

A Controlled Crossover Trial of Fenfluramine in Autism

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Abstract—We report a 12 month double-blind randomized crossover trial of fenfluramine in 20 children with the syndrome of autism. On active drug most of the children lost weight and blood serotonin levels fell by an average of 60%. There was a fall in urinary dopamine (DA) and noradrenaline (NA) levels and increased excretion of homovanillic acid (HVA). Some of the children showed improvement in tests of cognitive and language function, although the results did not achieve overall statistical significance. Event-related brain potentials (ERPs) were obtained in seven subjects on an auditory choice reaction time task. Side effects of the drug included irritability and lethargy. Fenfluramine may have a limited place in the management of some patients with autistic disorder.

Keywords: Fenfluramine, autism, neurotransmitters, event-related potentials

Introduction

There has been a vast amount of literature on the subject of autism but the aetiology remains obscure and management of the condition has relied heavily on behavioural interventions. Various psychopharmacological agents have been used with either limited short-term success, or in some cases no effect (Cohen & Young, 1977). These have included dopamine-blocking or -inhibiting compounds such as the phenothiazines (Campbell, Cohen & Anderson, 1981) and haloperidol (Campbell *et al.*, 1978; Anderson *et al.*, 1984). Dopamine agonists such as D-amphetamine, L-amphetamine and L-dopa have also been used with variable results (Campbell, Perry, Small & Green, 1987). Naloxone, an opiate antagonist, was reported to reduce stereotypy and self-mutilating behaviour in a few retarded autistic children (Davidson, Kleene, Carroll & Rockowitz, 1983; Sandman *et al.*, 1983; Bernstein, Hughes & Thompson, 1984).

A number of studies of neurotransmitters in autism indicate an over-activity of

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dopaminergic pathways, which may be associated with the increased stereotypy of children with autistic disorder (Cohen & Young, 1977). A recent Swedish study (Gillberg & Svennerholm, 1987) found increased concentrations of homovanillic acid (HVA) in the cerebrospinal fluid of children with the syndrome of autism. Garreau *et al.* (1988) have also reported increased urine HVA in autistic children. However, they found considerable individual variation in urinary catecholamines and their metabolites. This is in accord with a number of other laboratories including our own.

Elevated blood serotonin was found in a group of retarded children with autistic disorder by a number of investigators (Schain & Freedman, 1961; Ritvo *et al.*, 1970; Takahashi, Kanai & Miyamoto, 1976; Hanley, Stahl & Freedman, 1977; Anderson *et al.*, 1987). Geller, Ritvo, Freeman and Yuwiler (1982) suggested that up to 40% may have elevated blood serotonin (5-hydroxytryptamine, 5-HT) levels when compared with controls of the same age and sex.

To test whether lowering blood serotonin levels would have a beneficial effect on children with autistic disorder, Geller *et al.* (1982) assessed the effect of the anorectic agent, fenfluramine, in three boys with the syndrome. They reported improvements in behaviour and IQ in their subjects which appeared related to a marked lowering of blood serotonin levels. Since this original report there have been a number of reports on the effects of fenfluramine in autism (Ritvo *et al.*, 1984; August, Raz & Baird, 1985; Klykylo, Feldis, O'Grady, Ross & Halloran, 1985; Ho, Lockitch, Eaves & Jacobson, 1986; Ritvo *et al.*, 1986; Stubbs, Budden, Jackson, Terdal & Ritvo, 1986). An evaluation of these trials suggested that the role of fenfluramine in the management of autism remained unclear; we therefore carried out a randomized double-blind trial of fenfluramine in 20 children with autistic disorder using a comprehensive protocol and tight methodological criteria. The reason for embarking on the trial was that a large number of parents had read reports about the use of fenfluramine and were keen to try it with their children. Some parents had contacted their own doctors to ask for prescriptions of the drug. After detailed explanations and full and comprehensive discussions with parents, they agreed that a carefully controlled trial was safer because the effects of the drug would be carefully monitored throughout the trial. The majority of the children had been tried on various psychoactive drugs in the past, with evidence of side effects in some cases.

Methods

Following informed parental consent, 20 children with autistic disorder were enrolled in the trial. The trial was approved by the Ethics Committee of the Adelaide Children's Hospital and had the support of the Autistic Association of South Australia. Criteria for the diagnosis of autism were those of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (1980). There were 14 males and six females. Their ages ranged from 4 yrs 9 months to 17 yrs 3 months with a mean age of 10.0 yrs and a median age of 9.10 yrs. One child moved to another state half way through the trial, 19 children completed the trial.

All the children had been previously under the care of paediatricians and paediatric neurologists. A number had also been assessed by paediatric psychiatrists. In every case the final diagnosis was of infantile autism with or without mental retardation. There were no cases of progressive neurological disease. Investigations had included EEGs which were carried out in 13 of the subjects. Ten were normal, two were poorly developed for age and one was grossly abnormal with multiple epileptiform discharges

in a severely retarded epileptic girl. Biochemical investigations had also been carried out in 13 of the children. These included amino acid screen, blood ammonia, organic acids and white cell enzymes. No abnormalities were detected. Results of computerized axial tomography were available in seven cases. Three were normal, two showed mild asymmetry of the lateral ventricles, one showed mild cerebral atrophy, and one showed slight widening of the fourth ventricle and basal cisterns. All the subjects had been screened for chromosomal anomalies including the fragile X chromosome. No chromosomal abnormalities were detected in our cohort. Fifteen subjects were on no medication, three were on anticonvulsants, one was on a benzodiazepine and one on the contraceptive pill. The medications were continued during the trial. The only other drugs used were for intercurrent infections.

All the investigators were "blind" as to which children were on active drug or placebo. At the beginning of the trial all the children had an in-depth medical and family history taken and a full medical examination including height and weight measurements. Two baseline serotonin estimations were carried out on each child. Baseline psychometric assessments were carried out as appropriate for chronological and mental age; these included the Leiter International Performance Scale (Leiter, 1969), the Merrill-Palmer Scale (Stutsman, 1948) and the British Ability Scales (Elliott, 1984). Tests of language included the Reynell Developmental Language Scales (Reynell, 1977), the Test of Language Development—Primary (TOLD—P) (Hammill & Newcomer, 1985) and the Test of Adolescent Language (TOAL) (Hammill, Brown, Larsen & Wiederholt, 1980). Other instruments used with all subjects included the Vineland Social Maturity Scale (Doll, 1952), the Ritvo-Freeman Real Life Rating Scale (Freeman, Ritvo, Yokota & Ritvo, 1990) and the Conners Teachers Rating Scale (Conners, 1969). At the onset the parents were given a diary to enter regular observations of their child's behaviour, to keep a record of the tablets given and to record any side effects noticed. The psychometric tests were used at 6-monthly intervals only so that practice effects on cognitive and language measures, evident in other studies, would be eliminated. Details of the subjects' baseline assessments are shown in Table 1. [The Congalton Scale (Congalton, 1963) was used for social class.]

