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The effects of growth hormone on attention in children with hypopituitary short stature

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THE EFFECTS OF GROWTH HORMONE ON ATTENTION IN CHILDREN WITH HYPOPITUITARY SHORT STATURE

Christopher M. Gillman

1983
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THE EFFECTS OF GROWTH HORMONE ON ATTENTION IN CHILDREN WITH HYPOPITUITARY SHORT STATURE

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in partial fulfillment of the requirements for the degree of Doctor of Medicine
ABSTRACT

This study considered the hypothesis that children who receive human growth hormone (GH) for the treatment of hypopituitary short stature are subject to disturbances in attention, activity, and the regulation of impulsivity phenomenologically akin to the DSM-III entity of Attentional Deficit Disorder (ADD). Suggestions of this sort arise from anecdotal reports from parents receiving GH and from the commonalities between the neurotransmitter systems implicated in the neural control of GH secretion and in ADD. The literature on these two areas is reviewed.

The study consisted of a double blind administration of GH and placebo to six subjects in a crossover design. Subjects were tested on a variety of paper-and-pencil and computerized attentional tasks and were rated by mood self-reports and teacher and parent ratings on a pretreatment basis and under both treatment conditions. Findings suggest the existence of a GH-associated attentional deficit (GH-AD) although small sample size makes the trends observed in our tests a tentative basis for definitive conclusions. Directions for further investigation are suggested.
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For my father —
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Exogenously-derived human growth hormone (GH) is used in the therapy of childhood growth failure due to GH deficiency, either of an isolated kind or in combination with other pituitary abnormalities. GH is presently in short supply and expensive, originating entirely from cadaveric pituitaries. The numbers of children who receive it are small. Idiopathic GH deficiency occurs in about one child in 5000 in the general population (Vimpani et al., 1977), i.e. about 2% of children below the third percentile in height for age (Crawford, 1981).

However, the recent development of recombinant DNA techniques for the production of human GH from E. coli promises that it may soon be available in much less restricted amounts. Moreover, it has recently been suggested (Crawford, 1981; editorial [Lancet], 1981) that the constituency of children appropriate for GH treatment may be ten times as large as those for whom it is presently indicated. From among children with normal variant short stature (NVSS; a group that represents 30-50% of those below the third percentile on the growth charts), Rudman et al. (1981) have identified a proportion estimated at 15-30% whose anabolic and linear responses to GH are in the same range as those of children with GH deficiency. While this group of NVSS children has normal levels of plasma GH by radioimmunoassay (RIA) both at baseline and in response to standard provocative tests, levels by the more sensitive
radioreceptor assay are low, as are immunoassayable somatomedin-C levels. A prompt elevation in somatomedins and rapid growth are provoked by the administration of exogenously-derived GH. Presumably these children represent those whose NVSS can be attributed to a conformational abnormality in their native GH molecule but the retention of normal tissue sensitivity to conformationally sound GH. These developments in both indications for and availability of GH suggest the likelihood that the number of children treated with GH will be significantly augmented in the near future.

Under such circumstances, it would be useful to understand any possible complications of GH therapy. Little is known about the possible behavioral effects of its administration. Anecdotal reports (Dr. B.A. Shaywitz, personal communication) have suggested that children receiving the hormone for short stature may be subject to disturbances in attention, activity and regulation of impulsivity phenomenologically akin to the syndrome known as Attentional Deficit Disorder (ADD). This syndrome is the most common behavioral abnormality in school-age children, affecting an estimated 5-10% of this group (S.E. Shaywitz et al, 1978). Clinically, ADD is characterized by a variety of disturbances in attention and impulse control; a subset (ADD-H) show hyperactive motor activity as well. The syndrome has a long history under such designations as minimal brain dysfunction (MBD) and hyperactive child syndrome, but its etiological and pathogenetic status have remained unclarified. Recent evidence
discussed below from epidemiological, pharmacological and clinical studies in children as well as investigations with animal models of the disorder has led to the suggestion that irregularities in CNS neurotransmitter (NT) function may be central to the manifestations of the syndrome in affected children.

Evidence from both human and animal studies, discussed below, indicates that alterations in various monoaminergic brain systems affect the secretion of GH. As these are the same NT systems implicated in ADD, it may be reasonable to view them as a nexus of possible connections between the interactions of GH with the CNS on the one hand and the symptoms of ADD on the other. This notion has served as a central impetus for the present study of the attentional capacities of children receiving GH for the treatment of short stature.

