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ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY (ADDH): THE CONTRIBUTION OF CATECHOLAMINERGIC ACTIVITY

ROBERT D. OADES

Department of Physiology, Flinders University Medical Centre, Bedford Park, S.A. 5042, Australia

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1. Introduction

From the middle of the nineteenth to halfway through the twentieth century an association between insanity and hyperkinesia was commonly described (Ireland, 1877; Tuke, 1892; Ingram, 1956; Ounsted, 1955). The clinical picture of an attention deficit disorder with hyperkinesia, recognizably similar to that in use today (ADDH), was first widely identified as a common result of Von Economo's encephalitis in children after the first world war ("post-encephalitic disorder"). Currently the diagnostic and statistical manual of the American Psychiatric Association (DSM III, 1980) notes that the primary features of "childhood attention disorder with hyperactivity" are inattention (poor concentration), impulsivity and excessive motor activity (cf also Utah criteria; Wender *et al.*, 1984). In North America this concept, at least in name, replaced the more limited concept denoted by the "hyperactive child syndrome" (Laufer *et al.*, 1957; Stewart *et al.*, 1966).

Until recently, related diagnoses have been made less frequently in Europe (review, Weiss and Hechtman, 1979; incidence U.S.A. = 3–10%, U.K. = 1.2%; Thorley, 1984). The results of Australian work suggest there is a difference between the diagnostic practice in the U.S.A. and elsewhere which reflects the degree of symptom severity that is accepted as diagnostically significant rather than a categorical difference of incidence in and outside the U.S.A. (Glow, 1984; Glow and Glow, 1980). In practice the emphasis on motor activity in the syndrome has been formally retained (International Classification of Diseases, ICD 9, WHO, 1978). This probably reflects the history of the association between brain damage and hyperkinesia. However, as Barkley (1982) has emphasized, the American practice is to exclude any overt neurological component. This is fair, as recent computer tomographic studies have failed to find any consistent differences in the brain density, ventricular volumes or ratios of groups of ADDH subjects (Harcherik *et al.*, 1985; Shaywitz *et al.*, 1983).

This review will not consider the dimensions of defiance-aggression and anxiety-fear that appear on some rating scales (cf Conners, 1973; Werry, 1968). Indeed Thorley (1984; also Weiss and Hechtman, 1979) distinguishes an aggressive "conduct disorder" group from a hyperkinetic group with attentional and articulatory disturbances. Even those who emphasize the lack of a clear-cut distinction between ADDH children, adults with a residual symptomatology and groups with related symptoms nevertheless characterize them in a separable manner (e.g. Steinhausen and Goebel, 1985; Table 1). Thus I shall not discuss whether the syndrome of ADDH should and whether the disease entity does include features of conduct disorder. Rather for the purposes of research into the bases of ADDH (and of this article) it is useful to try to isolate a group of subjects primarily showing the symptoms of ADDH alone. This is analogous to similar research strategies that have been advocated for schizophrenia (Taylor and Abrams, 1975; Oades, 1982a). The emphasis here is to establish the separate features of attentional dysfunction and hyperkinesis and evaluate studies of the potential neurobiological concomitants.

Under consideration are children, usually boys (boy:girl ratio 3–9:1, Mannuzza and Gittelman, 1984) aged 5–13 years of whom more than half have shown symptoms for several years before treatment (Weiss and Hechtman describe the earlier stages of development). It has been claimed that girls make up a higher proportion of subjects in adolescence (Gittleman and Mannuzza, 1985).

Typically ADDH-children have short attention spans, are distractible and perform poorly on vigilance tasks (e.g. continuous performance task, CPT, Sykes *et al.*, 1973; Thorley, 1984). High levels of behavioral activity are seen in both unstructured playrooms and structured classrooms (review, Solanto, 1984). A certain amount of uncoordinated or clumsy behavior may also be present (Wender, 1971). ADDH-children have been followed up as adults where a residual syndrome consisting more of attentional than hyperkinetic symptoms may remain (Caresia *et al.*, 1984; Weiss, 1985; Wender *et al.*, 1985a). It has only recently been emphasized that symptoms of hyperactivity may not always disappear with age (Safer and Krager, 1985).

I shall now consider the functional and neurobiological concomitants of this syndrome as it is reflected in ADDH-subjects, some related conditions and potentially similar animal models, with particular emphasis on the catecholaminergic (CA) components.

TABLE 1. GENERAL CHARACTERISTICS RECORDED FOR ADDH (CHILDREN) COMPARED TO CONDUCT DISORDER GROUPS AND ADD-RT (ADULTS), (AFTER STEINHAUSEN AND GOEBEL, 1985; GUALTIERI *et al.*, 1985, RESPECTIVELY)

ADDH	ADD-RT
high motor activity	restless
developmental retardation learning	impulsive
early onset and persistence of motor and speech retardation	distractible
	emotional lability
soft signs of sensorimotor incoordination	problems with work and interpersonal relations
less anti-social	more anxiety, depression (self-rated)

2. Psychostimulant Treatment—Neurochemical Response

2.1. THE PSYCHOSTIMULANTS

Bradley (1937) originally observed some 50 years ago that psychostimulant drugs such as amphetamine could have a calming effect on ADDH-children. For the psychomotor stimulants, amphetamine and methylphenidate (but not caffeine, Elkins *et al.*, 1981) the beneficial results of treatment have been reported many times (reviews, Solanto, 1984; Wender, 1971; e.g. amphetamine, 0.1–0.6 mg/kg; methylphenidate, 0.25–2.0 mg/kg).

The effect of the indirect dopamine (DA) agonist amphetamine is often described as paradoxical. But, in hindsight one may say there was good reason to have tried it out. "Post-encephalitic" subjects, who had often shown some Parkinsonian-like symptoms, were later found on post-mortem examination to show degeneration in the substantia nigra. Later this area was recognized to contain the A9 DA neurons.

At low to moderate doses amphetamine and methylphenidate promote CA utilization in the synapse by facilitation of synthesis and release, by the blocking of CA reuptake and inhibition of the catabolic enzyme monoamine oxidase (MAO). Of these effects methylphenidate preferentially blocks reuptake but amphetamine affects other mechanisms more potently (Axelrod, 1970; Szporny and Garog, 1961). Amphetamine facilitates release from reserpine-resistant neuronal pools of CA but methylphenidate may be more effective on vesicular pools of CA in certain brain structures (reviews, Langer and Arbiller, 1984; Solanto, 1984). Studies of the binding of the tritiated ligands in neostriatal preparations found that amphetamine sites tended to be post-synaptic and threo-methylphenidate sites pre-synaptic (Hulihan-Giblin *et al.*, 1985). Amphetamine inhibits electrically-induced DA release but facilitates electrically-induced NA release (Langer and Arbilla, 1984).

Widely used names for stimulatory agents in use are Dexedrine (amphetamine), Ritalin (methylphenidate), Cylert (pemoline), and Eutonyl for the MAO inhibitor pargyline. Commonly experienced side-effects of the conventional stimulants are anorexia, insomnia, weight loss and stomach pains (Golinko, 1982).

2.2. THE NEUROCHEMICAL RESPONSE

The response of neurotransmitter metabolism to pharmacological treatment of ADDH-children has been sought in the metabolite levels of various body fluids. Ethical considerations usually preclude more invasive techniques to investigate the CSF or neural sites. Thus the neurochemical data of the following discussion must be regarded as only an indirect reflection of central nervous changes, being, as they are in the main, measures from the plasma or urine. It has been reported that 20–60% of urinary MHPG (NA metabolite) reflects central CA metabolism. It is unfortunate that the precise contribution of central NA activity to urine or plasma NA levels remains, quantitatively, obscure. Nonetheless in normal mammals there is a growing body of evidence of an interactive link between central and sympathetic NA activity (e.g. Maas, 1984). It has been argued that 33% (urine) to 45% (plasma) of HVA, a DA metabolite, reflect central DA metabolism (e.g. Kopin, 1978). Urinary HVA is derived from plasma with no contribution from renal DA metabolism (Elchisak *et al.*, 1978), (cf also Maas *et al.*, 1979; Kopin, 1978; Kopin *et al.*, 1984; Swann *et al.*, 1980 and discussion in Commissiong, 1985; Sternberg *et al.*, 1983).

With regard to the contribution of serotonin (5-HT) of central origin to levels in the plasma or urine the situation is far more problematic. There is a disproportionate amount of 5-HT in the periphery with the CNS containing 1–2% of endogenous levels of 5-HT (review, Raskin *et al.*, 1984).

