concentration per million cells decreased. Astrocytoma cells were also rich in VIP, but the peptide concentration in these cells was less than half that in neuroblastoma cells. Buffer solution in which cells were suspended, and the medium in which they were grown, contained nondetectable levels of the peptide. After incubation for at least 1 day, however, immunoassayable VIP was demonstrable in cell-free medium, in concentrations of approximately 200 pg/ml.

Vasoactive intestinal polypeptide immunoreactivity was also present in normal neural tissue (Table 2), being highest in cortex from frontal and occipital lobes, and hypothalamus, moderately high in hippocampus and white matter from frontal lobe, and lowest in cerebellum, brainstem, and vagus nerve. Peptide concentrations per gram wet weight were lower in duodenum, ileum, and colon than in the richest nervous tissues, raising the possibility that the VIP content in gastrointestinal organs may be partly due to the innervation of these organs. Skeletal muscle and liver contained traces or nondetectable levels of the peptide. This distribution of VIP resembles in some respects (for example, its paucity in cerebellum and liver) the tissue distribution of norepinephrine (*8*).

Extracts of frontal lobe cortex and of neuroblastoma cells (C46 clone) were assayed for VIP-like biological activity, based on their ability to relax isolated, superfused rat stomach strip and guinea pig gallbladder (*4*). The bioassay confirmed the presence of biologically active peptide. The high levels of VIP or a related peptide in both gray and white brain matter correlate with its presence in tumor cell lines of both neuronal and glial origin. These findings, and the selective distribution of the peptide in the central and autonomic nervous systems, suggest a possible function for this peptide, or one that is similar to it, in the nervous system. Until additional data are available, including the possible effects of the peptide on neural function, its physiologic role remains speculative. Such a role could include a modulator, trophic, growth-promoting (*9*), or transmitter action (*10*). An endothelial proliferative factor, elaborated by clonal cell lines of neural origin (*11*), is probably distinct from VIP, since this factor is reported to be destroyed by heating to 56°C for 10 minutes, while VIP resists boiling for that period (*1*). Pertinent to our results are the recent findings that substance P, another vasoactive peptide that was originally discovered in intestine (*12*), also occurs in the central nervous system (*13*) and may have a modulator or transmitter function (*14*); that gastrin immunoreactivity occurs in brain (*15*); and that somatostatin (growth hormone release–inhibiting hormone) (*16*) is found both in the central nervous system and the gastrointestinal tract (*17*).

Table 2. Distribution of VIP immunoreactivity in nervous, gastrointestinal, and other tissues from dogs. Values are in nanograms per gram, wet weight.

Tissue	VIP
Nervous tissues	
Frontal lobe cortex	61
Frontal lobe white matter	35
Temporal lobe cortex	24
Occipital cortex	66
Cerebellar cortex	2
Hippocampus	39
Thalamus	2
Hypothalamus	65
Pons	1.3
Medulla	2.5
Midbrain	3.3
Sympathetic nerve	6.4
Vagus	0.6
Gastrointestinal tissues	
Duodenum	13.2
Ileum	14.0
Ascending colon	10.6
Liver	<0.06
Other tissues	
Skeletal muscle	0.1

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Human Handedness: A Partial Cross-Fostering Study

Abstract. *The hand preference of college students correlated significantly with the writing hand of their biological parents but not that of their stepparents. The results are consistent with a genetic theory of the origin of human handedness.*

In contrast with nonhuman mammals, which show no preference (*1*), at least 90 percent of the humans in those cultures studied prefer to use the right hand for most skilled activities (*2*). There is indirect evidence of right-handedness in prehistoric man (*3*) and even in Australopithecus (*4*). The left cerebral hemisphere controls the right hand and language in most right-handers (*5*). In addition, the two cerebral hemispheres are anatomically asymmetrical (*6*), and some of the observed asymmetries correlate with preferred handedness (*7*). Handedness and cerebral organization are also related in that left-handers, as compared to right-handers, have less clear-cut laterality of virtually all cognitive functions (*5*, *8*).