The CNS stimulant methylphenidate (MPH; Ritalin®) is often a principal component of the treatment approach to children with ADD, despite concerns in both the medical and the at-large community over risks of drug toxicity and dependency and misgivings that a pharmacological approach may "oversimplify a complex problem, ignoring perhaps remediable social and educational efforts" (S.E. Shaywitz et al, in press; Douglas, 1980). The notion of the involvement of the GH axis with the brain systems affected by the stimulants used in treating behavioral difficulties receives support from the growth suppression noted in children chronically treated with high-dose
stimulants (Hunt et al, 1982). Moreover, in a recent study (S.E. Shaywitz et al, in press) which demonstrated a correlation in ADD children between plasma MPH levels and degree of improvement on behavioral measures as well as between the biological half-life and previously-described "behavioral half-life" of the effects of the drug, plasma GH peaked in parallel with MPH levels. In combination with a dip in prolactin, this led the authors to conclude that MPH probably affects these hormone levels by virtue of its dopamine (DA) agonist properties, which may also account for the drug's effectiveness in ADD. Gualtieri et al (1981) also demonstrated a rise in circulating GH in response to single-dose MPH administration to children with ADD-H, adults with the DSM-III diagnosis of "ADD, residual type" (American Psychiatric Association, 1980) and normal adult controls. The GH increment was correlated with MPH levels in all groups and was dose-related in the children.

So serum GH may be taken as an indication of the central effects of a "probe" such as MPH on monoaminergic systems -- at least specifically in the hypothalamus and tuberoinfundibular system -- and, at least indirectly, on attentional behavior (Young et al, 1982). One might expect differential behavioral responses to MPH to be reflected in the sensitivity of GH responses to another provocative stimulus like clonidine after MPH treatment, as recently demonstrated (Hunt et al, 1982); or in the degree of GH response to the drug itself. In this light is noted the report that GH release in seventeen normal males
following MPH administration was highly correlated with their subjectively experienced euphoria (Brown, 1977). Indications that GH may in this way provide valuable information on CNS function may prove useful especially if the population clinically diagnosed as having ADD is heterogeneous from a neurochemical point of view, although differential response to MPH might just as well indicate pharmacokinetic heterogeneity. Recent studies (reviewed in Hunt et al, 1982) show variations in peak time and peak levels of MPH after single-dose administration to ADD children. Failure to achieve an early peak level may mean diminished effectiveness of the drug, since its major effect seems to be the rather prompt facilitation of the release of stored catecholamines (CAs). Persistent MPH levels (as opposed to prompt peaking) were not correlated with persistent clinical effects in this study.

The relationship between possible biochemical and social/emotional influences on behavioral problems associated with hypopituitary short stature is poorly understood. As Rotnem et al (1977, 1979) have shown, GH replacement therapy is often perceived as a failure relative to expectations of both these children and their parents. The authors describe a pattern of problems in the regulation of self-esteem, socialization and the modulation of anger and aggression in twenty-five of these patients studied during and after a year of GH therapy. Abbot et al (1982) found that the intelligence and academic achievement of a group of GH-deficient children were independent of their
condition of hypopituitarism but that their subjects demonstrated a lag in the development of visual-motor integration skills on paper-and-pencil tasks. However, they cautioned that the small sample size and heterogeneity of their group make their results tentative.

Steinhausen & Stahnke (1976) studied psychological parameters in children with short stature, comparing groups with and without GH deficiency. While concluding that there was a similar occurrence of psychological alterations in both groups which should thus be attributed to the subjects' short stature rather than to any endocrine effect, they did note the increased incidence in the hypopituitar group of behavioral symptoms of the "psychoendocrine syndrome" including disturbances of appetite and thirst, hypersensitivity and impulse reduction. The latter occurring in response to a GH deficit is of particular note to the present focus on the relationship between exogenously supplied GH and ADD-like symptoms which include increased impulsivity. Clopper et al (1976) found deficits in "pair-bonding behavior and socializing" in post-pubertal hypopituitary patients without hypogonadotropinism who had completed a course of GH replacement therapy. While favoring an interpretation of these deficits as a response to their stilted social environment, the authors do not rule out the possibility that deficient pituitary function may be an adjunct to a deficit in adjacent hypothalamic pathways which participate in "the special type of pair-bonding and mating behavior known as falling in love," as they put it; or
that the lack of GH may prevent a postulated prenatal interaction with gonadotropins on the neural substrate necessary for the patterning of pair-bonding and erotic behavior.

While these behavioral effects of GH deficiency or GH replacement in short-statured children are not strictly in the realm of the modulation of attention, it is not unreasonable to expect such effects mediated by alterations in monoaminergic systems which are spread widely through the CNS to be broad or varied in appearance and scope. Moreover, the bounds of the psychological concept of attention are imprecise (Koella, 1978; Douglas, 1980) and such a basic psychological system as attention is of course implicated in the performance of a constellation of cognitive and behavioral operations.

It is unclear whether the ADD-like disturbances attributed to children receiving GH are produced de novo in an otherwise healthy child by some direct or indirect effect of the hormone, or whether the hormone injections evoke a preexisting disturbance, perhaps related to long-standing GH deficiency, which might or might not be subtly manifest in the performance of these children even when they are not taking GH. The present study will investigate these questions by characterizing both the baseline and post-treatment (GH and placebo) performance of a group of GH-deficient subjects on multiple measures of attentional processes.