2.2.1. *Catecholamines (CA)*

Up to ten years ago there was no indication of changed CA metabolic rates in ADDH-subjects judged by the levels of urinary metabolites (Solanto, 1984). In 1976

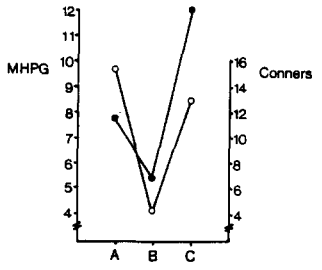

FIG. 1. Mean urinary MHPG excretion ($\times 100\,\mu g/24$ hr) (●) and mean Conners clinical rating score (○) of distractibility, attention span, impulsivity and hyperactivity for 73 hyperactive children (DSM III): (A) before, (B) after 3 weeks treatment with methylphenidate (0.3 mg/kg/day) and (C) 3 weeks after end of treatment. Mean MHPG levels for male and female controls were 1029 and 848 μg respectively. Diagnosis did not exclude those with a history of brain damage (n 35), but this group showed no significant differences of metabolite levels, (adapted from Shen and Wang, 1984).

Wender suggested subdividing ADDH-subjects on the basis of decreased DA or NA metabolism. Since then many correlations have been reported. This apparent success is probably due in part to more careful measurement. Thus the variable body areas of young subjects were taken into consideration and more than one sample would be taken precluding the variability of metabolite excretion at different times of day. The bad news is that the correlations found do not always agree between studies.

The results of recent studies are complex, but suggest the following pattern in which the presence of a positive therapeutic response is crucial. First I describe the results from several laboratories, which form a consensus, even though not all the studies were strictly controlled. There follow two dissenting results of controlled studies, which are themselves not beyond criticism.

ADDH-children may excrete normal or low levels of MHPG. Irrespective of the level of MHPG, those subjects responding to amphetamine showed a drop of MHPG levels (Hunt, 1982; Shekim *et al.*, 1979). A recent open study with an unusually large number of subjects (73 with ADDH-related diagnosis vs 57 controls, Shen and Wang, 1984) found that hyperactive children showed 20% lower urinary levels of MHPG and those that responded to methylphenidate showed a further 20% decrease (with large standard deviations). Unusually this Chinese study included girls (n 11) who showed a trend toward lower MHPG levels than boys in both groups. Together such results suggest that changes of NA metabolites *alone* cannot account exclusively for symptoms and symptom changes, despite the reported correlation between the neurochemical response and clinical improvement (Fig. 1).

In subjects that responded to treatment, HVA levels are the mirror image of MHPG levels (i.e. normal MHPG, low HVA: low MHPG, normal HVA: cf Table 2). Shekim and coworkers (1982, 1983) found that, in subjects responding to amphetamine, normal HVA levels decreased and low HVA levels increased. This result gives the impression of a drug-induced homeostatic effect. But, surprisingly, the reference HVA/MHPG relationship

TABLE 2. LEVELS OF CA METABOLITES AS PERCENTAGE OF CONTROL LEVELS AFTER AMPHETAMINE TREATMENT (2 WEEKS, 0.5 mg/kg, TWICE DAILY) OF HYPERACTIVE CHILDREN (CLINICAL CRITERIA FOR HYPERKINESIS) AND THE CA METABOLITE RATIO BEFORE AND AFTER TREATMENT (ADAPTED FROM SHEKIM *et al.*, 1982)

	MHPG	HVA	HVA/MHPG ratio before	after
Non-responders (n, 6)	108%	106%	5.1	4.9
Responders (normal MHPG) (n, 9)	57%	150%	2.5	5.5
Responders (low MHPG) (n, 6)	76%	82%	5.5	6.0
Controls (n, 12)	929 $\mu g/m^2$	3068 $\mu g/m^2$	3.3	

achieved with treatment seemed to be closer to that of non-responders than that of healthy untreated controls (Table 2). Shetty and Chase (1976) also found that treatment reduced levels of HVA. This reduction correlated highly with clinical improvement (0.96) recalling the similar correlation with MHPG levels reported in the Chinese study (Shen and Wang, 1984). These results are supported by one of CSF HVA levels, where, after probenecid treatment the level of HVA was found to be reduced (Shaywitz *et al.*, 1977).

Wender's laboratory reported that in ADDH-subjects of the residual type (ADD-RT) methylphenidate reduced CSF-HVA in responders but increased it in non-responders to drug treatment (Reimherr *et al.*, 1984; Wender *et al.*, 1984).

Thusfar the conclusion is that amongst responders to psychostimulant therapy (in admittedly sometimes rather broadly diagnosed ADDH groups) there are those with low NA metabolism and a second group with low DA metabolism. Curiously in both groups improvement is associated with a further lowering of metabolite levels which suggests that the CA metabolic anomaly is contingent on a third, as yet unknown, factor. Further there is a third group of subjects consisting of non-responders to psychostimulants.

Two recent studies, one with adults (ADD-RT, Mattes *et al.*, 1984) and one with children (ADDH, Zametkin *et al.*, 1985), appear at first sight to confuse this consensus.

In the first study Mattes reported a low success rate after methylphenidate treatment (ADD-RT; 16/61 responders). They could find no correspondence between therapeutic response and childhood history, personality disorder and depression. But as a number of responders were known for their abuse of drugs, they suspected that a history of "self-medication" may have been helpful in these cases. Perhaps with decreasing plasticity of the nervous system in late adolescence, psychostimulant therapy is less efficacious and useful only if persistently administered. Pre-exposure to psychostimulants is well known to be able to sensitize future responses to either stimulants themselves or stressful stimuli (Angrist *et al.*, 1980; Antelman *et al.*, 1980; MacLennan and Maier, 1983).

In the study of children, Zametkin and colleagues report on a mixed group of subjects that included children with conduct disorder, after treatment with methylphenidate (n 10) or amphetamine (n 12). In the former group all measures of NA and DA metabolism increased and in the latter they decreased. However as DA measures were more variable the changes did not prove to be significant (although they were of the same magnitude as those for NA). For supporters of the NA hypothesis the only problem was that there was no correlation between neurochemical and clinical response. It is unfortunate that a specific test of attention was not administered. However the data are not quite as paradoxical as they seem. If the data are viewed in terms of utilization (metabolite:CA) both drugs tended to suppress NA and DA utilization (above) (e.g. HVA/DA = 13%, MHPG/NA = 19% for methylphenidate). Broadly, amphetamine showed less of an effect on NA than on DA utilization. But the more individually variable DA response, which may well reflect separate sites for the action of these drugs, was less closely investigated.

It is perhaps important to remember that acute treatments of animals' mesolimbic and mesostriatal areas with psychostimulants is reported to produce changes in the opposite direction from the above report on ADDH children (e.g. Nielsen *et al.*, 1983). Chronic treatment exacerbates the acute effect of amphetamine treatment (Kokkinidis and Anisman, 1980; Segal *et al.*, 1980). In the above ADDH study it is less important whether utilization decreased than that it did not increase, as might have been expected. It may be that part of the problem is a neurochemical analog to rate dependency of behavioral response (see below) (i.e. low and normal metabolic levels are stimulated, high anomalous levels are inhibited). Relevant here is a recent study (Archer *et al.*, 1985) showing decreased rat motor activity in response to amphetamine treatment following depletion of NA. The effects of psychostimulants depend in a complex way on dose and regional CA levels. Here much work still remains to be done in animals.

2.2.2. *Serotonin (5-HT)*

Is it wise to ignore a possible dysfunction in ADDH subjects of the closely related monoamine neurotransmitter 5-HT? As has often been pointed out, just as treating the

symptoms of rheumatic fever with aspirin informs little about the cause, so might the treatment of ADDH subjects with psychostimulants be uninformative and misleading with regard to the CA contribution.

But the indications do not favour a role for anomalous 5-HT metabolism in ADDH. Despite early reports of decreased platelet 5-HT (Bhagavan *et al.*, 1975) and blood 5-HIAA (metabolite) (Coleman, 1971), these results have not been replicated (Rapoport *et al.*, 1974; Ferguson *et al.*, 1981). Further, no differences in the levels of the metabolite have been found either in urine of ADDH children (Wender *et al.*, 1971) or in the CSF with (Shetty and Chase, 1976) or without probenecid pretreatment (Shaywitz *et al.*, 1977).

2.3. Electrophysiological Indices of Cognition

What is the nature of the attentional and motor improvement that "responders" to psychostimulants show? It is unfortunate that for the interpretation of the results of cognitive performance, such studies have not yet been published where the effects on CA metabolism were also documented.

