PLASMA DOPAMINE-BETA-HYDROXYLASE IN IDENTICAL TWINS DISCORDANT FOR SCHIZOPHRENIA

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DOPAMINE-beta-hydroxylase (EC 1.14.2.1) (DBH), the final enzyme in the synthetic pathway of norepinephrine (KAUFMAN and FRIEDMAN, 1965), is released stoichiometrically with norepinephrine from peripheral sympathetic nerves (WEINSHILBOUM *et al.*, 1971). The enzyme is present in a stable form in human serum and has been used as an experimental and diagnostic tool. The activity of the enzyme varies widely among individuals, but in a given subject is relatively unaffected by external stimuli, diet or circadian rhythm (MILLER *et al.*, 1973).

The onset of psychotic symptoms in alcoholics treated with disulphiram (ANGST, 1956), a known DBH inhibitor (GOLDSTEIN, 1964), the increase in psychotic symptoms in schizophrenics with the same treatment (HEATH *et al.*, 1956), the STEIN and WISE (1971) theory of schizophrenia and our suggestion that a central overload of dopamine due to DBH inhibition leading to an increased number of occupied dopamine receptors could cause schizophrenic symptomatology (LAMPRECHT, 1973) have caused us to focus our attention on DBH in this illness. Previous studies of schizophrenic patients (DUNNER *et al.*, 1973; SHOPSIN *et al.*, 1972) did not reveal a relationship between DBH activity and psychopathology. In the present study, we examined the activity of DBH in the plasma of 12 pairs of monozygotic twins discordant for schizophrenia to determine (1) if plasma DBH activity in this group of schizophrenics is normal and (2) if plasma DBH activity in schizophrenic patients is genetically determined.

All twin pairs were part of previous studies at the National Institute of Mental Health (POLLIN, 1972; POLLIN and STABENAU, 1968). The schizophrenic index twins had all been hospitalized on one or more occasions with the diagnosis of schizophrenia. Only one was currently hospitalized, and five were considered to be in remission. The diagnosis and degree of impairment were established on the basis of an interview at the time of blood sampling and a review of our previous records (POLLIN, 1972; POLLIN and STABENAU, 1968; HOFFER and POLLIN, 1970). Except for one individual with borderline psychosocial functioning, the nonschizophrenic cotwins had never been hospitalized for a behavioural disorder, were not taking drugs and were generally functioning well within their families and communities. Seven index twins were receiving phenothiazines (Table 1), and only one pair was living in the same household at the time of the study. Blood samples were obtained by venipuncture at the subjects' homes or at hospitals in various parts of the country. The plasma was prepared by previously described methods (WYATT *et al.*, 1973). The

TABLE 1. CLINICAL CHARACTERISTICS, PLASMA DOPAMINE-BETA-HYDROXYLASE ACTIVITY AND IMPAIRMENT FOR 12 DISCORDANT MONOZYGOTIC TWINS

I, index twin with schizophrenia; NS, nonschizophrenic twin. Diagnoses were CUS, chronic, undifferentiated schizophrenia; CPS, chronic paranoid schizophrenia; AUS, acute, undifferentiated schizophrenia; and APS, acute, paranoid schizophrenia. The severity of schizophrenic impairment was rated 1 to 5 by historical review. The ratings were 1, history of poor functioning at work and in interpersonal relationships, or hospitalisation for a transient illness, or both; 2, hospitalisation with a clearly schizophrenic illness lasting longer than 1 month but less than 1 year, but subject has functioned well since (multiple hospitalisations within 1 year categorised here); 3, two or more clearly schizophrenic episodes separated by at least 1 year, but subject able to function at work or as a housewife while in remission; 4, inability to function at work or as a housewife even between hospitalisations; and 5, continuous hospitalisation for the last 5 years. In the forced rank order of index twins, the highest number was assigned to the most ill.)