The significance of a consideration of GH is not without precedent in the study of other behavioral disorders. The diminished GH response to various provocative stimuli in severe
depression is well-established and taken to support the monoamine hypothesis of the pathogenesis of certain types of affective disorder (Charney et al., 1982a, 1982b; van Praag, 1978; de la Fuente & Wells, 1981; Brown et al., 1978). Emotional deprivation (reviewed in Money et al., 1976; Brown, 1976), anorexia nervosa, stress disorders, and alcoholism (de la Fuente & Wells, 1981; Brown et al., 1978) have all been associated to various degrees with meaningful alterations in GH level or response. Janowsky et al. (1978) have even examined specific MPH-induced changes in GH in other diagnostic groups such as schizophrenics and drug abusers. However, the necessity of controlling for the effects in these studies of such confounding factors to GH as estrogen status, age and nutritional status has been cautioned (Halbreich et al., 1982; Brown et al., 1978). Nevertheless, a convergence of neuroendocrine and neurotransmitter lines of research in psychiatry would seem to have significant value.

Thus this study employs a variety of measures shown to be sensitive to ADD and to drug-related improvements in the clinical status of ADD children. These measures of attention are applied here to the study of attention deficits in children receiving GH for the treatment of short stature secondary to GH deficiency. The study, its findings and their implications are discussed in chapters 5, 6 and 7 after introductory reviews of the literature on the interaction of GH and the CNS (chapter 2), the nature of the deficits in ADD (chapter 3) and current thinking about its biological substrate (chapter 4).
GH is a species-specific pituitary peptide hormone of 191 residues whose actions, largely mediated at the tissue level by somatomedins, increase lineal growth as well as regulating various metabolic processes. The latter category of action includes "insulin-like" acute effects (stimulating amino acid and glucose uptake peripherally) and "diabetogenic" delayed effects (Frohman, 1981). Activity resides in fragments from several portions of the molecule, and forms of GH with molecular weights larger than the basic molecule have been described both in the pituitary and in the circulation. The hormone is primarily cleared by the liver, with a serum half-life on the order of 20-25 minutes and an average clearance of 110 ml/m²/min. Secretion averages from 350-500 microgram/m²/24h are noted (Frohman, 1981). Fig. 1 (reproduced from Table 7-4 in Frohman, 1981, p. 170) summarizes the various physiological and pharmacological influences on GH secretion.

The secretory pattern of GH, under a complex interaction of stimulatory and inhibitory influences, is basically pulsatile. In humans and animals, the burst profile -- a sharp onset with a decline suggestive of the known half-life of the hormone -- implies a brief duration of active secretion (Martin, 1976). The bursts are independent of fluctuations in corticosterone, prolactin and TSH levels (Martin et al, 1974a).

Development of a RIA for plasma GH has allowed extensive
investigation both in lab animals and human subjects of the factors controlling and influencing its secretion. Several excellent reviews of these studies exist (Martin, 1974, 1976; Muller, 1974). I will summarize the picture which emerges from this work.

Basal GH levels in fasting rested adults are <2 nanograms per ml. Because this basal level is often near the lower limit of detectability in the assays employed (Frohman, 1981), inhibitory effects which may act on the tonic level are sometimes hard to demonstrate without the concomitant use of a stimulatory agent. An additional problem is created by the stress-responsiveness of GH levels, necessitating stress-minimizing experimental conditions (Krulich, 1979). Furthermore, there are important species-related differences in GH responses to many stimuli (Martin, 1974), best characterized with regard to stress. In man and other primates, stress provokes an increase in circulating GH although not as great as the rise in prolactin. In contrast, rodent GH levels fall in response to stress and the dog and pig apparently show little or no stress-provoked GH response (Martin, 1976).

Such a secretory pattern, consisting of bursts superimposed on a baseline, especially when the frequency of bursts is age-dependent, adds to the difficulty of assessing the effects of stimulating agents. It appears that the major part of the acute physiological stimulation of GH secretion is accounted for by sleep, exercise, stress and postprandial insulin-induced
hypoglycemia as well as a residuum of "spontaneous" bursts (Martin, 1976). Physiological variations in glucose, free fatty acids and amino acids do not appear to be important, and Martin concludes (1976) that glucose homeostasis probably does not represent a teleological reason for the GH system. However, these substances in pharmacological magnitudes are significant, and their effects are summarized in a review by Martin (1976).

With these provisos in mind, it is possible to derive much information about the neural control of GH secretion from several types of investigations. With the ability to selectively lesion hypothalamic nuclei without concomitant damage to the median eminence (ME) and hypothalamic-pituitary portal circulation, several features of the hypothalamic influence on pituitary GH secretion were elucidated.

