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Evidence suggesting that the odortypes of pregnant women are a compound of maternal and fetal odortypes

(body odor/olfaction/kin recognition/histocompatibility/population genetics)

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ABSTRACT **Odortypes—namely, body odors that distinguish one individual from another on the basis of genetic polymorphism at the major histocompatibility complex and other loci—are a fundamental element in the social life and reproductive behavior of the mouse, including familial imprinting, mate choice, and control of early pregnancy. Odortypes are strongly represented in urine. During mouse pregnancy, an outcrossed mother's urine acquires fetal major histocompatibility complex odortypes of paternal origin, an observation that we took as the focus of a search for odortypes in humans, using a fully automated computer-programmed olfactometer in which trained rats are known to distinguish precisely the odortypes of another species. Five women provided urine samples before and after birth, which in each case appropriately trained rats were found to distinguish in the olfactometer. Whether this olfactory distinction of mothers' urine before and after birth reflects in part the odortype and hence genotype of the fetus, and not just the state of pregnancy *per se*, was tested in a second study in which each mother's postpartum urine was mixed either with urine from her own infant or with urine of a different, same-aged infant. Responses of trained rats were more positive with respect to the former (congruous) mixtures than to the latter (incongruous) mixtures, implying that, as in the mouse, human fetal odortypes of paternal genomic origin are represented in the odortype of the mother, doubtless by circulatory transfer of the pertinent odorants.**

Odortypes—i.e., genetically determined body odors that distinguish individual members of a species—were first discovered by fortuitous observation of their involvement in the social behavior of mice—namely, the usual preference of males to consort and mate with females of an unfamiliar major histocompatibility complex (MHC) type (1). Only later were test systems, the Y-maze (2) and the automated olfactometer (3), devised to reveal and study odortypes regardless of any behavioral context.

Early notions of special MHC-linked genes for odortype individuality were abandoned when it was found that class I genes of the MHC themselves determine odortypes (4), implying that odortype specification is a secondary function of polymorphic genes with other primary functions, one that has utility in species that depend highly on olfaction but that is expected to be found also in species with little or no sense of smell. Thus the existence of human odortypes (5) is of intrinsic interest regardless of the uses they may serve in a species depending mostly on sight.

As a potentially informative model for an exploration of human odortypes, we chose the observation that when an outbred pregnant mouse carries fetuses with a paternal MHC haplotype that is different from the maternal MHC haplotype, as is the case in all but a few human pregnancies, then the odortype specified by that haplotype can be detected in the mother's urine (6).

Genetic analysis of mouse odortypes has been focused mainly on the MHC (*H-2*), at least three sectors of which specify independent odortypes (7). But unidentified odortype-determining loci are known to be present elsewhere throughout the autosomal genome (8) and on both sex chromosomes (9), and their united contribution to odortype determination may approach that of the MHC. Thus indications of human odortypes reported here probably relate to both the MHC and other loci.

MATERIALS AND METHODS

Urine Donors. See Table 1.

Trained Rats. Four female Harlan–Sprague–Dawley rats, initially about 2 months of age and weighing 200–250 g, were housed individually in a large tub cage and had access to Purina Rat Lab Chow at all times. The trained rats were maintained on 12–15 ml of water daily, and after a training session, in which 2–3 ml of water was earned, they received supplemental water in the home cage.

The Automated Olfactometer. The apparatus described in detail elsewhere (13) and shown in Fig. 1 was adapted from Slotnick and Nigrosh (14).

Training and Testing Procedures. Rats were first trained to make a touch response of 0.3-s duration to obtain a 0.05-ml water reinforcement. After the rats were responding successfully in this task, only responses made in the presence of an odor were reinforced. Odor stimulus presentations were next made dependent upon a trial-initiating response, which required the interruption of the infrared photobeam located on the sides of the conical tip of the funnel next to the odor delivery port.

In a go/no-go discrimination training session, urine from one of two alternative sources (see below) was assigned to be the reinforced (S+) stimulus. Bar touches within 3 sec in the presence of this stimulus were rewarded with 0.05 ml of water. For each rat, urine from the other alternatives was designated as S− (unreinforced); bar touches in the presence of this odor were never reinforced. S+ and S− trials were alternated in a random manner with the restriction that no more than three of either type would occur consecutively. After the rat successfully discriminated between a pair of S+ and S− stimuli, each collected on a single day, a second pair of stimuli from the same individuals but collected on different days was added. As soon as the trained rats were responding positively to those two

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Abbreviations: MHC, major histocompatibility complex; S+, reinforced; S−, unreinforced.