Twin pair No.	Age/ Sex*	Diagnosis		Impairment ratings	Forced rank order		Phenothiazine		DBH (Units)	
		I	N.S.	I		N.S.	I	N.S.	I†	N.S.‡
1	33F	CUS	None	4	9	0	Yes	No	1053	1106
3	28F	CUS	None	5	12	0	Yes	No	444	814
5	37M	CPS	None	4	8	0	Yes	No	1427	1057
7	34F	AUS in Remission	None	2	1	0	Yes	No	1062	1127
8	30M	CPS	None	4	11	0	No	No	1036	1228
10	42F	CPS	None	3	3	0	No	No	948	418
14	25F	CUS in Partial Remission	None	3	6	0	Yes	No	267	266
17	37F	CPS	None	3	7	0	No	No	99	98
18	51F	APS in Remission	None	2	2	0	No	No	406	489
21	44F	AUS in Remission	None	3	5	1	Yes	No	774	699
22	37F	CPS in Remission	None	3	10	0	Yes	No	229	280
23	31M	CUS	Borderline	4	4	1	No	No	335	384

Mean values ± S.E.M.: Normal = 498 ± 78; *36 ± 2; †673 ± 123; ‡663 ± 113.

plasma preparations were then coded and assayed by a different investigator who was unaware of their origins.

DBH activity was measured by a coupled enzyme assay as described elsewhere (WEINSHILBOUM and AXELROD, 1971a) but with a modified pH of 5·5 (in lieu of pH 6·0). Results are expressed in units (1 unit equals 1 nmole of phenylethanolamine formed/hr/ml plasma). Thirty-four normal blood donors were matched for age and served as controls. The severity of schizophrenic impairment was rated as described in the legend to Table 1.

The DBH activity was 498 ± 78 units for the 34 controls. The mean values of the index twins (673 ± 123 units) and of the nonschizophrenic twins (663 ± 113 units) were almost identical; both were slightly, but not significantly, elevated when compared with controls. There was a highly significant correlation ($r = 0{\cdot}84$, $P < 0{\cdot}01$) between enzyme activities in schizophrenic and nonschizophrenic cotwins. Neither a relationship between the severity of impairment and the levels of the enzyme activity (Fig. 1) nor an effect of the phenothiazines could be demonstrated (Table 1).

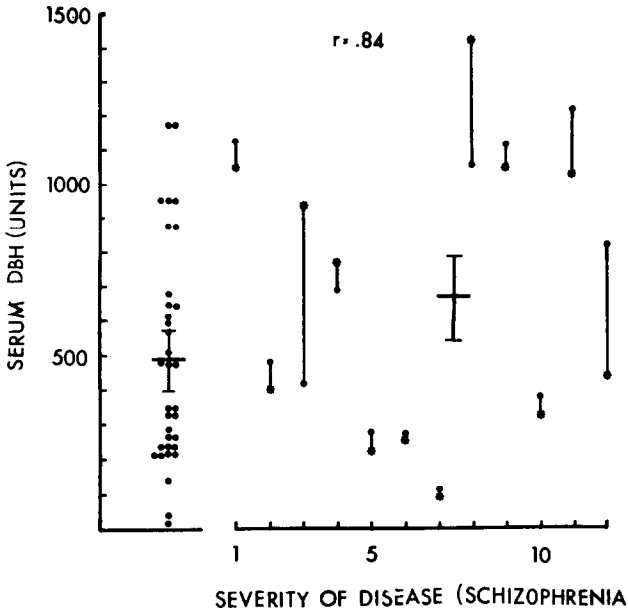

FIG. 1.—Serum dopamine-beta-hydroxylase (DBH) in 34 normal controls compared with 12 monozygotic twins discordant for schizophrenia. The schizophrenic twins are indicated by an asterisk (*), and the normal cotwins' values are indicated by a connecting line (see also Legend to Table).

Since blood samples were taken at different times and cotwins of nine of the twin pairs investigated lived in different cities, these results strongly suggest that environmental factors play a minor role in influencing DBH activity and that plasma DBH activity may be genetically determined. Family studies of individuals with torsion dystonia (WOOTEN *et al.*, 1973) and dysautonomia (WEINSHILBOUM and AXELROD, 1971c) have also suggested that genetic factors are important determinants of DBH activity in blood. No pathophysiological relationship between plasma DBH activity and schizophrenia has been demonstrated. Catecholamine-related enzymes can be increased in the central nervous system without concommitant peripheral changes (LAMPRECHT *et al.*, 1972) and an almost complete destruction of central noradrenergic neurons by intraventricularly administered 6-hydroxydopamine had no effect on serum DBH levels (LAMPRECHT *et al.*, 1973). Thus, it does not necessarily follow from the data presented that brain DBH is unaltered in schizophrenia since plasma DBH is mainly derived from peripheral sympathetic nerves (WEINSHILBOUM and AXELROD, 1971b) and separate genetic loci may control plasma and central nervous system DBH.

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