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Scent of A man

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IT ALL started with a bit of harmless T-shirt sniffing. A group of women were asked to sniff T-shirts that had been worn by a group of unknown and unwashed men. All they had to do was say which shirts smelled best. The experiment, run by Claus Wedekind, a young Swiss scientist then at the University of Bern, was designed to find out if humans, like mice, use body odour to identify genetically appropriate mates. But it revealed something more worrying.

As Wedekind predicted, most female volunteers had equivalent preferences to their rodent counterparts. Numerous studies in mice have shown that, given the choice, they sniff out mates with genes for immunity that differ from their own, and that this seems to increase their chances of producing healthy offspring. But among Wedekind's volunteers there was a startling exception to this trend. Women on the contraceptive pill showed the reverse preference. Instead of being attracted to the scent of dissimilar men, they chose men whose genes for immunity were closest to their own.

If humans are using smell to find a good partner for reproduction, and the Pill is turning things upside down, then there could be serious consequences. By tricking users into falling for the wrong guy, the Pill could be giving women better protection than they bargained for—making it harder for them to have kids long after they stop taking it.

It's a contentious idea. For a start, not everyone agrees that the human brain can register such smells, let alone that they might influence our behaviour. But if they do, then does the Pill interfere with this form of sexual chemistry? "It's a reasonable question," says Wayne Potts, a biologist at the University of Utah in Salt Lake City, who specialises in mate choice. His colleague, Dustin Penn, goes further: "It wouldn't surprise me if sabotaging our reproductive machinery would lead to faulty mate choice."

The genes at the centre of the debate are a large cluster called the major histocompatibility complex, or MHC. Each person has a unique combination of MHC genes that encode various components of their immune system. These include genes for histocompatibility antigens—which determine, for instance, whether your body will reject a foreign tissue graft—and for proteins called complements, which help fight off disease. The idea is that the more varied an individual's MHC, the more robust their immunity. And if your parents have widely varying MHC genes, your own MHC is more likely to be diverse. Parental differences may even increase the chances of your being born in the first place.

Kunio Yamazaki at the Monell Chemical Senses Center in Philadelphia has found that mouse embryos conceived by parents with dissimilar MHCs are more likely to make it to term. And at the Reproductive Science Center of the Bay Area in San Ramon, California, Louis Weckstein found that human couples who fail to conceive after two or more attempts with IVF shared significantly more MHC genes than successful IVF couples.

If olfactory cues about MHC genes are so important, why do women taking the Pill seem to respond so differently from other women? "My guess is that the Pill simulates pregnancy and that maybe during pregnancy, odour preferences change," says Wedekind. This appears to be what happens in mice, he points out. The theory is that during pregnancy, a female is attracted to the smell of her own relatives, who have similar MHCs to her own. After all, family members have the greatest interest in seeing her offspring survive. Pregnant women—and women whose bodies are tricked into thinking they're pregnant—might have the same tendency, says Wedekind.

The implications are not lost on Marian Petrie from the University of Newcastle upon Tyne. "Potentially, women might affect their chances of becoming [pregnant], not by something that's an

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obvious means," she says. "It might be important generally to infertility problems." In the next few months, she and her colleague Craig Roberts will run a follow-up to Wedekind's study to find out whether the Pill really does skew women's smell preference. They will ask 80 women who are planning to start taking oral contraceptives to do the T-shirt test, both before and a few months after they go on the Pill. The researchers will also run the same test on 80 women trying to get pregnant, both before and after conception.

To date, almost all the work on MHC differences, mate choice and their effects on offspring viability has been done on rodents. But geneticist Carole Ober from the University of Chicago has come up with a cunning way to explore some of the same questions in humans. For over a decade, she has been studying a North American religious community known as the Hutterites. Following Wedekind's revelations about the women's preference for certain odours in an artificial laboratory setting, Ober aimed to get information about real partnerships.

In many ways, Hutterites are the perfect study group for "natural" mate choice among humans. They are a socially isolated group who work on communal farms, marry within their own community, and can trace their roots back to a handful of European ancestors in the 16th century. Single men and women visit neighbouring Hutterite colonies, and often end up working or celebrating special occasions alongside potential spouses. They don't use perfumes or deodorants. "They are absolutely maximising the importance of MHC," says Ober. They marry once—divorce is strictly prohibited—and, claims Ober, they marry for love. Once paired off, they place a high value on big families, and seldom use contraception.