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Table 1. Mothers donating urine

Mother	Age of mother, years	Sex of infant	Exclusive feeding
M1	39	Male	Breast
M2	32	Female	Formula
M3	37	Male	Breast
M4	31	Female	Breast
M5	30	Female	Breast

Five healthy pregnant women were recruited from the University of Pennsylvania community and from advertisements in local newspapers. All were multiparous except M2. All study procedures were approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania, and informed consent was obtained from each woman. Urine was collected during the early morning on at least 10 separate days during the last 7 weeks of pregnancy, during the 8th–11th week postpartum, and from each infant on at least 4 separate days at 8–11 weeks of age by use of a sterile, urine collecting bag (Hollister, Libertyville, IL). Each urine sample was placed in a sterilized glass container and immediately frozen. Because sulfurous volatiles found in the diet can alter the odor of bodily fluids (10–12), subjects were instructed to eat a bland diet low in sulfur-containing foods during each of the two collection periods (see ref. 12 for detailed methods). To encourage compliance, subjects were asked to record, in terms of household measure, all foods and beverages consumed. Mothers were also asked to refrain from using any vaginal products or scented lotions on themselves and scented lotions or powder on their infants during the collection period.

pairs of samples (i.e., ≥80% touch to S+ and ≥80% no touch to S−), four different samples of S+ and four different samples of S− urine were employed, two pairs for the first half of a test session and two pairs for the second half. Four S+ and S− samples were used each day to be sure that the trained rats learned to distinguish between classes of odors rather than to some random difference that may have distinguished any two individual samples collected from the same individual.

The particular stimulus jars used for S+ and S− responding were varied from day to day. Touching the bar during S+ trials and not touching the bar during S− trials were recorded as correct or positive responses, and the other possible responses were recorded as errors. Accuracy scores for S+ and S− stimuli were combined for the 140–160 trials in each daily session. Reinforcement for S+ trials for the first several sessions was 100%; thereafter, it was reduced to a random 50% schedule. Once accuracy scores of about 80% for both S+ and S− were obtained on the 50% reinforced schedule during the training session, the animals were considered trained, and critical generalization trials, as described below, were initiated.

Generalization. The purpose of generalization (see refs. 2 and 8) is to introduce urine samples that have never been used in training and for which the trained rats have never been reinforced. Positive generalizations to these new samples (touch to samples of the same putative class as S+ and no touch to samples of the putative class represented by S−) further ensure that the learned response involved the distinction in question, in the present case pregnancy status or infant odortypes, and not some incidental factor such as a varied diet. Positive generalization also implies that the stimuli used in the generalization trials resemble (have elements in common with) the training stimuli.

Order of Training and Testing. The rats were first trained to distinguish between two unrelated inbred mouse strains,

