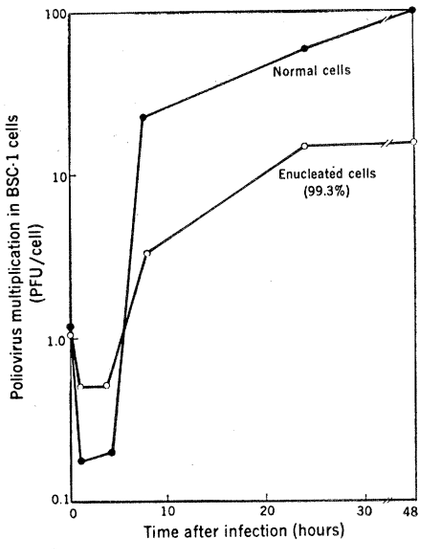
Fig. 2. Titer of poliovirus in infected cover slips of untreated and enucleated BSC-1 cells. Cultures were infected at a multiplicity of 100 PFU per cell for 30 minutes. At times thereafter, dishes with a cover slip in 1 ml of medium were frozen to −190°C and thawed. The thawed medium was sonicated and titered for plaque-forming units on BSC-1 monolayers (*8*).

with 10 percent calf serum was then added, and the infection was allowed to proceed at 37°C. Untreated BSC-1 cell cultures responded with a typical cytopathic effect: 4 hours after infection, cells began to come off the cover slip and lyse. Poliovirus had similar cytopathic effect on the enucleated cells, but it was delayed until about 8 hours after infection (Fig. 1).

At different times after infection, cover slips and medium were frozen to −190°C for later plaque titration of total infectious virus (Fig. 2). Other infected and control cover slips were fixed in acetone : methanol (3 : 1) immediately after infection and 4 and 8 hours afterward. These were stained with monkey antibody to poliovirus type 1, counterstained with fluorescein-conjugated equine antibody to monkey gamma globulin, and examined for fluorescence under dark-field ultraviolet illumination at ×400 magnification. Cells with fluorescent cytoplasm were considered to contain newly synthesized viral capsid antigen (Fig. 1). Newly synthesized poliovirus was detected in enucleate populations both by immunoassay (Fig. 1) and plaque assay (Fig. 2).

Only half of the enucleated cells contained detectable amounts of viral capsid antigen 8 hours after infection, at which time more than 90 percent of the untreated cells had synthesized detectable antigen. The number of infectious viruses per cell increased about 30-fold in the enucleates, as compared with a 300-fold increase in infected untreated cells (Fig. 2). Thus, enucleates supported capsid synthesis and virus growth less efficiently than did cells with nuclei. Cover-slip cultures subjected to cytochalasin B for 1 hour but not centrifuged, or cultures centrifuged in the absence of the drug, permitted virus growth at a rate indistinguishable from that of untreated cells.

The final yield of poliovirus per fluorescent enucleate cell was about one-fifth the final yield of poliovirus per fluorescent untreated cell (Fig. 2). A reduced yield was expected because



some cytoplasm was lost from each cell during enucleation (*2*), and because both infected and uninfected enucleated cells shrank in size with time in culture (Fig. 1). The number of enucleates never fell by more than 50 percent in the first 12 hours after enucleation. The yield of poliovirus was high enough to exclude the possibility that infectious virus was released only from the small minority of nucleate cells present on treated cover slips (*8*).

Enucleated cell fragments made from L cells by cytochalasin B treatment have been used to show that the host cell nucleus is not necessary for uncoating of vaccinia virus and establishment of viral DNA synthesis (*9*). These data show that monkey cell nuclei are not necessary for uncoating, translation, and replication of poliovirus RNA, and for the assembly of infectious virus.

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8. The time course of synthesis of whole virus in both untreated and enucleated BSC-1 cells is slower than that reported for HeLa cells infected at similar multiplicities (*6*). This is probably because monolayers, rather than cells in spinner culture, were infected here.
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Reduced Monoamine Oxidase Activity in Platelets: A Possible Genetic Marker for Vulnerability to Schizophrenia

Abstract. *Monoamine oxidase activity in blood platelets was measured, with [^{14}C]tryptamine as substrate, in 13 monozygotic twin pairs discordant for schizophrenia and in 23 normal volunteers. The monoamine oxidase activity of both schizophrenic and nonschizophrenic co-twins was significantly lower than it was for the normals, and it was highly correlated between twins. In addition, there was a significant inverse correlation between a measure of the degree of the schizophrenic disorder and the monoamine oxidase activity. These data suggest, but do not prove, that reduced platelet monoamine oxidase activity may provide a genetic marker for vulnerability to schizophrenia.*

Twin and adoptive studies of schizophrenic individuals indicate that this behavioral disorder is at least partly genetically transmitted (*1*). No biological marker, however, has been consistently associated with the syndrome (*2*). With regard to a biological marker, we recently described a marked reduction of monoamine oxidase (MAO) activity in blood platelets in a group of 33 patients with chronic or acute schizophrenia (*3*). In that and subsequent studies, attempts to assess whether influences secondary to the process of being schizophrenic—such as diet, drugs, and hospitalization—might affect platelet MAO activity have been hampered by the inseparability of these secondary factors from the chronic illness. We attempted to bypass conventional means of controlling such artifacts by examining monozygotic twins

