC type and relative preference for the perfume ingredients. This shows that individual perfume preferences are consistent even after 2 years This finding supports the hypothesis that these preferences are individual traits that are immune to fashion to some extent which would hardly be expected under the null hypothesis.

A detailed analysis showed that the two most common HLAs, HLA-A2 and -A1, for which we had probably the highest statistical power, interacted significantly with the rating of the 36 scents in the first study, as well as with the 18 scents in the second study when evaluated for self in both women and men. There was hardly any significant result when these analyses where repeated for the evaluation of the 18 scents for "partner." This is what we expect (our hypothesis 2) if perfume ingredients are selected to be used on oneself in order to support in any way the individual MHC-related body odor. As a rule customers try and buy perfumes for their own use (Le Norcy, 1991) as has been the habit in the past (Jellinek, 1951).

We found significant effects of taking oral contraceptives on the interaction between rating the scents and HLA type with indications of both sensitizing and reversing the preferences for the scents. An increased sensibility for scents (including a perfume) has been found in pregnant women (Gilbert and Wysocki, 1991; Hudson et al., 1996). This agrees with our result if the pill mimics pregnancy. A trend of a reversed

Table 4

Second study: MANOVAs on the pleasantness of 18 scents evaluated for "self" and for "mate," with three groups of smellers analyzed only for the most common HL-antigen A2

Source of variation	df	"Self" *F*	"Mate" *F*
Between subjects			
Group of smeller	2	1.2	2.7
HLA-A2	1	0.3	0.1
Group of smeller × HL-antigen	2	<0.1	1.3
Error: "self," 106; "mate," 104			
Within subjects (18 scents evaluated)			
Scent	17	32.4***	24.9***
Scent × group of smeller	34	2.5***	0.9
Scent × HLA-A2	17	2.1**	1.0
Scent × group of smeller × HLA-A2	34	0.6	0.6
Error: "self," 1802; "mate," 1768			

Men, women not on the pill, and women on the pill were included in this analysis. *** $p \leq .001$; **$p \leq .01$; all other *F*-values are not significant (Huynh-Feldt corrected).

Table 5

Second study: MANOVA's on the pleasantness of 18 scents (first trial factor) and evaluated for "self" and for "mate"(included as second trial factor), with two groups of smellers, analyzed for the two potential haplotypes found in our study population

		Potential haplotypes	
		A1B8	A3B7DR15
Source of variation	df	*F*	*F*
Between subjects			
Gender	1	0.2	0.1
Haplotype	1	1.8	0.3
Gender × haplotype	1	2.1	<0.1
Error	94		
Within subjects (18 scents evaluated for "self" and for "mate")			
Self-mate	1	<0.1	0.3
Self-mate × gender	1	8.4**	3.0
Self-mate × haplotype	1	1.1	<0.1
Self-mate × gender × haplotype	1	0.4	0.1
Error	94		
Scent	17	31.3***	12.4***
Scent × gender	17	1.8*	1.9*
Scent × haplotype	17	0.4	0.9
Scent × gender × haplotype	17	0.6	1.4
Error	1598		
Self-mate × scent	17	1.7*	2.5***
Self-mate × scent × gender	17	3.3***	3.5***
Self-mate × scent × haplotype	17	1.9*	1.6
Self-mate × scent × gender × haplotype	17	1.7*	1.8*
Error	1598		

Women not on the pill and men were included; women on the pill were not included in this analysis. *** $p \leq .001$; ** $p \leq .01$; * $p \leq .05$; all other *F*-values are not significant (Huynh-Feldt corrected).

preference for scents corresponds with earlier findings that showed a reversed preference for MHC-correlated body odors in women taking the pill (Wedekind and Füri, 1997; Wedekind et al., 1995). The evidence for the effect of oral contraceptives in these studies, including the present one, is, however, correlational.

We found significant effects mainly for those antigens for which we had the highest statistical power to find any effect if it existed. This power estimation assumes that, in the context of our study, the antigens are comparable to each other with respect to a correlation to scent perception. Many of the results from other antigens, for which we had less statistical power, were close to being statistically significant, which suggests that significant interactions of scent preferences with other antigens may exist and may become detectable with larger sample sizes.