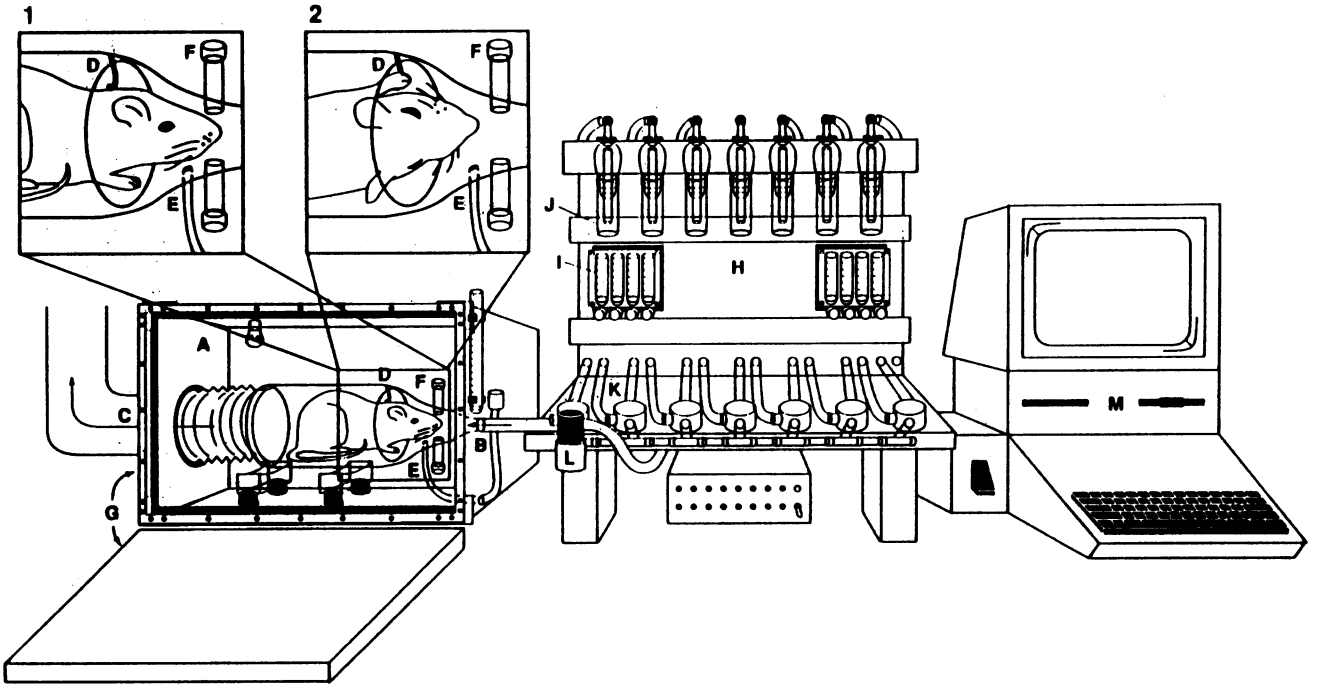

FIG. 1. Automated olfactometer. The odor chamber (A) admits odorized air at one end (B), which exhausts at the other end (C). A response manipulandum, a solid metal bar connected to an electronic touch circuit (D), and a water reservoir (E) are positioned inside the odor chamber. A high-output infrared LED and an infrared phototransistor are placed on opposite sides of the nose of the odor chamber (F), near the air ports, creating an infrared photobeam. Interruptions in the photobeam are detected by an electronic circuit. The odor chamber is completely enclosed in a sound-attenuating chamber (G). An exhaust fan removes any extraneous odors from inside the enclosure and provides a masking noise; the entire enclosure is illuminated by a 15-W red light bulb. The odor delivery system (H) is adjacent to this chamber but outside the enclosure. Compressed air is filtered through activated charcoal and distributed to each flowmeter (I). Metered quantities of air are then delivered to the urine samples. A 0.5-ml sample of urine is placed in the bottom of a glass impinger jar (J). All impinger jars, except one that is always for clean air, could contain urine samples. Incoming air odorized by the urine samples is normally shunted to exhaust unless the appropriate three-way solenoid valve (K) is activated. When an odor channel is opened in this way, odorized air is mixed with the clean air that always flows through the mixing manifold (L). Simultaneous activation of an odor valve with the final valve allows for mixing of the stimulus with the clean air before its delivery to the test chamber; odor flow is indicated by the arrows (see *Training and Testing Procedures*). All stimulus presentation and response monitoring and data analysis are performed by an Apple II/e computer (M). Insets show rat sampling odors (1) and touching the bar (2).

then between two MHC-congenic strains, as detailed elsewhere (3). Details of the training procedure are presented in the legend to Fig. 1.

RESULTS

The data shown in this report are restricted to generalization trials. Although these unrewarded trials of samples not encountered before, inserted between series of rewarded familiar training samples, represent only a small proportion of the rats' total experience of trials, generally no more than 10%, they are the prime criterion of the specificity of the odor in question.

First Study: Olfactory Distinction of Mothers' Urine Before and After Birth. The purpose of this first study was to find out whether human gestation is accompanied by any characteristic change in the scent of mothers' urine, as a prelude to approaching the question of whether such a change may include indication of the odortype, and thus genotype, of the fetus.

Part 1. As detailed in Table 2, each of four rats was assigned to distinguishing urine samples taken before birth and after birth from each of four mothers (M1–M4; Table 1). All four rats were successful, and each then successfully distinguished new samples from the same mother without reward (first generalization in Table 2). Each rat was then retrained and repeated this successful performance with each of the three other mothers, making a total of 16/16 positive distinctions of maternal urine before and after birth, the generalization data for which are given in Fig. 2.

Serial retraining in this manner did not affect performance; performance scores for first training sets did not differ significantly from the three following sets.

Part 2. Each of the same four rats, after having distinguished samples of the training mother in Part 1, was presented, in the same unrewarded manner, with before-birth and after-birth urine samples of four nontraining unfamiliar mothers (M2–M5; second generalization detailed in Table 2). Combined data for this second group of 16 test modes are given in Fig. 3 in comparison with the combined data from Table 2. These data show that the rats were significantly less successful in distinguishing the state of pregnancy, probably because training with a single mother rather than several mothers introduces the here-unwanted factor of her idiosyncratic odortype (see *Discussion*).

