

# Attention Deficit Disorder and Hyperkinetic Syndrome: Biological Perspectives

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## INTRODUCTION: THE CONDITION

What is the nature of the condition, referred to as attention deficit disorder (ADD) or childhood hyperkinesia in this chapter? Recent categorical descriptions in diagnostic manuals are widely felt by clinicians to be misleading (e.g. ADD, minimal brain dysfunction, childhood hyperkinesia). Indeed in contrast to conditions like Parkinsonism, there is little clear knowledge of the underlying disorder. There are symptoms. But no single one is indispensable for diagnosis and the number necessary varies with the authority.

The measurable items of interest include motor activity, attentional strategies, context-dependent motivation and psychostimulant responsiveness. An arbitrary degree of deviation from the norm for several of these items currently forms the basis for diagnosis (e.g., from fidgetiness to pervasive hyperkinesia) and hence leads to the rather different estimates of the incidence of the condition around the world (Weiss & Hechtman, 1979; Thorley, 1984).

If we seek biological concomitants or symptoms to model we cannot overlook the questions raised by differences of clinical opinion. For example, at the mild end of the scale, is there a symptom in "underachievement" (cf. Shaywitz & Shaywitz, this volume)? This is a question for society and for the laboratory investigator. Is it relevant that after a given intervention an animal learns more slowly or that learning one task interferes with learning another? At the severe end of the scale, should the investigator be more concerned with pervasive hyperkinesia and/or autistic behaviour, mental handicap and/or responsiveness to psy-

chostimulants? Clearly biological correlates for each of these symptom pictures should be sought separately, and if possible, sometimes in combination. With a symptom-oriented strategy, there will remain doubts about the interpretation of the biological correlates in terms of the underlying cause of the disorder. But eventually one hopes that such studies will clarify the relationships between the components of a potential category, of the condition under consideration.

However there are some sobering caveats for the exclusive use of a symptom-oriented strategy without reference to knowledge about categories of symptoms and their epidemiology. For example, whilst classical childhood autism may improve slightly after neuroleptic treatment, autism associated with the fragile X chromosomal condition can benefit from psychostimulant treatment. The reverse is more usually true for childhood hyperkinesis, given that there is a response to treatment at all.

Nonetheless, let us concentrate on the symptoms and consider what indicators of changed biological function, associated with the symptoms of ADD, might be useful and then look for correlations with the behavioral items of interest from animal studies.

## BIOLOGICAL INDICATORS

There are different requirements of biological indicators in diagnosis and treatment on the one hand and for providing clues to those investigating the biological bases underlying any symptom on the other. For instance there is a high incidence of subtle brain damage in hyperactive children (Taylor, this volume). Whilst the use of major neurological soft signs is felt not to be useful in diagnosis and management, more reports of refined and intelligent use of soft signs (e.g., multiple measures of cognitive performance) would be most welcome for the laboratory investigator of hyperactive children or animal models (cf. Milner, 1971; Carpenter, Strauss, & Bartko, 1981; Kolb & Wishaw, 1983). To illustrate the point, it is only through such reports that a rational argument for measuring frontal cerebral blood flow can be advanced to confirm anomalous biological function.

*Electrophysiology.* Electrophysiological investigations also illustrate the dichotomy between the value of diagnostic and investigatory tools. The main clinical use of the EEG lies not in diagnosis per se, but in the separation of a subgroup for pharmacotherapy (e.g., methylphenidate vs valproate; Morag, Frank, & Myslobodsky, paper presented at the Workshop on Attention Deficit Disorder, Oslo, 1987). But averaging the EEG after stimuli or events in a task situation (event-related potential, ERP) has not received appropriate or intensive study. Such studies may provide a useful investigatory tool, despite methodological difficulties.