All the children were given placebo for a month to get them used to the routine of taking tablets regularly. The pharmacist then randomly allocated the children into two groups of equal size, one was given fenfluramine (the proprietary drug is racemic fenfluramine) and the other placebo for a 5-month period. The dose of fenfluramine was 1.5 mg/kg/day given in two divided doses, morning and evening. At the end of this time period all children were given placebo for 2 months to allow serotonin levels to return to pre-treatment levels before the groups crossed over for the second 5-month period.

Following two baseline serotonin estimations, measurements of serotonin, fenfluramine and norfenfluramine were carried out at intervals shown in Fig. 1. Blood for serotonin determination was collected by venepuncture or finger-prick into EDTA-containing vacutainer tubes, an earlier study having shown no significant difference between venous and capillary (finger-prick) collection (Badcock, Spence & Stern, 1987). Whole blood serotonin values were determined in duplicate by the protein precipitation-HPLC method of Anderson, Young, Cohen, Schlicht and Patel (1981). Plasma fenfluramine and norfenfluramine levels were determined in duplicate using gas chromatography with nitrogen detection (Morris & Reece, 1983). Twenty-four hour collections of urine were obtained in 11 children. Aliquots of 100 ml were taken and frozen (-80°C). Separate analyses were performed for noradrenaline (NA), dopamine (DA) and homovanillic acid (HVA) using HPLC with electrochemical detection (Smedes, Kraak & Poppe, 1982; Soldin, 1982; Oades, Stern, Walker, Clark & Kapoor, 1990).

The standardized psychological tests were repeated at 6 and 12 months. Conners Teacher Rating Scales (Conners, 1969) were carried out during the baseline period and repeated at the end of each treatment period, and the Ritvo-Freeman Real Life Rating Scales (Freeman *et al.*, 1990) on average every 4 weeks. Five children, considered by parents and teachers to have high activity levels, had their activity monitored on active drug and placebo by the use of a pedometer which registered the distance covered by the child over several hours of the day. Other children had different activities quantitatively monitored such as flicking, tap-turning or lightswitching.

Seven of the subjects who functioned at the highest level completed an auditory choice reaction time task while event-related potentials were recorded from seven standard EEG sites during placebo and active drug phases of the study. The auditory paradigm is adapted from Pfefferbaum, Ford, Wenegrat, Roth and Kopell (1984). The subjects were required to press a button in response to a low "target" tone and to ignore a rare high and a common tone. For a more detailed description of the method refer to Oades *et al.* (1990) and Oades, Walker, Geffen and Stern (1988).

Table 1. Baseline assessments

Subject number	Sex	Age	Social class (Congalton)	Baseline weight percentile	Baseline IQ (Merrill-Palmer BAS)	Baseline social scale (Vineland)	Baseline language quotient (Reynell, TOAL, TOLD—P)
1	F	8.9	6	26	48	51	29
2	M	9.2	6	17	93	86	88
3	M	5.4	6	25	40	55	16
4	M	8.6	4	67	63	80	53
5	F	14.3	4	80	40	36	14
6	M	9.8	4	50	18	26	12
7	M	14.1	5	99	41	39	16
8	F	8.8	6	75	21	23	12
9	F	5.8	3	20	33	47	18
10	F	11.3	3	50	26	28	14
11	M	10.3	4	75	24	25	14
12	M	13.9	1	10	30	36	24
13	M	10.5	1	7	47	60	32
14	M	11.3	7	37	61	52	24
15	M	4.7	2	97	63	89	46
16	M	14.2	6	30	95	75	80
17	M	7.2	6	62	50	36	21
18	M	4.8	3	62	72	88	24
19	M	7.5	1	37	120	69	72
20	F	17.3	5	88	90	75	70

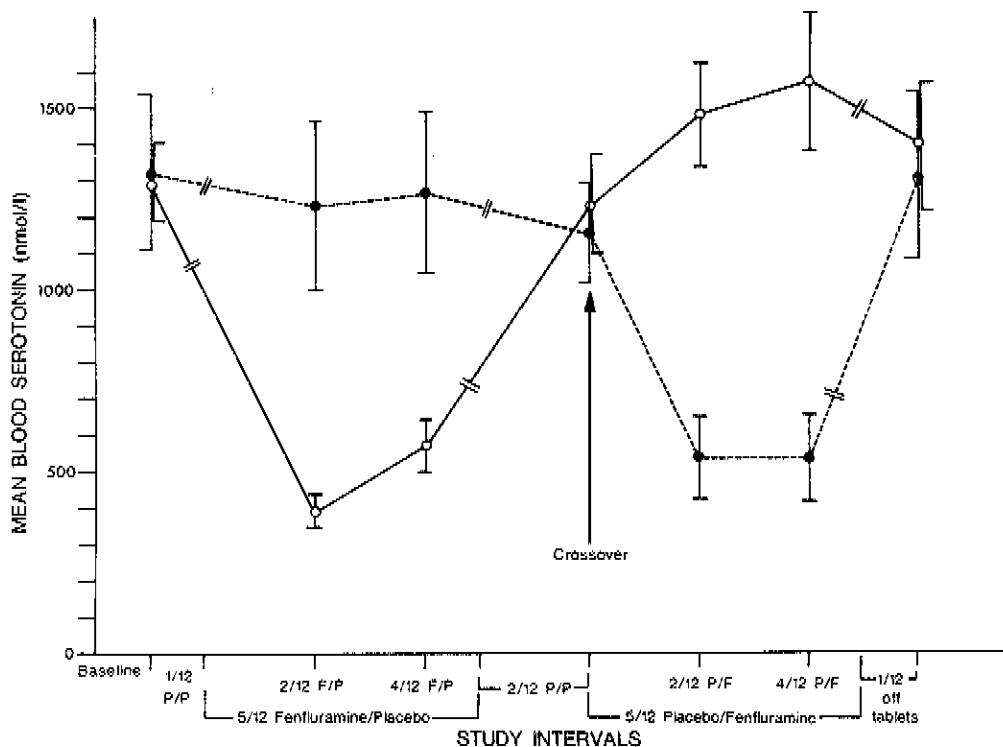


Fig. 1. Effect of fenfluramine on blood serotonin concentration. ○—○ Means (\pm SEM) of nine autistic children receiving fenfluramine (F) followed by placebo (P). ●—● Means (\pm SEM) of 10 autistic children receiving placebo (P) followed by fenfluramine (F).