So do Hutterites tend to marry people who have dissimilar MHCs? To answer this question, Ober and her colleagues studied 411 couples drawn from 31 Hutterite colonies. They made two separate calculations of how many couples would end up matching for certain haplotypes, or "linked" MHC genes found close together on chromosome 6, if there was no active avoidance of mates with similar MHCs.

In the first, they predicted how many Hutterite couples with similar MHCs would just happen to end up together, having taken into account factors such as the way women always move to their husband's colony after marriage, that Hutterites never marry first cousins and that siblings often marry into the same family. In the second, they used the exact genealogy of each of the volunteers to establish that there would have been between 60 and 80 unrelated "ancestral" haplotypes for this particular chromosome among their founding ancestors. They then ran a computer simulation based on this genealogy to see how many couples with similar MHCs you would expect to find if Hutterites married at random.

Next, the researchers compared these calculations with the actual situation. As they had suspected, the Hutterite men and women they studied tended to avoid pairing off with mates who had similar MHC genes to their own. Despite the lack of genetic variation within this isolated population, only 44 of the couples matched for any haplotype—significantly fewer than the 65 predicted from the first calculation. The genealogy study backed that up: if mate selection were random the probability that only 44 couples would have matched was only about 5 per cent. Ober's group concludes that genes in this region of DNA may indeed influence mate choice in humans.

The findings were published in 1997, along with a review by Yamazaki and his colleague Gary Beauchamp, director of Monell, who were delighted that at last there was some evidence in humans for the effect they had found in rodents. Their enthusiasm was dampened, however, by results from another excellent study published alongside Ober's paper, which had examined the same question and come to a different conclusion. Philip Hedrick of Arizona State University in Tempe and Francis Black at Yale University studied 194 couples from 11 Amazonian Indian tribes and found that people seemed to pair off randomly. Yamazaki and Beauchamp suggested that the large number of Hutterite couples studied and the special characteristics of the culture may have made this group better than the Amazonian tribes for detecting a small but real effect.

The next question for Ober was whether couples with similar MHCs actually have reduced fertility. Some of her early research on Hutterites had hinted that couples who had a large number of MHC

matches took longer to conceive. She decided to look at this effect more carefully, asking 111 Hutterite women to keep diaries recording all their menstrual periods. If they didn't have a period on the day expected, the women took a pregnancy test and recorded the result. The women were also asked to note whether they were nursing other infants, practising birth control of any kind or were ill—any of which could affect the likelihood of conception. During the course of the study—the first to examine possible links between MHC and miscarriage in humans—she collected information on 251 pregnancies.

Of the 111 women, 27 had miscarriages, and there were 38 miscarriages altogether. None of the couples was completely infertile—all but one had already had at least one child, and none had more than two consecutive miscarriages. But when Ober scrutinised the MHC genes from the women and their husbands at 16 separate genetic sites, she found that miscarriage rates were highest for couples who matched at all these sites. And there was an increased risk even where there was matching at just some of the sites.

"The effects we see in the Hutterites are pretty clear," says Ober. But she adds that Hutterites are an isolated population, and they have a limited repertoire of certain MHC genes. "At this point, it's difficult to say whether the same is true of out-bred couples," she says. A Hutterite couple is much more likely to have matching DNA at these particular miscarriage black spots than a couple who do not live in a genetically isolated community. Even so, Ober believes that the actual risks associated with having one or two such genetic matches could be similar in any population.

The fertility gods may well frown on couples with similar MHCs. But where does all this leave Pill users? Even if using oral contraceptives alters a woman's sense of smell, does smell itself really play such a big part in choosing a man? The effect may be subtle and subconscious, argues Penn, but that doesn't mean smell is unimportant. He points out that chemosensory signals are used to attract and select mates in many species, from bacteria to plants to mice. "What we know about mate choice in other species tells us they use lots of different information," he says. "They use everything—everything they can."

