The model is also at variance with those currently popular positions which hypothesize a variable unilateral (left- or right-sided) representation of speech in the LH (*6-8*). This type of position would generate an EUL value identical to that of the RH (50 percent), which would not account for the raised incidence of aphasia reported for the LH (*14*). The results demonstrate that this increased incidence could be produced only by an increase in the number of the LH who, because of an incomplete functional lateralization of speech (bilateral), are more sensitive to the effects of an acute unilateral brain lesion. The model would also help explain clinical reports of a raised incidence of aphasia in the LH after injury to the left hemisphere (*5*). Approximately 85 percent of them would be expected to have at least partial representation of speech in the left hemisphere.

This model would also be compatible with studies that have reported a more dramatic remission of aphasia in the LH following unilateral brain injury (*1, 4*). If the majority of the LH (approximately 70 percent) have bilateral representation of speech, this atypical organization would spare them from the more severe and prolonged effects of a unilateral lesion that would be seen in an RH person whose speech mechanisms are more laterally differentiated (*15*). Would the recovery course in those LH (approximately 30 percent) who are predicted (Table 3) to have a more variable unilateral representation of speech (left- or right-sided) be similar to that of RH patients? Recent evidence linking familial left-handedness (in sinistrals) to bilateral cortical speech (*16*) provides one approach, albeit indirect, to these questions.

One final caution should be noted. This model of cortical speech organization in the LH represents merely the best fit with the observed data on the frequency of aphasia after unilateral injury to the brain. Although these studies comprise all of the known reports between 1935 and 1978, they represent only one of several inferential approaches to speech-brain asymmetry in the LH. It is, however, one approach that lends itself to more quantitative inferential test.

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13. This estimate also approximates closely the observed incidence of dysphasia after an operation on the left hemisphere in right-handed (73 percent) and left-handed (72 percent) patients as reported by Penfield and Roberts (*5*). It also approximates the value computed by M. Annett [*Cortex* **11**, 305 (1975)] and J. Levy [in *Hemisphere Function in the Human Brain*, J. Dimond and J. Beaumont, Eds. (Wiley, New York, 1974)].
14. Any model which postulated a unilateral or variable unilateral mode of speech (left- or right-sided) would generate an EUL value of 50 percent, regardless of differences in the proportions of speech representation between hemispheres.
15. The proportions derived from Table 3 closely approximate the findings of a recent study of bilateral intracranial arteriograms in left- and right-handers [F. Hochberg and M. LeMay, *Neurology* **25**, 218 (1975)]. The authors found that the right sylvian point angle was greater than the left by more than 10° in the majority of right-handed patients. However, in the left-handed patients, the majority (71 percent) had comparatively equal right and left sylvian point angles.
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Enduring Changes in Dopamine Receptor Cells of Pups from Drug Administration to Pregnant and Nursing Rats

Abstract. *A decrease in specific [^3H]spiroperidol binding to rat caudate tissue and a parallel decrease in sensitivity to apomorphine in eliciting stereotyped behavior was observed in the offspring of rat mothers treated with either haloperidol or α-methyl-p-tyrosine-methyl ester during pregnancy. In contrast, evidence of increased dopamine-receptor sensitivity was observed in the pups if haloperidol was administered to their mothers postpartum during nursing rather than during pregnancy.*

Although mechanisms for the storage and synthesis of dopamine are present at a very early stage of ontogeny (*1-3*), dopamine-containing neurons gradually develop their functions during fetal life and the first 4 weeks of postnatal life (*4*). The activity of tyrosine hydroxylase, the concentration of dopamine, and the activity of dopamine-stimulated adenylate cyclase in the striatum at birth, represent only 20 percent of adult levels for these neurochemical markers of dopaminergic activity, which achieve adult levels at the age of 3 to 4 weeks of postnatal life (*2, 5*). Cell bodies for dopaminergic neurons are extrinsic to the striatum, and changes in their neurochemistry reflect an ingrowth, proliferation, and development of terminals (*1*). The fetal and early postnatal periods in rats may, therefore, be vulnerable stages in the functional maturation of the central dopaminergic system (*6-8*). In the study described here we demonstrated that certain drugs, administered during these two periods related to the maturation of dopaminergic mechanisms, have pronounced prolonged effects on central dopamine receptors and on the response to a dopaminergic agonist.

