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Catecholamines Metabolism in Infantile Autism: A Controlled Study of 22 Autistic Children[1]

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In a group of 22 autistic children aged 5 to 16 years and a group of normal controls matched for age and sex, catecholamines metabolism was investigated in plasma, platelets, and urine. This investigation was part of a research project in which several biological parameters (including serotonin) were explored simultaneously in the same children. In the autistic group, epinephrine and norepinephrine were significantly elevated in plasma, while epinephrine, norepinephrine, and dopamine were significantly lower in isolated platelets. No significant difference was found between the two groups for the urinary excretion of epinephrine, norepinephrine, dopamine, DOPAC, and MHPG. Other differences between the two groups in the statistical correlations of several biochemical parameters also suggest abnormalities of bioamine metabolism in the platelets of autistic children.

INTRODUCTION

Over the last two decades, numerous studies have attempted to find specific neurometabolic disorders in childhood autism. The most consistent result of these works is the finding of hyperserotonemia in 30–50% of autistic

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children (Hanley, Stahl, & Freedman 1977; Launay et al., submitted). However, the origin of this excess of serotonin remains unclear.

Catecholamines metabolism has also been investigated, with less consistent results. Homovanillic acid (HVA) the main metabolite of dopamine has been measured in CSF of autistic patients: In 1974, Cohen, Shaywitz, Johnson, and Bowers reported higher post-probenecid HVA levels in the CSF of autistic and atypical children, compared with epileptics. In 1977 the same authors (Cohen, Caparulo, Shaywitz, & Bowers 1977a) found no difference between autistic and other diagnostic groups of children; in this study HVA levels tended to be higher in children with greater locomotor activity and more severe stereotypies. Leckman et al. (1980) also failed to find a difference in CSF HVA between subjects diagnosed with "child psychosis (largely autism)" and subjects with "perceptual cognitive disorder." On the contrary, Gillberg, Svennerholm, and Hamilton-Hellberg (1983) reported elevated HVA in the CSF of 18/22 psychotic children; in 13 autistic children of this group, this increase was isolated, while it was associated with a rise of 5-HIAA in the 9 children with other types of psychoses. In this study, raised concentrations of HVA were also observed in the CSF of children affected by progressive encephalopathy of meningitis. In urine, Lelord et al. (1978) also found elevated free HVA levels, whereas Landgrebe and Landgrebe (1976) found "large amounts" of dihydroxyphenylacetic acid (DOPAC) in the urine of 88% of 74 autistic patients. These results might suggest an increase of dopamine activity, at least in some autistic patients. But they have not been confirmed by De Villard and Dalery (1979) who found urinary excretion of HVA and iso-HVA not significantly different in autistic and in normal children.

Several authors have studied dopamine-β-hydroxylase (DBH), the enzyme that controls the conversion of dopamine to norepinephrine. This enzymatic activity is considered an index of noradrenergic activity. Its measure in autism has also led to conflicting results: Whereas Goldstein, Manahand, Lee, and Coleman (1976) and Lake, Ziegler, and Murphy (1977) found a decrease, compared to controls, Young, Kyprie, Ross, and Cohen (1980) found no difference. In one study (Belmaker, Hattab, & Ebstein, 1978) plasmatic DBH activity was superior in children with various types of psychoses than in children with organic cerebral disease or mental retardation. Recently, Garnier et al. (1983, 1986) again studied this parameter: They found no difference in DBH activity between controls and autistic children as a group; however a significant increase was observed in autistic subjects without mental retardation compared with patients in which autistic syndrome was associated with signs of mental deficiency.

Few studies have examined norepinephrine and its metabolites. Lake et al. (1977) found an elevation of the plasmatic level of norepinephrine in

autistic children, while Young, Cohen, Brown, and Capparulo, (1978, 1979; Young et al., 1981) reported a decrease of urinary free catecholamines and 3-methoxy-4-hydroxyphenylglycol (MHPG), suggesting a reduction in noradrenergic activity.