Results

Compliance was checked regularly in the parent diaries using a monthly date and time chart. It was confirmed at the end of the trial by the fenfluramine blood levels. There was excellent compliance throughout the trial helped by good parent motivation.

Side effects: parents were informed of the major possible side effects and asked to note in their diary any unusual increases and decreases in characteristic behaviours. As many parents were quite sensitive to changes in the areas known to show side effects, good indications of their occurrence could be ascertained from the diaries. Lethargy was not uncommon in a mild form, was reported in eight children, and was marked in one child. Irritability was a feature in two children, necessitating a reduction in dosage in one.

Fenfluramine is a known anorectic agent and 14 subjects lost weight; this varied from 0.1 to 6.6 kg. All the subjects regained their original percentile weights within 2 months following withdrawal of fenfluramine. Five subjects gained weight while on fenfluramine from 0.1 to 5.2 kg. There was a significant correlation between plasma fenfluramine (but not norfenfluramine) level and drop in weight percentile from baseline to active periods ($r = 0.56$, $p = 0.01$). However, there was no significant

correlation between percentage reduction in blood serotonin and weight percentile drop ($r = 0.32$, $p = 0.10$).

The effect of fenfluramine on mean blood serotonin levels is shown in Fig. 1. This shows the marked drop in mean serotonin level of 66% at 2 months and 57% at 4 months, with a return towards pre-treatment levels after the drug was discontinued. There was evidence of a "rebound" effect for the group receiving fenfluramine in the first half of the trial. The group receiving fenfluramine in the second half did not have serotonin levels monitored over a similar period at the conclusion of the trial. Using the method of Armitage and Hills (1982), comparisons of mean serotonin levels at the end of each treatment period with the respective pre-treatment baselines showed that subjects receiving fenfluramine during the first treatment period had significantly higher serotonin levels at the end of the second period (placebo or non-treatment for that group) (Table 2). This is in keeping with previous research (Ritvo, Freeman, Geller & Yuwiler, 1983; Stahl & Levin, 1982).

Table 2. Comparison of changes in serotonin levels between first and second treatment periods using the method of Armitage and Hills (1982)

Order	Serotonin level (nmol/l)	
	Difference between start & end period 1	Difference between start & end period 2
Drug in first period	- 817.00	+ 256.44
Drug in second period	- 57.00	- 615.90

Effect of order along, $F = 0.46$ (1 df), $p = 0.51$ (NS); difference between changes in each period, $F = 7.13$ (1 df), $p = 0.02$ (significant) and effect of drug (interaction), $F = 103.05$ (1, 17 df), $p < 0.001$ (significant).

The relationship between percentage decrease in blood serotonin concentration and plasma fenfluramine and norfenfluramine levels after 4 months medication is shown in Fig. 2. There was significant correlation between fenfluramine level and percentage decrease in serotonin level from baseline to active periods ($r = 0.45$, $p = 0.05$), but not with norfenfluramine level ($r = 0.144$, $p = 0.20$). Results of the 24 hour urinary NA, DA, HVA and HVA/DA estimations are shown in Table 3. These indicate decreased levels of NA and DA, increased levels of HVA and increased DA metabolism (HVA/DA) on fenfluramine.

Psychometric assessments

Leiter International Performance Scale. Using Repeated Measures Analysis of Variance, no statistically significant increase in IQ was found for the group of 18 subjects while on fenfluramine, in comparison with placebo (Table 4). However, seven subjects showed clinical improvements of five or more IQ points from placebo to treatment periods (subjects 1, 2, 10, 11, 14, 18, 19).

Merrill-Palmer Scale. For the 13 children tested, there was no overall significant increase in IQ across the group while on fenfluramine as demonstrated by Repeated

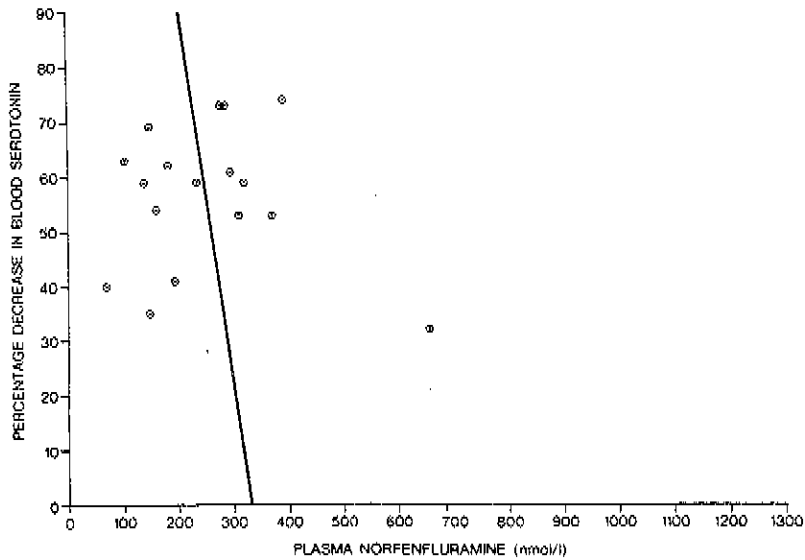
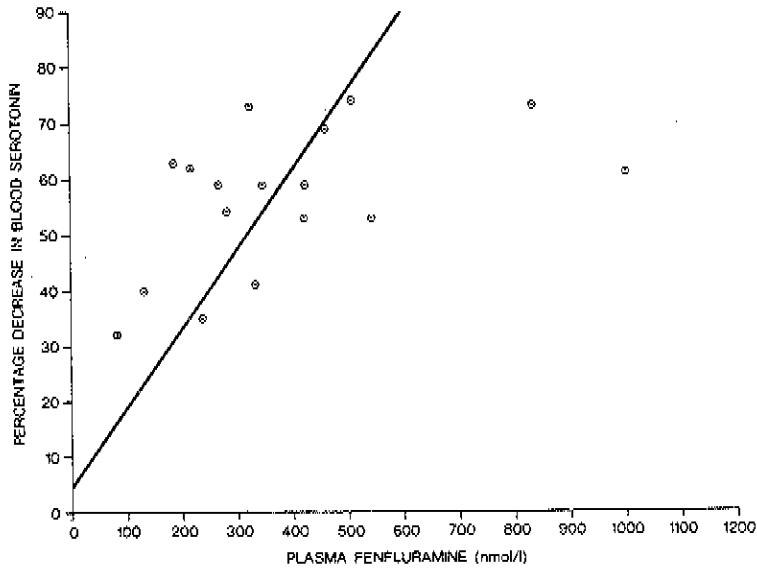