Studies in female rodents have shown that the scent of a male can sometimes speed up puberty, activate ovulation and even induce miscarriage. Humans also use odour cues in at least some matters related to reproduction. For instance, Martha McClintock at the University of Chicago showed in 1998 that when women who live together synchronise their menstrual cycles, they do it through chemical signals known as pheromones. McClintock has recently teamed up with Ober to further explore the impact of the Pill on chemical communication.

As far as anyone can tell, whatever chemical signals do pass between people are subconscious. Nonetheless, Rachel Herz from Brown University in Providence, Rhode Island, decided to ask people about it directly. She polled 166 women about what makes a man attractive—specifically, attractive enough to go to bed with. Out of a variety of factors, including appearance, the sound of his voice and how his skin feels, women respondents said that a man's scent was paramount. Body odour was particularly important, the volunteers reported, in decisions not to have sex with a certain individual.

The question is not whether there are human MHC smells—that is more or less resolved. Rats in the labs of Beauchamps and Yamazaki are able to distinguish between people with different MHC types simply by sniffing their urine. This is strong evidence, the researchers say, that MHC genes influence body odour in humans just as they do in rodents. The genes may affect the concentrations of volatile acids in body fluids, such as urine, blood, breast milk or even sweat. These in turn could act as sexual odorants.

The real question is, even if these odours are advertising what kind of MHC a person has, do humans still have the capacity to pick up the scent and act on it? Rodents have something called a vomeronasal organ (VNO)—a region high in the nose that can detect chemosensory signals. That system bypasses conscious centres of the brain and has direct access to the amygdala and hypothalamus, which govern sexual behaviour. In most animals with a VNO, reproductive behaviour is disrupted if you cut this part of the nose out.

There is still a debate raging about whether humans even have a VNO (New Scientist, 25 January 1997, p 36). We do seem to have a structure similar to a VNO during early development, but there is no strong evidence that the vestige that remains into adulthood is functional. Maybe we don't need one. Pigs, rabbits and sheep have a VNO, but detect some pheromones through their main olfactory system. It's possible that humans do too. After all, a functioning human pheromone receptor gene was identified last year ([New Scientist, 2 September 2000, p 7](#)). And proponents point out that humans have more scent glands than any other mammal. What for, if not to communicate? But there is still no consensus on whether humans have some kind of working chemosensory perception or just remnants from a once-elaborate system that evolution decided to phase out.

Still, Hutterites do tend to marry those with different MHCs. And women did respond differently to a sniff from those T-shirts when they were on the Pill. So it's not inconceivable that the Pill is meddling with whatever chemosensory perception we have. "It makes sense that if you change the hormonal environment, you change olfaction," says Ober.

At first glance, the Pill's glittering record should be enough to quash the whole discussion. Oral contraception has been in use since 1960, and there is no evidence so far that women who have taken the Pill have lower fertility when they stop. Several large studies looking at tens of thousands of women have been reassuring, says Martin Vessey, an epidemiologist at the University of Oxford. "Studies haven't suggested an association between fetal loss and Pill use," he says. But then, no study has looked specifically at women who found life partners while on the Pill, he admits. And it's only recently that women have been using the contraceptive pill from such a young age—sometimes from before their first sexual encounter straight through to the time when they want to have kids.

Then there's the fact that the Pill has so far been the darling of the developed world, where there are relatively few challenges to the immune system. Would its impact on fertility be more readily seen if women in the developing world took a shine to it? "There it might matter," says Wedekind. He cautions, however, that no research has been done in this area. "I think it's worth investigating," he adds. Clearly pathogens do affect mate choice in animals. Research by Wedekind and Thomas Rüllicke of University Hospital Zurich shows that when mouse colonies are infected with a mouse hepatitis virus, their offspring have more varied MHCs. The researchers believe this is partly due to the egg selecting specific sperm to maximise the survival chances of the resulting offspring.

Despite this, no self-respecting woman of the 21st century would want to disparage the Pill. For the past 40 years it has liberated us from the threat of unwanted pregnancy, leaving us free to earn degrees, climb corporate ladders and travel the world, all without having to swear off sex. Even so, it might be worth taking precautions. Herz suggests that if you are on the Pill and meet someone you want to have children with, you should stop taking oral contraceptives. "Go off," she says, "to see if you're still attracted."

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