Table 1. Clinical characteristics, impairment, and platelet monoamine oxidase (MAO) activity for 13 monozygotic twins discordant for schizophrenia; 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 hospitalization for a transient illness, or both; 2, hospitalization with a clearly schizophrenic illness lasting longer than 1 month but less than 1 year, but subject has functioned well since (multiple hospitalizations within 1 year categorized 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 hospitalizations; and 5, continuous hospitalization for the last 5 years. In the forced rank order of index twins, the highest number was assigned to the most ill.

Twin pair	Age	Sex	Diagnosis		Impairment			Current phenothiazine treatment		Platelet MAO activity (nmole per milligram of protein per hour)	
					Rating	Forced rank order	Rating NS				
			I	NS		I		I	NS	I	NS
1	33	F	CUS	None	4	10	0	Yes	No	5.59	7.98
2	30	M	CUS	None	4	13	0	Yes	No	3.98	2.79
5	37	M	CPS	None	4	9	0	Yes	No	4.02	9.49
7	34	F	AUS in remission	None	2	2	0	Yes	No	5.61	5.12
8	30	M	CPS	None	4	12	0	No	No	0.64	1.64
10	42	F	CPS	None	3	4	0	No	No	5.47	8.49
14	25	F	CUS in partial remission	None	3	7	0	No	No	1.63	1.58
17	37	F	CPS	None	3	8	0	Yes	No	0.31	1.77
18	51	F	APS in remission	None	2	3	0	No	No	5.33	4.14
22	35	F	CPS in remission	None	3	6	0	Yes	No	5.57	7.19
23	31	M	CUS	Borderline	4	11	1	No	No	1.56	0.72
21	44	F	AUS in remission	None	3	5	1	Yes	No	7.64	4.79
26	55	M	APS in remission	None	2	1	0	No	No	4.13	4.54
					Mean ± standard deviation						
	37 ± 9									3.9 ± 2.3*	4.7 ± 2.9

* Normal value: 6.4 ± 2.7 nmole mg^{-1} hr^{-1}.

discordant for schizophrenia (*4*). A high correlation between MAO enzyme activity in schizophrenic and nonschizophrenic co-twins was observed. Our results suggest that the platelet MAO activity reduction is not secondary to being schizophrenic, but may represent a genetic marker for increased vulnerability to schizophrenia.

Thirteen pairs of monozygotic twins discordant for schizophrenia and 23 normal nontwin controls were studied. Twelve of the twin pairs were part of previous studies at the National Institute of Mental Health over the last 10 years (*4, 5*). The remaining pair, living locally, was part of a twin cohort of the National Academy of Sciences –National Research Council (*6*).

The schizophrenic index twins had all been hospitalized on one or more occasions for abnormal behavior diagnosed as schizophrenia; only one was currently hospitalized, and five were considered to be in remission. The diagnosis and degree of impairment (Table 1) were established on the basis of an interview at the time of the blood sampling and a review of our previous records (*4–6*). Except for one individual with borderline psychosocial functioning, the nonschizophrenic co-twins had never been hospitalized for a behavioral disorder, were not taking drugs, and were generally functioning well within their families and communities. Only two of the twin pairs were living together in the same household at the time of the study; in nine cases the co-twins were living in different cities. Because many of the patients were receiving phenothiazines, the natural course of their illness was probably altered. The 23 normal controls had never had a psychotic illness.

Blood samples were obtained by venipuncture in the subjects' homes or in hospitals in various parts of the country, and the platelets were prepared for analysis at nearby facilities as described (*7*). The preparations were then coded and assayed by a different experimenter, who was unaware of their origins. Monoamine oxidase activity in platelets was determined by measuring the deamination of [^{14}C]tryptamine bisuccinate, and expressed as the amount of labeled metabolites formed per milligram of platelet protein per hour (*8, 9*). For the 23 normals (32 ± 11 years old), the enzyme activity (6.4 ± 2.7 nmole mg^{-1} hr^{-1}, mean ± standard deviation) was no different than that of 22 normals previously studied (6.4 ± 4.0 nmole mg^{-1} hr^{-1}). The MAO activity of schizophrenic twins (3.9 ± 2.3 nmole mg^{-1} hr^{-1}) was significantly lower than that of the 23 normals ($P < .005$, t-test). The values for the nonschizophrenic twins (4.7 ± 2.9 nmole mg^{-1} hr^{-1}) were also lower ($P < .05$). There was no significant difference in MAO activity between the schizophrenic and nonschizophrenic twins, and there was a significant Pearson correlation ($r = .67$; $P < .01$) between enzyme activities in schizophrenic and nonschizophrenic twins.