Fig. 2. Relationship between percentage decrease in blood serotonin concentration and plasma fenfluramine (top) and norfenfluramine (bottom) concentration after 4 months medication

Table 3. Levels of noradrenaline (NA), dopamine (DA), homovanillic acid (HVA) and DA metabolism (HVA/DA) in 24 hours. Urine samples collected at the end of placebo (P) and fenfluramine (F) trial periods (mg/g creatinine per m²)

	NA (SEM) n11	DA (SEM) n11	HVA (SEM) n11	HVA/DA (SEM) n11
P	37.0 (4.0)	497.8 (79.0)	48.4 (11.6)	0.104 (0.023)
F	26.3 (4.6)	422.1 (89.7)	58.1 (9.1)	0.258* (0.072)

* $t = -1.9$, $p < 0.05$.

Measures ANOVA (Table 4). However, three subjects showed a clinical improvement of 5 or more IQ points (subjects 1, 10, 18). Four increased IQ more on placebo than on fenfluramine.

British Ability Scales. Six children possessed sufficient verbal abilities to complete a balanced number of verbal and non-verbal subtests on these scales (subjects 2, 4, 14, 16, 19, 20). Repeated Measures ANOVA showed significant differences between IQ on fenfluramine and both placebo and baseline periods (Table 4). Three subjects showed excellent overall improvement in IQ and cognitive functioning as reflected in their total and subtest scores (subjects 2, 14, 19) while the other three showed scattered improvements.

Language Scales. Significant improvement in language functioning was recorded across the whole group using Repeated Measures ANOVA (Table 4). To perform this analysis, the language quotients from the Reynell Developmental Language Scales (mean of Expressive and Comprehension Scales), the TOLD—P and TOAL were pooled because different age and ability subgroups had been tested on different measures. As the numbers involved in the TOLD—P and TOAL analyses are small, their language quotients were analysed separately. Separate Repeated Measures ANOVAs were performed on the Reynell Comprehension and Expressive Subscales, revealing significant differences across the trial on both.

Vineland Social Maturity Scale. A significant effect of fenfluramine on overall social functioning was shown using Repeated Measures ANOVA (Table 4). Eight subjects showed an increase of five or more points in Social Quotient (SQ) (subjects 1, 13, 14, 15, 16, 18, 19, 20).

Conners Teacher Rating Scale. (Table 4) This scale does not produce a composite score summarizing behaviour as a whole; instead various subscales are extracted allowing investigators to focus on aspects of behaviour where improvement is desired. Using Repeated Measures ANOVA, no significant effect of fenfluramine was recorded across the whole group on the subset of questions measuring the "hyperactivity" factor (which was the sole concern in this study).

Ritvo-Freeman Real Life Rating Scale. Observation sessions were 30 minutes in length and were carried out in the child's classroom. Initial reliability was assessed using

Table 4. Repeated measure ANOVAs on IQ, language and social scales (means for each phase of trial \pm standard error)

Test used	<i>N</i>	Baseline	Placebo	Fenfluramine	<i>p</i> value
Using IQ Scores:					
Leiter International Performance Scale	18		64.17 ± 7.25	65.72 ± 7.73	0.35 NS
Merrill-Palmer Scale	13	42.69 ± 4.25	46.38 ± 4.90	44.69 ± 4.87	0.11 NS
British Ability Scales	6	80.57 ± 8.86	84.71 ± 9.29	88.00 ± 7.73	0.004 ^a
Using language age: (in months)					
Reynell Developmental Language Scales					
(a) Comprehension subscale	14	(a) 22.14 ± 2.58	23.42 ± 3.32	27.42 ± 4.31	0.013 ^a
(b) Expressive subscale		(b) 21.57 ± 2.53	23.07 ± 2.75	26.93 ± 3.16	0.001 ^a
Language quotient:					
TOLD-P and TOAL	5	72.6 ± 5.84	73.2 ± 4.27	80.2 ± 6.34	0.019 ^a
Combined language quotients	19	35.11 ± 5.58	36.42 ± 5.71	41.11 ± 6.32	0.001 ^a
Social quotient:					
Vineland Social Maturity Scale	19	55.42 ± 5.06	57.68 ± 5.71	60.53 ± 6.53	0.02 ^a
Mean score:					
Conners Teacher Rating Scale	19	13.89 ± 1.32	12.53 ± 1.18	12.61 ± 1.53	0.50 NS
Ritvo-Freeman Real Life Rating Scale	19	0.71 ± 0.09	0.69 ± 0.11	0.68 ± 0.09	0.50 NS

NS - Not significant; ^a = significant *F* for the repeated measure.

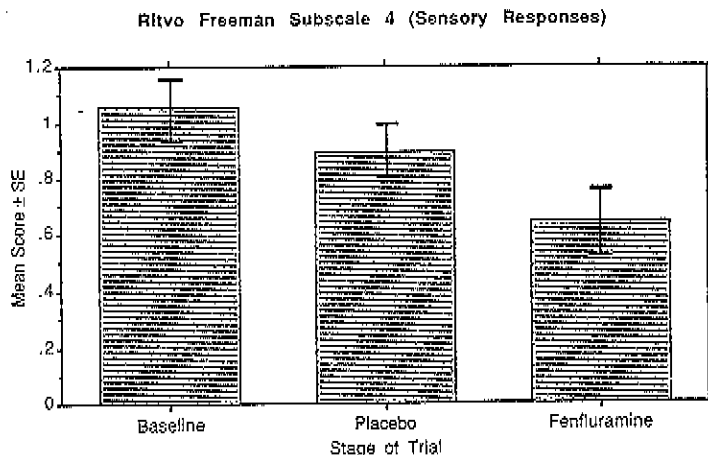


Fig. 3. Results of sensory responses subscale (subscale 4) of Ritvo–Freeman Real Life Rating Scale. (Reduction in score indicates improved adaptive response to sensory input.)