Second Study: Fetal Contribution to the Scent of Mothers' Urine. Here the aim was to determine whether some part of the altered scent of pregnant women's urine can be ascribed to the genetically determined odortype, and hence genotype, of the fetus. To eliminate factors common to pregnancy *per se* and to simulate the state of pregnancy but featuring only fetal components, we adopted the approach already applied successfully in the mouse in identifying fetal contributions to maternal odortype (6). Accordingly, as detailed in Table 3, the postpartum urine of each selected mother was combined in measured proportion with urine of either her own infant or of a different, comparable infant. These samples, differing only in the infants' contributions, were then presented, in the usual unrewarded generalization mode, to rats whose training (as in the first study above) had involved the congruous fetus or an incongruous fetus. In bold terms, if the contribution of the fetus to the odor of maternal urine were nonspecific, then the odortype of the fetus should be immaterial, and the rat should not distinguish one infant from another in the present context. In fact, as Fig. 4 shows, there was preferential recognition of the congruous infant, representing the fetus of training, over the incongruous infant/fetus, which constitutes provisional evidence that, as in the mouse (6), the odortype and pertinent genotype of the fetus are evident in the urine of the human mother. The fact that the incongruous infant/fetus was recognized to a lesser extent—relevant performance scores were not totally random, as Fig. 4 indicates—is discussed below.

Table 2. Outline of first study, showing the four modes of training and testing that were presented in sequence to each of four rats (rats 1–4), using urine obtained from mothers M1–M5 before and after birth

Test mode	Urine donors: Training*	Generalization to same donors†	Generalization to different donors‡
1	M1:bb vs. M1:ab	M1:bb vs. M1:ab	M2:bb vs. M2:ab
2	M2:bb vs. M2:ab	M2:bb vs. M2:ab	M3:bb vs. M3:ab
3	M3:bb vs. M3:ab	M3:bb vs. M3:ab	M4:bb vs. M4:ab
4	M4:bb vs. M4:ab	M4:bb vs. M4:ab	M5:bb vs. M5:ab

bb, Before birth; ab, after birth. In all cases M:bb was S+, and M:ab was S−. Generalization tests to different donors followed completion of generalization tests to the same donors.
*Rewarded; data not given.
†Not rewarded; data in Fig. 2.
‡Not rewarded; data in Fig. 3.

DISCUSSION

Drawing on our studies in mice (for reviews, see refs. 15 and 16) and other studies on rats (for reviews, see refs. 17 and 18),

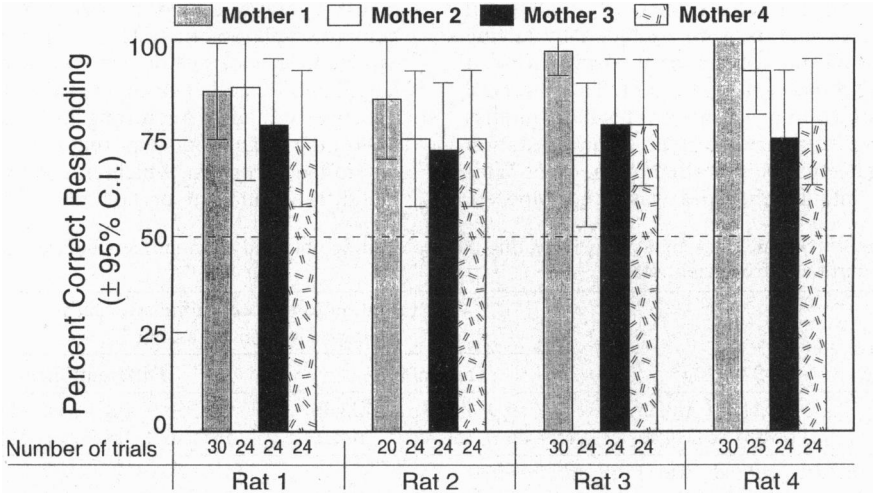

FIG. 2. Study 1: distinction of antepartum urine from postpartum urine. The results of generalization trials to the same donors used in training (see Table 2) are shown. Mean value plus 95% confidence intervals (C.I.) are shown for each rat tested with each mother. These data show that each rat generalized significantly (>50%) to each set of novel samples from the same donor (binomial test on 16 separate tests: all $z > 1.65$, all $P < 0.05$; all tests combined, $P < 0.001$).