An early report provided initial evidence of a latent excitability of the nervous system of hyperkinetic children (broad selection criteria: Laufer *et al.*, 1957). The threshold for the induction of a myoclonic jerk by stroboscopic stimulation during metrazol infusion was determined. The rather low threshold obtained in this group was increased under amphetamine treatment. At the least this result is compatible with the electrophysiological inhibition of DA neurons observed after the treatment of animals with amphetamine. But the implications do not seem to have been followed up in ADDH groups.

A number of early EEG studies of ADDH-children reported the presence of excessive amounts of slow wave activity, but that such "dysrhythmias" disappeared as the subjects grew up (Burks, 1964; Capute *et al.*, 1968; Hechtman *et al.*, 1978). More recently Caresia *et al.* (1984) reported on adult subjects. Non-responders, like ADDH-children, showed increased activity in the 6–8 Hz band and decreased activity at 10–13 Hz. In contrast, responders showed a decrease for the 6–10 Hz and an increase for the 10–13 Hz bands. These changes are consistent with the increased ability of the responders to concentrate.

Unexpectedly, Caresia and colleagues could find no significant effects in their sample of ADDH-children where eight out of nine responded to pemoline. However, their data did at least show a trend for these subjects towards higher beta activity. Such an effect is also seen in healthy subjects (Finch, 1968). (Of course reports of apparently conflicting results for relatively small samples are not unexpected where records from normal subjects vary considerably with emotional state, between individuals and depend on the state of maturation.)

Records of auditory evoked potentials from the brain stem of ADDH children have not shown a consistent impairment in the registration of sensory stimuli (Gualtieri *et al.*, 1985). But studies of event-related potentials (ERPs) show that the psychostimulants can affect both the cognitive and motor symptoms of ADDH-subjects, although it seems that methylphenidate may primarily improve response selection rather than stimulus evaluation. (Recent evidence suggests that auditory P3b and slow wave amplitudes, possibly reflecting the perceived significance of stimuli, are often smaller in ADDH-children (Holcomb *et al.*, 1986).)

A Californian laboratory has reported on the effects of three doses of methylphenidate on ADDH-children (7–13 years: Elliott *et al.*, 1978; Halliday *et al.*, 1979; 1983). Visual ERPs were elicited by flashes of light of varying brightness in situations that did or did not require a response (active and passive attention). This group found, with increasing dose, a decreasing negativity of the anticipatory N2 complex in older, but an increasing positivity in the younger children (10 year). They also reported a small but opposite effect of the stimulant on attention-related processes as a function of either increasing age or course of the condition. But surprisingly they could find no difference of latency for the N2 and P3 complex despite subjects showing improved reaction times after treatment.

More recently this laboratory has confirmed that N1 latency did not differ between ADDH- and normal children and there was no differential effect after methylphenidate

treatment (Callaway and Halliday, 1982). (But it should be remembered that where reaction times improve with maturity by ca. 1 msec, so ERP latencies normally decrease by 0.5 msec.) Thus these results seem to show that there was a response related effect of the drug (reaction time) separate from that on attention-related processes (N1/P3 complex) in their ADDH subjects. This result was recently confirmed for the P300 wave (Naylor *et al.*, 1985). However it is appropriate to remark here that it is a common finding, in a situation where latencies decrease, that reaction times shorten far more (Johnson *et al.*, 1985). Thus in view of the complexity of the stimulus and maturation variables involved, a negative result for an effect of psychostimulants requires further replication.

2.4. BEHAVIORAL INDICES OF COGNITION

Psychostimulants have been consistently found to improve social behavior, activity and learning in a little over half of ADDH-children (e.g. Bradley, 1937; Burks, 1964; Hechtman, 1985) and adolescents or adults with residual signs (Varley, 1985; Wender *et al.*, 1985b) despite the absence of convincing support from electrophysiological studies of the potential mechanisms (above). Indeed some authors prefer to emphasize that despite reports of improvements on tests of attention following treatment, educational advance does not necessarily follow and serious personality problems can develop (e.g. Gualtieri *et al.*, 1985). What are the characteristics of the poor learning performance attributed to ADDH-children that have been reported to be improved by psychostimulants?

On choice tasks with warning signals that do not require much attentional effort, ADDH-subjects are reported not to show much impairment. But they are more impaired on serial or self-paced reaction time tasks. On the CPT that requires the selection of a rare target during a long presentation of stimuli, they make both more errors of omission (a problem of concentration) and more redundant responses (motor control or stimulus evaluation problem). Stimulants increase the number of correct responses (Goldberg and Konstantareas, 1981; Klorman *et al.*, 1979; Kupietz, 1976; Sykes *et al.*, 1971, 1972, 1973).

The administration of stimulants to normal children reduces the number of CPT errors of omission. Thus it has been claimed by one laboratory that from a therapeutic and research viewpoint the decrease of errors of commission is more significant (Rapoport *et al.*, 1978, 1980; Zahn *et al.*, 1980). However this is far from established. One of the tasks most frequently administered to ADDH-subjects is the matching of familiar figures (MFFT) test of cognitive style (Glow *et al.*, 1983). Methylphenidate clearly improves the performance of ADDH-subjects on this task (Ballinger *et al.*, 1984). A study relating CPT and MFFT performance showed that both types of CPT error correlate with MFFT latency to first response (negatively) and total MFFT errors (positively); only with the overall MFFT latency measure was there a difference (Table 3; Klee and Garfinkel, 1983)

TABLE 3. (A) CORRELATIONS BETWEEN CONTINUOUS PERFORMANCE TASK (CPT) AND OTHER PSYCHOMETRIC VARIABLES FOR CHILDREN WITH ADDH, CONDUCT AND AFFECTIVE DISORDERS (DSM III, *n*, 51). CONNERS TEACHER RATING SCALE (CTRS), MATCH FAMILIAR FIGURES TEST (MFFT), WECHSLER INTELLIGENCE SCALE FOR CHILDREN—REVISED (WISC-R)

	Partial order controlling for age						
	CTRS	MFFT 1st	MFFT total	MFFT errors	WISCR coding	WISCR arithmetic	age
Omission errors	0.32*	−0.28*	−0.09	0.31*	−0.32*	−0.37†	−0.52†
Commision errors	0.36[2]	−0.35[2]	−0.33*	0.34*	−0.25	−0.12	−0.49†
CPT total errors	0.38[2]	−0.36[2]	−0.26	0.28*	−0.31*	0.05	−0.56†

(B) PARTIAL CORRELATIONS BETWEEN CPT AND CTRS FACTOR SCORES

Factors	Conduct	Inattention	Anxiety	Hyperactivity	Sociability
Omission errors	−0.05	0.31	−0.10	0.36†	0.21
Commission Errors	−0.03	0.33	−0.01	0.34*	0.05
CPT total errors	−0.04	0.33*	−0.04	0.35†	0.12

* $p < 0.05$.
† $p < 0.01$.
After Klee and Garfinkel, 1983.

(this study reported on a mixed group of hyperkinetic children). Indeed in support of the contention that MFFT results after treatment reflected measures of cognitive style rather than mere impulsivity (Glow *et al.*, 1983) signal detection measures have also shown that methylphenidate will improve target detection and target discrimination ratios of normal adults on dichotic listening tasks (Clark *et al.*, 1984).

There are two points here. The first is that psychostimulants may improve poor performance on a task of attention and learning but not that ADDH-subjects necessarily have a peculiar or specific deficit. For example, a recent study of 400 college students reported that the poor CPT performance of the bottom 5% correlated both with ADDH-related features in their history and other attentional measures (e.g. ERP and Stroop test: Buchsbaum *et al.*, 1985). This suggests that there is a quantitative rather than a qualitative difference in the symptoms under study.

The second point is that, taken with the electrophysiological data of the previous section, these results emphasize that there are two significant factors in ADDH and that stimulant treatment can (but may not) improve both. They may be termed response control (cf reaction time latencies) and the control of vigilance, an attention-related factor (cf CPT/MFFT errors, Table 3).

This distinction between response and attention/vigilance factors in ADDH may seem elementary for it is reflected in terms of the rating scales in clinical practice (Conners and Wells, 1979; Conners teacher scale, Table 3). But it is an important point to be made in some quarters and is capable of being developed into a valuable distinction for the future establishment of diagnosis and for research into the underlying factors.