To test the prenatal effects of drugs, we injected pregnant female Wistar rats intraperitoneally with either haloperidol (2.5 mg/kg-day) (*6*), α-methyl-*p*-tyrosine-methyl ester (α-MT) (50 mg/kg-day) (*9*), or saline. The injections were given for 16 days, beginning on day 4 or 5 after conception. No rat mother died during the treatment and none appeared to be ill or suffering from an adverse reaction. These doses of haloperidol and α-MT produced no apparent sedation, nor did they interfere with eating or drinking. Each pregnant rat was placed in a separate cage 4 to 5 days before she was expected to give birth. Within 12 hours after birth runts were discarded and all litters culled to ten pups. All pups were weighed at 1 week of age and weekly thereafter until they were killed. Dopamine receptor function was assessed in the pups by measurement of specific binding of [^{3}H]spiroperidol in caudate homogenate (*10*) by a modification of the method of Fields *et al.* (*11*). The stereotyped behavioral response to apomorphine was assessed with a five-point scale (*12*), which was a modification of a scale developed by Tarsy and Baldessarini (*9*). We also studied the effect of haloperidol on pups whose mothers were first allowed to give birth and then were

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Table 1. Specific binding of spiroperidol to striatal dopamine receptors of offspring of rat mothers subjected to various treatments. Values are expressed in femtomoles of [^{3}H]spiroperidol bound per milligram of protein. For the statistical analysis we used a two-tailed Student's t-test. The radioactivity in duplicate assays of caudates from 21-day-old control rat pups was typically as follows: total, 2362 and 2423 count/min; nonspecific, 890 and 856 count/min; mean difference, 1519 count/min, per 300 μg of protein (corrected for efficiency = 213 femtomoles of [^{3}H]spiroperidol bound per milligram of protein). N.S., not significant.

Group	At 14 days		At 21 days		At 28 days		At 35 days		At 60 days	
	Binding	N	Binding	N	Binding	N	Binding	N	Binding	N
Haloperidol-treated during pregnancy	75.0 ± 5.0	14	80.7 ± 7.1	10	93.5 ± 9.3	12	155.0 ± 9.3	12	173.0 ± 9.2	3
Saline controls	190.0 ± 12.1	20	199.2 ± 6.4	14	250.7 ± 10.7	12	241.0 ± 14.3	8	222.1 ± 12.4	3
Probability level	.001		.001		.001		.001		.05	
α-MT-treated during pregnancy	60.0 ± 11.4	6	147.8 ± 7.1	6	247.8 ± 12.1	6				
Saline controls	197.0 ± 9.3	6	192.8 ± 10.7	6	260.7 ± 10.0	6				
Probability level	.001		.01		N.S.					
Haloperidol-treated during nursing							340.7 ± 10.7	12		
Saline controls							241.4 ± 14.3	13		
Probability level							.001			

injected daily with haloperidol (2.5 mg/kg-day); mothers of control pups received injections of saline.

We found no significant difference in number of pups born to mothers treated during pregnancy with haloperidol, α-MT, or saline. There was also no difference in the weights of the pups at 1 week of age, or in their weight gain during the first 4 weeks of postnatal life (Student's t-test, two-tailed). During this period there were 10 deaths in the 112 pups born to haloperidol-treated mothers, 11 deaths in the 120 pups born to control mothers, and 3 deaths in the 27 pups born to α-MT-treated mothers (χ^2, not significant).