In rats, lesioning the hypothalamic ventromedial nucleus (VMN) was shown to decrease both pituitary and circulating GH levels; levels were inversely correlated with lesion size (Frohman & Bernardis, 1968). Martin et al showed that it is the pulsatile GH release that these lesions affect (1974a); pituitary levels were not always affected (Martin et al, 1975b). [There is evidence (discussed below) that tonic levels and pulsatile secretion are controlled separately, perhaps by differing NT systems.]

Without affecting basal GH levels, lesions of the ME in monkeys prevented insulin-induced GH release (Abrams et al, 1966) and the GH response to capture and ether anaesthesia. In
contrast, lesions to the monkey optic chiasmatic area enhanced the GH response to ether stress, presumably by the removal of an inhibitory tone (Brown et al., 1971). Rats who had had their medial-basal hypothalamus surgically isolated demonstrated an increase in linear growth and markedly elevated non-stress plasma levels of GH (Mitchell et al., 1973).

The evidence gained in lesioning studies has found corroboration in experiments which applied electrical stimulation directly and selectively to various brain areas. Stimulation of the rat VMN, the adjacent arcuate nucleus and the ME induce prompt increases in plasma GH (Frohman et al., 1968b; Martin, 1974) and other hypothalamic sites are thoroughly ineffective. [This includes the supraoptic; thus vasopressin, which Martin notes has been shown to be released by supraoptic stimulation, does not despite long-standing suspicions function as a physiological CRF.] The implication of these studies is that the VMN/arcuate system represents a final common pathway mediating CNS control of pituitary GH secretion. Electrical stimulation studies have also shown hypothalamic anatomic specificity for the regulation of the other individual anterior pituitary hormones (Martin, 1976).

Electrical stimulation of the hippocampus (HP) and amygdala of the rat have varying positive and negative effects on GH release, presumably via their efferents to the VMN (Muller, 1974). A wide variety of points in the dorsal and ventral HP augment plasma GH levels in comparison to sham-stimulation or
stimulation of adjacent cortical areas (Martin, 1972). Stimulation of the basolateral amygdala (BLA) in rats produces a GH response equivalent to VMN stimulation and blocked by bilateral VMN lesions (Martin, 1974), indicating that the BLA effects are mediated through the latter.

Martin has also shown (1976) that the inhibitory effects of corticomedial amygdala (CMA) stimulation are comparable to those of preoptic stimulation, suggesting mediation of CMA effects by the latter via the stria terminalis. Interruption of the stria has been shown to increase circulating GH levels and lateral growth in rats (Mitchell et al., 1972). Overall, the data point toward the limbic system as a modulator of basic GH release processes.

Hypothalamic influences on the pituitary secretion of GH are mediated chemically through both releasing and inhibiting factors in the portal circulation. Both releasing and inhibiting factor activities can be demonstrated in various hypothalamic preparations with bioassay systems (see reviews in Guillemin, 1974; Muller, 1973) and, as this discussion will show, the evidence points toward a physiological role for both in in vivo GH release.

Krulich et al. (1972) showed that growth inhibiting factor (GIF) activity by bioassay is confined within the hypothalamus to the ME, VMN, preoptic and arcuate; and growth releasing factor (GRF) activity to the lateral VMN. Within the ME, GIF localized to portal capillary nerve terminals (Pelletier et al., 1974).
Soon after the isolation and synthesis of somatostatin (SS) by Guillemin and associates (Brzeau et al, 1973) it was shown to prevent the GH response to electrical stimulation of the VMN and ELA after subcutaneous or intravenous introduction in rats (Martin, 1974). SS represents only one of several bioactive GIF fragments, so there may be other hypothalamic substances with GIF activity (Martin, 1976). However, the implication of SS in the neural mediation of GH inhibition has steadily been elaborated. In rats, electrical stimulation of the preoptic area, which decreases GH, leads to increased SS in the portal circulation; stimulation of the VMN does not change portal SS levels. The preoptic area has been shown to have a high incidence of cell bodies of neurons which project directly to the ME and use SS as a NT. In contrast, the SSergic neurons also found in the VMN do not project to the ME (Arimura and Fishback, 1981). A short review of SS effects (Martin, 1976) indicates that it inhibits GH release secondary to phenobarbitol, thorazine, morphine (rats); L-dopa (humans, primates, dogs); insulin-induced hypoglycemia (man, primates); arginine, and sleep (man), with no effects on levels of any other pituitary hormone.