The genesis of handedness in humans is unclear. Collins (*9*) and Provins (*10*) have hypothesized that learning is primarily responsible. Nagylaki and Levy (*11*) have refuted much of Collins's (*9*) evidence that genetic factors are not involved, although studies of twins have never provided clear evidence for a genetic factor (*11*). They report that the frequency of left-handedness in twins, both dizygotic and monozygotic, is significantly higher than in singletons; that finding calls into question the results of heritabil-

Table 1. Mean laterality quotients as a function of handedness of the biological parent, handedness of the stepparent, and sex of the biological parent. The number in parentheses is the number in each group.

Biological parent handedness	Stepparent handedness		
	Right	Left	None
	Father		
Right	84.89 (9)	86.43 (7)	82.00(11)
Left	55.51 (6)	68.40 (5)	54.40 (5)
	Mother		
Right	83.80(45)	85.63(11)	93.57(23)
Left	71.86(15)	67.59(10)	73.02 (4)

ity studies of this trait in twin populations. The increased frequency of left-handedness in twins may in part result from both their higher rate of perinatal brain damage and, in monozygotic twins, to situs inversus (*11, 12*), sources of nongenetic variance in twins absent in nontwins. Family studies [for example, (*13, 14*)] have repeatedly demonstrated that left-handedness runs in families but not in any obvious, single locus Mendelian pattern. This enables environmental theorists to claim that the familial resemblance occurs through learning (*9, 10*). However, close examination of familial resemblance casts doubt on the learning hypothesis. Annett (*13*) notes that 84 percent of all left-handers have two right-handed parents, 72 percent of the mothers with a left-handed offspring are themselves right-handed, and roughly 50 percent of the offspring of two left-handed parents are right-handed.

In our study we followed a partial cross-fostering design (*15, 16*). The handedness of college students was correlated with the handedness of their biological parents and, in some cases, their stepparents. A handedness inventory (*17*) was administered to college students enrolled in psychology courses at the University of Texas at Austin and the State University of New York at Albany between 1973 and 1975. In addition, the students indicated which hand each parent wrote with and whether each parent was biologically related or was a stepparent. Of the 1252 students questioned, 1101 (87.94 percent) had two biological parents (BP), 108 (8.63 percent) had one biological and one stepparent (SP), and 43 (3.43 percent) had only one biological parent and no stepparent. The mean age of the students was 20.18 years (standard deviation = 2.47), and this did not differ significantly ($P > .05$) across parental groupings. Students who had a stepparent with whom they had lived had a mean of 7.24 years (standard deviation = 3.12).

In the preliminary analysis, the laterality quotients (LQ) of the students were correlated with the handedness of the parents of (BP + BP) families and the parents of (BP + SP) families. A parent was assigned a score of 1.0 for right-handed writing (R) and 0.0 for left-handed writing (L). Thus, R × R, R × L, L × R, and L × L parental groups were assigned midparental scores of 1.0, 0.5, 0.5, and 0.0, respectively. (The first symbol represents the writing hand of the father.) The correlation between midparental value and LQ was .52 for (BP + BP) families, and .38 for (BP + SP) families. The difference between these two correlations is significant [Fisher r to z transformation (*18*); $z = 1.762$, $P = .0392$; one-tailed test]. This result is consistent with a genetic or prenatal interpretation, but it is not conclusive.

The correlation of .38 between (BP + SP) midparental handedness and LQ of the child is significant. The first test of the contribution of the stepparent to this relationship was to correlate the length of time the student spent with the stepparent with the stepparent's handedness (*19*) ($r = -.03$, $P > .10$, not significant). The next analysis was done in order to test for any effect of handedness of a stepparent on that of the child.