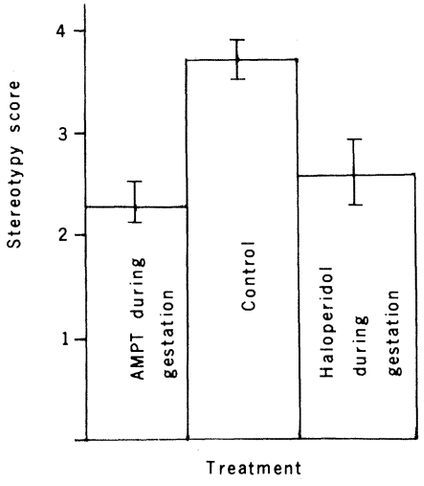

Fig. 1. Apomorphine-induced stereotyped behavior. Apomorphine (0.3 mg/kg) was administered to the offspring of saline-treated control rat mothers and the offspring of rats treated with haloperidol or α-MT during pregnancy. The stereotypy score represents the mean number of stereotyped movements observed during a 1-minute period. Observations were made every 10 minutes for a total of 60 minutes after apomorphine treatment. A statistically significant decrease was observed in 28-day-old offspring of haloperidol and α-MT-treated animals when compared with 28-day-old offspring of controls. Values are expressed as means ± standard error, $N = 6$ in each group ($P < .02$, Student's t-test, two-tailed for both treatment groups).

A significant decrease was found in [^{3}H]spiroperidol binding in the striatum of animals born to mothers treated with haloperidol during pregnancy (Table 1). The decrease was still apparent at day 60 of postnatal life, when we made the last measurement. In both the drug-treated and the control groups, however, a gradual increase in specific binding occurred over the 8-week postnatal period, with the offspring of haloperidol-treated mothers slowly catching up with the offspring of controls.

Two additional experiments were carried out in which Scatchard plots were made from specific binding studies. In experiment 1, with 14-day-old pups treated with haloperidol prenatally, the dissociation constant, K_d, was 0.37 nM; for saline-treated controls, $K_d = 0.40$. In experiment 2, with similar pups, for those treated with haloperidol $K_d = 0.65$, and for those treated with saline, $K_d = 0.65$. The number of binding sites per unit of protein in the haloperidol-treated rats in experiments 1 and 2 was, respectively, 34 and 47 percent of control. Apomorphine produced significantly less stereotypy in 28- and 35-day-old rats exposed to haloperidol prenatally, compared to age-matched controls (Figs. 1 and 2). Stereotypy was not determined at younger ages.

In the offspring of α-MT-treated mothers, we also observed a significant decrease in [^{3}H]spiroperidol binding to striatal tissue; however, the decrease in binding was less pronounced and of shorter duration than in the haloperidol group (Table 1), returning almost to control values after 28 days. A significant decrease in sensitivity to apomorphine was observed in the offspring of α-MT-treated rat mothers when they were tested at 28 days of age (Fig. 1), and the difference from controls was significant. Stereotypy was not assessed at other ages.

When the mothers were injected with haloperidol after they gave birth (*6*, *7*), their pups were 20 percent heavier at the age of 3 weeks than the pups of control mothers ($P < .001$). At age 35 days (2 weeks after termination of treatment of the mothers) these pups demonstrated a significant increase in [^{3}H]spiroperidol

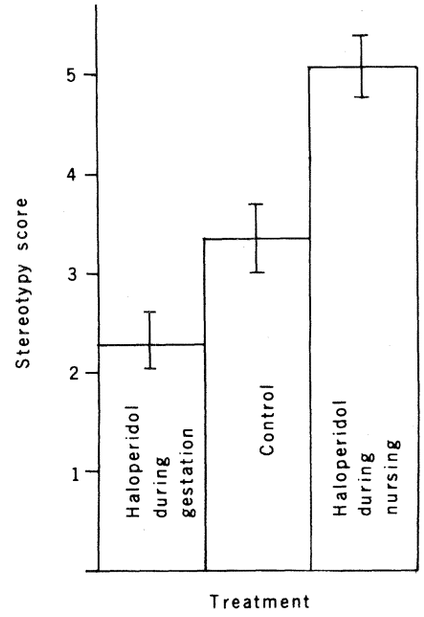

Fig. 2. Apomorphine (0.3 mg/kg)-induced stereotyped behavior. A statistically significant increase in stereotypy was observed in 35-day-old rats that received haloperidol during nursing ($P < .001$, Student's t-test, two-tailed, $N = 6$), whereas a statistically significant decrease in stereotypy was observed in the 35-day-old offspring of rat mothers that received haloperidol during pregnancy ($P < .02$, $N = 6$).

binding and in sensitivity to apomorphine (Table 1 and Fig. 2), the effect of haloperidol being similar to that observed in adult rats (*13*).