If the function of perfume use is to signal the possession of specific MHC alleles, then, if anything, the ability to choose specific mixtures of scents that mimic or fortify one's own odors could have been developed. It should be extremely difficult for a person to find the mixture from the hundreds of brands that comes closest to the ideal fit with own odor. In agreement with this is that it seems to be a difficult and long lasting process during which a person finds "her" or "his" perfume, usually affording many visits to a perfume shop (Le Norcy, 1991). According to our hypothesis the ideal perfume would be individually composed for any person as actually has happened in former times: "Our great grandmothers would consult with their perfumer. He would make, exclusively for them, a special perfume. The formula was secret and our great grandmothers would never tell anyone what their delightful perfume was, *so much was it part of their personality*" (Le Norcy, 1991, italics ours).

There is compelling evidence that MHC genes influence body odors, although it is still unclear how. Various hypotheses exist (review in Penn and Potts, 1998b). The peptide-microflora hypothesis (Penn and Potts, 1998b) is consistent with available data: MHC molecules influence odor by binding unique subsets of peptides, which are then carried to, for example, the axillary region where their metabolites are made volatile by commensal flora. Singer et al. (1997) found in MHC congenic mice that the MHC-determined urinary odor is composed of a mixture of volatile carboxylic acids occurring in relative concentrations that are characteristic of the MHC odor type. This is consistent with the peptide-microflora hypothesis (Penn and Potts, 1998b).

Do perfume ingredients resemble body odors? The scents of, for example, jasmine and rose apparently differ from human body odors. However, a natural flower oil may contain over 400 different odorants (Dodd, 1991) and there are more than 270 known constituents in rose oil (Ohloff, 1978). The perfumer Jellinek (1951) described subscents ("Beigerüche") of many classic ingredients of natural origin as reminiscent of human body odors (see also Köster et al., 1986). These subscents do not need to have the same structure as body odors because structurally unrelated odorants can have similar odor (Beets and Theimer, 1970). Starting as a "sensory bias" (Ryan et al., 1990) preferences for such subscents may have been developed. It may be because of their subscents that specific ingredients have a long tradition of being used for perfumes. Stoddard (1990) wonders why only about a hundred plant species have been used traditionally, which is an insignificant proportion of the total number of plant species in the world. "This suggests there may be something very special about them" (Stoddard, 1990), which may be the possession of specific subscents. However, the subscent-hypothesis is only one among various potential mechanisms for the correlation between individual preferences for perfume ingredients and MHC type.

Why perfumes? First, perfumes may be used as amplifiers of MHC-correlated body odors to overcome the smelly noise of human civilization (Vollrath and Milinski, 1995). Although Wedekind et al. (1995) and Wedekind and Füri (1997) asked their volunteers to avoid any odoriferous contact such as tobacco, perfume, and so on while wearing the test shirt, there was a telling exception: one of the six t-shirt wearers in Wedekind and Füri (1997) elicited strong associations to both tobacco smoke and perfume in the smellers. Nevertheless, a good correlation between the dissimilarity of this person's MHC alleles to the smellers' and the scored pleasantness of his t-shirt odor overall, and the best correlation in women not using oral contraceptives, was found for this person (Wedekind and Füri, 1997). If perfumes are used only to enhance body odors, an alternative strategy would be to enhance body odor itself or the perception of it. We would have to assume that constraints exist that render this alternative strategy less feasible. Second, perfumes may be used strategically to signal the possession of specific MHC alleles when specific infectious diseases are around. Rülicke et al. (1998) found experimentally in mice that the gamete fusion was dependent on the MHC type of sperm, and conditional on a pending infection with mouse hepatitis virus, which confirmed an earlier observation (Wedekind et al., 1996). Infected mice (Kavaliers and Colwell, 1995; Penn et al. 1998) as well as ill humans (review, Penn and Potts, 1998a) are perceived as such by their changed odor which may become masked with the "healthy" perfume signal.