Children with attentional problems are reported to show larger negative slow waves over frontal sites (CPT, Friedman, Cornblatt, Vaughan, & Erlenmeyer-Kimling, 1986) and a well-controlled group of ADD (both with and without hyperactivity) showed smaller P3b and late positive components over posterior sites (auditory odd-ball task, Holcomb, Ackerman, & Dykman, 1986). In this context it is of interest to discover that cerebral glucose utilization has been studied (Shaywitz & Shaywitz, this volume). A decreased utilization is reported in frontal regions and increased utilization in posterior regions. What might be the relation between ERPs, glucose utilization and mental (attention or response) effort?

Mental effort or the evaluation of events, as indexed by P3b latency, is said not to be influenced by methylphenidate (Callaway & Halliday, 1982). But others have shown and replicated an enhancement of the evaluation process (P3b latency) under such medication in certain forms of the Sternberg memory scanning task (Brumaghim, Klorman, Strauss, Lewine, & Goldstein, 1987). What is the fine distribution of these ERP changes (mapping) and their sensitivity to treatment in ADDH-subjects who respond and not respond to psychostimulant therapy? Does the severity of performance deficits correlate with ERP changes and are ERP changes subject to manipulation of the motivational interest of ADD subjects? Is the decrease in amplitude of late positive components in autistic children performing an auditory odd-ball task (Oades, Walker, Geffen, & Stern, 1988) related to the similar phenomenon in ADD children? Results of such studies will inform us about the nature of the attention-related phenomenon, its locus and the sub-group showing such changes.

*Stimulants and Arousal.* It may be that psychostimulant responsiveness should form a part of the diagnostic process (Rutter, this volume). It cannot be doubted that the separation of subjects for further study into those responding and not responding to amphetamine or methylphenidate treatment is crucial for progress in understanding the biology of the hyperkinetic syndrome. (Although the use of this type of separation should not exclude under-used methods for group separation, e.g. on the basis of mental or developmental retardation, autonomic arousal, peptide excretion or "food allergy").

Are hyperactive children under—or over-aroused? Is the therapeutic effect of psychostimulant medication paradoxical? What happens to catecholamine (CA) metabolism in underaroused and psychostimulant responders? Kløve (this volume) has capably summarised the conflicting literature on the arousal hypothesis. But Pandora's box has been opened. The measures (heart rate, skin conductance inter alia) not only vary between individuals and medication status (Brand & van der Vlugt, this volume), but according to stimulus salience, anticipatory set, motivation, stimulus consequence, age, institutional status and a host of other factors. To define the effect of medication requires the study of the individual as his/her

own control and a truly enormous investigation controlling for each situational factor. More tellingly one must have reservations on the predictive power of such investigations of a global construct.

Resolution of the so-called paradoxical effect of psychostimulants does not lie in the determination of the status of a global construct such as arousal and its change with treatment. The effect of stimulant treatment is the sum of the numerous changes it induces in a wide range of measures. Some of these changes appear on the surface to be paradoxical. Psychostimulants can decrease urinary/plasma MHPG levels (metabolite of noradrenaline (NA), increase HVA levels (metabolite of dopamine (DA) or simply decrease HVA levels in hyperkinetic subjects with low MHPG (Shekim, Javaid, Dekirmenjian, Chapel, & David, 1982; see also Table 2, Oades, 1987). They can increase the prolactin response without affecting growth hormone levels (Shaywitz & Shaywitz, this volume). Behaviorally, as Robbins, Jones, and Sahakian (this volume) indicate, methylphenidate treatment of hyperactive children may increase perseverative errors in a Wisconsin card sorting task yet improve visual search on the Lafayette battery.

Some of these paradoxes rest on an assumption about the underlying substrate treated. For example, the neurophysiological effect of amphetamine is inhibitory, yet it stimulates the release and activity of CAs. Resolution of the conflict lies in separating pre- and post-synaptic mechanisms. Again, the beneficial effect of amphetamine was first seen in hyperactive subjects suffering from von Economo's encephalitis. In hindsight one can say that this was not paradoxical, for these subjects showed some Parkinsonian symptoms and post-mortem study showed some degeneration of the substantia nigra.