The only consistent results concern monoamine oxidase (MAO) activity, which controls the catabolism of both serotonin and catecholamines: platelet MAO activity of those with autism has always been found in the normal range (Boullin, Bhagavan, O'Brien, & Youdim, 1976; Campbell, Friedman, Green, Small, & Burdock, 1976; Cohen, Young, & Roth, 1977b). Several factors might explain the inconsistency of the results on catecholamines investigations in autism. First, in many studies the patient group is small. Another factor is the large interindividual variance of most of these parameters (particularly, age is an important factor of variance). Methodological problems, such as differences in the specificity of the assays used, might also affect these results. Therefore we considered it useful to investigate the metabolism of catecholamine in plasma, platelets, and urine, in a group of 22 autistic children, carefully selected on the basis of DSM-III criteria, in comparison to controls matched for age and sex. The study reported here is part of a research project in which other biochemical (including serotonin) and immunological parameters were explored (reports of other investigations are in preparation).

METHODS

Subjects

Twenty-two children, ages 5 to 16 years (mean: 10.5 years), diagnosed as having infantile autism, according to the criteria of the DSM-III, were enrolled in this study. Neurologic examination and CT scan were negative except for two children whose encephalic lesions (ventricular dilatation in one case, corpus callosum agenesis in the other) were previously known. Controls, matched for sex and age, were selected among patients hospitalized or consulting for somatic diseases. None had psychiatric symptoms nor disease or treatment known to interfere with bioamine metabolism; two patients were treated by psychotropic drugs: thioridazine in one case, carbamazepine phenobarbitone and pericyazine in the other. The influence of these drugs was tested *in vitro* on each of the parameters studied. No interference or modification was found with the following final concentrations: 3.5×10^{-5} M thioridazine, 8.2×10^{-4} M pericyazine, 5.6×10^{-3} M phenobarbitone, 5.5×10^{-3} M carbamazepine.

Procedure

Blood and urinary samples were collected after 2 days of a controlled diet excluding tryptophan and serotonin-rich foods (chocolate, bananas, nuts, and tomatoes). Venous blood was drawn from fasting children between 8:30 and 9:30 a.m. using ACD A as anticoagulant (1v/9v). Platelet-rich plasma (PRP) and plasma were obtained by 10 minute centrifugations at 4°C (300 *g* and 2,300 *g*, respectively). Platelets were isolated from PRP by centrifugation (2,300 *g*, 10 minutes, 4°C) and by washing with a modified Tyrode buffer (Gadd & Clayman, 1972). Urine aliquots, most often corresponding to overnight urine, were collected on 5 ml of concentrated hydrochloric acid.

Standard techniques were employed: Platelet counts were determined by contrast phase microscopy and their protein content was measured by the procedure described by Lowry, Rosebrough, Farr, and Randall (1951); unconjugated epinephrine, norepinephrine, and dopamine in plasma, isolated platelets, and urine were measured by radioenzymology (Da Prada & Zurcher, 1979) as well as MAO activity in isolated platelets (Murphy et al., 1976). One unit of enzymatic activity corresponds to the transformation of 1 micromole of substrate (benzylamine) per minute. Dihydroxyphenylacetic acid (DOPAC) and methoxyhydroxy phenylglycol (MHPG) were measured in urine by high-performance liquid chromatography (HPLC; Krstulovic, 1982). Urinary creatinine was determined colorimetrically on a GSA II D autoanalyser (Kuffer, Takkinen, & Jaag, 1975).

Wilcoxon (W) and Kolmogorov-Smirnov (KS) nonparametric tests (Siegel, 1956) were used for the comparisons between autistic children and controls (chosen level of significance: $p < .05$). Limits of frequent values were determined from the data obtained in controls by the "box plot" method of Tukey (1977).

RESULTS

The results are summarized in Tables I and II.

