pression probably reflect an extension of damage into the cortex of the final motor pathway; relatively greater receptive deficits extend into storage portions of the short-term verbal memory system. Agrammatism may indicate damage to areas we identify with syntax. And "conduction aphasia," now recognized as largely a short-term verbal memory defect, most commonly follows lesions at the parietal-temporal junction, where we found storage aspects of the memory system (*14*). The data from our stimulation studies also suggest that phylogenetic development of language is characterized by the appearance of lateralized sequential motor and memory systems. Evidence for memory systems has been obtained in the monkey (*15*). We predict the presence of lateralized sequential motor systems in higher primates who can be taught manual communication systems.

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4. Lidocaine local anesthesia was used so that the epileptic focus could be identified by electrocorticography.
5. Naming, reading, short-term memory, and—in patients B and D—facial movements were measured during this intracarotid amobarbital testing. These functions changed after perfusion of the left carotid only, except for short-term memory changes after perfusion of either side in patient D.
6. Tests of orofacial movement and phoneme identification were research studies, whereas tests of naming were an integral part of the operation, performed to localize the language cortex. A limited number of sites were selected in advance for the research studies so as not to prolong the operation greatly. Procedures used for obtaining informed consent for research are reviewed annually in advance by the University of Washington Biomedical Sciences Review Committee in accordance with Public Health Service guidelines for human experimentation.
7. Phoneme identification was omitted at one site in patient C for clinical reasons.
8. Such individual variability in the exact cortical location of language functions has been quantified for naming. Only cortex immediately in front of the motor strip showed changes in evoked naming in all of the series of left-brain-dominant patients tested. Elsewhere in the classical peri-Sylvian language cortex, 20 to 70 percent of patients sampled showed no naming changes [G. Ojemann and H. Whitaker, *Brain Lang.* **6**, 239 (1978); G. Ojemann, *J. Neurosurg.* **50**, 164 (1979)].
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10. The finding of sites in the dominant cortex where stimulation alters short-term verbal memory, the differential locations where stimulation during input or storage and output alter memory, and the general separation from other language behaviors is identical to that reported for six other patients [G. Ojemann, *Brain Lang.* **5**, 331 (1978)].
11. There is a high degree of functional specificity in the language cortex. Thirty-five sites outside of the final motor pathway for speech showed naming, reading, or memory changes; only four have all three and five, any two. Thus, at three-quarters of the sites, only a single language-related function was altered.
12. An example of a jargon error is the response "It is searnesy sucky," to the sentence, "If it is sunny next Saturday she . . . beach."
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Sibling Matings in a Hunting Wasp: Adaptive Inbreeding?

Abstract. *Upon emergence as adults, brothers of* Euodynerus foraminatus *compete among themselves for the microterritory around their natal nest. The winning male inseminates his sisters as they emerge several days later. Unlike most species that inbreed in a similar fashion, both sexes of this common wasp are strong fliers. The possibility is raised that siblings may be preferred as mates even when outbreeding is possible.*

Among sexually reproducing animals, outcrossing is the rule. Indeed, high frequencies of close inbreeding are known for only a few forms such as gregarious parasitoid Hymenoptera, among which choice seems largely restricted to siblings (*1*). In these generally tiny insects, siblings develop in close proximity on the same host. Males are often flightless (indicating inability to join a general mating pool), reach adulthood before the females, remain in the natal area, and inseminate their sisters, which then seek out new hosts on which to oviposit. Because of the near universality of outbreeding by sexual organisms and its known benefits (*2*), biologists have tended to consider sibling mating systems as forced (in an evolutionary sense) on the species in question by low population densities and thus low chances of females finding suitable mates away from the natal area (*3*). I here report frequent brother-sister matings in an abundant, nonparasitic, solitary wasp, *Euodynerus foraminatus* (Saussure) (Vespidae), which does not seem forced to inbreed since both sexes are strong fliers and capable of dispersing widely. This case raises questions because inbreeding has important genetic consequences with regard to sex determination (*4*), sex ratios (*5*), the maintenance of sexual reproduction (*2*), and rates of evolution (*6*) and speciation (*7*); it is not obvious that costs are offset by benefits.