Besides MHC-correlated odor preferences there are further facets of the psychology of fragrance selection (e.g., Mensing

and Beck, 1991). Stoddart (1990) cites evidence that some perfume ingredients mimic mammalian steroidal sex pheromones that might unconsciously "stimulate the mind." Such effects, however, can hardly explain the great individual differences in preferences for perfumes. We found a strong MHC-independent gender effect on perfume preference. Although there is no indication that the MHC is gender-specific, which agrees with our result, natural odors have some relation to gender. Humans are able to "detect" gender from natural axillary odors which are stronger in males than in females (Doty, 1981; Schleidt et al., 1981). This ability may depend on quantitative rather than qualitative aspects of the odor, because the stronger the axillary odor is, the more likely it is assigned to a male gender category, regardless of the true sex of its donor (Doty, 1981; Wedekind and Füri, 1997). Since male and female perfumes contain almost the same range of ingredients, there seems to be no ingredient that determines the "gender" of a perfume (Glöss, 1995). However, relative quantities and frequencies of specific ingredients differ statistically between male and female perfumes, whereas numerous cultures never distinguished between female and male perfumes (Jellinek, 1994). Our test persons had a gender bias for some reason.

Tremendous progress has recently been made in understanding chemosensory mechanisms (e.g., Bargmann 1996; Buck and Axel, 1991; Fan et al., 1995; Prasad and Reed, 1999; Reed, 1998; Zhao et al., 1998) so that the physiology that underlies the correlation between oneself's MHC genotype and the preference for specific mixtures of perfume ingredients for self and (with changed sign) for body odors of potential mates might be understood in the near future.

APPENDIX

First study: MANOVAs on the pleasantness of 36 scents, with two groups of smellers analyzed for the two potential haplotypes found in our study population

		Potential haplotypes	
Source of variation	df	A1B8 *F*	A3B7DR15 *F*
Between subjects			
Gender	1	0.9	0.2
Haplotype	1	<0.1	<0.1
Gender × haplotype	1	0.1	<0.1
Error	110		
Within subjects (36 scents evaluated)			
Scent	35	30.0***	13.5***
Scent × gender	35	1.6*	1.8**
Scent × haplotype	35	1.1	0.9
Scent × gender × haplotype	35	0.9	1.1
Error	3850		

Women not on the pill and men were included; women on the pill were not included in this analysis. *** = $p \leq .001$; ** = $.001 < p \leq .01$; * = $.01 < p \leq .05$; all other *F*-values are not significant (Huynh-Feldt corrected).

We thank the participants for their cooperation, A. Paepke for standardizing the dilution of the perfume ingredients, R. Eggler, S. Maurer, J. Rauch, and P. Stettler, for technical help. We thank the referees for helpful comments, and the Swiss National Science Foundation and the Roche Research Foundation for financial support. C.W. is now supported by an IHP fellowship of the Swiss National Science Foundation.

REFERENCES

Apanius V, Penn D, Slev PR, Ruff LR, Potts WK, 1997. The nature of selection on the major histocompatibility complex. Crit Rev Immunol 17:179–224.

Bargmann C, 1996. From the nose to the brain. Nature 384:512–513.

Beets MGJ, Theimer ET, 1970. Odour similarity between structually unrelated odorants. In: Taste and smell in vertebrates (Wolstenholme GEW, Knight J, eds). London: Churchill; 313–321.

Behan JM, Macmaster AP, Perring KD, Tuck KM, 1996. Insight into how skin changes perfume. Int J Cosmet Sci 18:237–246.

Bender K, 1991. The HLA system, 5th revised version. Dreieich, Germany: Biotest AG.

Blaustein AR, 1983. Kin recognition mechanisms: phenotype matching or recognition alleles? Am Nat 121: 749–754.

Brown JL, 1997. A theory of mate choice based on heterozygosity. Behav Ecol 8:60–65.

Brown JL, Eklund A, 1994. Kin recognition and the major histocompatibility complex: an integrative review. Am Nat 143:435–461.

Buck L, Axel R, 1991. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65:175–187.

Cohen J, 1988. Statistical power analysis for the behavioral sciences, 2nd ed. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Daly CD, White RS, 1930. Psychic reactions to olfactory stimuli. Brit J Med Psychol 10:70–87.

Dodd GH, 1991. The molecular dimension in perfumery. In: Perfumery: the psychology and biology of fragrance (Van Toller S, Dodd GH, eds). London: Chapman & Hall; 19–46.

Doty R, 1981. Olfactory communication in humans. Chem Senses 6: 351–376.