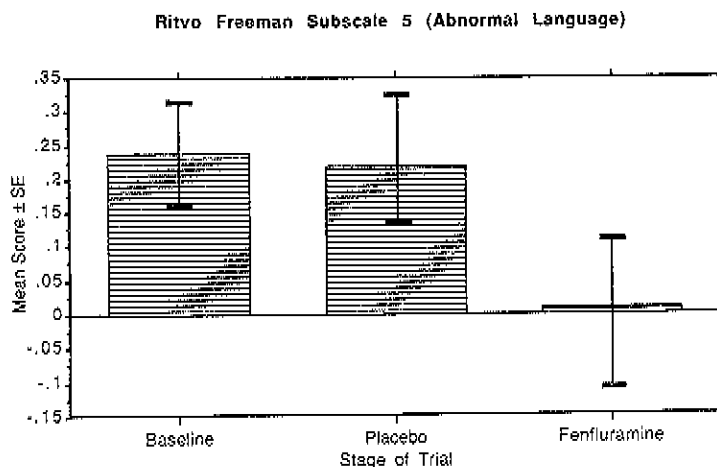


Fig. 4. Results of language subscale (subscale 5) of Ritvo–Freeman Real Life Rating Scale. (Reduction in score denotes improvement in communicative skills.)

videotapes of several children who had also been observed “live”. Correlations for particular behaviours on two occasions ranged from 0.79 to 1.00 (using Pearson’s Correlation Coefficient). No significant differences in total scores on this scale were apparent during the trial (Repeated Measures ANOVA) (Table 4). There were however significant decreases in “abnormal” behaviours on two subscales during active drug compared with both baseline and placebo periods: subscale 4 (Sensory Responses) and subscale 5 (Language). Using the combination of increase in overall verbal ability as shown on the Reynell Developmental Language Scales and the decreased abnormal language behaviours measured by the Ritvo Language subscale, the ratio of normal to abnormal language increased.

Drug order effects were analysed and found to be non-evident except with the combined language quotients, where by chance, a higher functioning group all received the drug during one period and the lower functioning group received it during the alternate period. Overall, there appear to be greater increases for the ones with a higher initial baseline. The planned comparisons performed on the Repeated Measures ANOVAs indicate where changes were due to increases during drug or placebo periods when compared to baseline and can be seen from the means in Table 4. Where planned or *post hoc* analyses reveal the exact location of a change in scores, these are included in the table.

Parent diary

The written entries in the diary (when subjected to frequency counts of content categories such as "new words used", "child helping around the house") showed good concurrence with the Conners Scale, IQ improvements and Social Quotients. It was not considered statistically valid to subject these diary results to statistical analysis because of the variation in styles and completeness. However, the improvements in behaviour on fenfluramine (and many deteriorations while on placebo and after the official end of the trial) are clearly evident in parents' behavioural descriptions. For four children with IQs ranging from 65 to 127, there is clear mention of reduction of stereotypic play on fenfluramine, but no such indication for children with lower IQ. There did not appear to be a reduction in repetitive activities such as tapping, lightswitching and tap-turning, as recorded by frequency counts in the parent diaries, nor in flicking as recorded by time sampling by the psychologist.

Pedometers

Measuring activity level (in mean steps per minute), Repeated Measures ANOVA showed a non-significant reduction between placebo and drug periods in the five children tested ($F = 6.58$, $p = 0.08$). The equipment was not available during the "baseline" period. Three children, however, showed a marked reduction in mean steps per minute.

Auditory choice reaction time task and ERPs

On fenfluramine, errors of omission decreased by 27%. N1 latency increased by a mean of 6% with all three stimuli (rare target, and both rare and frequent non-target). Non-target P3 latency increased by a mean of 7%. Three subjects with abnormally long target P3 latencies showed a large latency decrease from 600 to 400 milliseconds. A multivariate analysis of variance for N1 amplitude showed a main effect of drug ($F = 11$, $p < 0.002$) and a drug tone interaction ($F = 5.2$, $p < 0.02$). N1 amplitude decreased with all three stimuli (Fig. 5), the largest decrease being after the rare non-target tone ($p < 0.05$, Tukey's test). An ANOVA showed that P3 amplitude increased with all three stimuli ($F = 11$, $p < 0.002$) (Fig. 5), with a significant effect for the rare non-target tone ($p < 0.05$, Tukey's test).

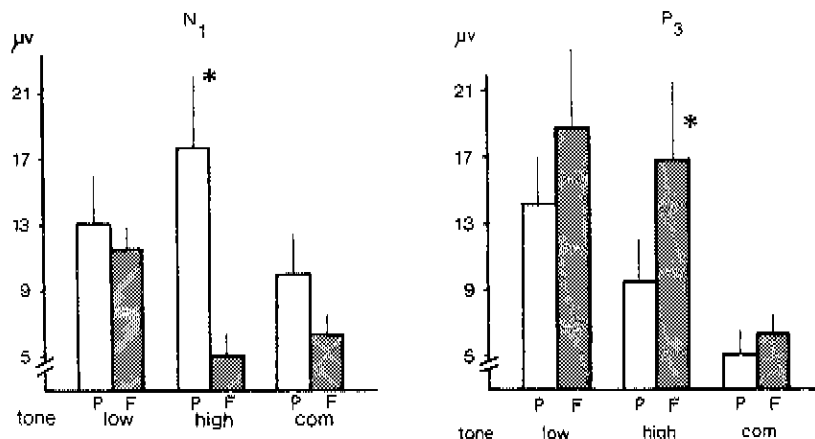


Fig. 5. N1 and P3 amplitude (μV) elicited by low (target), high (rare non-target) and frequent (common) non-target tones with placebo (P, open columns) and fenfluramine (F, hatched columns).

Discussion

In a recent annotation on fenfluramine treatment of autism, Campbell (1988) divided the reports into two groups; those in partial agreement with Ritvo and those which are in complete disagreement. Our results would be in partial agreement with Ritvo's findings, and will be compared with the results of previous trials and with reference to the known and presumed properties of fenfluramine. In our study, although not all the subjects improved on all functional measures, 10 subjects responded significantly in at least two areas. Four of these improved significantly in cognitive, language and social parameters. Six others responded significantly in two of the three functional areas. Improvements were noted from a few days, to 2–3 weeks after initiation of fenfluramine and were noted in children across the whole ability range.

Auditory discrimination performance improved on fenfluramine with fewer errors of omission. However, contrary to expectation, this was not matched by improved attention to the target, although there was greater overall response to non-target stimuli, as shown by ERP amplitude changes. This may indicate that on fenfluramine, unusual environmental stimuli command more attention and help decrease the supposed overselectivity of response characteristic of many autistic individuals (Hermelin & O'Connor, 1970; Rutter, 1979). Allowing for methodological differences, we can compare our results with those of August *et al.* (1984). We would agree that the main effects of fenfluramine were on the N1 and P3 components elicited by non-target stimuli. An analysis of the differences between N1 and P3 amplitudes after non-target and target tones suggests an improved differentiation at the earlier, but a worse differentiation at the later stages of processing measured by these two components. Since a separate analysis of the urine samples from these subjects showed significant decreases of NA in addition to the increased excretion of HVA and correlations between changes of the N1 peak and dopamine metabolism were noted (Oades *et al.*, 1990),

we speculate that information processing assessed by the evoked potentials is affected by the effects of fenfluramine on catecholamine activity. While published studies differ on the extent to which urinary measures reflect central (as well as peripheral) catecholamine metabolism, a partial relationship is reported (Kopin, Bankiewicz & Harvey-White, 1988).