In plasma, no significant difference between autistic children and controls was observed for dopamine; epinephrine and norepinephrine were significantly elevated in the autistic group. Considering individual data (Figure 1), plasma epinephrine was above the upper limit of frequent values (determined from control values) in 16 patients and 3 controls; it was normal or low in 4 patients and 16 controls. A high level of norepinephrine was observed in 16 patients and 5 controls, whereas a normal level was found in 5 patients and 17 controls. Finally, 15 controls and only 2 patients presented with normal values for both epinephrine and norepinephrine.

Table I. Levels of Free Catecholamines in Plasma and Platelets of Autistic Children and Controls (Matched for Age and Sex)

Catecholamines	Control group				Autistic group				p^b	
	No.[a]	Mean ± *SD*	Median	Sup. quart/ inf. quart[c]	No.[a]	Mean ± *SD*	Median	Sup. quart/ inf. quart[c]	W	KS
Plasma										
Epinephrine (nM)	19	0.09 ± 0.17	0.05	0.06/0.03	20	0.20 ± 0.19	0.11	0.35/0.08	<.02	<.001
Norepinephrine (nM)	22	0.20 ± 0.17	0.16	0.24/0.10	21	0.66 ± 0.43	0.51	1.02/0.30	<.01	<.001
Dopamine (nM)	22	0.05 ± 0.08	0.05	0.06/[e]	21	0.06 ± 0.07	0.03	0.09/[e]	ns	ns
Isolated platelets[d]										
Epinephrine										
(10^{-22} mole/pl)	19	3.47 ± 2.46	3.88	4.97/0.35	21	1.77 ± 2.39	1.12	2.07/0.34	<.01	<.01
(10^{-13} mole/mgPP)	19	1.07 ± 0.82	1.08	1.68/0.08	21	0.44 ± 0.56	0.30	0.56/0.06	<.05	<.02
Norepinephrine										
(10^{-21} mole/pl)	22	1.84 ± 1.12	1.47	2.63/1.08	21	1.34 ± 0.74	1.37	1.76/0.76	<.05	ns
(10^{-12} mole/mgPP)	22	0.52 ± 0.32	0.38	0.86/0.30	21	0.35 ± 0.28	0.20	0.67/0.15	ns	<.02
Dopamine										
(10^{-22} mole/pl)	22	7.15 ± 6.64	7.79	12.69/[e]	21	1.87 ± 3.57	[e]	2.30/[e]	<.01	<.01
(10^{-13} mole/mgPP)	22	1.93 ± 1.86	1.58	3.99/[e]	21	0.63 ± 1.39	[e]	0.43/[e]	<.05	<.01
MAO										
(10^{-12} U/pl)	22	6.25 ± 3.61	5.60	7.95/3.92	20	5.59 ± 3.60	5.34	7.80/2.18	ns	ns
(10^{-3} U/mgPP)	22	2.05 ± 2.22	1.34	2.76/0.59	20	1.51 ± 1.98	0.92	1.55/0.54	ns	ns

[a]Number of determinations.
[b]Probability of the null hypothesis according to the Wilcoxon (W) or to the Kolmogorov-Smirnov (KS) test; ns = nonsignificant difference, $p > .05$.
[c]Sup. quart. = superior quartile; inf. quart. = inferior quartile.
[d]U = unit of enzymatic activity; pl = platelet; mgPP = milligram of platelet protein.
[e]No detectable.

Table II. Levels of DOPAC, MHPG, and Free Catecholamines in Urines of Autistic Children and Controls (Matched for Age and Sex)

Catecholamines in urine	Control group				Autistic group				p^b	
	No.[a]	Mean ± *SD*	Median	Sup. quart/ inf. quart[c]	No.[a]	Mean ± *SD*	Median	Sup. quart/ inf. quart[c]	W	KS
Epinephrine (nmole/nmole creatinine)	19	5.11 ± 3.92	4.11	5.40/2.72	20	4.97 ± 5.34	3.11	5.96/1.48	ns	ns
Norepinephrine (10^{-6} mole/mole creatinine)	19	1.39 ± 1.24	1.12	1.54/0.69	20	1.06 ± 0.86	0.95	1.65/0.38	ns	ns
Dopamine (10^{-7} mole/mole creatinine)	19	2.23 ± 1.35	2.25	2.84/1.31	20	1.82 ± 1.40	1.36	3.12/0.97	ns	ns
MHPG (μmole/mole creatinine)	19	5.06 ± 4.01	4.03	5.80/2.23	20	3.79 ± 2.51	3.51	5.77/1.76	ns	ns
DOPAC (μmole/mole creatinine)	19	4.84 ± 4.37	3.88	5.66/1.71	20	5.13 ± 3.34	4.72	7.05/1.93	ns	ns