Normally, females of *E. foraminatus* nest in vacant insect tunnels in wood. Within the tubular hole, a female sequentially constructs and provisions a series of linearly arranged cells separated by mud partitions. Inside each cell she first lays an egg and then provides enough paralyzed caterpillars for the complete growth of the single wasp larva. When foraging, a female may fly several hundred meters to locate and sting caterpillars. Nesting wasps readily accept sticks with drilled holes (trap nests) as nest sites. Through the use of such nests, population density can be manipulated, and trap nests can be opened for study (*8*). Female wasps usually rear both sexes in the same nest hole; females in the innermost and males in the outer cells. The sexes are not intermixed (*9*). Controlled arrangement of the sexes is possible because of the haplodiploid genetic system found in the Hymenoptera. Diploid females are produced when eggs are fertilized at the time of oviposition by sperm stored in the female's spermatheca. Haploid males are produced when sperm are withheld so that unfertilized eggs are deposited. Even though females are provisioned first, males in the outer cells develop more rapidly and emerge from the nest several days ahead of their sisters. Emergence occurs in the morning, and it is usually synchronized so that all individuals of the same sex exit on the same morning within a fairly short period.

When a single nest produces two or more males, they interact aggressively; one brother drives away the others. The fights are brief, and in a matter of seconds the issue is permanently decided. The dominant male becomes resident at the nest and assumes an activity pattern that he maintains for about a week. He usually spends nights away from the nest; but each morning, as the temperature rises, he returns and awaits the emergence of his sisters. He may make periodic short flights from the nest and patrol nearby flowers or vegetation, but he returns to the nest after a few minutes. As the morning passes, these flights away from the nest increase in frequency and duration; and by noon the male no longer returns to the nest but continually patrols plants. The subordinate brothers spend the entire day patrolling vegetation; though they may remain in the area of the natal nest, they do not again challenge their territorial brother.

The females' emergence from the nest is heralded by vibrations they make as they chew through the mud partitions between the cells. At this time the resident male remains standing over the nest hole. As a female exits, the male mounts and copulates with her for 1 to 2 minutes. After mating, if the female has carried him away, the male returns directly to the nest hole and waits for the next female. If another female is already out of the nest, the male initiates copulation directly. Females do not wait for the male and sometimes leave the nest area without copulating. I saw 42 females emerge from 19 nests while each nest was being attended by a resident male. Thirty-three females mated with the resident males (nearly four-fifths), three emerged and flew off while the male was away temporarily, and six emerged and departed while the resident was occupied with another female at the nest. Thus, a male resident at his natal nest inseminates a high proportion of his emerging sisters. Females, after leaving the nest and whether mated or not, usually fly to a nearby leaf or flower where they groom or feed on nectar. At these locations, patrolling males probably find and inseminate the willing females.

Significant inbreeding will result from sibling matings if females do not mate more than once. Were females to mate again after dispersal, it is likely that their mates for these copulations would not be closely related. The available evidence, however, indicates that females of *E. foraminatus* mate once and are thereafter unreceptive. (i) That males compete to be the first to mate with females suggests that subsequent matings by females either do not occur or are less important to the production of offspring. (ii) Freshly mated females successfully reject males by curling their abdomens forward under their thoraxes so that males cannot link genitalia. (iii) Nesting females are not sexually receptive. I never observed males frequenting areas where females were provisioning nests, but on several occasions I saw females initiate nests in holes where males were waiting, at their natal nest, for the emergence of virgin sisters. These nesting females and waiting males were always quarrelsome and never mated.

Table 1. Classification of 104 females from 36 nests with respect to sibling and nonsibling matings.