Other types of experimental study also point to this distinction and that treatment with psychostimulants improves both information processing and response organization. Such studies have measured performance on Porteus mazes (sensitive to cognitive strategies) and stylus mazes (sensitive to fine motor control) (Conners, 1972; Conners *et al.*, 1969; Epstein *et al.*, 1968; Knights and Hinton, 1969). Indeed to emphasize the distinction between these two factors one may remark that the ADDH-subjects who show improved learning after stimulant treatment are not necessarily those who show less of a motor impairment (Weingartner *et al.*, 1982). Where subjects show both improvements, the cognitive effect may deteriorate long before the calming effect of treatment wears off (Solanto and Conners, 1982).

A last piece of evidence for the distinction between these two factors comes from clinical experience. It has been reported that optimal cognitive effects are produced by a lower dose of methylphenidate (ca 0.3 mg kg^{-1}) whereas higher doses (ca 1.0 mg kg^{-1}) are needed to produce favorable changes of social behavior (Sprague and Sleator, 1977). (There is an inverse U-curve relationship for the improvement of learning with dose, but a linear relationship for the improvement of classroom activity with dose). The sum of these observations support the idea of two groups of symptoms with variable sensitivity to psychostimulant therapy.

2.5. Responses to Other Monoaminergic Agents

In view of the evident changes after psychostimulant treatment of psychomotor performance on the one hand and CA metabolism on the other, it makes sense to investigate the therapeutic potential of other CA active agents in ADDH. But so far the potential of such agents has been assessed more according to clinical rating scales rather than on specific experimental test performance.

With "stimulant" as the key word in the success of pharmacotherapy, albeit that the improvement is of a short-lived nature and restricted to a proportion of subjects, it has been natural to follow two experimental strategies. The one is treatment with a transmitter precursor, the other is the blocking of MAO in order to prolong the synaptic life of the transmitter.

2.5.1. *Precursors (L-DOPA and amino acids)*

The first strategy has not been successful. In children, CA precursors (e.g. L-DOPA) exert a rather nonspecific sedative effect (Gross, 1977; Jackson and Pelton, 1978). In a controlled study, a rather mild alleviation of symptoms was found which at best permitted a reduction of the level of Ritalin administered (Langer *et al.*, 1982). In residual type subjects a clear but temporary alleviation has been registered. But this was soon followed by a refractory period (Wender *et al.*, 1984; Wood *et al.*, 1982).

The administration of tyrosine, the amino acid essential for the biosynthesis of CAs, would be less beset by the untoward effects of L-DOPA. From animal studies it is encouraging to know that there is a dose-dependent relationship between levels of tyrosine and the amount of electrically-induced DA released from the neostriatum (Milner and Wurtman, 1985). Wood *et al.* (1985) report on an open study (*n* 12 adults) where *l*-tyrosine improved target symptoms with a delayed onset similar to that seen after treatment of depression with tricyclic drugs (ca. 21 days). But improvements had disappeared within 6 to 10 weeks. An absence of a lasting therapeutic effect has also been found by Nemzer and Arnold (cit. McConnell, 1985). The report by Wood and his colleagues included a double blind crossover trial of *dl*-phenylalanine (the *l*-isomer can be hydroxylated to tyrosine). The effect was milder. Mood proved less labile. There was a rapid onset and again a disappearance of the therapeutic effect. This, along with the apparent ineffectiveness of the natural *l*-isomer, led the authors to suggest a nonprecursor mode of action for the racemate. At best, amino-acids might be construed as helpful adjuncts to the use of other agents, having less side effects than, for example, neuroleptics.

2.5.2. *Monoamine oxidase (MAO)*

For the second strategy two enzymes may be targeted, MAO A (with NA as substrate) and MAO B (with DA and phenylethylamine as substrate) (Houslay *et al.*, 1976). Concentrating on the DA aspect, Wender and his colleagues (1985a, b) conducted open trials with pargyline (ca. 20 mg/day) and deprenyl (ca. 30 mg/day). Improvement was recorded in 11 out of 16 and 6 out of 9 subjects respectively. (A lower dose of deprenyl has proved less efficacious (Donnelly cit Rapoport *et al.*, 1985). In Wender's adult subjects activity was reduced and attention span improved (Wender *et al.*, 1983). Unfortunately because of the dangers from numerous side effects (especially hypotension and the 'cheese' effect) these agents are unlikely to find wide application. Nonetheless a DA component would seem to be indicated in the symptoms of some subjects.

Rapoport and her colleagues (1985) investigated the combined effects of clorgyline (MAO A action) and tranylcypromine (mixed MAO A & B action) in a double blind trial. In contrast to the antidepressive effects of the drugs and the relatively slow appearance of the therapeutic effects reported by Wender, an improvement with rapid onset was found. But this was restricted to the factor of "impulsive hyperactivity" as indicated by the Subject Treatment Emergency Symptoms Scale.

A larger scale study with the NA uptake inhibitor DMI showed there was an improvement on the Conners teacher rating scale but not on the CPT (Rapoport *et al.*, 1985; cf also Waizer *et al.*, 1974; Winsberg *et al.*, 1972). Unlike the authors I find this result to be disappointing. Firstly the indication for an NA component in ADDH is indirect. There were no measures of metabolism reported and they merely claim that clorgyline alone was also effective. Secondly an improvement was restricted to one aspect of the syndrome. Further, because of the potential for drug-abuse, therapy with these agents is contraindicated. Another study of the usefulness of imipramine (3–7 mg kg^{-1} day^{-1}) to block reuptake found it did not help non-responders to methylphenidate (Conners teacher/parent rating scales, Winsberg *et al.*, 1980). Indeed these authors had more success with this group when they used the neuroleptic thioridazine.

2.5.3. *Alternative directions*

Other ideas for pharmacotherapy have been tried out with little (e.g. neuroleptics see above) or no success (e.g. Lithium, Phenobarbital (Wender, 1971), Fenfluramine (Donnelly cit Rapoport *et al.*, 1985) and Evening Primrose oil (Gibson personal communication)). Nonetheless there are individuals who may respond to such drugs. Thus, for example, Cole (1978) has reported some positive responses from adult subjects treated with lithium or with benzodiazepines. But such results are probably restricted to those individuals with additional problems with behavior, personality or affect. In general, these studies indicate that factors ranging from sedation and affect, to the availability of serotonin and the prostaglandins are not strongly indicated in ADDH.

There is perhaps one further idea that perhaps has potential for development. Taking into account the joint effects of stimulants on NA and DA metabolism, the anti-hypertensive effects of pargyline and the usefulness of the hypertensive rat as a model for the ADDH syndrome (see below), it would be of interest at least at the research level to study the usefulness of "atypical" CA agonists. One example is the ergoline bromocriptine. This agent is a mixed DA agonist/antagonist with a certain affinity for D2 receptors and, at least after acute administration to animals, it depresses levels of NA and reduces systolic and diastolic blood pressure (Mannelli *et al.*, 1984). Administration of another ergoline, pergolide, produces a drop in tension, which is blocked by the D2 antagonist sulpiride but not by the NA anatagonist yohimbine (Barrett and Lokhandwala, 1983). Other ergolines with alpha antagonist and D2 agonist properties that reduced blood pressure are also being developed (e.g. Morales-Olivas *et al.*, 1984). Starting with the model of vasomotor action, the development of such agents may yet produce a balance between the unwanted systemic and the desirable neuropharmacological effects in ADDH.

3. Similarities and Differences with Other Disorders of Catecholamines and Attentional Function

It is of interest to compare briefly the disorders of three other syndromes to show where there are similarities between clinical symptoms and CA dysfunction, but more importantly to stress that there are limits to speculation about the potential correlations.

3.1. PHENYLKETONURIA

There is widespread agreement that patients suffering from phenylketonuria show an increased turnover of phenylethylamine (PEA, an unusual metabolite of NA with a structure similar to amphetamine). Indeed PEA contributes to the symptoms of hyperactivity, excitability, lability of mood and short attention span shown by those with phenylketonuria (Wolf and Mosnaim, 1983).

On the one hand it may be no surprise that subjects with phenylketonuria show a broad range of symptoms when there is such a widespread pathological deposition of phenylalanine. On the other hand it is striking that these particular symptoms should be apparent.

Is a putative PEA-attention dysfunction link relevant for ADDH subjects? Recently Zametkin *et al.* (1985) reported that a 1600% increase in the excretion of PEA was found after treating ADDH-children with amphetamine (but not methylphenidate). The first implication is clearly that one should look for PEA excretion in further studies of ADDH subjects and particularly one should look to see if it is enhanced by treatment with the structurally similar amphetamine. Secondly, abnormal CA metabolism is implicated. Thus as MAO inhibitors should promote the elimination of this amine, there is good reason to explore this therapeutic strategy further (cf PEA is a substrate for MAO B). The opposite might be said about the wisdom of increasing the activity of DA or treatment with DA precursors that could lead to an increase of PEA if this abnormal metabolic pathway is more usual in ADDH subjects.