Doty RL, Ford M, Preti G, Huggins G, 1975. Human vaginal odors change in pleasantness and intensity during the menstrual cycle. Science 190:45–60.

Egid K, Brown JL, 1989. The major histocompatibility complex and female mating preferences in mice. Anim Behav 38:548–550.

Engen T, McBurney D, 1964. Magnitude and category scales of the pleasantness of odors. J. Exp Psychol 68:435–440.

Erlich HA, Bergström TF, Stoneking M, Gyllensten U, 1996. HLA sequence polymorphism and the origin of humans. Science 274: 1552–1554.

Fan W, Liu Y-C, Parimoo S, Weissman SM, 1995. Olfactory receptor-like genes are located in the human major histocompatibility complex. Genomics 27:119–123.

Gilbert AN, Kemp SE, 1996. Odor perception phenotypes: multiple, specific hyperosmias to musks. Chem Senses 21:411–416.

Gilbert AN, Wysocki CJ, 1991. Quantitative assessment of olfactory experience during pregnancy. Psychosom Med 53:693–700.

Glöss W, 1995. H&R Fragrance Guide. 3rd ed. Hamburg: R. Glöss.

Hudson R, Koch B, Heid B, Laska M, 1996. Veränderungen der Geruchswahrnehmung während der schwangerschaft: eine Längsschnittstudie. In: Schwangerschaft, geburt und der ubergang zur elternschaft (Brähler E, Unger U, eds). Opladen: Westdeutscher Verlag; 174–191.

Jellinek JS, 1994. Eine Neubewertung. In: Die psychologischen grundlagen der parfümerie, 4th ed. (Jellinek PJS, Jellinek JS, eds). Heidelberg: Hüthig Verlag: 235–256.

Jellinek P, 1951. Die psychologischen grundlagen der parfümerie. Heidelberg: Hüthig Verlag.

Kavaliers M, Colwell DD, 1995. Discrimination by female mice between the odours of parasitized and non-parasitized males. Proc R Soc Lond B 261:31–35.

Kirk-Smith MD, Booth DA, 1987. Chemoreception in human behaviour: experimental analysis of the social effects of fragrances. Chem Senses 12:159–166.

Köster EP, Jellinek JS, Verhelst ND, Mojet J, Linschoten MRI, 1986. Odorants related to human body odor. J Soc Cosmet Chem 37:409–428.

Labows JN, Wysocki CJ, 1984. Individual differences in odor perception. Perfum Flavor 9:21–27.

Le Norcy S, 1991. Selling perfume: a technique or an art? In: Perfumery: the psychology and biology of fragrance (Van Toller S, Dodd GH, eds). London: Chapman & Hall: 217–226.

Maynard Smith J, 1989. Evolutionary genetics. New York. Oxford University Press.

Mensing J, Beck C, 1991. The psychology of fragrance selection. In: Perfumery: the psychology and biology of fragrance (Van Toller S, Dodd GH, eds). London: Chapman & Hall: 185–204.

Ober C, Weitkamp LR, Cox N, Dytch H., Kostyu D, Elias S, 1997. HLA and mate choice in humans. Am J Hum Genet 61:497–504.

O'Connell RJ, Stevens D A, Akers RP, Coppola DM, Grant AJ, 1989. Individual differences in the quantitative and qualitative responses of human subjects to various odors. Chem Senses 14:293–302.

Ohloff G, 1978. The importance of minor components in flavors and fragrances. Perfum Flavor 3:11–22.

Penn D, Potts WK, 1998a. Chemical signals and parasite-mediated sexual selection. Trends Ecol Evol 13:391–396.

Penn D, Potts W, 1998b. How do major histocompatibility complex genes influence odor and mating preferences? Adv Immunology 69:411–436.

Penn DJ, Potts WK, 1999. The evolution of mating preferences and major histocompatibility complex genes. Am Nat 153:145–164.

Penn D, Schneider G, White K, Slev P, Potts W, 1998. Influenza infection neutralizes the attractiveness of male odour to female mice (*Mus musculus*). Ethology 104:685–694.

Potts WK, Manning CJ, Wakeland EK, 1991. Mating patterns in seminatural populations of mice influenced by MHC genotype. Nature 352:619–621.