The 151 students not from (BP + BP) families were assigned to the cells of a 3 by 2 by 2 design (Table 1) with dimensions of handedness of the stepparent, handedness of the biological parent, and the sex of the biological parent. Sex of the child was ignored in this analysis because of the lack of data in some cells. An unweighted-means analysis of variance (*18*) indicated that the handedness of the biological parent was significant [$F(1,139) = 44.436$, $P < .001$]. (Only unweighted LQ means, the ones from the analysis, are reported in the text.) Children of a right-handed biological parent had more preference for use of the right hand (mean LQ = 86.06) than those of a left-handed biological parent (mean LQ = 65.13). The only other significant effect was for sex of the biological parent [$F(1,139) = 5.419$, $P < .025$]: The students had a higher mean LQ when the mother was the biological parent (79.25) than when the father was (71.94). The handedness of the stepparent had no significant effect, nor did it interact significantly with either of the other variables. As the hypothesis of no relation between the stepparent's handedness and that of the child cannot be rejected, there is no support for a learning theory of handedness.

Table 2. Mean laterality quotients as a function of handedness of the biological mother, handedness of the biological father, and sex of the child. The number in parentheses is the number in each group.

Sex of child	Handedness of father	Handedness of mother	
		Right	Left
Male	Right	84.16(382)	71.87(31)
	Left	62.44 (23)	39.48(15)
Female	Right	87.39(541)	74.90(44)
	Left	76.88 (52)	36.69(13)

An unweighted-means analysis of variance was also calculated on the LQ's of children from (BP + BP) families (Table 2). The handedness of the fathers was related to that of the children [$F(1,1093) = 173.121$, $P < .001$], with children of right-handed fathers having a greater preference for use of the right hand (mean LQ = 79.58) than those of left-handed fathers (mean LQ = 53.87). Likewise, children of right-handed mothers expressed greater right-handed preference (mean LQ = 77.72) than those of left-handed mothers (mean LQ = 55.74) [$F(1,1093) = 126.585$, $P < .001$]. These two variables were not additive; having two left-handed parents produced disproportionately less preference for use of the right hand (mean LQ = 38.09) with reference to the norm of two right-handed parents (mean LQ = 85.78), than would be predicted from discordant matings (mean LQ's = 69.66 and 73.38, for children of L × R and R × L parents, respectively). Girls were more right-handed (mean LQ = 68.97) than boys (mean LQ = 64.49) [$F(1,1093) = 5.252$, $P < .025$]. Right-handedness in the mother was more strongly related to right-handed preference in girls (mean LQ = 82.14) than in boys (mean LQ = 73.3), whereas left-handedness in the mother produced no difference between girls (mean LQ = 55.79) and boys (mean LQ = 55.68) [$F(1,1093) = 4,974$, $P < .05$]. Finally, there was a significant three-way interaction between handedness of the father, handedness of the mother, and sex of the child [$F(1,1093) = 4.748$, $P < .05$]. The interaction may be due to a smaller effect of the fathers' handedness on girls than on boys when the mother is right-handed, and the reverse when the mother is left-handed (Table 2).

In summary, a parent's handedness is predictive of that of the offspring only if the parent is biologically related to the child. In discordant matings, there is no evidence that left-handed mothers produce more left-handed children than do

left-handed fathers. The former result is contrary to a learning theory of handedness, and the latter is contrary to a prenatal hypothesis. The data are consistent with a genetic hypothesis.

Because we cannot conceive of any suitable prenatal nongenetic process, we believe that the most parsimonious explanation of our data is that genetic factors are important in the origin of human handedness. However, there is also substantial evidence that handedness is related to early brain damage (*20*), and, perhaps, cultural factors (*13*). The present data certainly do not preclude the operation of such factors.