It remains, however, that the predominant influence of the brain on GH secretion, as inferred primarily from stalk section and hypothalamic lesion studies, is stimulatory (Martin, 1976). Nevertheless, the substance associated with bioassayable GRF activity has not been characterized in hypothalamic extracts or pituitary portal blood. One confounding factor may be the GIF
activity in the same fractions. In any case, the evidence is consistent with control by a physiological GRF and not just by GIF and its inhibition (Martin, 1976); see below for an elaboration of this point. The isolation, characterization and biosynthetic replication of a GRF from an acromegaly-inducing human pancreatic tumor has recently been reported (Guillemin et al., 1982). While it has been difficult to collect enough hypothalamic GRF to characterize and compare structurally with the tumor-derived product, it is noted by the authors that other ectopic tumor-produced active peptides have been found to be identical to the physiological product (or a fragment of it) whose effects they duplicate.

In contrast to physiological regulators of GH release, most investigators have utilized pharmacological stimuli in an attempt to focus in on the monoamine NT systems implicated in GH regulation. L-dopa, a precursor of both dopamine (DA) and norepinephrine (NE) which crosses the blood-brain barrier, increases circulating GH levels in patients with Parkinson's disease (Boyd et al., 1970) and in normal volunteers (Cavagnini et al., 1972). This effect is blocked by phentolamine, an alpha-adrenergic blocker (Kansal et al., 1972) and potentiated by beta-adrenergic blockade with propranolol (Muller, 1974). Alpha-blockade has also been shown to prevent the rise in GH consequent to ECT in psychiatric patients (Vigas et al., 1976), arginine (Buckler et al., 1969), insulin-induced hypoglycemia, vasopressin and exercise (Muller, 1974). Muller also showed facilitation of
these effects by beta-blockade.

Clonidine, a central alpha-agonist, increases GH levels (Lal et al, 1974, 1975a). Because clonidine's alpha-adrenergic activity also stimulates peripheral glucagon release, thus raising plasma glucose, its central effect on GH may be somewhat antagonized in vivo and actually even more intrinsically powerful than observed (Martin, 1976). Noradrenergic involvement in GH regulation is further supported by the observed GH response to electrical stimulation of the rat locus coeruleus, the origin of NE tracts to the medial hypothalamus (Martin, 1974); and to intracerebroventricular (icv) NE in rats (Vijayan et al, 1978). Alpha-blockade with phenoxybenzamine as well as the administration of alpha-methyltyrosine (a-MT, a competitive inhibitor of tyrosine hydroxylase leading to central DA and NE depletion) abolish pulsatile secretory surges in rats; GH release after a-MT can be restored with clonidine but not with apomorphine, a DA agonist (Martin et al, 1978). The implication is that NE represents the major secretory driver (Krulich, 1979).

Willoughby & Day (1981) showed that the GH secretory pattern, abolished in rats by icv 6-hydroxydopamine (6-OHDA, a neurotoxin which destroys presynaptic catecholamine [CA] terminals), returned to normal by day 7 after 6-OHDA and could then be suppressed by alpha-blockade with phenoxybenzamine but not by the DA-antagonist butaclamol. So either NE is more important than DA or DA control had not recovered so rapidly. The former interpretation was favored by the fact that butaclamol
at day 7 was effective in increasing prolactin levels, an observation consistent with the intactness at that stage of DA mechanisms which affect prolactin secretion.

A number of studies address the question of the locus of NE actions in the control of GH secretion. Release of the hormone in response to direct stimulation of the rat VMN is not prevented by pharmacological manipulation of NE (or DA or serotonin, 5-HT) but the response to stimulation of the HP or amygdala was prevented by reserpine (Martin, 1972), a-MT (Martin et al, 1973), alpha- (but not beta-) adrenergic blockers, and para-chlorophenylalanine (PCPA, an inhibitor of 5-HT synthesis) (Martin, 1976). It seems clear that it is these higher influences on the hypothalamic GRF- and GIF-producing neurons, viz. the influence of the limbic system, that is mediated by alpha-receptors. Guillemin et al (1982) note that the newly-characterized ectopic GRF causes GH secretion in rats with VMN lesions as well as in normal animals.

Dopaminergic involvement in GH regulation is also evident. Martin (1972) showed a GH response to electrical stimulation of the ventral tegmental area of Tsai around the interpeduncular nucleus in the rat (the site of the DA cell bodies of tracts to the higher brain). Icv DA (Vijayan et al, 1978) and systemic apomorphine in small doses (Mueller et al, 1976) were both effective stimuli for GH release in the rat. Willoughby et al (1977) showed that the DA receptor blocker butaclamol decreases the GH pulse amplitude but not its frequency or pattern. In contrast, Stewart et al (1981) found that while alpha-blockade
in baboons decreased tonic serum GH levels but maintained discernable but small peaks at the usual frequency, a-MT increased peak frequency while decreasing circulating GH levels. Because of its simultaneous stimulation of prolactin, the authors conclude that this a-MT effect acted via a decrease in DA and that DA is an inhibitor of pulsatility. Pimozide, a DA receptor blocker, also increases pulse frequency, they note, in patients with diabetes mellitus. In the rat, Willoughby & Martin (1976) report that hypothalamic deafferentation which produces an isolated medial basal hypothalamus allows persistent episodic secretion with normal peak amplitude and normal or increased frequency. Such deafferentation results in unmeasurable hypothalamic NE levels but maintains normal DA concentrations. 5-HT levels are also significantly reduced, suggesting to the authors that if 5-HT plays a role it is only modulatory. The isolated medial basal hypothalamus also, incidentally, supports the pulsatile secretion patterns of other anterior pituitary hormones, bolstering the hypothesis that this small area contains a number of neural pacemakers.