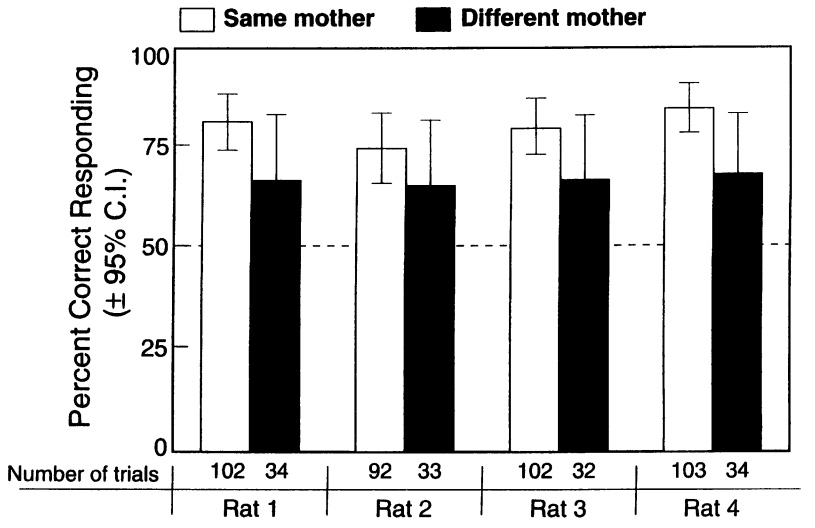

FIG. 3. Study 1: distinction of antepartum urine from postpartum urine. The results of generalization trials to the same donors used in training (□; mean values from Fig. 2) are compared with results of generalization trials to different (novel) mothers (■; see far right column in Table 2). Generalization scores to different mothers are significantly lower than responses to the same mother ($\chi^2 = 10.52$; $P < 0.01$); however, positive responses to different mothers are significantly greater than chance (binomial test on four sets of combined data: all $z > 1.65$; all $P \leq 0.05$). C.I., confidence intervals.

we believe that odortypes are composed mainly of normal metabolites that happen to be odorous and whose outputs are subject to genetic variation, giving rise, secondarily, to compound odors—i.e., odors distinguished from one another by differing proportional assortment of the same set of constituent odorants, broadly as with color vision, where innumerable secondary colors are derived from the three primary colors (19). In this view, odortypes are no more surprising than the visual individuality of all humans except identical twins, both being facets of genetic developmental variation. By the same token, it is not essential to invoke new odorants to explain the olfactory distinction of pregnancy from nonpregnancy, in this case physiologic rather than genetic.

That the olfactory distinction of pregnancy was more pronounced in response to urine samples from the mother that the rats had experienced in training, as compared with samples from other mothers, suggests that the response in training included recognition of that mother's odortype. If necessary, to achieve an olfactory response more specific for pregnancy, odortype factors could be eliminated by training on samples from a randomized set of mothers.

Conversely, in searching for fetal odortypes in maternal urine, nonfetal pregnancy factors were excluded by testing each mother's postpartum urine when combined with urine of her own infant versus that of a different infant. The observed successful olfactory distinction of infants on this basis implies that a part of the mother's urinary odortype during gestation stems from the paternal genotype inherited by the fetus. This evident distinction of infant genotypes was superimposed, however, on lesser but substantial recognition of all infants' urine presented in the same context. But in light of the small numbers, and the sampling of a freely segregating population, it is uncertain to what extent this seemingly general recognition of a fetus also may depend on differing fetal/infant genotypes rather than on fetal physiology *per se* or on nonvariable fetal genetics.

Odortypes were discovered originally by fortuitous observation of a behavioral trait—namely, that male mice generally prefer to consort and mate with females of a different MHC type, later shown to be a consequence of familial imprinting (20). May odortypes have any influence in human populations?

Urine, apparently the source of unique odortypes, is a suitable vehicle for individual identification of mice (2) and is so used also for the marking of territory (21), but it hardly fits the case for the civilized human population. However, the presence of an evidently unique odortype in mouse urine may be misleading. From the studies in mice, it is known that the kidney does not formulate the odortype. For instance, in mice, the urine of radiation chimeras acquires the MHC odortype of the bone marrow donor (22), just as the urine of the pregnant mouse acquires the MHC odortype of the fetus. Thus the hematolymphopoietic system is one source of odorants already assorted for odortype determination before reaching the kidney. Doubtless other or all organs contribute to joint urinary odortype similarly. Accordingly, in simple terms, the uniqueness of the urinary odortype may stem simply from the kidney's physiologic program, which entails that different elements of the filtrate, odorant or not, must be subject to differential