This study confirms our earlier one (*3*) indicating that some individuals with the schizophrenic syndrome have lower platelet MAO activities than do most normals. The present group of patients was not homogeneous with respect to either diagnosis or enzyme activity. The earlier, more homogeneous group contained largely phenothiazine-resistant patients with chronic schizophrenia who had been hospitalized continuously from 2 to 15 years. The low MAO values (< 2 nmole mg^{-1} hr^{-1}) in four index twins, however, suggest that some of the twins are representative of the group previously studied. These four index twins were among the most ill. The severity of impairment was rated on a five-point scale, based primarily upon the number and duration of hospitalizations, by a rater with no knowledge of the results of the platelet MAO assays (Table 1). A forced rank order was made between the numerical ratings, with highest number assigned to the most ill patient. This order, when compared to the MAO activities, produced a Spearman rank-order correlation (*10*) of − .54 ($P < .05$).

The high correlation for platelet

MAO activities between index twins and their nonschizophrenic co-twins indicates that the low MAO activities are not solely secondary to being schizophrenic but may be genetically determined. We have also found a high correlation ($r = .94$) in platelet MAO activity between nine pairs of normal monozygotic twins, as have Nies and Robinson (*11*). In addition, the mean value for the normal twin pairs was no different from other normals who were not twins. Because the present twins are discordant for schizophrenia, it appears that low platelet MAO is not a marker for the disorder, but rather may be a genetic marker for the vulnerability to schizophrenia. A smaller reduction in platelet MAO activity is sometimes observed for patients with bipolar depression but not for those with unipolar depression; this suggests that there may be a common factor affecting MAO activity in bipolar depression and schizophrenia (*9*). The evidence indicating a reduction in MAO activity in some schizophrenic patients and their relatives is so far confined to blood platelets, and there are no data to indicate whether MAO activity may also be reduced in brain or other tissue. Whatever platelet MAO activity may reflect regarding brain function, it can be at most only one part of a complex system leading to schizophrenia. Prior studies have shown that although genetic factors are important, they can account for less than half of the disposition to become schizophrenic (*1*). Thus, there is no essential contradiction between our results indicating that MAO activity is related to severity of impairment and is also correlated between co-twins discordant for schizophrenia.

It cannot be concluded that low MAO activity in platelets is a primary genetic alteration in schizophrenia. While such an alteration could be involved in the pathogenesis of this disorder, the alteration could be secondary to other genetic factors that might regulate MAO activity in platelets or might be incidentally related but genetically linked to the actual pathogenetic mechanism of schizophrenia. It is also conceivable that a factor occurring in utero or in early life could yield this difference in MAO activity. It should be possible to determine whether relatives of schizophrenic individuals also have reduced MAO activity and, if so, how this alteration is transmitted. Also, it would be useful to know whether the difference in platelet MAO is representative of a generalized deficiency in MAO or one of its isoenzymes, and, specifically, whether there is a deficiency in brain MAO. Since a generalized deficiency in MAO activity would be consistent with many current theories relating to abnormalities in indoleamine and catecholamine metabolites (*2, 4, 9, 12*) in schizophrenia, it will be of interest to determine which of the many substrates for MAO is most affected by this abnormality.

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Multilane Vehicular Traffic and Adaptive Human Behavior

Abstract. *The parameters in a statistical theory of multiple-lane traffic have been determined from two independent sets of data. The numerical values of the parameters calculated by four different methods of estimation are in essential agreement with one another. The data suggest the important role of adaptive human behavior in determining the characteristics of congested flow.*

Traffic flow on a multiple-lane highway has been studied in recent years by using various approaches (*1, 2*). The manner in which human behavior is involved in this problem makes it one of the most interesting in the theory of traffic flow, and in addition, similar features are likely to appear in other complicated problems of sociology and economics. In this connection it has been stated in a monograph (*1*, p. 87) on the theory of multilane traffic: "We have here an example of a game in which the rules are not fixed once for all, but vary according to circumstances. The modification of the rules implies a modification of behavior of the entire collectivity of participants." The main intent of the theory of traffic we have presented (*1*) is to permit us to gain some insight into the mechanisms through which the change of concentration on a highway leads to modification of the traffic pattern. We have discussed the theory (*3*) with respect to data obtained from two different sources (*4, 5*). As it is of great importance to validate our theoretical approach with respect to experimental data (*6*), we examine here a comparison of theory and data from a somewhat different viewpoint. We have estimated from the data the numerical values of the parameters included in our description of the multiple-lane traffic. The values of the parameters calculated in various independent ways from the lower moments of the speed distribution function are in satisfactory agreement with one another; moreover, the variations of the parameters with concentration are along lines predicted by the theory.

Qualitative conclusions are also drawn from the cumulative distribution of the observed speeds. The dominating effect of the "adaptive behavior" of the drivers exhibited in the speed distributions at high concentrations is observed. It appears that one of the basic problems regarding congested flow is to describe quantitatively the adaptive behavior brought about by the interactions between drivers. This pattern of behavior illustrates the essential nonlinearity of human behavior involving the continuous interplay between "program" and "realization."