It is particularly interesting that investigations of the potential contribution of PEA to the above named symptoms of phenylketonuria and to thought disturbance in schizo-

phrenia have shown a tendency for it to be accumulated in neostriatal and limbic structures. These are two subcortical areas that are particularly important for the evaluation of sensory information and its use in organizing adaptive behavioral strategies (review, Oades, 1982a; Oades *et al.*, 1985a; Wolf and Mosnaim, 1983). Clearly CA metabolism and function in these brain regions merits particular attention.

3.2. TOURETTE'S SYNDROME

A second disorder, Tourette's syndrome may be mentioned in the present context. Recalling the way ADDH was first perceived, Tourette-like symptoms quite often follow encephalitic infections (review, Messiha and Carlson, 1983). Suggestions for biological dysfunction in Tourette's syndrome remain controversial, but include DA hyperfunction in the neostriatum (cf oral stereotypies, Stahl and Berger, 1982). An increased cortical excitability has also been proposed on the basis of evoked potentials recorded from the scalp. However it should be noted that such potentials can reflect activity in the septohippocampal region from which abnormal excitability has been recorded in attention disordered schizophrenics (Heath, 1966).

Amongst the various symptoms of Tourette's syndrome, clinicians often encounter hyperactivity associated with a decreased attention span. The more dominant symptoms of motor (and phonic) tics, associated with dysfunction of the basal ganglia, are alleviated by haloperidol treatment. However such treatment exacerbates the ability to process temporal information (Goldstone and Lhamon, 1976) and generally blunts cognitive ability (Werry and Aman, 1975). From this it would seem as if excessive mesostriatal DA activity had been normalised but normal mesolimbic DA activity attenuated. In contrast clonidine, an inhibitory alpha NA agonist, although less efficacious in general, does produce less cognitive blunting (Shapiro and Shapiro, 1982). Although the mechanism of action of clonidine is poorly understood, the results do imply that a judicious manipulation of the interplay between cortical NA and DA could assist attentional function. At the least, as there are parallel DA projections to the neostriatal and septal regions a closer comparison of symptoms between this syndrome and ADDH could be helpful for subjects with impaired DA metabolism.

3.3. LESCH–NYHAN SYNDROME

Finally in order to show that there are severe limits to speculative proposals for explaining the CA bases of ADDH, it is worth discussing briefly the Lesch–Nyhan syndrome (Lesch and Nyhan, 1964). Seegmiller and coworkers (1967) demonstrated that a specific inborn deficiency of purine metabolism is responsible for the syndrome. But reduced DA function in several brain regions has been reported from Lesch–Nyhan subjects post-mortem (Lloyd *et al.*, 1981). CSF measures taken at intervals during development of four subjects showed consistently lower levels of HVA (Silverstein *et al.*, 1985).

The biochemical results are partly consistent with what is known about the neurobiological bases of the main symptoms of hypertonicity, choreoathetoid movement, self mutilation behavior and mental retardation (Baumesister and Frye, 1985; Kelley and Wyngaarden, 1983). Indeed Breese and his colleagues (1984) have now modelled this symptom picture remarkably closely in the rat by depleting DA levels neonatally and additionally stimulating the *hypersensitive* system with *DA agonists* later in development.

On the surface it seems that the syndrome and the model demonstrate comparable behavior but opposite changes of DA metabolism. However the lesson here is that one does not know precisely what happened to the DA system (e.g. local utilization and binding changes). Indeed in either case it seems that an increase or a decrease of DA function, by different criteria, can give rise to a symptom picture quite different to ADDH. This should be surprising if one wishes to maintain that apparently similar biochemical changes in ADDH and a putative animal model (cf below) result in comparable changes

of cognitive and motor performance. The matter would perhaps be resolved by a clarification of both the descriptor "mental retardation" in the case of the clinical condition and quantification of the parameters of DA change in the animal model. Nonetheless the warning that arises out of the present results is pertinent both to postulates of what the changes are that underlie ADDH as well as to the direction that proposed pharmacotherapeutic strategies should take.

4. Parallels to Experimental Animal Studies

4.1. Attention-Related Symptoms

On search-learning tasks many ADDH children readily understand the requirements and indeed get as far as achieving reinforcement, but they may take very many trials to actually reach criterion (Dykman *et al.*, 1979, 1980). Such subjects were also reported to show many inter-trial responses. A recent review of animal studies (Oades, 1985) described how the similar problem of achieving a respectable learning criterion on a number of different tasks has been reported after damage to the dorsal NA bundle. NA-depleted animals may quite rapidly attain a 66% criterion but take a very long time to reach 80–90% correct performance. Indeed depletion of NA can also lead to distractability and irrelevant responses, so long as the depletion occurs before decisions about the performance have to be made and the task acquired (Oades, 1985). The parallel seems quite striking.

A10 lesions in the midbrain of rats, that can lead to DA receptor supersensitivity in the forebrain (Simon *et al.*, 1980) or even amphetamine administration (Oades *et al.*, 1985b), can induce increases of irrelevant collateral behavior during task performance. These changes have been interpreted as indicating an attentional dysfunction arising from uncontrolled DA activity. This in turn interferes with learning. Also pertinent is the finding that treatment with DA antagonists can impair incentive learning in animals (review, Beninger, 1983). These manipulations change DA activity in different ways. They appear to affect the function of different behavioral mechanisms. But in both cases learning is impaired.

Recalling the difficulties ADDH-subjects are reported to have on Porteus mazes (above) and the use of the search task as a soft sign for frontal damage, it is of interest that disruption of the mesocortical DA projection interferes with the development of task-solving strategies by rats searching for food on a holeboard or in a maze (Oades, 1981, 1985; Oades *et al.*, 1985a, b; Simon, 1981).

From studies of the performance on paired associate learning tests there is evidence that ADDH-subjects employ a different cognitive style or different strategies for information processing (Weingartner *et al.*, 1980, 1982). These authors have suggested that amphetamine could act by "strengthening" the memory traces produced by the particular dominant processing strategy in the individual subject. However they also noted that the drug-induced improvement could be stronger during the acquisition stage, particularly when effortful attentional processes were required.

Without trying to establish the validity of an attention- vs a memory-related hypothesis, we may note parallels for both types of cognitive style in studies of animal information processing ability. The first suggestion is reminiscent of the facilitation of retrieval of maze performance, learned three weeks previously, in rats after treatments with CA agonists that promoted the release of NA in hippocampal and neocortical areas (e.g. Sara *et al.*, 1984). The second effect parallels some of the effects of lesions of the A10 DA region. For example, lesioned animals can learn a simple visual discrimination but not the more effortful delayed alternation (Simon *et al.*, 1980). Such animals can acquire a preference for the *first* of four correct food-hole visits on a holeboard with 12 empty holes, but not develop a normal, but more complex, preferred *sequence* of four food hole visits (Oades, 1982b; Oades *et al.*, 1985a).

Finally Crider and his colleagues (1982) showed that treatments which induce DA receptor supersensitivity in mesolimbic projection areas such as the nucleus accumbens can