Nest situation	Mated with brother	Left without mating
No male at nest		
No males produced		41
Abandoned by males		11
Brother at nest		
Females observed	14	5
Other females	24	9
Total	38	66

I estimated the proportion of sibling matings by scoring the emergence of females from trap nests placed in the field at stations 50 feet apart. Forty-five nesting females provisioned 71 nests, and 198 adult wasps emerged from 50 of these nests. From this total, 104 females emerged from 36 nests (*10*). Table 1 categorizes these females as to whether or not they mated with a brother before dispersal. Forty-one females emerged from 16 nests from which males failed to emerge (*11*), and 11 females emerged from five nests from which males emerged but failed to wait at the nest for their sisters. These 52 females probably mated with unrelated males at flowers. The remaining 52 females emerged from 15 nests while the nest was attended by a brother. I could keep only one nest under observation at a time; consequently, some females emerged and left their nests while I was away temporarily. I observed the actual emergence of 19 of these females; 14 of the 19 mated with a brother (three-fourths), and five flew away without mating. By extrapolating, I assigned the remaining unobserved 33 females as sibling mating (24 females) or nonsibling mating (9 females) according to the proportion of females observed mating. Thus, approximately two-fifths of the copulations were between siblings as estimated for the wasps from these 50 nests (Table 1).

The distribution of nesting females, and thus the distribution of emerging males and virgin females, affects the extent of sibling mating. When females nest in isolation, their sons emerge and readily become established at their natal nest; once established as resident, a male is resistant to being displaced. Occasionally, patrolling males attacked resident males, but the residents prevailed and returned to their position after a skirmish. However, males that have just emerged from the nest seem to be driven off easily by intruders, who then assume typical resident behavior at the nest they have usurped (*12*). Vulnerability of callow males to displacement is apparent only during their first morning out of the nest, perhaps because they are not yet oriented to the area. When nests provisioned by different females of the parental generation are nearby, the chance that callow males will be discovered and driven away by intruders increases because territorial males are constantly in the area, and males are less able to monopolize their emerging virgin sisters. Sometimes, males from nearby nests emerge and become established before discovering each other. Once established, these males are reluctant to yield, and over a period of several days they may fight many times during the morning hours without one's finally driving off the other. When males were distracted by constant quarreling, females were more likely to emerge and disperse before mating; when rival males are in the area constantly, copulations may be interrupted, further reducing the amount of sibling mating.

Reports on the behavior of other abundant, strong flying species suggest sibling mating is probably more important than generally realized (*13*), and inbreeding by species that are not constrained by a scarcity of mates after dispersal indicates that the evolutionary role of sibling mating needs to be more carefully considered. A female that mates with a brother increases her relatedness to her offspring, and thus may increase her genetic representation in subsequent generations relative to outcrossing females (*2, 14*). A male gains because he encounters more females by remaining at the natal nest but still participates in a general mating pool. Also, the sex ratio control afforded by haplodiploid genetic systems allows hymenopteran females to gain further by shifting their reproductive effort toward daughters once inbreeding has begun (*5, 10*).

The selective forces acting on these wasps may be similar to those that led to an alternation of sexual and asexual generations in organisms such as aphids or gall wasps. Inbreeding combined with sex ratio control and bias toward females is comparable to parthenogenetic reproduction; reproductive effort is diverted from "excess" sons to the production of more daughters which are genetically more similar to the parents. This results in a higher rate of increase for the genetic line than would occur under outbreeding, but it occurs at the expense of genetic variability. The regular occurrence of mating between nonrelatives at flowers ensures that new genetic combinations are continually generated. It seems that for *E. foraminatus* the costs of reduced genetic variability, resulting from partial inbreeding, are outweighed by the benefits of large numbers of daughters with high genetic relatedness to the parents.

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10. The sex ratio is 0.47 (94 males per 198 total wasps). Since parents provide an average of 0.204 g of caterpillars to individual daughters and 0.130 g to individual sons (*8*), the sex ratio of parental investment is 0.37 for those wasps that reached adulthood. Even though this is not the primary sex ratio of investment, there is a female bias as is expected to occur with inbreeding (*4*).
11. The circumstances under which only females emerged from nests were when no male eggs were laid or when all of the males died before reaching adulthood.
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Antipsychotic Drug Action in Schizophrenic Patients: Effect on Cortical Dopamine Metabolism After Long-Term Treatment