The "paradox" of hyperactivity being attenuated by stimulant treatment receives only partial solution by consideration of the rate-dependent effects of psychostimulants on behaviour (c. 30%, Robbins & Sahakian, 1979). Global effects of the stimulants on behavioural activity reflect baselines of transmitter activity. Low baselines increase after stimulant treatment. High baseline transmitter activity is relatively unaffected or often reduced by stimulant drugs. More important will be the neuronal innervation patterns in regions governing specific and separately organised responses (e.g., response and error monitoring, the search for a stimulus relevant for task solution and the control of vegetative activities such as hormone production). For example, as amphetamine can inhibit electrically induced DA release, but facilitate electrically induced NA release (Langer & Arbilla, 1984), behavioral activities depending on the neostriatum (mainly DA innervation) will be affected differently from those depending on active contributions from the prefrontal cortex or nucleus accumbens (related DA and NA innervation).

The true paradox of psychostimulant therapy yet presents itself when the biochemical and behavioral changes resulting from treatment are interpreted exclusively in terms of the known effects of these agents on blocking CA reuptake, stimulating CA release and attenuating monoamine oxidase (MAO) activity. Why

are treatments with CA precursors and MAO inhibitors disappointing in the long term? It is curious that neurological soft signs, where present, do not predict stimulant responsiveness. Even where psychostimulants effectively reduce hyperactivity, such a decrease is a poor predictor of the ultimate outcome. Even where it is found that stimulants or MAO inhibitors do improve behavior and there is a behavioral rebound after drug withdrawal, MHPG levels remain as low as ever. These are some of the paradoxes and uncomfortable issues that need to be addressed. Elsewhere I have elaborated on the possibility that these issues point to a third "non-catecholamine" etiological factor in the hyperkinetic syndrome (Oades, 1987). These issues recall Baldessarini's remark (1977) that an understanding of the action of thiazide diuretics would not necessarily lead to an important insight into the pathophysiology of congestive heart failure.

*Metabolism.* Issues that have been addressed all too infrequently concern metabolites as biological indicators. Of interest are the breakdown products of the conventional monoamine transmitters (e.g., HVA, MHPG, 5-HIAA) of the neuropeptides (e.g., opioids) and of certain dietary constituents (e.g., casein).

Considering the relative and non-invasive ease with which urinary and plasma specimens may be obtained, it is regrettable that this practice is not more routine. Particularly taking into account that it is possible to increase the proportion of metabolites of central origin by prior use of debrisoquin, a mild monoamine oxidase inhibitor with largely peripheral action (Shaywitz & Shaywitz, this volume). The technique could provide valuable epidemiological data and illustrate more clearly the relevance of stimulant treatment. It could also highlight productive avenues for further study by providing correlations with some of the anomalous developmental or behavioural features of hyperactive children.

Why, amongst stimulant-responders, are MHPG levels low and not improved by pharmacotherapy? Do these levels reflect low turnover, low sympathetic arousal and a reduced ability to tune central neural processing to task relevant stimuli (cf. Oades, 1985)? Certainly there is evidence supporting enduring low "arousal" in hyperkinetic children (cf. Kløve, this volume) and the reduced P3 amplitude of the ERP (Holcomb et al., 1986) is modulated by locus coeruleus activity (Foote, personal communication). But the answer may be "No" to all three questions. MHPG levels may not be a good indicator of NA neural activity (Commissiong, 1985). Sympathetic and central arousal levels are likely to be reflected by other metabolites (e.g., VMA) and other transmitters (e.g., the amino acids). The P3 component is affected by many other neurotransmitters (e.g., acetylcholine; Hammond, Meador, Aung-Din, & Wilder, 1987).