In monkeys, L-dopa and clonidine evoked a GH response but apomorphine was effective only in emetic doses (Brown et al., 1973). Because this was accompanied by a simultaneous rise in cortisol, the authors attribute the apomorphine results to the effects of emesis-associated stress.

In humans, apomorphine is effective without an associated rise in cortisol and in subemetic doses (Lal et al., 1972, 1975b).
Haloperidol (Haldol®), a DA antagonist, blunts the insulin-hypoglycemia-induced GH response (Kim et al., 1971). Bansal et al. (1981) showed evidence for dopaminergic effects on GH secretion both at the level of the hypothalamus and the ME-pituitary (respectively inside and outside the blood-brain barrier). GH response correlated with circulating L-dopa or DA levels after oral administration of L-dopa, but not after L-dopa plus carbidopa (a peripheral decarboxylase inhibitor which therefore allows only central conversion of L-dopa to DA and therefore preferentially elevates central but not peripheral DA levels). DA infusions, which act only peripherally because DA itself does not cross the blood-brain barrier, also cause GH release but the authors conclude that central stimulation is more important since the GH response during GH infusion was less despite higher peripheral DA levels than after L-dopa administration.

However, because of the ability of DA to displace 5-HT from cerebral stores (Ng et al., 1970), central dopaminergic influences may act via 5-HT release. 5-hydroxytryptophan (5-HTP), a 5-HT precursor, elevates GH in rats (Smythe et al., 1975), monkeys (Chambers & Brown, 1976) and humans (Lancranjan, 1977). Icv 5-HT and quipazine (a 5-HT receptor agonist) increase GH in rats; their effect is prevented with methysergide (Vijayan et al., 1978). Oral 5-HT, 5-HTP, or L-tryptophan increase plasma GH in man (Imura et al., 1973). Carcinoid-induced increases in 5-HT in humans stimulate GH release (Feldman & Lebovitz, 1972). The 5-HT receptor blockers methysergide and cyproheptadine block the GH
response to insulin-induced hypoglycemia (Bivens et al, 1973; Smythe & Lazarus, 1974) and sleep-related GH release (Chihara et al, 1976) as does imipramine, a tricyclic antidepressant which inhibits 5-HT and NE reuptake (Muller, 1974).

The possible GH-suppressing effect of imipramine-induced 5-HT excess is supported by the data suggesting that 5-HT synthesis blockade by PCPA may suppress REM sleep. Because this stage of sleep is associated with GH inhibition, its suppression allows increasing circulating GH levels. Reversal of the REM-inhibition of GH secretion can be obtained with the 5-HT precursor 5-HTP (Sassin et al, 1969; Wyatt et al, 1969). Thus, 5-HT may be inhibitory to sleep-associated GH release. This contrasts with animal studies which show that the serotonergic Raphe nucleus is involved in the initiation of SWS in cats (Jouvet, 1969) and rats (Martin, 1976) and that PCPA inhibition of 5-HT or Raphe lesioning lead to insomnia or decreased SWS. SWS has commonly been associated with the spontaneous nocturnal GH surge although a review by Martin (1976) of the human data finds this association less compelling than generally accepted.

If 5-HT pathways are involved in GH regulation, then they too are located at a higher level than the VMN-mediated final common pathway, as suggested above in the discussion of the hypothalamic deafferentation findings. PCPA blocks the GH response to electrical stimulation of the ELA but not the VMN (Martin, 1974).

Recent research has implicated other NT systems, to which
attention has more recently been turned, in GH regulation. The opioid peptides beta-endorphin, met-enkephalin and analogues stimulate GH secretion in rats. Naloxone and naltrexone both block opioid-induced GH secretion and decrease basal GH levels (reviewed in Martin, 1976). Katakami and colleagues (1981) have shown that alpha-adrenergic blockade (but not beta- or DA-blockade), reserpine and DBH antagonists prevent opioid-induced GH release in rats, indicating alpha-mediation. Furthermore, beta-endorphin reverses phenoxybenzamine suppression of GH release. Erikkson et al (1981) showed that morphine-induced GH release in the rat is potentiated by clonidine, prevented by yohimbine and reserpine, and that the reserpine-based antagonism is countered by pretreatment with tetrabenazine (which prevents reserpine monoamine depletion). Haloperidol and PCPA had no effect on this morphine-induced GH secretion. Substance P and neurotensin stimulate GH release, effects that are blocked by histamine-H1 receptor blockade but not by opioid receptor antagonists (reviewed in Martin, 1976).