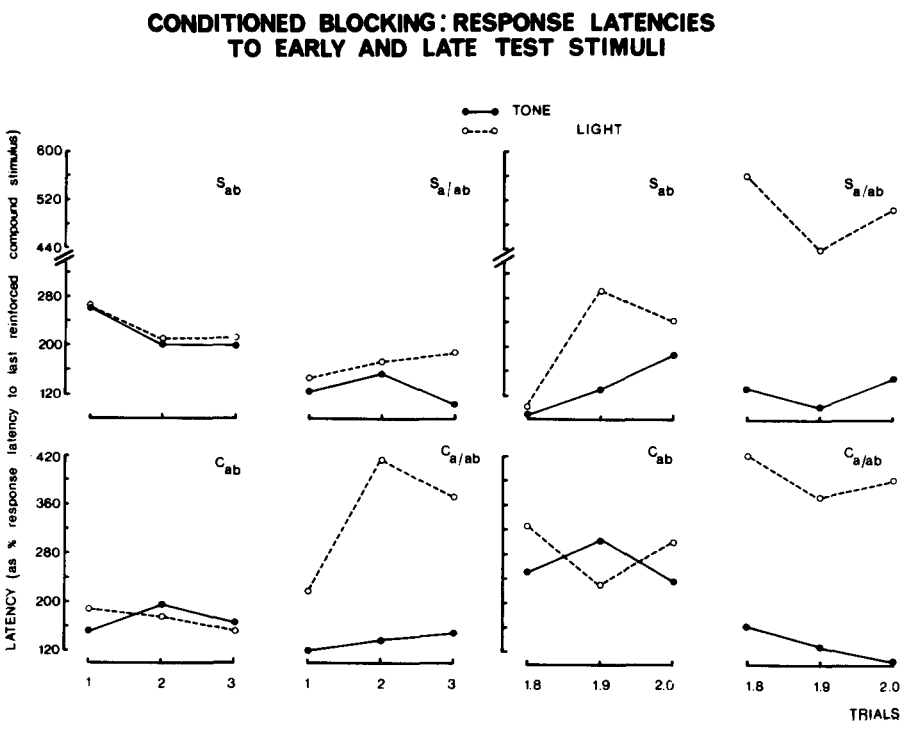

FIG. 2. Escape-response latencies of rats to the first (left) and the last (right) three presentations (20 test trials) of a non-reinforced tone (a: solid line) or light (b: broken line) in a shuttle box after avoidance training with stimuli "ab" or "a" followed by "ab". Latencies are shown as a percentage of that for the last reinforced (footshock) presentation of "ab". (Test sequence: a,b,a,ab,b,a,b,ab . . . .) S (n 11); septal lesion with 6-OHDA (DMI protection of NA terminals): C (n 18) injection of vehicle. Attenuation of blocking to "b"($S_{a/ab}$, trial 1–3, response to "a" and "b") preceded normal or exaggerated blocking ($S_{a/ab}$, trial 18–20, response only to "a"), $p < 0.05$.

result in the animals paying attention to redundant stimuli (e.g. latent inhibition, conditioned blocking). It has also been found that infusing a DA toxin (6-OHDA) into the septum or frontal cortex of rats can impair the performance of a conditioned blocking task (Oades *et al.*, 1985a, 1986; Fig. 2), which is claimed to be a measure of attentional function (Mackintosh, 1975).

These results indicate potential neurobiological bases (i.e. limbic and cortical CA activity) for some of the attention-related changes attributed to the ADDH syndrome.

4.2. HYPERACTIVITY SYMPTOMS

It is difficult to resist drawing a comparison between clinically observed hyperactivity and that which follows stimulation of lesion-induced DA supersensitivity in the nucleus accumbens, septum and perhaps frontal cortex of rodents (Carey, 1982; Dunnett *et al.*, 1984). Locomotor hyperactivity can reflect an imbalance between NA and DA activity in these areas (Fishman *et al.*, 1983; Oades *et al.*, 1986a).

However the lesion-induced syndrome should not be taken too literally as a model for the hyperactive ADDH syndrome. Although amphetamine treatment no longer stimulates locomotion in animals with lesions of the ascending A10-DA innervation, an actual reduction of locomotion is not usually recorded (Koob *et al.*, 1981).

Perhaps more relevant for comparison with the ADDH condition is an interesting genetic model (Helmeste and Seeman, 1982). There are strains of mice with unusually low or high densities of DA receptors. Such mice with high receptor densities, like rats with lesion-induced receptor supersensitivity, may show little abnormal daytime activity yet high levels of locomotion at night (their normal active period). Treatment of these mice

TABLE 4. THE HABITUATION OF ACTIVITY AND THE LATENCY FOR AVOIDANCE IN LEARNING A SHUTTLE BOX AVOIDANCE TASK FOR RATS AT ABOUT FOUR WEEKS OF AGE AFTER NEONATAL DEPLETION OF NA, DA OR BOTH CAs (AFTER RASKIN *et al.*, 1983)

	Time spent active: (% total time in activity cage)		Avoidance latency (sec): (Shuttle box)	
	1st trial	6th trial	1st trial	5th trial
Controls	32	24*	14	1–2‡
NA depleted	32	25*	24	14§
DA depleted	31	28†	19	14§
CA depleted	31	30†	23	23‖

* Normal habituation.
† Absence of habituation.
‡ Good.
§ Poor.
‖ No learning.

with amphetamine induces hypolocomotion. Such strains of mice, where in the Weaver mutation discrete effects on the A10 system may reflect a change in a single gene (Roffler-Tarlov and Graybiel, 1984) provide potentially useful animal models for symptoms of the ADDH condition which itself exhibits a genetic component (cf Shen and Wang, 1984). But it should be noted that the genetic features of the ADDH syndrome may show more similarity to the polygenetic transmission reported for the hypertensive rat discussed below (Louis *et al.*, 1969). It is rewarding therefore to see that increased DA binding has been reported in areas of the basal ganglia of hypertensive rats (Hellstrand and Engel, 1980).

The depletion of CAs in rats after the neonatal, intracisternal application of 6-hydroxydopamine (6-OHDA) has been proposed as an experimental model for ADD with hyperactivity (Raskin *et al.*, 1983; Shaywitz *et al.*, 1976; Smith *et al.*, 1983; but caveat Lesch–Nyhan model above). After such treatment (without pharmacological stimulation) hyperactivity appears in adolescent rats (day 14–23) and disappears in adulthood, in some ways similar to ADDH. The learning deficit of these animals shown on avoidance tasks remained in the adult, like ADD-RT. Raskin *et al.* (1983) compared the results from animals with specific protection or depletion of NA. The combined behavioral deficit (activity and learning) proved more marked and persistent if both CAs were depleted. Alone NA depletion produced only the learning deficit in adults (Table 4). An advantage of this model is that the activity of both CAs is affected by the manipulation. A disadvantage for experimental analysis is that the lesion technique produces very variable results. In addition it would be useful to have more information on the nature of the learning deficit than that as yet provided by shock avoidance performance.

Finally we may note a possible further reason for not regarding the relative success of amphetamine treatment as paradoxical. Certainly low doses of amphetamine in animals usually increase locomotion. But it is well-known that when baselines of operant responding are high, amphetamine treatment reduces response rates (reviews of rate dependency, Dews and Deweese, 1977; Sanger and Blackman, 1976). Note that in practice, whether increases or decreases of exploratory locomotion are recorded depends both on the basal level of DA activity (Costall *et al.*, 1980) and on the dose of amphetamine (Fishman *et al.*, 1983; Scheel-Kruger, 1971).

A precise test of the explanatory value of the rate dependency hypothesis for ADDH subjects, linking psychostimulant dose, baseline CA activity and behavioral activity in all conditions has not been published. To be sure, there are claims that support the hypothesis. On a mixed fixed ratio/delayed response schedule low baseline responders increased whereas high baseline responders did not increase response rate after methylphenidate treatment (in comparison with placebo treatment: Weber, 1985). However others have reported inconsistent results (e.g. a variable responsiveness on fixed interval and an unpredicted increased responsiveness on variable ratio schedules: Rapport *et al.*, 1985). A re-analysis of some studies (Robbins and Sahakian, 1979) suggested that perhaps 30% of the variance recorded could be attributed to rate dependency effects. In the light of what,

at best, could be considered a minor contributing effect, and what still might prove to be a statistical artifact, it simply does not seem that the rate dependency hypothesis has much explanatory value in the case of the symptoms of ADDH (but cf Green and Warschauer, 1981 vs Millard and Standish, 1982).

5. An Animal Model—Spontaneous Hypertension

In contrast to some of the animal studies described above, a good animal model should represent not just one, but a spectrum of the symptoms found in the condition to be modelled. For the ADDH condition two animals have received attention recently—the Telomian-Beagle hybrid and the spontaneously hypertensive rat.

The interest shown by Bareggi and his coworkers (1979) in the hydrid dog is supported by the demonstration in these animals of distractibility, learning impairments and hyperactivity that superficially resemble such characteristics of the ADDH syndrome. Further it is striking that some, but not all of these animals respond favourably to amphetamine treatment by showing improved learning abilities. Such successful treatment is reported to result in decreases of central DA levels and CSF-DA metabolites. However it is not clear if there is an NA component to the anomalous behavior shown by these dogs. This model does not yet seem to have come into widespread use.

5.1. The Spontaneously Hypertensive Rat (SHR)

There has been growing interest shown in comparing behavioral and biochemical parameters in normotensive Wistar-Kyoto rats (WKY) with those of the hypertensive Okamoto strain (SHR). (Other SHR strains have also been developed.)