The decrease in [^{3}H]spiroperidol binding and apomorphine-induced stereotypy in the offspring of rats treated with haloperidol during pregnancy does not appear to be the result of malnutrition or retarded growth. Inasmuch as haloperidol restricts the access of dopamine to the receptor and α-MT blocks dopamine synthesis, it may be that normal receptor development is contingent on exposure of developing receptor cells to dopamine. When pups receive haloperidol postnatally in the milk of their mothers, they demonstrate supersensitivity on haloperidol withdrawal. This is similar to the effect in mature rats and presumably reflects the effect of blockade of more mature receptors.

The fact that moderately high doses of a neuroleptic administered to pregnant or nursing rat mothers produces prolonged sensitivity changes in their offspring may have implications for the offspring of human mothers treated with neuroleptics.

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HCN Did Not Condense to Give Heteropolypeptides on the Primitive Earth

Matthews and co-workers propose that (i) heteropolypeptides are formed directly from hydrogen cyanide (HCN) (*1*, *2*) and (ii) these polypeptides were formed on the primitive earth as well as such extraterrestrial environs as the moon and Jupiter (*3*). I briefly outline earlier data, which they do not cite, and other results that show their hypothesis is incorrect.

The available experimental evidence in support of the proposal that polypeptides and their precursors are formed directly from HCN is tenuous (*1-4*). There are two findings (i) that hydrolysis of HCN oligomers gives amino acids and (ii) that HCN oligomers exhibit infrared absorption at a frequency where the carbonyl and imine group is known to absorb. However, many compounds release amino acids on hydrolysis—a notable example is the formation of glycine by hydrolysis of diaminomaleonitrile, a tetramer of HCN, while infrared absorption in the carbonyl region does not prove that peptides are present (*5*).

Two different laboratories reported experiments that were specifically designed to test for the presence of peptide bonds in the HCN oligomers; these experiments yielded completely negative results, which were not cited by Matthews *et al.* (*6*, *7*). Of particular significance is the absence of oligomer hydrolysis catalyzed by Pronase, an enzyme that will even catalyze the hydrolysis of diglycine to glycine. If peptide links are present in the HCN oligomers, a significant number should be diglycine units, which would be susceptible to Pronase catalyzed hydrolysis. Matthews (*3*) cites unpublished work in which the enzymatic hydrolysis of HCN oligomers is claimed (*3*). This study (*3*) remains unpublished.

Matthews' recent papers (*1*, *2*) do not even acknowledge that the formation of heteropolypeptides has been disputed. The hydrolysis of the reaction product of poly(α-cyanoglycine) and H^{13}CN to yield ^{13}C-labeled amino acids is discussed (*2*). But, since poly(α-cyanoglycine) already contains peptide links, no data concerning the presence of peptides in the HCN oligomers can be obtained from these experiments. The incorporation of deuterium in the amino acids released on hydrolysis of the HCN oligomers with DCl in D_2O is also reported (*1*). These data do not provide evidence for peptides or peptide precursors since it is noted that deuterated glycine is released on deuterolysis of diaminomaleonitrile [(reference 14 in (*1*)]. Since diaminomaleonitrile has a central role in the formation of HCN oligomers (see below), it is not surprising that deuterolysis of the HCN oligomers yields deuterated glycine.

Azacyclopropenylidenimine, a dimer of HCN, is claimed to be the monomer unit that condenses to give the HCN oligomers (*1*, *2*, *8*). First, no mention was made of the iminoacetonitrile structure for the HCN dimer, which has been shown to be the most stable dimer of hydrogen cyanide by a variety of theoretical calculations (*9*). Second, since only a low steady-state concentration of the HCN dimer, be it iminoacetonitrile or azacyclopropenylidenimine, will be produced from HCN it is highly unlikely

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