The lack of a specific target gland for GH secretion suggests that it might act on pituitary or hypothalamic receptors to autoregulate its own secretion, either directly or through an intermediary. Elucidation of the mechanism of such an effect of GH on the CNS would be of particular interest to the current investigation of the possibility that the administration of exogenous GH may affect such CNS functions as the modulation of attention. In the rat, GH infusion or implant or the transplant
of GH-producing tumors block the GH response to insulin-induced hypoglycemia (Müller, 1973). ICV GH acts centrally to decrease circulating levels and pulse amplitudes of GH, in contrast to ICV saline control (Tannenbaum, 1980). In the monkey, Sakuma & Knobil (1970) showed that a two-hour i.v. infusion of GH also inhibits GH secretion in response to insulin, as does six days of GH administration to humans (Abrams et al, 1971). The GH responses to exercise and arginine were shown to be inhibited by the pre-existing elevation of circulating GH consequent to a prior provocative stimulus or to direct i.v. GH infusion (Hagen et al, 1972). These studies suggest both central and peripheral negative feedback effects of GH but the question remains open as to the physiologic sites of action. The ME is an obvious candidate because of its position so-to-speak astride the blood-brain barrier (Weindl & Joynt, 1972). Tannenbaum (1980) suggests the possibility of retrograde transport in the pituitary stalk vasculature, which has been demonstrated for other pituitary hormones; and Passaro et al (1982) have shown that ICV GH seeps across the blood-brain barrier and into the hypophyseal portal system to act directly on the pituitary somatotrophs.

It is likely that at least one mechanism of this negative-feedback autoregulation is a "short loop" via hypothalamic SS. In rats, ME SS is depleted by hypophysectomy-induced GH depletion and restored following the administration of exogenous GH. i.v. and ICV GH administration to rats increases SS concentrations in the hypothalamus and hypophyseal portal blood and in vitro GH
administration releases SS from incubated rat hypothalamic tissue (reviewed in Tannenbaum, 1980).

But there are also suggestions of a "long-loop" feedback via tissue-produced somatomedins. Laron et al (1966) showed increased plasma GH in children unable to make somatomedins, the so-called Laron dwarfs. Rats infected with *Spirometra mansonioides* (a worm which induces somatomedin production and skeletal growth by the elaboration of a non-immunoreactive competitive inhibitor of GH) demonstrate decreased circulating GH levels (Daughaday & Garland, 1972). And *in vitro*, somatomedin-C rapidly stimulates cultured rat-hypothalamic cells to secrete SS. After a lag of about 24 hours, somatomedin-C will inhibit cultured rat-pituitary cell release of GH in response to GRF derived from pancreatic adenomas and also in response to dibutyryl cAMP (Berelowitz et al, 1981). If SS-mediated GH inhibition is time-limited secondary to down-regulation of SS receptors, it might be complemented by the delayed effect of somatomedin. This suggests that the latter's actions on the pituitary somatotrophs represent an alteration in cellular metabolism rather than simply a secretory block. Tannenbaum et al (1983) have recently demonstrated that icv administration of a somatomedin-rich preparation markedly reduces GH secretory episodes in rats while insulin and albumin have no such effects. Together with the findings of Berelowitz et al, this suggests an *in vivo* negative feedback loop via the inhibitory mechanism of hypothalamic SS release and perhaps additional inhibitory effects on GRF and/or direct pitui-
tary effects, in light of Passaro et al's (1982) above-mentioned demonstration of the rapid crossing of the blood-brain barrier by centrally administered peptides.

Martin (1976) observes that SS is widely distributed in the brain in a number of regions — preoptic, amygdala, cortical, thalamic, cerebellar, brainstem, cord and pineal — beyond the hypothalamus. Antidromic activation of ME SS terminals shows that many neurons whose axons synapse on the portal vessels have widely-reaching collateral axons in these other regions. These might represent recurrent feedback loops that might complicate our elucidation of the mediation of pulsatile GH secretion and/or might have other important effects on neurophysiological functioning and on behavior. Moss (1979) has reviewed the behavioral effects of SS in the CNS and concludes that it probably acts on a variety of systems as a general depressant of activity. Such properties might mediate the behavioral/cognitive effects of exogenous GH administration.