Gillberg and Wahlstrom (1985) reported that 47% of 66 psychotic children had major or minor chromosomal aberrations, with 25% of boys with autistic disorder showing the fragile X (G27) marker. None of our subjects showed any chromosomal abnormality. This is more in accord with Matsuishi *et al.* (1987) who found an incidence of fragile X of only one in 38 subjects. This may reflect differences in populations with autistic disorder which fulfill the DSM III criteria.

Comparing our results with those of Ritvo *et al.* (1986) in their multicentre trial, they found significant correlations between low initial blood serotonin concentrations, high baseline performance IQ and good clinical response. We were not able to replicate these findings. On the tests used they reported significant mean improvements on verbal and performance IQ. Thirty-three per cent of their subjects were rated as showing "strong clinical improvements", 52% "some improvements" and 15% "absolutely no changes". Klykylo *et al.* (1985) found no increases in functioning on behavioural measures and no change in IQ. They reported clinical improvements in three of their 10 subjects, but this was not supported statistically.

August *et al.* (1985) in a study of nine outpatients found no increases in verbal or performance IQ, but improvements in areas such as hyperactivity, distractibility and motor disturbances in some of the subjects. Ho *et al.* (1986) found increases in non-verbal IQ of 5-8 points in three boys of initially higher functioning but no overall improvements across their group of 31 subjects. They also found a slight increase in short-term auditory memory in higher functioning children and some increases in receptive language. Their results are confounded by short test-retest intervals. Stubbs *et al.* (1986) studied eight subjects. Three patients with IQs < 20 showed no change, four with IQs > 39 had "small increases". On the Ritvo-Freeman Real Life Rating Scale, a decrease in abnormal motor behaviour was the only significant effect. They did not find a correlation between baseline serotonin levels and clinical improvement.

Fenfluramine is an anorectic drug with mild sedative properties (Rowland & Carlton, 1986). The D-isomer, reminiscent of the effects of amphetamine on catecholamines, stimulates the release of 5-HT, and reduces the levels of 5-HT and its metabolite 5-HIAA (Costa, Groppetti & Revuelta, 1971; Invernizzi, Berettera, Garattini & Samanin, 1986). The α -isomer is reported to reduce level of DA and NA and raise levels of their metabolites. These claims of increased catecholamine utilization and increased levels of acetylcholine are reminiscent of the effects of various neuroleptics (Consolo, Forloni, Garattini, Ladinsky & Tirelli, 1979; Garattini *et al.*, 1979; Invernizzi *et al.*, 1986) and are consistent with our findings from urinary measures following treatment with the racemate.

A number of papers have outlined the side effects of fenfluramine in children with autistic disorder (Volkmar, Paul, Cohen & Shaywitz, 1983; Piggott, Gdowski, Villanueva, Fischhoff & Frohman, 1986; Realmuto *et al.*, 1986), the most frequently reported symptoms being irritability, agitation and lethargy. In the non-autistic,

drowsiness, dizziness, diarrhoea, dry mouth, nausea, vomiting and urinary frequency have been described (Veltri & Temple, 1975). Sanders-Bush, Bushing and Sulser (1975) and Seiden, Fischman and Schuster (1976) have shown that degenerative lesions of 5-HT neurones are caused by parachloroamphetamine and methylamphetamine, respectively. Fenfluramine neurotoxicity has been described in a number of species including the rat (Harvey & McMaster, 1977) and the rat, guinea pig and Rhesus monkey (Schuster, Lewis & Seiden, 1986). Whilst the dosage used by Harvey and McMaster (1977) approximated that used in humans, the doses used by Schuster *et al.* (1986) ranged from 6.25 to 50 mg/kg per injection. Duhault and Boulanger (1977) in contrast, found that the decrease of brain 5-HT in long-term treated rats is rapidly reversible and dispute the neurotoxic effect of fenfluramine. They ascribe the conflicting results to differences in methods or in strains. In their study of fenfluramine and brain serotonin, Clineschmidt *et al.* (1978) point out that "It is not known if the smaller but repeated dosage of fenfluramine used in man will cause a long-term reduction in brain 5-HT. Such an effect might explain, at least partially, tolerance, withdrawal depression and perhaps other actions of this drug reported in humans".

Our findings suggest that fenfluramine may bring about modest improvements in cognitive function, language and behaviour in a proportion of children with autistic disorder. It is obvious that our knowledge of both the short- and long-term effects of fenfluramine is still incomplete. Clinicians using this drug need therefore to weigh the risk/benefit ratio in every individual case before embarking on its use, keeping in mind the reported neurotoxicity with long-term use in animals. We were unable to determine any clinical or laboratory criteria that defined a subgroup of individuals with autistic disorder who would respond to fenfluramine, as improvements occurred in both high- and low-functioning individuals. To design an ideal study of fenfluramine in autism, one should try to obtain a much larger group of more homogeneous history and baseline functioning. As with studies of any rare and variable clinical condition, this ideal is seldom achievable.

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References

- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd edn). Washington: American Psychiatric Association.
- Anderson, G. M., Freedman, D. X., Cohen, D. J., Volkmar, F. R., Hoder, E. L., McPhedran, P., Minderas, R. B., Hansen, C. R. & Young, J. G. (1987). Whole blood serotonin in autistic and normal subjects. *Journal of Child Psychology and Psychiatry*, **28**, 885-900.
- Anderson, G. M., Young, J. G., Cohen, D. J., Schlicht, K. R. & Patel, N. (1981). Liquid-chromatographic determination of serotonin and tryptophan in whole blood and plasma. *Clinical Chemistry*, **27**, 775-776.
- Anderson, L. T., Campbell, M., Greca, D. M., Perry, R., Small, A. M. & Green, W. H. (1984). Haloperidol in the treatment of infantile autism: effects on learning and behavioural symptoms. *American Journal of Psychiatry*, **141**, 1195-1202.

