netic 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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8. I placed trap nests, made from 25 by 25 by 152 mm pine sticks, each with a hole drilled longitudinally to a depth of 140 mm, in a field in southeastern Michigan. I gave nesting females individual marks. Shortly before the young wasps were likely to eclose as adults (about 25 days after the mother sealed the nest), I brought the nests into the laboratory and split the sticks to reveal the contents. After eclosing as adults, wasps remain quiescent within the nests for about 3 days while their exoskeletons harden. During this period, I opened the nests and gave each group of brothers a distinctive mark or marked each male individually, measured the wing lengths, resealed the nests, and replaced them in the field. I marked 152 males from 70 nests by this method (D. P. Cowan, thesis, Univ. of Michigan, 1978).
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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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2 May 1979; revised 13 July 1979

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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Table 1. Homovanillic acid concentrations (micrograms per gram of tissue) in brain regions from schizophrenics and controls. Long-term treatment with antipsychotic drugs (chlorpromazine, perphenazine, fluphenazine, trifluoperazine, thioridazine, and haloperidol, separately or in combination) had been given for periods ranging from 6 months to 17 years. For controls, the average age was 61.2 ± 1.6 years; for schizophrenics, 65.6 ± 3.4 years. No significant effects of sex or age were seen on the concentration of HVA in the brain regions examined. Statistical analysis by modified t-test [which considers the difference in variance between groups (*17*)] was performed for those regions in which the variance was inhomogeneous between groups. The difference in variance between groups was estimated by an F-test in which the F value was the quotient of the larger of the two unequal variances divided by the smaller. A significant F value indicated the existence of different variances—as was the case for the three cortical regions. In all cases, this variability was due to a large variance among the drug-treated groups, which is understandable considering the widely varied durations of treatment. For the putamen and the nucleus accumbens (which produced F's at a $P > .05$), statistical analysis was carried out by conventional group t-test. S.E.M., standard error of the mean; N, number of cases in each group.

Brain region	Control group		Schizophrenics			
			Antipsychotic drug treatment		No antipsychotic drug treatment	
	Mean ± S.E.M.	N	Mean ± S.E.M.	N	Mean ± S.E.M.	N
Temporal cortex (area 38)	0.18 ± 0.01	22	0.29 ± 0.03*	18	0.23 ± 0.06	3
Cingulate cortex	0.33 ± 0.04	20	0.66 ± 0.11†	18	0.23 ± 0.05	3
Orbital frontal cortex (area 12)	0.15 ± 0.02	20	0.23 ± 0.03‡	19	0.20 ± 0.03	3
Putamen	8.93 ± 0.43	28	10.48 ± 0.73§	25	6.66 ± 0.55	3
Nucleus accumbens	8.36 ± 1.07	7	11.02 ± 1.04§	5		

*P = .001. †P = .01. ‡P = .02. §P = .10.

cantly increased in the cingulate gyrus (area 24), the perifalciform region of the temporal lobe (area 38), and the orbital frontal cortex (area 12) of schizophrenics who had received long-term treatment with antipsychotic drugs (Table 1). In the putamen and the nucleus accumbens, no significant difference in HVA content was observed between treated schizophrenics and controls. The HVA content in schizophrenics who had not been treated with antipsychotic drugs was within the control range. The number of specimens in this group was small, so we do not consider this negative evidence to be conclusive. The data from the treated schizophrenics suggest a remarkable similarity between the response of the human brain to the long-term administration of antipsychotic drugs and the response of other primates or lower animals to such drugs.

The increased HVA concentration in the cortical regions of schizophrenics who had been treated with antipsychotic drugs suggests that an effective blockade of dopamine receptors had occurred and been maintained in those regions. The HVA concentration had not increased significantly in the projection areas of the nigrostriatal and mesolimbic dopamine pathways, the putamen, and the nucleus accumbens, suggesting that tolerance to the effects of antipsychotic drugs had developed in those neuronal systems. Because the therapeutic actions of antipsychotic drugs are not diminished by tolerance, the sustained biochemical alterations in dopamine metabolism in cortical regions are probably involved in antipsychotic drug action.

These findings add anatomical specificity to the dopamine hypothesis of schizophrenia, insofar as they implicate specific cortical regions in the therapeutic actions of antipsychotic drugs and thus suggest possible loci for the pathophysiology of schizophrenia. For example, the cingulate gyrus is part of a neuroanatomical system that regulates emotion (*14*), and the orbital and perifalciform cortical regions are associative areas involved in higher mental function. Since schizophrenia is characterized by cognitive and affective disturbances, abnormalities in the function of those brain regions may lead to schizophrenic symptoms. Unfortunately, the exact nature of the abnormality that leads to schizophrenic disease is not known. Our findings that HVA concentrations in brains of schizophrenics who had not received antipsychotic drugs did not differ significantly from concentrations in the controls supports the view that the endogenous deficit of dopamine in schizophrenia probably does not involve mechanisms regulating the presynaptic release of dopamine, but rather the sensitivity of postsynaptic dopamine receptors.