[a]Number of determinations.
[b]Probability of the null hypothesis according to Wilcoxon (W) or to the Kolmogorov-Smirnov (KS) test; ns = nonsignificant difference, $p > .05$.
[c]Sup. quart. = superior quartile; inf. quart. = inferior quartile.

In isolated platelets, dopamine and epinephrine, expressed either as per platelet or per milligram of platelet protein, were significantly lower in the autistic group. Norepinephrine was also significantly lower in patients but only according to one statistical test (KS) and depending on the mode of expression (Table I, Figure 2). MAO activity did not differ between the two groups. In the control group, the platelet content of each catecholamine increased with age until 11–13 years; by contrast, in the autistic group, individual values were in the same range whatever the age of the children (Figure 3).

In urine, no significant difference between the two groups was obtained for the excretion of each of the free catecholamines and their metabolites DOPAC and MHPG. No significant difference was found either when the following sums were considered: dopamine + norepinephrine + epinephrine,

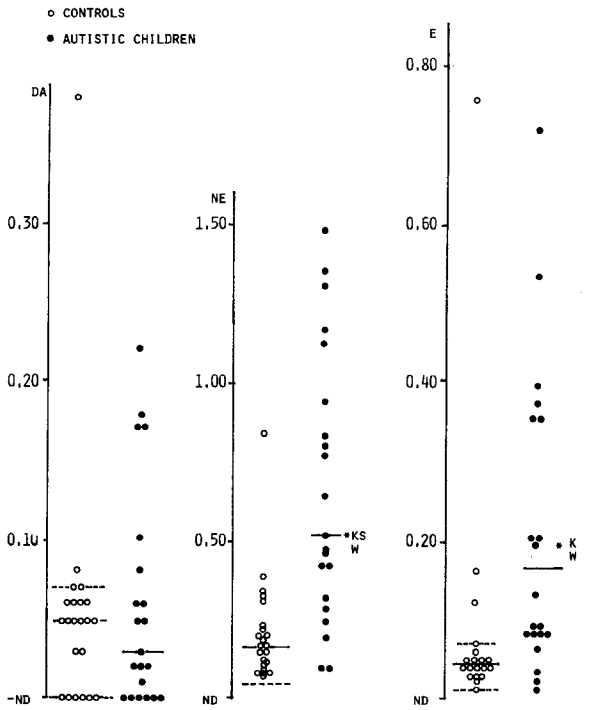

Fig. 1. Plasma unconjugated catecholamines: $nmoles^{-1}$, DA = dopamine, NE = norepinephrine, E = epinephrine. ND = not detected; significative difference ($p < 0.05$) according to Wilcoxon (W) or Kolmogorov-Smirnov (KS) tests; solid line = median, dashed line = 95% confidence limits according to the "box plot" of Tukey (1977).