In any case what are the behavioral differences between stimulant responders and the non-responders who show normal levels of MHPG? Why is the urinary HVA/MHPG ratio 50-100% higher in both responders and non-responders than in healthy controls? Perhaps these changes reflect an imbalance, not of the transmitter-CAs, but of the trophic-CAs. An imbalance of trophic properties might

explain anomalous regional innervation patterns, some functional retardation and the progress, development and amelioration of different symptoms with maturity. It is not clear to what extent metabolite imbalance attenuates with age and if this is related to symptom changes.

The excretion of a range of N-substituted peptides and their relation to diet and psychiatric disorder was touched on by Reichelt et al. (paper presented at the Workshop on Attention Deficit Disorder, Oslo, 1987). They claim to be able to distinguish subjects with ADD, ADHD, conduct disorder and autism according to the pattern of peptide excretion (e.g., Reichelt, Saelid, Lindback, & Boeler, 1986). These results are provocative, suggesting perhaps a range of peptidase insufficiencies. The potential causes are legion. They range from the reduced availability of nutrients necessary as enzymic cofactors (e.g., zinc) to changed levels of neuropeptides which inhibit enzymes such as enkephalinase and angiotensin converting enzyme (e.g., beta endorphin and substance P; McGeer & Singh, 1979; Hui, Graf, & Lajhta, 1982). The functional relevance is hinted at by McGaugh (paper presented at the Workshop on Attention Deficit Disorder, Oslo, 1987). NA release is modulated by opioid activity. Thus changes of learning abilities, dependent on adrenergic activity, may be influenced by abnormal central opioid activity (Izquierdo, Dias, Souza, Carrasco, Elisabethsky, & Perry, 1980).

Challenges have been made. The metabolic pathways need to be examined. I have already raised the question of an involvement of angiotensin on the basis of hypertensive animal models and the psychological profile of some hypertensive people (Oades, 1987). More circumstantial evidence can be derived from the claim that a large proportion of hyperactive children show unusual thirsts (I. Colquhoun, personal communication). Are these items all merely coincidental? Are other neuropeptides such as cholecystokinin and neuropeptide Y involved? These peptides are associated with DA and NA neurons respectively; they can also modulate motor activity and hypertension.

## ANIMAL MODELS

Two main types of model are used to illuminate ADHD. The first one draws on the implied CA dysfunction and describes the effects of interfering with CA function on the major symptoms of attention and behavioural activity. Symptoms relating to impulsivity and motivation have received less study. The second draws more broadly on the symptom picture and arguably can be said to attempt to model the disorder. Here I refer to spontaneously hypertensive animals and manipulations during the development of animals. I briefly mention a third category of model that seems to have been neglected, namely that of other childhood disorders with features in common with ADD.

### Symptom Models

*Noradrenaline (NA)*: The problem has been and remains that it is difficult to show or describe attentional or learning impairments that animals have when depleted

of central NA. They are quite capable of learning: it is just in some situations that they are less efficient and less adaptive. Is this not remarkably similar to the situation with hyperactive children?

Burning the midnight oil in Södertälje and Cambridge has been rewarded by interesting findings (see the chapters by Archer and Robbins et al. for details). Firstly, performance on sensory preconditioning and latent inhibition - two tasks that experimental psychologists have proposed as indicators of attentional and selective learning ability - is impaired after the reduction of forebrain NA. I believe such studies have succeeded (e.g., Archer, Mohammed, Danysz, & Jonsson, 1986; Mohammed, Callenholm, Järbe, Swedberg, Danysz, Robbins, & Archer, 1986; Lorden, Rickert, & Berry, 1983) where others have failed (e.g., Tsaltas, Preston, Rawlings, Winocur, & Gray, 1984; Robbins & Everitt, 1985) because of the use of multiple cues. As I have suggested (Oades, 1985), only where demands are placed on NA to tune the relative importance between *several* potentially relevant stimuli will behavioural impairments be demonstratable after NA depletion. But for the sake of the model one must go further. Would non-sedative doses of pharmacological agents that result in low MHPG excretion produce similar results?