Table 3. Outline of second study, indicating the use of urine obtained from mothers before and after birth and from their infants

Test mode	Training*	Generalization to mother's urine after birth combined with infant's urine†	
		Own infant	Different infant
5	M3:bb vs. M3:ab	(M3:ab + Inf. 3) vs. M3:ab	(M3:ab + Inf. 1) vs. M3:ab
6	M4:bb vs. M4:ab	(M4:ab + Inf. 4) vs. M4:ab	(M4:ab + Inf. 5) vs. M4:ab

bb, Before birth; ab, after birth; Inf, infant.
*Rewarded; data not given.
†Generalization in test mode 5 followed directly after completion of generalization in test mode 3 (Table 2), and generalization in test mode 6 followed directly after completion of generalization in test mode 4 (Table 2). The order of the testing was own, different, different, own (test mode 5) and different, own, own, different (test mode 6). The proportion of mother urine to infant urine was 1:4.

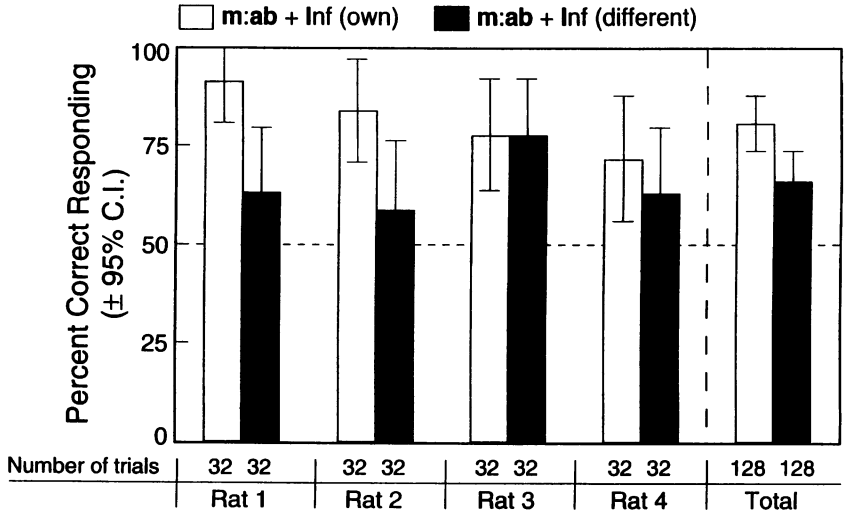

FIG. 4. Study 2: distinction of fetal odortypes. The results of generalization trials with each mother's postpartum urine combined with urine from either her own infant (□) or a different infant (■) are shown (see Table 3). Results are presented for each rat (1–4) and, on the right, for all four rats combined (Total). Positive responsiveness to mixtures containing urine from the mother's own infant [Inf (own)] are significantly greater than to mixtures containing urine from a different infant [Inf (different)] (open bars greater than solid bars: combined data $\chi^2 = 7.39$; $P < 0.01$). When presented with mixtures, rats bar-pressed on 73% of own-infant trials but on only 44% of different-infant trials. ($\chi^2 = 9.93$; $P < 0.002$; data not shown). Although they were significantly different from each other, responses to both own-infant ($z = 7.09$; $P < 0.001$) and different-infant ($z = 3.50$; $P < 0.001$) trials were significantly greater than chance (50%) levels. C.I., confidence intervals; m:ab, mother after birth.

controls over resorption and excretion. Hence, the kidney's participation may rest only or mainly in translating received information into new terms without altering the message.

It follows that discrete "untranslated" odortypes should be expressed by organs that supply primary odorants to the kidneys and by secretions—discrete odortypes that escaped discovery in the mouse because urine was the easiest material for study. In the human population, saliva, milk, and sweat would seem more appropriate odortype vehicles, each probably requiring definition, without necessarily any direct correspondence with the joint-"translated" urinary odortype.

Just as the fetus imparts its paternal odortype to the mother, so presumably must the mother impart her odortype to the fetus. Thus at birth the odortypes of mother and infant should briefly be the same, composed of both maternal and paternal elements. Recently parturient women having little exposure to their infants can nevertheless distinguish their own from other infants by scent, implying that merely transient exposure is sufficient to establish individual identity (23–25). But perhaps such identification has already been learned before birth, by means of odortypes exchanged during gestation, representing possibly an important early factor in parent–infant bonding.

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