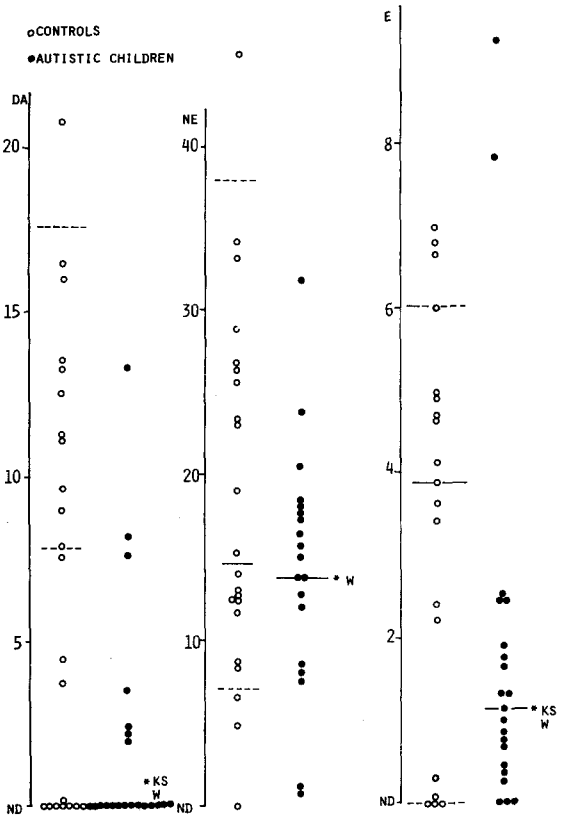

Fig. 2. Platelet unconjugated catecholamines: 10^{-22} mole platelet^{-1}, DA = dopamine, NE = norepinephrine, E = epinephrine. ND = not detected; * = significant difference ($p < 0.05$) according to Wilcoxon (W) or Kolmogorov-Smirnov (KS) tests; solid line = median, dashed line = 95% confidence limits according to the "box plot" of Tukey (1977).

dopamine + DOPAC, norepinephrine + epinephrine + MHPG, DOPAC + MHPG, and norepinephrine + epinephrine + dopamine + DOPAC + MHPG.

Correlations

In the control group, a positive correlation between platelet norepinephrine and dopamine (Table III) and a negative correlation between platelet norepinephrine and serotonin (Table III) were observed. (Values reported in Ferrari et al., 1985, and in Launay et al., submitted.) These correlations were not found in our group of patients in which, by contrast to

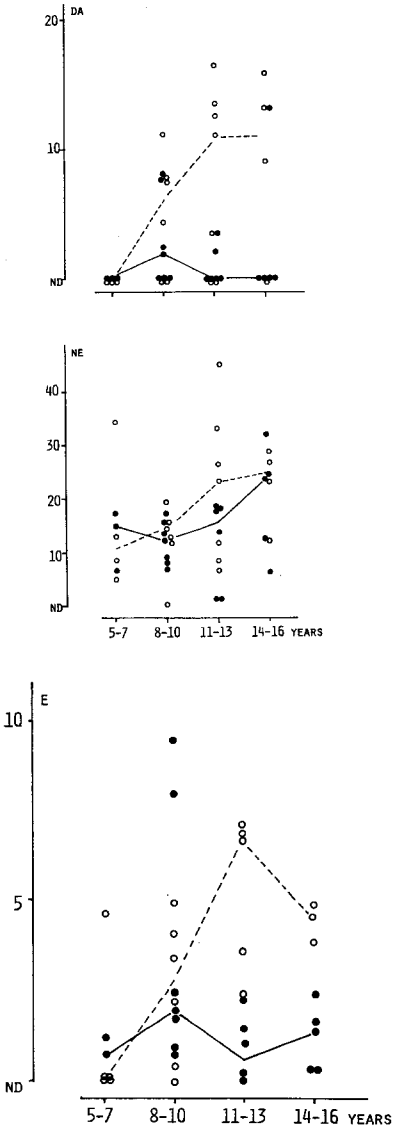

Fig. 3. Variations of platelet unconjugated catecholamines according to age: 10^{-22} mole platelet^{-1}, DA = dopamine, NE = norepinephrine, E = epinephrine; -----○ = controls; ● = autistic children; ND = not detected.

Table III. Correlations Found in Autistic Children and Controls[a]

Variable	Control group	Autistic group
Platelet NE/platelet DA	$p < .01$	ns
Platelet NE/platelet 5-HT	$p < .05$	ns
Platelet NE/platelet MAO	ns	$p < .01$
Plasma DA/platelet MAO	ns	$p < .01$

[a]For additional details on these correlations, contact the authors.

the control group, were found positive correlations between platelet MAO activity and either plasma norepinephrine (Table III) or plasma dopamine (Table III).