The second finding of interest is that animals depleted of forebrain NA can take an unusually long time in reaching strict learning criteria on some forms of discrimination task. In this context it is not surprising that agents of "arousal" that might be expected to challenge CA systems (e.g., white noise before presentation of discriminanda or amphetamine treatment of the nucleus accumbens) can impair the discrimination performance of lesioned animals (Robbins et al., this volume; Robbins & Everitt, 1985).

In connection with these results it is perhaps pertinent to note that intact animals respond to mild stressors or novel stimuli by releasing NA transiently in the terminal regions (c. 20%, Gold & Zornetzer, 1983; Svensson & Ahlenius, 1983). Such a neural response seems designed to control inappropriate reactions. One would expect that such neural and behavioural responses would not only be absent in lesioned animals, but perhaps reduced in children with low levels of MHPG. The lesson surely is that NA activity is important for cognitive performance to be appropriate and adaptive. It might prove instructive to examine further the strategies of exploration of *novel* objects in *novel* environments, - preferably structured to facilitate a comparison of studies of performance in lesioned animals and hyperactive children.

*Dopamine (DA)*: Attention-related information processing is anomalous in a number of human conditions where DA activity is significantly altered. This has been shown by ERP studies of schizophrenia (for review see Oades, 1982), Parkinsonism (Wright, 1988), childhood autism (Oades, Stern, Walker, & Kapoor, submitted) and ADD/ADDH (Holcomb et al., 1986). Shaywitz and Shaywitz (this volume) has pointed out that a group of hyperactive children do show changes of HVA levels in samples of CSF, urine and plasma. Changed DA activity is

a factor in the attentive processes (e.g., effort) of healthy students where neuroleptic effects are reversed by methylphenidate (Clark, Geffen, & Geffen, 1986). The role of DA activity in hyperactive children is also shown by the relative success of psychostimulant treatment and the fact that the effects can be blocked by neuroleptic pretreatment (Levy, personal communication). The efficacy of very low doses of neuroleptics in such children (Werry & Aman, 1975; Gittelman Klein & Abikoff, this volume), receives support from animal studies. Very low doses of sulphiride (like amphetamine treatment) eliminate latent inhibition (Feldon, Weiner & Ben-Shahar, 1987). In animal studies a variety of DA manipulations affect both latent inhibition and conditioned blocking (Weiner, Lubow, & Feldon, 1984; Crider, Blockel, & Solomon, 1986; Oades, Rivet, Taghzouti, Kharouby, Simon, & Le Moal, 1987). Yet it remains unclear just what the contribution of DA might be.

The chapters by Robbins et al. and Beninger (this volume) imply, respectively, that changes in DA activity could partly be responsible for the impulsivity and altered motivational control seen in many hyperactive children. Robbins et al. describes a 9-hole box where rats have to wait for the correct stimulus, then respond to the correct hole and pick up a reward elsewhere. Commission, omission and premature errors are recorded. He draws an analogy with the continuous performance task in which hyperactive children perform poorly on signal detection measures. The analogy is plausible. Amphetamine treatment increases premature responses, apparently decreasing beta, the response criterion of signal detection theory. This impairment is attenuated by chemical lesion of the DA innervation of the nucleus accumbens. This is an elegant demonstration implicating the role of DA activity. However as an explanation for the behavior of hyperactive children, it is "upside down". The performance of hyperactive children that show a low response criterion can be improved by amphetamine treatment. Of course there are many examples whereby the nature of the change is altered by training before or after a manipulation or by altering the sequence of events in the protocol. But although it may be worthwhile exploring these alternatives, it may be better to look at the role of another DA-innervated region such as the septal nuclei or the frontal cortex.