The appeal of the SHR as a model for ADDH lies with their behavioral responsiveness and the underlying neurobiological anomalies. They are hyperactive, hyperreactive but often hypoexploratory (Low *et al.*, 1984). These changes (including hypertension) may result from differences of NA and DA activity, and also potentially of a third transmission factor in the CNS (see below). As may be expected from any model, on closer examination there are more reasons for drawing the parallel with ADDH. But differences also become apparent. Foremost among potential differences would be the central nervous changes associated with hypertension. Let us first consider these and consider the possibility that they also may contribute to the picture which *is* the model of ADDH.

5.2. Neurobiology of Hypertension: Participation in SHR Behavior?

5.2.1. *Noradrenaline (NA)*

First of all there is the major contribution of NA activity to hypertension. An analysis of the content of a limited number of brain nuclei in the genetically hypotensive mouse showed increases of NA in the A1, A2, A6 nuclei, the anterior and posterior hypothalamus and *septum*. The comparison was drawn with both randomly bred and hypertensive animals (Denoroy *et al.*, 1985). Pharmacological studies show that both the alpha agonist clonidine (which decreases the firing of NA cells) and the neuroleptic chlorpromazine (which has marked alpha antagonistic properties) have hypotensive effects in the SHR. In contrast the stimulation of supersensitive alpha receptors results in hypertension (Cerrito *et al.*, 1984; Peroutka and Snyder, 1980).

Electrophysiological work broadly supports this inverse relationship between parameters of NA activity and blood pressure. SHRs have more slow firing neurones in the noradrenergic A6 nucleus than WKY control rats. Even in normal rats as the blood pressure rises the firing of A6 neurones decreases (Olpe *et al.*, 1985). Two crucial areas for blood pressure control are the posterior hypothalamus and the nucleus of the solitary tract (NTS). In the former, an important area for sympathetic regulation, NA release is reduced in the SHR (Tuomisto *et al.*, 1983) despite there being an apparent increased NA

innervation during development (Winternitz *et al.*, 1984). In the latter area 6-OHDA lesion renders blood pressure labile and electrolytic, nonspecific damage further abolishes the baroreceptor reflex (review, Reis and Talman, 1984). This latter result implies that there is an additional involvement of a non-NA transmitter.

5.2.2. *Glutamate, neuropeptide Y and serotonin*

One good candidate for the "non-NA" modulation of hypertension, and in particular the baroreceptor reflex, is *l*-glutamate. Reis and Talman (1984) showed that administration of glutamate to the NTS induced hypotension. Another candidate is neuropeptide Y which is reported to have similar effects to glutamate (and clonidine) after intracisternal infusion (Zini *et al.*, 1984). Neuropeptide Y is stored in the same neurons as adrenaline in the NTS and reticular system, where clonidine is claimed to act to reduce tension (Atkinson *et al.*, 1984). Concentrations of neuropeptide Y are lower in SHR than WKY rats in the cortex and brain stem (Maccarone and Jarrott, 1985).

The contribution of 5-HT to the characteristics of the SHR and/or central hypertension is difficult to pin down. Pressor and depressor effects have both been frequently reported after administration of the transmitter or precursor to normo- and hyper-tensive rats (Chalmers, 1982). The synthetic enzyme for 5-HT is abnormally active in the spinal cord and medulla of young but not older SHRs (Smith *et al.*, 1979). At one month of age 5-HT levels are high in the hypothalamus of the SHR. By two months these are restricted to the posterior region and no differences are found in the fore or mid brains, pons/medulla or spinal cord (Howe *et al.*, 1982). Indeed in contrast to the levels of the CA synthetic enzyme tyrosine hydroxylase, that of tryptophan hydroxylase outside the hypothalmus is no different even under conditions of stress (Ikeda *et al.*, 1984). Evidence from electrical stimulation of the raphe (pressor response) and lesion with specific toxins (e.g. 5,7,dihydroxytryptamine: depressor response in SHR) is suggestive of a contribution to blood pressure changes from 5-HT innervation of the hypothalamus alone (Wolf *et al.*, 1981; Chalmers, 1982).

5.2.3. *Dopamine (DA)*

Of the other transmitters whose activity may be associated with blood pressure changes (e.g. GABA, histamine, adrenaline: Tuomisto *et al.*, 1983) DA is probably the most important. Thus, for example, after treatment with phencyclidine at a dose that induced acute hypertension, DA levels were found to fall and DA transmission in the NTS was enhanced (Bayorh *et al.*, 1984). Indeed infusion of DA (icv 0.4 mg) leads to a decrease of blood pressure in rats and rabbits (Hutchinson and Mok, 1984).

Initially surprising was the finding of low striatal levels of DA in mice with high blood pressure (Denoroy *et al.*, 1985). Alone this result does not inform us about DA activity. But it may be taken as consistent with the result of phencyclidine (above) which enhanced DA transmission. This interpretation is also consistent with the report that kainic acid lesions of the neostriatum lead to hypertension and tachycardia (Wu *et al.*, 1984). Curiously the neostriatum was the one area found to show increased levels of neuropeptide Y in the SHR with respect to WKY rats (Maccorone and Jarrott, 1985). These changes are in a region of the brain well situated for affecting the activity and reactivity of animals.

What about other brain regions? The apparent difference between the effects of DA in the neostriatum and the brain stem is mirrored within the hypothalamus. One group has reported a reduced release of DA from the posterior hypothalmus of SHRs but the opposite from the anterior region (Dietl *et al.*, 1981; Tuomisto *et al.*, 1983). Therefore it would be unwise to speculate or to generalize about CA changes in other brain regions (e.g. septum). Finally the potential involvement of the neocortices should not be overlooked. Areas such as the cingulate (Burns and Wyss, 1985) and insular cortex (Ullan,

1983) are involved in vasomotor regulation (e.g. electrical stimulation studies), are directly connected with known blood pressure control centers (e.g. posterior hypothalamus and NTS) and receive major NA and DA innervation. Both regions are involved in the integration of sensory information as well as the organization of motor responses.

5.3. THE LINK WITH BEHAVIOR AND COGNITION

Is there a connection between blood pressure changes and cognitive function? Certainly in some forms of hypertension in man (e.g. high renin, as in the pituitary of SHRs: Naruse *et al.*, 1985) psychological symptoms of sensitivity, hostility and psychotic thought disorder can occur (Thailer *et al.*, 1985). Differences in vasomotor reactivity and in regional cerebral blood flow have been reported in ADDH-subjects (Butter *et al.*, 1984; Lou *et al.*, 1985). In both studies methylphenidate treatment normalised both of these anomalies and the children showed improved indices of learning and activity. Are there parallels in the animal model? Certainly SHRs are highly sensitive to sensory stimulation as shown by measures of heart rate and blood pressure (Hallbach and Folkow, 1974; Yamori *et al.*, 1969). Further, slow electrical activity in the hippocampus has been reported to be associated with sympathetic and pressor effects whereas fast activity was associated with parasympathetic activity and the lowering of blood pressure (Toru and Kawamura, 1960). There is a large literature on the potential relationship between rhythmic slow activity in the hippocampus and the attention-related processing of information (e.g. review Oades, 1982a).

What are the behavioral features of the SHR rat? Broadly speaking their increased levels of activity and reactivity recall the similar features of rats with non-specific damage of the DA and non-DA elements of the A10 area (Gaffori *et al.*, 1980; Le Moal *et al.*, 1976). In the open field SHRs can show both increased motor activity and exploratory investigation of novel stimuli (Knardahl and Sagvolden, 1979; McCarty and Kirby, 1982). This is particularly marked in the center of an open field whereas WKY rats are more active around the edges (Hard *et al.*, 1985, Table IV). These changes were correlated with individual blood pressure levels. Sutterer and coworkers (1984) also found a considerable increase of rearing in SHRs to sudden changes of light (500 W) or sound (96 dB) stimulation. But the amplitude and duration of the immobility response (6 sec of a 95 dB bell) was shorter than that for either WKY or normotensive rats (Hard *et al.*, 1985). Thus both hypertensive rats and humans (Brod, 1963; Falkner *et al.*, 1979) can show a marked physiological response to environmental stimulation. However neither Whitehorn *et al.* (1983) nor Sutterer found a precise correlation with blood pressure. But a big problem with the SHR model is that the WKY "controls" also appear abnormal. They are unusually emotional, do not move or rear much, are not good at noticing novel stimuli, rapidly habituate motor responses and freeze in response to sudden environmental stimuli (Sutterer *et al.*, 1980, 1981, 1984; Delini-Stula and Hunn, 1985; Hard *et al.*, 1985). The question of appropriate controls for the behavioral characteristics of SHRs needs closer attention in future work.