- Armitage, P. & Hills, M. (1982). The two-period crossover trial. *The Statistician*, **31**, 119-131.
- August, G. J., Raz, N. & Baird, T. D. (1985). Effects of fenfluramine on behavioural, cognitive and affective disturbances in autistic children. *Journal of Autism and Developmental Disorders*, **15**, 97-107.
- August, G. J., Raz, N., Papanicolaou, A. C., Baird, T. D., Hirsh, S. L. & Hsu, L. L. (1984). Fenfluramine treatment in infantile autism: neurochemical electrophysiological, and behavioural effects. *Journal of Nervous and Mental Disease*, **172**, 604-612.
- Badcock, N. R., Spence, J. G. & Stern, L. M. (1987). Blood serotonin levels in adults, autistic and non-autistic children with a comparison of different methodologies. *Annals of Clinical Biochemistry*, **24**, 625-634.
- Bernstein, G. A., Hughes, J. R. & Thompson, T. (1984). Naloxone reduces the self-injurious behavior of a mentally retarded adolescent. Paper presented at the Annual Meeting of the American Academy of Child Psychiatry, Toronto.
- Campbell, M. (1988). Fenfluramine treatment of autism. *Journal of Child Psychology and Psychiatry*, **29**, 1-10.
- Campbell, M., Anderson, L. T., Meier, M., Cohen, I. L., Small, A. M., Samit, C. & Sachar, E. J. (1978). A comparison of haloperidol, behaviour therapy and their interaction in autistic children. *Journal of the American Academy of Child Psychiatry*, **17**, 640-655.
- Campbell, M., Cohen, I. L. & Anderson, L. T. (1981). Pharmacotherapy for autistic children. A summary of research. *Canadian Journal of Psychiatry*, **26**, 265-273.
- Campbell, M., Perry, R., Small, A. M. & Green, W. H. (1987). Overview of drug treatment in autism. In E. Schopler and G. B. McSibov (Eds), *Neurobiological issues in autism* (pp. 341-356). New York: Plenum.
- Clineschmidt, B. V., Zacchei, A. G., Totaro, J. A., Pflueger, A. B., McGuffin, J. C. & Wishousky, T. I. (1978). Fenfluramine and brain serotonin. *Annals of the New York Academy of Sciences*, **305**, 221-241.
- Cohen, D. J. & Young, J. G. (1977). Neurochemistry and child psychiatry. *Journal of the American Academy of Child Psychiatry*, **16**, 353-411.
- Congalton, A. A. (1963). *Occupation status in Australia* (Studies in Sociology No. 3). Sydney: University of New South Wales Press.
- Conners, C. K. (1969). A teacher rating scale for use in drug studies with children. *American Journal of Psychiatry*, **126**, 884-888.
- Consolo, S., Forloni, G. L., Garattini, S., Ladinsky, H. & Tirelli, A. S. (1979). Differential effects of the isomers of fenfluramine and norfenfluramine on rat striatal acetylcholine content. *Journal of Pharmacy and Pharmacology*, **31**, 706.
- Costa, E., Groppetti, A. & Revuelta, A. (1971). Action of fenfluramine on monoamine stores of rat tissues. *British Journal of Pharmacology*, **41**, 57-64.
- Davidson, P. W., Kleene, B. M., Carroll, M. & Rockowitz, R. J. (1983). Effects of naloxone on self-injurious behavior. A case study. *Applied Research in Mental Retardation*, **4**, 1-4.
- Doll, E. A. (1952). *Vineland social maturity scale* (revised edition). Princeton NJ: Educational Testing Service.
- Duhault, J. & Boulanger, M. (1977). Fenfluramine long-term administration and brain serotonin. *European Journal of Pharmacology*, **43**, 203-205.
- Elliott, C. D. (1984). *British Ability Scales*. London: NFER.
- Freeman, B. J., Ritvo, E. R., Yokota, A. & Ritvo, A. (1990). A scale for rating symptoms of patients with the syndrome of autism in real life settings. *Journal of the American Academy of Child Psychiatry* (in press).
- Garattini, S., Caccia, T., Mennini, T., Samanin, R., Consolo, S. & Ladinsky, H. (1979). Biochemical pharmacology of the anorectic drug fenfluramine: a review. *Current Medical Research and Opinion*, **6**, 15-27.
- Garreau, B., Barthelemy, C., Jouvc, J., Bruncau, N., Muh, J. P. & Lelord, G. (1988). Urinary homovanillic acid levels of autistic children. *Developmental Medicine and Child Neurology*, **30**, 93-98.
- Geller, E., Ritvo, E. R., Freeman, B. J. & Yuwiler, A. (1982). Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys. *New England Journal of Medicine*, **307**, 165-169.
- Gillberg, C. & Svennerholm, L. (1987). CSF monoamines in autistic syndromes and other pervasive developmental disorders of early childhood. *British Journal of Psychiatry*, **151**, 89-94.