Intact innervation of the frontal cortex exerts an inhibitory control over the innervation of the nucleus accumbens (Pycock, Kerwin, & Carter, 1980; Tassin, Reibaud, Blanc, Studler, & Glowinski, 1984). The increase of limbic DA activity induced by frontal damage may be attenuated by the rate dependent action of amphetamine. One notes from studies of hyperactive children that glucose utilization is lower in the frontal regions of some subjects (Shaywitz & Shaywitz, this volume). Further, in the context of a putative frontal impairment and the so-called paradoxical action of psychostimulants, a recent result from Robertson (1986) is provocative. Unilateral cortical damage or chronic amphetamine treatment downgrades neostriatal DA receptors by between a fifth and a third. But together the treatments result in the upgrading of DA receptors by 50%.



The study of impulsivity in a 9-hole box after manipulation of DA-projection regions may yet prove productive in modelling human impulsivity, as could further study of both NA and DA influences on the nature of task-solving strategies. For example, hippocampal and DA activity can differentially affect errors and sequences of holevisits in a 16-holeboard (Oades & Isaacson, 1978). The technique, in the form of a pegboard, has been used for studying schizophrenic performance (Oldigs, Ularadt, & Rey, 1981). It could be useful in the study of hyperactive children.

### Disorder Models

A model is an experimental compromise, a simplified preparation created to help understand a larger, more complex phenomenon (McKinney & Moran, 1981). With this in mind, the use of *icv* 6-hydroxydopamine (6-OHDA), environmental deprivation and the spontaneously hypertensive rat will be briefly discussed. But it should not be forgotten that similar behaviors in various species (or in separate situations) may exist for different reasons and therefore have different meanings (Kornetsky & Markowitz, 1978). The question must continually be raised whether the simplification or comparison is appropriate and relevant.

*icv* 6-OHDA. At first sight the investigations of Seiden, Miller and Heffner (this volume) of the behavioral effects of the chemical toxin 6-OHDA in the cerebral ventricles of neonatal rats seem attractive. They showed that hyperactivity may be induced and, depending on the dose, may gradually disappear in adulthood. The hyperactivity was attenuated by amphetamine treatment and increased by water deprivation (cf. the frequent incidence of thirst in hyperactive children, see above). Further, his animals were slower to acquire a simple lever press-task.

But one must ask what DA parameters are being changed by the different doses of 6-OHDA and amphetamine? Breese, Baumeister, McCown, Emerick, Frye, Crotty, and Mueller (1984) depleted DA levels neonatally and treated the adults with DA agonists. They suggest that this is a model for the Lesch-Nyhan syndrome (including self-mutilation, choreoathetoid movements). In their hands both neonatal and adult treatment with 6-OHDA depleted DA and DOPAC levels by a factor of 10, but altered neither D1 nor D2 receptor binding in the nucleus accumbens (Breese, Duncan, Napier, Bondy, Iorio, & Mueller, 1987). After neonatal lesions they stimulated locomotion in adults with selective D1 rather than D2 agonist treatment. But opposite results were obtained by varying the age for 6-OHDA treatment and by administering the agonists systemically or to the nucleus accumbens.

As exciting as this approach is, it is generating more than its fair share of questions. Before this type of treatment can be claimed as a model for any-condition, one must study the potential bases for how behavioral supersensitivity is achieved

without receptor upgrading (cf. Fleming, 1988). Under what conditions does icv-6-OHDA induce receptor supersensitivity? What mechanisms are the various direct and indirect agonists affecting? What constitutes the significant difference between various routes of administration and how do D1 and D2 receptors interact during development and in the adult?

*Developmental Environment.* The role of the environment in development is often studied by following the effects of three types of influence: isolation vs social housing, regular vs no handling and simple vs enriched (object) environment. The simple and isolated environments are often similar. It is assumed that early deprivation could lead to a hyperactive syndrome in development. There is very little evidence for this supposition (Taylor, this volume). Let's suppose it is true. What happens after using the different rearing conditions?