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Catecholamine Enzymes in the Degenerative Neurological Disease Idiopathic Orthostatic Hypotension

Abstract. *Discrete brain areas and sympathetic ganglia obtained at autopsy from patients with idiopathic orthostatic hypotension were assayed for tyrosine hydroxylase and dopamine β-hydroxylase. Dopamine β-hydroxylase activity was decreased 7.5-fold in sympathetic ganglia, while tyrosine hydroxylase activity was reduced more than 50-fold in the pontine nucleus locus coeruleus. These observations indicate that noradrenergic neurons of both brain and ganglion are affected in idiopathic orthostatic hypotension, but suggest that the central and peripheral biochemical deficits differ.*

Although degenerative disorders of the nervous system contribute significantly to human morbidity and mortality, little is known about the biochemical abnormalities underlying these diseases (*1*). We have been studying a rare but clinically well-defined degenerative neurological disease, idiopathic orthostatic hypotension (IOH) (*2*), the Shy-Drager syndrome (*3*). This progressive degenerative disorder characteristically strikes during middle age, causing a profound fall in blood pressure upon standing (orthostatic hypotension) that commonly results in fainting. Urinary and fecal incontinence, sexual impotence, loss of sweating, extraocular palsies, and a disorder of movement that may resemble Parkinson's disease may also occur. Including the original autopsy report in 1927 (*4*), only 19 cases have been subjected to postmortem anatomical examination (*3*, *5*). These studies have revealed variable neuronal degeneration of cranial nerve nuclei, striatum, substantia nigra, pontine nuclei, inferior olives, cerebellar cortex, and spinal cord intermediolateral columns in the central nervous system, and of autonomic ganglia in the periphery.

Since many of the symptoms of IOH could result from dysfunction of catecholamine-containing neurons, and since many of the histopathological changes are found in monoaminergic systems, we elected to study two enzymes involved in catecholamine biosynthesis. Tyrosine hydroxylase (TOH), the apparent rate-limiting enzyme in catecholamine biosynthesis (*6*), catalyzes the conversion of L-tyrosine to L-dopa and is restricted to neurons synthesizing dopamine or norepinephrine. In contrast, dopamine β-hydroxylase (DBH), which converts dopamine to norepinephrine, is localized to noradrenergic nerves (*7*). This report describes the results of postmortem analysis of these enzymes and histological examination of the nervous systems of patients with IOH.

Brain tissue and sympathetic ganglia were obtained from three patients with IOH and from seven controls who died from other causes at New York Hospital–Cornell Medical Center. Because there is normally a rapid postmortem decrease in TOH activity (*8*), only patients from whom specimens could be obtained within 10 hours of death were examined. Postmortem delay (time between death and freezing of dissected tissue) was 4.9 ± 0.32 hours for the control group and 5.2 ± 2.46 hours for the IOH group ($P > .05$). At autopsy the brain and sympathetic ganglia were hemisected; one portion was used for histological examination and the other for biochemical studies. Sympathetic ganglia of the cervical and thoracic chains, the nucleus locus coeruleus of the rostral pons, substantia nigra, and head of caudate were dissected at autopsy by methods previously described (*8*, *9*), with an atlas as a guide (*10*). Tissues were immediately frozen on Dry Ice and stored at −90°C. When these methods were employed enzyme activities remained stable for at least 6 months, and repeated assays of the same specimen on different days yielded results that differed by less than 10 percent. Assays of TOH and DBH activities were carried out according to slightly modified versions of methods previously described (*11*, *12*). After they were weighed, samples were assayed in triplicate, and the results reported are the means of these determinations. Results were similar whether they were expressed per unit of weight or per unit of total protein. To ensure reproducibility, TOH obtained from pooled rat superior cervical ganglia and DBH obtained from pooled loci coeruleus were included in all assays as external standards.

Patients with IOH and controls were comparable not only with respect to postmortem delay time, but also with respect to age: controls were 62.3 ± 6.75 years, and the IOH patients were 58.7 ± 9.02 years ($P > .05$). All patients and controls were American-born Caucasians. There were five males and two females in the control group and two males and one female in the IOH group. Primary dis-