DISCUSSION

Our data are in accordance with previous reports of a "normal" platelet MAO activity in autism (Boullin et al., 1976; Campbell et al., 1976; Cohen et al., 1977b) and with the results of Lake et al. (1977) who found plasmatic norepinephrine significantly elevated in autistic children. In our study, plasmatic epinephrine and/or norepinephrine are elevated in most of the autistic subjects (19/21), whereas a high level of the same parameters is less frequent in the matched controls (7/22) (Table I, Figure 1).

Our observation of a significantly lower level of catecholamines in platelets of autistic children has not been published before. The difference is highly significant for epinephrine and dopamine, but less significant for norepinephrine (Table I, Figure 2). Our data on urinary excretion (Table II) of catecholamines are somewhat at variance with the results previously published by other authors. We found no significant difference between autistic children and controls for epinephrine, norepinephrine, and dopamine or their metabolites MHPG and DOPAC. No significant difference appears when the sums of either free catecholamines or their metabolites or both are compared between the two groups. Thus we cannot confirm the results of the uncontrolled study by Landgrebe and Landgrebe (1976) who found "large amounts" of DOPAC in the urine of autistic subjects, nor the results of Young et al. (1978, 1979, 1981) who found a lower excretion of catecholamines and MHPG in autistic boys compared to normal children. A possible explanation for the discrepancy of the results concerning urinary catecholamines might be a difference in the specificity of the analytical procedures used.

We must, of course call for caution in the interpretation and generalization of our results, which need to be confirmed in larger groups of autistic children. For the moment, it remains difficult to answer the numerous questions coming out of these data. The high level of plasmatic epinephrine and norepinephrine in autistic children could be explained by an enhanced stress

reaction in these subjects. However the lower level of platelet catecholamines and the high level of platelet serotonin (Ferrari, et al., 1985), measured simultaneously in the same children, suggest that the elevated plasmatic concentration of norepinephrine and epinephrine might be, at least partly, due to their less efficient storage in platelets. In fact, in thrombocytes several biochemical mechanisms are common for catecholamines and serotonin: Dopamine and serotonin uptakes depend on the same membrane carrier (Omenn & Smith, 1978) and accordingly platelet uptakes of serotonin (Launay et al., submitted) and dopamine (Boullin & O'Brien, 1972) are "normal" in autistic children. Epinephrine, norepinephrine, dopamine, and serotonin are costored in the same "dense granules" (Da Prada, Richards, & Kettler 1981) which possess a "maximal packet size" (Costa et al., 1978). Thus the storage of catecholamines might be diminished in platelets already filled with serotonin, with the consequence of elevated plasmatic, and low platelet concentrations of catecholamines (Table I, Figures 1 and 2). The correlations found in controls between platelet serotonin, norepinephrine, and dopamine (Table III) support this hypothesis. This might also explain our results about plasma and platelet norepinephrine and epinephrine. Feldman and Davis (1981) found that platelets from subjects with carcinoid syndrome have the same catecholamine content as normals even though platelet 5-HT is six times normal. However the two pathological situations might not be comparable since an increase of the number and size of dense granules have been reported in carcinoid patients (Da Prada et al., 1981); on the contrary, the number and the size of these organelles appeared normal in seven of our hyperserotonemic patients, as assessed by mepacrine-induced fluorescence microscopy (Launay et al., submitted).