- Gillberg, C. & Wahlstrom, J. (1985). Chromosome abnormalities in infantile autism and other childhood psychoses: a population study of 66 cases. *Developmental Medicine and Child Neurology*, *27*, 293-304.
- Hammill, D. D., Brown, V. L., Larsen, S. C. & Wiederholt, J. L. (1980). *Test of adolescent language (TOAL)*. Los Angeles: Western Psychological Services.
- Hammill, D. D. & Newcomer, P. L. (1985). *Test of language development—primary (TOLD—P)*. Los Angeles: Western Psychological Services.
- Hanley, H. G., Stahl, S. M. & Freedman, D. X. (1977). Hyperserotonemia and amine metabolites in autistic and retarded children. *Archives of General Psychiatry*, *34*, 521-531.
- Harvey, J. A. & McMaster, S. E. (1977). Fenfluramine: cumulative neurotoxicity after chronic treatment with low dosages in the rat. *Communications in Psychopharmacology*, *1*, 3-17.
- Hermelin, B. & O'Connor, N. (1970). *Psychological experiments with autistic children*. Oxford: Pergamon Press.
- Ho, H. H., Lockitch, G., Eaves, L. & Jacobson, B. (1986). Blood serotonin concentrations and fenfluramine therapy in autistic children. *Journal of Pediatrics*, *108*, 465-469.
- Invernizzi, R., Berettera, C., Garattini, S. & Samanin, R. (1986). D- and L-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. *European Journal of Pharmacology*, *120*, 9-15.
- Klykylo, W. M., Feldis, D., O'Grady, D., Ross, D. L. & Halloran, C. (1985). Clinical effects of fenfluramine in ten autistic subjects. *Journal of Autism and Developmental Disorders*, *15*, 417-423.
- Kopin, I. J., Bankiewicz, K. & Harvey-White, J. (1988). Effect of MPTP-induced Parkinsonism in monkeys on the urinary excretion of HVA and MHPG during debrisoquin administration. *Life Sciences*, *43*, 133-141.
- Leiter, R. G. (1969). *Manual for the revised Leiter international performance scale*. Chicago: Stoelting Co.
- Matsushita, T., Shiotsuki, Y., Niikawa, N., Katafuchi, Y., Otaki, E., Ando, H., Yamashita, Y., Horikawa, M., Urabe, F., Kuriya, N. & Yamashita, F. (1987). Fragile X syndrome in Japanese patients with infantile autism. *Pediatric Neurology*, *3*, 284-287.
- Morris, R. G. & Reece, P. A. (1983). Improved gas-liquid chromatographic method for measuring fenfluramine and norfenfluramine in heparinized plasma. *Journal of Chromatography*, *278*, 434-438.
- Oades, R. D., Stern, L. M., Walker, M. K., Clark, C. R. & Kapoor, V. (1990). Event-related potentials and monoamines in childhood autism: effects of fenfluramine. *International Journal of Psychophysiology* (in press).
- Oades, R. D., Walker, M. K., Geffen, L. B. & Stern, L. M. (1988). Event-related potentials in autistic and healthy children on an auditory choice reaction time task. *International Journal of Psychophysiology*, *6*, 25-37.
- Pfefferbaum, A., Ford, J. M., Wenegrat, B. G., Roth, W. T. & Kopell, B. S. (1984). Clinical application of the P3 component of event-related potentials. *Electroencephalography and Clinical Neurophysiology*, *59*, 85-103.
- Piggott, L. R., Gdowski, C. L., Villanueva, D., Fischhoff, J. & Frohman, C. F. (1986). Side effects of fenfluramine in autistic children. *Journal of the American Academy of Child Psychiatry*, *25*, 287-289.
- Realmuto, G. M., Jensen, J., Klykylo, W., Piggott, L., Stubbs, G., Yuwiler, A., Geller, E., Freeman, B. J. & Ritvo, E. (1986). Untoward effects of fenfluramine in autistic children. *Journal of Clinical Pharmacology*, *6*, 350-355.
- Reynell, J. (1977). *Reynell Developmental Language Scale (revised)*. London: NFER-Nelson.
- Ritvo, E. R., Freeman, B. J., Geller, E. & Yuwiler, A. (1983). Effects of fenfluramine on 14 outpatients with the syndrome of autism. *Journal of the American Academy of Child Psychiatry*, *22*, 549-558.
- Ritvo, E. R., Freeman, B. J., Yuwiler, A., Geller, E., Yokota, A., Schroth, P. & Novak, P. (1984). Study of fenfluramine in outpatients with the syndrome of autism. *Journal of Pediatrics*, *105*, 823-828.
- Ritvo, E. R., Freeman, B. J., Yuwiler, A., Geller, E., Schroth, P., Yokota, A., Mason-Brothers, A., August, G. J., Klykylo, W., Leventhal, B., Lewis, K., Piggott, L., Realmuto, G., Stubbs, E. G. & Umansky, R. (1986). Fenfluramine treatment of autism: UCLA—collaborative study of 81 patients at nine medical centers. *Psychopharmacology Bulletin*, *22*, 133-140.
- Ritvo, E. R., Yuwiler, A., Geller, E., Ornitz, E. M., Saeger, K. & Plotkin, S. (1970). Increased blood serotonin and platelets in early infantile autism. *Archives of General Psychiatry*, *23*, 566-572.
- Rowland, N. E. & Carlton, J. (1986). Neurobiology of an anorectic drug: fenfluramine. *Progress in Neurobiology*, *27*, 13-62.

- Rutter, M. (1979). Language, cognition and autism. In R. Katzman (Ed.), *Congenital and acquired cognitive disorders* (pp. 247-264). New York: Raven.
- Sanders-Bush, E., Bushing, J. A. & Sulser, F. (1975). Long-term effects of *p*-chloroamphetamine and related drugs on central serotonergic mechanisms. *Journal of Pharmacology and Experimental Therapeutics*, **192**, 33-41.
- Sandman, C. A., Datta, P. C., Barron, J., Hochler, F. K., Williams, C. & Swanson, J. M. (1983). Naloxone attenuates self-abusive behavior in developmentally disabled clients. *Applied Research in Mental Retardation*, **4**, 5-11.
- Schain, R. J. & Freedman, D. X. (1961). Studies on 5-hydroxyindole metabolism in autistic and other mentally retarded children. *Journal of Pediatrics*, **58**, 315-320.
- Schuster, C. R., Lewis, M. & Seiden, L. S. (1986). Fenfluramine: neurotoxicity. *Psychopharmacology Bulletin*, **22**, 1148-151.
- Seiden, L. S., Fischman, M. W. & Schuster, C. R. (1976). Long-term methamphetamine induced changes in brain catecholamines in tolerant rhesus monkeys. *Drug and Alcohol Dependence*, **1**, 215-219.
- Smedes, F., Kraak, J. C. & Poppe, H. (1982). Simple and fast solvent extraction system for selective and quantitative isolation of adrenaline, noradrenaline and dopamine from plasma and urine. *Journal of Chromatography*, **321**, 25-39.
- Soldin, S. J. (1982). High performance liquid chromatography: applications in a children's hospital. *Advances in Chromatography*, **20**, 139-166.
- Stahl, S. M. & Levin, B. (1982). Serotonin depletion by fenfluramine in the carcinoid syndrome (letter). *New England Journal of Medicine*, **306**, 429.
- Stubbs, E. G., Budden, S. S., Jackson, R. H., Terdal, L. G. & Ritvo, E. R. (1986). Effects of fenfluramine on eight outpatients with the syndrome of autism. *Developmental Medicine and Child Neurology*, **28**, 229-235.
- Stutsman, R. (1948). *The Merrill-Palmer Scale of mental tests*. New York: Harcourt Brace and World.
- Takahashi, S., Kanai, H. & Miyamoto, Y. (1976). Reassessment of elevated serotonin levels in blood platelets in early infantile autism. *Journal of Autism and Childhood Schizophrenia*, **6**, 317-326.
- Veltri, J. C. & Temple, A. R. (1975). Fenfluramine poisoning. *Journal of Pediatrics*, **87**, 119-121.
- Volkmar, F. R., Paul, R., Cohen, D. J. & Shaywitz, B. A. (1983). Irritability in autistic children treated with fenfluramine (letter). *New England Journal of Medicine*, **309**, 187.