Rats reared in isolation tend to show increased motor activity (Robbins et al., this volume). Intriguingly this is attenuated by treatment with amphetamine. Could this imply increased DA activity and a rate-dependent action of the stimulant? For rats, enriched housing is an advantage in learning mazes (Archer, this volume). Depletion of central NA reduces the advantage. So different housing conditions may affect CA activity and behavioural abilities differentially. Certainly NA and amphetamine can enhance sensory function in the cortices of deprived animals at a neurophysiological level. But to what extent are the effects due to neurotransmitter function, the trophic effects of CA agents and/or compensatory action for other numerous and perhaps more important structural changes? Extremes of developmental housing conditions have been correlated with the numbers of dendritic spines and cortical morphology (Diamond, Greer, York, Lewis, Barton, & Lin, 1987).

Feldon and colleagues have reported at the ADD workshop in Oslo and elsewhere that non-handled male rats (in contrast to females) did not show latent inhibition (an index of attentive capability: Weiner et al., 1985). This was counteracted by isolation experience. These results are intriguing for pointing out potential complex interactions between various experiential factors and in particular pointing to the difference in sensitivity between the sexes. They are valuable for advancing our knowledge of developmental processes. But they may be too preliminary to provide a model in the absence of an underlying hypothesis or evidence for a phenomenon to be paralleled. Far too little is understood of the far reaching biological changes wrought by these environmental manipulations. Further, not enough is known about the interactions of neurotransmitter activity, hormone secretion and heterogenic brain development between the ages of 3 and 8 in children.

*The Spontaneously Hypertensive Rat (SHR).* As reported by Sagvolden and colleagues (this volume) the appeal of SHRs lies with their behavioral hyperactivity, hyperreactivity and performance on certain tasks. SHRs show changed cen-

tral NA and DA activity and reactivity (Hellstrand & Engel, 1980; Ikeda, Hirata, Fujita, Shinzato, Takahashi, Yagyu, & Nagatsu, 1984; Koulou, Saavedra, Niwa, & Linnoila, 1986).

Questions about the appropriateness of the comparison of SHR with childhood hyperkinesia arise when the motor activity increase is by day and not by night and task performance may vary as a function of sensitivity to electric shock (Knardahl & Sagvolden, 1979, 1982; Knardahl & Karlsen, 1984). Adding to the problems are a number of conflicting reports on the behavioral reactivity of SHR (Sutterer, DeVita, & Rykaszewski, 1981; Hard, Carlsson, Jern, Larsson, Lindh, & Svensson, 1985). Here one of the major problems may be the choice of the Wistar-Kyoto control for the Okamoto strain of SHR. In some studies the control animals have been hypoactive and/or emotional (Sutterer et al., 1981; Hard et al., 1985; Sutterer, Stoney, & Sanfillipo, 1984; Delini-Stula & Hunn, 1985). Recent investigations include Sprague-Dawley normotensive rats as a second control group. (Of course the parallel problem for studies of childhood hyperkinesia exists. Should one use control groups comprising, say, conduct disorder or dyslexia as well as healthy children?)

Sagvolden et al. (this volume) have taken these problems into account and with careful and persistent work shown that an analysis of the response patterning of SHR and hyperactive children does hold promise. Both groups show deviant responding, the nature of which depends on the schedule of reinforcement (e.g., interval schedules). It is stimulating and relevant that Sergeant and van der Meere (this volume) reported that the performance of hyperactive children is particularly sensitive to variable interval schedules. Here there is clearly a phenomenon that is modelled and one eagerly awaits the results of investigations of the biological variables controlling this type of appropriate response organization.

Crucial investigations of the future on the role of psychostimulants in the model must take into account regional as well as general changes of CA metabolism. Biochemical changes may be region specific and some relevant changes may be specific to a particular developmental period (cf. Sutterer et al., 1984; Oades, 1987). The comparison of these regional and developmental changes with situation-specific task performance is one of the exciting challenges for the development of the SHR model.