Abstract. *In the brains of deceased schizophrenics who underwent long-term treatment with antipsychotic drugs, the concentration of homovanillic acid (a dopamine metabolite) was significantly increased in the orbital frontal, cingulate, and temporal tip areas of the cortex, but not in the putamen or the nucleus accumbens. The concentration of homovanillic acid was normal in the brains of schizophrenics who were not treated with antipsychotic drugs.*

The dopamine hypothesis of schizophrenia (*1*) proposes that an abnormal increase in the activity of central dopamine neurons or in the sensitivity of dopamine receptors is an etiologic factor in schizophrenia. Although antipsychotic drugs exert their therapeutic actions by competitively inhibiting the binding of dopamine to its receptors in the central nervous system (CNS) (*2*), there is insufficient evidence to suggest excessive neuronal activity in the dopaminergic pathways in the CNS of schizophrenics (*3*). However, the administration of drugs that increase the synaptic availability of dopamine exacerbates schizophrenic symptoms in patients or precipitates a state in normal subjects that is similar to paranoid schizophrenia (*4*). Moreover, initial treatment of schizophrenics with α-methyltyrosine, a drug that lowers catecholamine concentration in the brain, reduces the dose of antipsychotic drug required to produce noticeable improvement (*5*).

Antipsychotic drug treatment increases the concentration of homovanillic acid (HVA), a dopamine metabolite, in the cerebrospinal fluid (CSF) of schizophrenic patients. This suggests a dopamine receptor blockade in the CNS of schizophrenics (*6, 7*). The increase in HVA, however, subsides after long-term treatment with antipsychotic drugs, although their therapeutic effects persist (*8*). Because HVA in CSF originates primarily from periventricular regions (*9*), its increased concentration in CSF does not necessarily reflect alterations of dopamine metabolism in other brain regions. Indeed, certain studies on rodents (*10*) suggest that tolerance to the effects of antipsychotic drugs on HVA concentration develops in periventricular brain structures such as the caudate nucleus and in deeper, limbic regions, but not in cortical areas. We have recently confirmed these findings in a primate species (*11*). The cingulate, temporal, dorsal frontal, and orbital frontal areas of the cortex maintained their responsiveness to the effects of haloperidol on HVA concentration, whereas tolerance to this effect developed in the putamen after 20 daily haloperidol injections (0.5 mg/kg, intramuscularly). The demonstration of an analogous regional specificity in the long-term effects of antipsychotic drugs in the human brain would provide the dopamine hypothesis of schizophrenia with a neuroanatomical basis essential to the further elaboration of the hypothesis. Not all dopaminergic pathways in the brain that have been described (*12*) can be implicated in the antischizophrenic action of antipsychotic drugs. Specifically, the development of tolerance to the ability of antipsychotic drugs to accelerate dopamine metabolism in brain regions innervated by the nigrostriatal and mesolimbic pathways excludes those pathways from the possible sites of therapeutic action and, therefore, from the possible loci of a primary lesion in schizophrenia.

We measured the concentration of the dopamine metabolites HVA and 3,4-dihydroxyphenylacetic acid (DOPAC) in cortical and subcortical brain regions obtained at autopsy from schizophrenic and normal subjects matched by sex, age, and autopsy interval. Brain regions were kept at −70°C until assay. Samples weighing between 150 and 250 mg were removed and homogenized in 4 ml of 0.1*N* formic acid containing 100 μg/ml Na metabisulfite and 100 ng/ml of two deuterated internal standards (HVA-d_2 and DOPAC-d_5 from Merck Sharp & Dohme, Canada). The supernatant obtained by centrifugation at 10,000*g* was saturated with NaCl and the acidic metabolites were extracted into 5 ml of ethyl acetate, which was then evaporated under a stream of dry N_2. The metabolites were derived and then quantitated by mass spectrometry (*13*). In the brain regions we examined, DOPAC constituted a small fraction of total dopamine metabolites and did not change with drug treatments; therefore, the results are discussed in terms of HVA. Brains from the schizophrenic group were divided into two subgroups: those from patients who had received long-term treatment with antipsychotic drugs and those who had not.

The concentration of HVA was signifi-

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