Potts WK, Manning CJ, Wakeland EK, 1994. The role of infectious disease, inbreeding, and mating preferences in maintaining MHC diversity: an experimental test. Phil Trans R Soc London 346:369–378.

Prasad BC, Reed RR, 1999. Chemosensation: molecular mechanisms in worms and mammals. Trends Genetics 15:150–153.

Pratt J, 1942. Notes on the unconscious significance of perfume. Int J Psychoanal 23:80–83.

Reed RR, 1998. Opening the window to odor space. Science 279:193.

Rice WR, Gaines SD, 1994 'Heads I win, tails you lose': testing directional alternative hypotheses in ecological and evolutionary research. Trends Evol Ecol 9:235–237.

Rülicke T, Chapuisat M, Homberger FR, Macas E, Wedekind C, 1998. MHC genotype of progeny influenced by parental infection. Proc R Soc Lond B 265:711–716.

Ryan MJ, Fox JH, Wilczynski W, Rand AS, 1990. Sexual selection for sensory exploitation in the frog *Physalaemus pustolosus*. Nature 343: 66–67.

Schleidt M, Hold B, Attili G, 1981. A cross-cultural study on the attitude towards personal odours. J Chem Ecol 7:19–31.

Singer AG, Beauchamp GK, Yamazaki K, 1997. Volatile signals of the major histocompatibility complex in male mouse urine. Proc Natl Acad Sci USA 94:2210–2214.

Stoddart DM, 1986. The role of olfaction in the evolution of human sexuality: an hypothesis. Man 21:514–520.

Stoddart DM, 1990. The scented ape: the biology and culture of human odour. Cambridge: Cambridge University Press.

Stoddart DM, 1991. Human culture: a zoological perspective. In: Perfumery: the psychology and biology of fragrance (Van Toller S, Dodd GH, eds). London: Chapman & Hall: 3–17

SYSTAT, 1992. Statistics, version 5.2. Evanston, Illinois: SYSTAT.

Van Toller S, Dodd GH (eds), 1991. Perfumery: the psychology and biology of fragrance. London: Chapman & Hall.

Vollrath F, Milinski M, 1995. Fragrant genes help Damenwahl. Trends Ecol Evol 10:307–308.

Wedekind C, Chapuisat M, Macas E, Rülicke T, 1996. Non-random fertilization in mice correlates with the MHC and something else. Heredity 77:400–409.

Wedekind C, Füri S, 1997. Body odour preferences in men and women: do they aim for specific MHC combinations or simply heterozygosity? Proc R Soc Lond B 264:1471–1479.

Wedekind C, Seebeck T, Bettens F, Paepke AJ, 1995. MHC-dependent mate preferences in humans. Proc R Soc Lond B 260:245–249.

Yamazaki K, Beauchamp GK, Shen F, Bard J, Boyse E, 1994. Discrimination of odortypes determined by the major histocompatibility complex among outbred mice. Proc Natl Acad Sci USA 91:3735–3738.

Yamazaki K, Beauchamp GK, Wysocki CJ, Bard J, Thomas L, Boyse EA, 1983. Recognition of H-2 types in relation to the blocking of pregnancy in mice. Science 221:186–188.

Yamazaki K, Boyes EA, Thaler HT, Mathieson BJ, Abbott J, Boyes J, Zayas ZA, 1976. Control of mating preferences in mice by genes in the major histocompatibility complex. J Exp Med 144:1324–1335.

Yamazaki K, Yamaguchi M, Andrews PW, Peake B, Boyes EA, 1978. Mating preferences of F2 segregants of crosses between MHC-congenic mouse strains. Immunogenetics 6:253–259.

Zhao H, Ivic L, Otaki JM, Hashimoto M, Mikoshiba K, Firestein S, 1998. Functional expression of a mammalian odorant receptor. Science 279:237–242.

Ziegler A, Ehlers A, Forbes S, Trowsdale J, Uchanska-Ziegler B, Volz A, Younger R, Beck S, 2000. Polymorphic olfactory receptor genes and HLA loci constitute extended haplotypes. In: Major histocompatibility complex—evolution, structure, function (Kasahara M, ed). Tokyo: Springer-Verlag; 110–130.