Yet there remains plenty of scope for comparative study of the SHR with other hypertensive animals (e.g., Bareggi, Becker, Ginsberg, & Genovese, 1979; Denoroy, Sautel, Schlager, Sacquet, & Sassard, 1985) and non-hypertensive strains of rats (e.g., Naples excitable strains, Sadile, Cerbone, & Cioffi, paper presented at the Workshop on Attention Deficit Disorder, Oslo, 1987). Such comparisons might help to distinguish the relevant from the irrelevant features of the hypertensive model.

### Comparative Models

The comparative approach to the study of the underlying biological mechanisms

has seldom been invoked for childhood psychiatric disorders. More often a range of disorders is cited for the distinguishing features. To be sure, for example, in Tourette's syndrome there are tics and language problems and in the Lesch-Nyhan syndrome there is self mutilation, in addition to involuntary motor impairments. But children with such syndromes often show learning disabilities and have difficulty in maintaining vigilance, motivation and effort (see Messiha & Carlson, 1983; Kelley & Wyngaarden, 1983 for reviews).

In Tourette's syndrome there can be both hyperactivity and reduced attention span (Fisarova, 1976). Certainly there have been comparative studies which showed no overt brain damage and impairments in path tracing, distractibility and performance of the digit-symbol sub-test of the WISC-R (Harcherik, Cohen, Ort, Paul, Shaywitz, Volkmar, Rothman, & Leckman, 1985; Harcherik, Carbonari, Shaywitz, Shaywitz, & Cohen, 1982). On the whole the problems were present in a milder form than in ADD. Reminiscent of ADD - DA, NA and opioid dysfunctions are implicated (see reviews, Sandyk, 1985; Caine, 1985; Haber, Kowall, Vonsattel, Bird, & Richardson, 1986). But reminiscent of childhood autism and the mirror image of ADD, - neuroleptics (and clonidine) are helpful in 80% of cases, whilst methylphenidate is likely to precipitate the condition (Sandyk, 1985).

The waxing and waning of behavioral symptoms in Tourette's syndrome may have more in common with Parkinsonism and striatal dysfunction than ADD. But potential dysfunctions of the mid-brain tegmentum (Devinsky, 1983), amygdala and cerebellar cortices (Haber et al., 1986) suggest closer comparisons with ADD and autistic subjects than has yet been sought. As I have suggested elsewhere (Oades, 1987), such comparisons would serve to sharpen our perception of the relationships between anatomical projection systems and their function or dysfunction.

## CONCLUSIONS

In looking at the present understanding of the biological features associated with the "hyperactive syndrome" and the way experimental manipulations of animals illuminate these changes, one must remark that progress has been made in the last ten years. Two important changes have been the rejection of the concept of minimal brain dysfunction and the study of hypertensive animals. Yet an understanding of what features make up the important symptoms and how the relative efficacy of psychostimulant therapy can be explained remains woefully inadequate.

Studies of the hyperactive syndrome have been blinkered by giving inadequate attention to the detailed biochemical and behavioural differences between the responders and non-responders to psychostimulant treatment. As argued by Sagvolden et al. (this volume) new behavioural studies would be well advised to look at situations that can be structured for both children and animals to facilitate the

type of dissection that is only appropriate for animals (e.g., correlates of learning strategies and learned inattention). For studies of children and of animals the adequacy of comparison groups should be more seriously questioned.

Studies of the effects of psychostimulants on monoamines and resultant behaviour require both methodological and quantitative refinement. They should be extended to include interactions of monoamines with brain damage (e.g., neo/archicortex) and other neuromodulators (e.g., peptides). In animal models there is scope for expanded studies of region specific differences and the trophic effects of CAs and CA agents. Within the next ten years both a broadening and a refinement of our knowledge of the biology of childhood hyperactivity and the attention-related problems is likely to be achieved.

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