Increased binding of dopamine receptor ligands has been found in the caudate nucleus of schizophrenics who did not receive antipsychotic drug treatment (*15*); it would be interesting to investigate the applicability of that finding to cortical areas. Antipsychotic drugs would reverse the functional deficit resulting from excessive activity at dopaminergic synapses, regardless of the presynaptic or postsynaptic origin of the disturbance. However, it is just as plausible that the biochemical abnormality in schizophrenia occurs in nondopaminergic neurons, and that the inhibition of the latter by antipsychotic drugs merely restores a dynamic equilibrium that was biased in favor of dopaminergic influences by the disease process.

These experiments provide the first direct experimental evidence that antipsychotic drugs accelerate the metabolism of dopamine in the human brain in a regionally specific manner. Because their therapeutic action is not reduced by their long-term use (*16*), sustained increases in HVA concentration in the cingulate, orbital frontal, and perifalciform regions of the cortex implicate those brain regions as possible sites of antipsychotic drug action. Moreover, the apparent lack of long-term alterations in the metabolism of dopamine in the putamen may explain why tolerance eventually develops to the extrapyramidal side effects initially induced by treatment with antipsychotic drugs.

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18. Supported in part by the State of Connecticut and grants MH-14092, MH-25642, and MH-30929 from the U.S. Public Health Service. We thank M. Rossor of Addenbrookes Hospital, Cambridge, England, for his help in obtaining some of the brain specimens used in this study.

4 December 1978; revised 4 May 1979

Pseudohermaphroditism in *Ilyanassa obsoleta* (Mollusca: Neogastropoda)

Abstract. *Field studies, a rearing and maintenance program, and a transfer experiment have shown that anomalous male traits found in some female* Ilyanassa obsoleta *are an expression of environmentally controlled pseudohermaphroditism. The particular pattern of pseudohermaphroditism discovered in this species has not been reported previously from any other group, but may be characteristic of the Neogastropoda.*

Females with a penis have been found in a number of apparently dioecious neogastropod species in which most individuals are clearly male or female (*1–12*). The female's penis is located on the head behind the right cephalic tentacle, just as the male's is; it is sometimes "vestigial," but in other cases resembles the male's organ in both size and shape (*1–9*). In some females a "sperm duct" leads up to the penis, and the oviduct is convoluted, resembling the male's vas deferens (*1–4*). Although they possess male sexual traits, these penis-bearing females are not simultaneous hermaphrodites. Dissections, gonadal smears, and histology have shown that they have a complete female system and produce ova, but their male system is incomplete, the testis being absent (*1–6*).

Several hypotheses have been proposed to explain this phenomenon. The most notable is that the snails are protandric hermaphrodites that first function as males, then change into females, losing the testis but keeping male secondary traits (*4, 12, 13*). But sex ratio and size frequency analyses done on populations of two species having some females with male structures have failed to provide any evidence of sex change (*6, 11*), and the hypothesis has not been tested experimentally.

The study of anomalous sex traits in neogastropods has been hampered by the similar coloration of the male and female systems in most species, which makes the distinction between males and penis-bearing females difficult (*6, 13, 14*). The mudsnail *Ilyanassa obsoleta*, a neogastropod in which some females have a penis (*3*), differs in this regard; males have a bright red-orange testis, whereas the females have a white ovary and a white egg capsule gland with red lips. It is thus simple to tell whether a dissected *I. obsoleta* with a penis is actually a male, or a female with male traits. This made *I. obsoleta* well suited for a study of anomalous sex traits.

I examined over 10,000 *I. obsoleta* from more than 70 populations during a 10-year period. Each snail was cracked and removed from its shell; its sex and any anomalous sexual traits were recorded. To assure the accuracy of sexual identifications, I examined the entire reproductive system, not just a single diagnostic feature.

Female *I. obsoleta* with male traits were found to be common; however, the percentage of females having a penial organ varied greatly between sites. Although a complete range of population types was found, at many sites no females with a penial structure were ever collected; in many other locations nearly all the females examined had a penis of some kind (Table 1). The two extreme population types showed no geographical pattern. They did not appear related to sex ratio, and males were not scarce at the sites where most females had a penis (*15*). Repeated samples revealed that male traits were present year round at the sites where females had them. The female's penis was lost at the end of the reproductive season, just as the male's was, but in both sexes a penial bump remained from which a new penis later developed.

Most populations, including some followed for 10 years, stayed the same year after year. At those sites where females originally lacked male traits (for example, Newport River Causeway, North Carolina), they continued to lack them during the survey period. Where females originally had a penis (for example, Bogue Sound, North Carolina), females had penial organs throughout the study. This was true even where populations of the two extreme types were located within the same sound or estuary and only a few kilometers apart. This consistency cannot be explained either by genetic isolation or by low recruitment rates, since the larvae of *I. obsoleta* have a long planktonic existence (*16*), and immature forms comprise a large portion of the populations each year.

Males with a female character, the eggcase-molding foot gland, were also found; this anomaly has not been reported before from any neogastropod. Such males were very rare, and their occurrence did not appear related to the presence of penes in females.

Immature *I. obsoleta* form distinct

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