Platelet dopamine is low in autistic children but its concentration in the plasma of these subjects does not differ significantly from the control group: this could be explained by a metabolization of the excess of dopamine into norepinephrine. This metabolic pathway is controlled by dopamine-β-hydroxylase. As seen previously, the measurement of the activity of this enzyme in the serum of autistc children has shown reduced or unchanged levels (Goldstein et al., 1976; Lake et al., 1977, Young et al., 1980). However, there is no evidence to support the hypothesis of the dopamine/norepinephrine interconversion in the plasma. Another metabolic pathway is the catabolism of dopamine by MAO and COMT into homovanillic acid (HVA). Lelord et al. (1978) have found higher levels of urinary HVA in autistic children, and other studies (Gillberg et al., 1983) have found elevated levels of HVA in the CSF of autistic patients. Since the excretion of epinephrine norepinephrine, and MHPG is not superior in the autistic group, our study gives no answer to the question of the catabolism of the large excess of epinephrine and norepinephrine found in the plasma.

If confirmed in larger groups, the different correlations found in the autistic group and the control group—plasmatic norepinephrine and dopamine correlated with platelet MAO activity in patients and not in controls (Table III), norepinephrine correlated positively with dopamine and negatively with serotonin in platelets of controls but not of autistic children (Table III)—as well as the absence of variation of platelet catecholamines with age in patients (Figure 3), might also suggest metabolic disturbances of bioamines in autistic patients.

The nature of the relationship between the clinical syndrome and these metabolic disturbances of bioamines is another important question but it remains also difficult to answer. Platelets are considered a model of serotoninergic neurons (Stahl, 1977; Pletscher, Affolter, Cesura, Erne, & Muller, 1984). It is thus tempting to suggest that the abnormal level of catecholamines and serotonin found in platelets of autistic children might reflect a disorder of CNS bioamines which might explain, even partly, the clinical syndrome. Some authors have attempted to produce such a model: Young et al. (1982) proposed that the brain dopaminergic system might play a role in the production of autistic symptoms. This hypothesis is supported by pharmacological observations: the partial therapeutic effect of neuroleptics (dopamine receptor blocking agents) and the deleterious effect of amphetamine-like drugs; these agents, which release dopamine and block its reuptake and degradation, aggravate autistic symptoms (general disorganization of behavior, increased stereotypies, etc.). According to these authors, animal studies have shown that stimulation of the brain dopaminergic system by stimulant drugs elicits a locomotor activation with stereotypies and "rotational behaviors" involving the nigrostriatal system. On the other hand, it has been suggested (Redmond & Huang, 1979) that brain noradrenergic systems might play a role in the attention process. Thus a deficit of noraadrenergic activity might contribute to explain the poor attention and the learning difficulties of autistic children. However, we emphasize that these models must be considered only as research hypotheses and that, for the moment, the data collected in autistic subjects are not sufficient to evaluate their validity.

We must emphasize that the finding of biochemical differences in a group of autistic patients does not prove *per se* that this anomaly is the direct and unique cause of their clinical symptoms nor that it can be taken as "hard evidence of primary CNS dysfunction," as pointed out by Gillberg et al. (1983). One must remember that such alterations of catecholamines are not specific of autism and other psychotic disorders: Gillberg and his co-workers found very high HVA levels also in children with meningitis and progressive encephalopathy. Monoamine disorders in autistic children might be related to other factors than autism itself (such as mental retardation, motor activi-

ty level, underlying organic disease). They might also reflect a primary general vulnerability to psychiatric morbidity, as indicated by Sedvall et al. (1980). The possibility that they might be a consequence of the psychotic disorders must also be considered. Some experimental studies give support to this hypothesis: in rats isolated for 2 months, changes in dopamine turnover are observed in several cerebral structures (frontal cortex, striatum, nucleus accumbens); these animals exhibit also higher biochemical and comportmental reactions to stress (Tassin, 1980).

Taking account of these remarks we believe that further studies of bioamines and their metabolites, in various types of psychotic and developmental disorders, should contribute to a better understanding of the biological processes implicated in pathological as well as normal development.

In summary, we found disturbances of catecholamines in both platelets and plasma of a group of autistic children. These disturbances of catecholamines might be related to the excess of platelet serotonin, but further studies are needed to clarify the origins of the abnormal levels of serotonin and catecholamines, the relationships between the disorders affecting both serotonin and catecholamines, and their possible relation to the clinical syndrome.

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