Surprisingly SHRs are reported to be more active by day but show no differences with respect to normotensive rats by night (e.g. Sasagawa and Yamori, 1975; Hard *et al.*, 1985). It is of interest to note in passing that a similar increase in daytime activity was the unexpected and, as yet, unexplained result of grafting DA containing cells into the nucleus accumbens of rats with A10-6-OHDA lesions (Dunnett *et al.*, 1984). It would be of value to make more comparisons of circadian rhythms of activity in both the model and the clinical condition. The importance would lie in the study of the functional correlates of activity in different transmitter systems. But deeper lying causal connections may not be found. Thus Hendley and coworkers (1983) did not find a genetic link for hyperactivity to the hypertensive gene system of the SHR.

5.4. THE SEPTUM?

Changes of exploratory motor behavior, sensory responsiveness and active avoidance acquisition of the SHR are not unlike those recorded in normal rats after electrolytic or

6-OHDA lesion of the A10 projection region of the septum (Clody and Carlton, 1969; Chafetz *et al.*, 1980; Oades *et al.*, 1985a). SHRs are hyper-responsive to noncontingent electrical footshock (Knardahl and Sagvolden, 1982). Such an increase of sensitivity may contribute to the facilitation of acquisition of an active and Sidman avoidance tasks (Knardahl and Sagvolden, 1982; Sutterer *et al.*, 1980; Takaori *et al.*, 1972).

Remembering that there is a potential role for glutamate and neuropeptide Y in hypertension, it is worth recalling that there is a major glutamergic (or aspartergic) input to the septum where there is also a moderate neuropeptide Y innervation.

A further parallel can be mentioned emphasizing specific chemical lesions in normal animals. SHRs learned a rewarded alternation faster than normotensive controls (Low *et al.*, 1984). A similar result was recorded for mice with septal-6-OHDA damage that resulted in increased acetyl choline activity in the hippocampus (Galey *et al.*, 1984). Oades and colleagues (1985a; Fig. 2) have reported that the depletion of septal DA can alter the time course for learning a conditioned blocking task on which performance is claimed to reflect selective attentional function (Mackintosh, 1975). On this task impaired attentional performance reveals itself in animals learning about redundant stimuli (i.e. impaired attentional control) and thus in this special case learning the task faster than controls. It would be interesting to know how ADDH subjects would perform on such a task.

The septal area that receives a copious innervation from NA and DA fibers would seem to be worthy of closer investigation in the SHR. Further reason for such study is that during development, changes of activity of angiotensin converting enzyme are reported to be particularly marked in the septum (cf developmental time course for ADDH: Chevillard *et al.*, 1984). Angiotensin II promotes drinking in the change of events arising after a drop of blood pressure. The septum is one site that is particularly sensitive to this peptide (Epstein *et al.*, 1970). Injections of the peptide to the septum elicit drinking. There are high levels of angiotensin II in the septum and hypothalamus (Israel *et al.*, 1984) and the adjacent stria terminalis and medial preoptic area (Weyhenmeyer and Phillips, 1982). Further there are high levels of radioligand binding in the septum, hypothalamus and neostriatum (Petersen *et al.*, 1984). Angiotensin II excites septal neurons (Huwyler and Felix, 1980) and stimulates the release of NA (Langer, 1978) and DA (Simmonnet and Giorguieff-Chesselet, 1979).

With respect to the SHR there are reports of increased levels of angiotensinogen in a number of brain regions (Naruse *et al.*, 1985) and less angiotensin converting enzyme, particularly in the cerebral blood vessels (Kobayashi *et al.*, 1985). Interference with the breakdown of angiotensin II heightens pressor responses (Wright *et al.*, 1985). Elsewhere it has been shown that the amount of CA released per impulse is higher in the SHR (Nilsson *et al.*, 1985). As angiotensin II is one of several factors that can also affect the quantal release of NA (Vanhoutte *et al.*, 1981) it seems appropriate that the consequences of anomalous CA activity in the septum should form one important direction of research into ADDH-like features modelled by the SHR.

Finally it is appropriate to record that there is a well known syndrome of hyperreactivity that follows lesion of the septum (Brady and Nauta, 1953). This syndrome is attenuated by activity of the gonadal steroid estrogen (Iovino *et al.*, 1983). (Estrogen as well as being the most abundant gonadal steroid in females is synthesized in males and is present as a functional metabolite of testosterone in some limbic sites.) The effect of estrogen is of interest for three reasons. Firstly estrogen can modulate DA receptor activity rather like a DA antagonist (Joyce *et al.*, 1984) and hence can modulate DA-mediated locomotion. Secondly estrogen tends to decrease responsiveness to angiotensin II and its binding in the preoptic-septal region (Fregly *et al.*, 1985; Jonklaas and Buggy, 1985). Thirdly the natural changes of hormone levels at puberty could, speculatively, lead to or contribute to the change between ADD with hyperactivity in children and the adult residual syndrome with reduced activity.

Thus in view of the marked developmental changes, the effects of both principle CAs and the change of responsiveness that this brings, it is suggested that the function of specific transmitter systems of the septum and related structures of the limbic system,

particularly in the SHR, may be crucial to an improved understanding of the ADDH syndrome.

6. Conclusions

It is naturally a difficult task to try to generalize on the ADDH condition where diagnostic practice has not been consistent and diagnosed subjects show highly variable measures on both cognitive tests and in neurochemical assays. From the research point of view what is needed are correlations of test performance (rather than mere clinical impression) with indicators of transmitter metabolism in controlled experiments using larger groups of subjects than has usually been the practice. What are the effects of treatments on learning *and* CA metabolism in normal and ADDH subjects?

There are two clinical conditions associated with the hyperactive syndrome. One of these (ADDH) portrays two major clusters of symptoms (attentional and motor disturbance) that seem to be both functionally and causally independent. In the ADDH condition there are, at least, two groups (psychostimulant responders and nonresponders), one of which, the responders, can show two effects of drug treatment on DA metabolism. Stimulants may raise, lower or decrease normal levels of HVA. In each case levels of MHPG fall. In view of this complexity it is little wonder that nondiscriminating pharmacological treatments have not proved highly successful in correcting maladaptive responsiveness, socialization and performance in ADDH subjects.

The results of current therapeutic strategies and studies of animal models suggest there is a double anomaly in NA and in DA metabolism. Neither serotonin nor GABA metabolism seem to be involved to any major extent. But since the ratios of CA metabolites remain anomalous even in responders, the possibility of a third neurochemical change is raised. Further animal studies are required both of the symptom, as produced by specific chemical brain lesion, and of the syndrome, as shown in animal strains. There are clues from such studies that CA interactions in the septum could be a source of the anomaly. With relatively few studies of the cognitive performance of the SHR on tasks of experimental psychology, information on how well this model fits the clinical picture is still lacking. How do animal models (e.g. SHR) respond on cued tasks, partial reinforcement and what sort of errors do these animals make on search-vigilance tasks? A comparison of such results with the effects of damage to specific septal neurotransmitter systems (e.g. 6-OHDA, ibotenic acid) on responding in similar tasks might be illuminating.

In animals the "typical" stimulants facilitate the release of CAs, improve incentive learning and assist in "tuning" the degree of stimulus selection and initiation or "switching" of the appropriate response: I refer here to fundamental roles that have been postulated for NA and DA transmission respectively (cf Beninger, 1983; Oades, 1985). In ADDH-subjects these agents modulate the utilization of CAs and help subjects to slow down and concentrate, for a while. Perhaps the use of atypical stimulants (e.g. the ergolines) that have both adrenergic and dopaminergic agonist properties combined with psychotherapeutic training of cognitive strategies would help to produce a longer lasting more favorable response.

7. Summary

An attention deficit disorder with hyperactivity in children (ADDH) is now recognized in most countries although diagnostic practices differ. Evidence is presented to show that the two cardinal symptoms of poor attentional performance and high motor activity may be functionally and causally separate. Both are temporarily relieved in a proportion of subjects that respond to psychostimulants. Beneficial treatment decreases noradrenergic metabolism and normalizes variable levels of dopaminergic metabolism. Parallels are drawn with other clinical syndromes arising from changed catecholaminergic activity and with behavioral interpretations of the result of damage to the dorsal noradrenergic bundle and dopaminergic A10 nucleus. Prognosis of ADDH subjects after treatment remains

poor. There may be a further defect of neurotransmitter metabolism in the ADDH syndrome. Research strategies are suggested based on the neurobiological correlates of the cognitive style of ADDH subjects and septal function in the animal model of the hypertensive rat.

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