The GH response to rat VMN electrical stimulation, Martin (1974) found, is not a direct effect but a rebound phenomenon. In fact, longer periods of VMN stimulation cause an initial fall in GH levels prior to the post-stimulation rebound surge. Noting that the time course of this fall is consistent with the short (about five minutes) half-life of GIF, Martin (1976) suggests that VMN stimulation results in the simultaneous release of GIF and GRF with GIF dominance during the stimulation. This is followed by a rebound increase in GRF and/or decrease in GIF. In
contrast, BLA stimulation, which results in a concurrent GH release, stimulates VMM GRF release directly (without an inhibition-rebound cycle which would suggest mediation solely by GIF and its inhibition). Martin et al (1975a) showed furthermore that rat VMM lesions prevent the rebound GH response after a GH infusion, despite normal pituitary GH levels, further suggesting the physiological importance of GRF. Ferland et al (1975) showed persistent pulsatile GH secretion in rats treated with anti-SS antiserum, and episodic secretion blocked by the alpha-antagonist yohimbine was not restored by anti-SS treatment (Arnold & Fernstrom, 1980), further delineating presumed GRF functions. Anti-SS antiserum does not prevent the restoration by clonidine of pulsatile GH secretion abolished by reserpine pretreatment. The pulsatile pattern is not altered by anti-SS alone although this does elevate basal GH tone, suggesting that SS exerts a tonic inhibitory effect and GRF mediates pulsatility (Labrie et al, 1970; Eden et al, 1981).

Muller (1974) proposes that some of the cross-species differences in neural control of GH, including the direction of the effects of stress and the ambiguous direction of DA influences, might result from phylogenetic changes in the hierarchy of stimulatory and inhibitory centers acting via GRF and SS. Rice & Critchlow (1975) showed that preoptic lesions in the rat blocked the stress-induced inhibition of GH secretion and allowed the emergence of a stress-induced stimulation of GH. Eden et al (1981) note the evidence that this stress-induced
inhibition of rat GH is considered to be under SS control, since it can be prevented with anti-SS antiserum. Now that GRF has been isolated and characterized (Guillemin et al., 1981), it would be informative to do studies with anti-GRF antiserum analogous to those discussed above with anti-SS.
Chapter 3: ADD: The Nature of the Disorder

A characteristic behavior pattern in children which has elements of motoric hyperactivity, impulsivity, emotional lability, low frustration tolerance and other associated manifestations has long been recognized. Such a complex was first identified as a behavioral syndrome in the demonstrably brain-damaged and continues to be recognized in association with well-defined metabolic and traumatic encephalopathies. Until quite recently, investigators assumed that all exemplars in children of the behavior pattern corresponded to an inferred organ pathology which was defined somewhat circularly, even with the remarkably uniform failure to demonstrate morphological evidence of CNS damage, as "minimal brain dysfunction " (MBD) (reviewed in Shaywitz & Shaywitz, in press; Porges & Smith, 1980).

More recently, the diagnostic entity of "hyperactivity" or "hyperkinesis" has prevailed, in light of the centrality of parents' and teachers' typical complaints that these children are "always on the move" or "can't sit still." This focus in turn has been supplanted by the diagnostic category of attentional deficit disorder (ADD), as investigators have been persuaded that, despite being the most obvious, hyperactivity is nevertheless only one of a constellation of critical symptoms and is in fact less central than such problems as an inability to sustain attention and to control impulsive responding (Douglas,
1972) — in short, alterations to the quality as well as the more evident quantity of the child's behaviors. In fact, the impression of hyperactivity may itself be partially a byproduct of the fragmented and disorganized flavor of the behavior of these children (Douglas, 1980).

Current diagnostic criteria for ADD with hyperactivity (ADD-H) are stipulated in DSM-III (American Psychiatric Association, 1980) as including inattention (failure to finish or difficulty concentrating on tasks, inability to stay with a play activity, not listening, easy distractibility), impulsivity (a tendency to act before thinking, excessive shifts between activities, disorganization in work, needing supervision, difficulty awaiting turn in school and other group activities) and hyperactivity (excessive running, climbing or fidgeting, difficulty staying seated or still). A related diagnostic category of ADD without hyperactivity exists and embodies the criteria in the first two categories without those of hyperactivity.

Diagnoses in these categories are only applicable if the manifestations appear before the age of seven and have persisted for at least six months; these manifestations are not indicative of ADD in a patient with schizophrenia, affective disorder or severe developmental disorder. The male:female ratio for the diagnosis is in the range of 10:1 (American Psychiatric Association, 1980) and it should be noted here that most of the research data presented herein derive entirely from males, considered by most investigators to be more representative of the
syndrome. Henker & Whalen (1980) suggest that the antecedents, course and outcome for female hyperactivity may be different for those in males.

Typically, symptomatology in any given child with ADD varies with situation and time. Group settings or the demands for more organized and complex goal-directed behavior that occur in school may emphasize such a child's difficulties, or cause them to emerge. The fact that a child has such a problem may often not come to anyone's attention until (s)he begins to interact significantly with groups of peers and/or attend school although, as noted below, the converse -- a resolution of earlier problems under the influence of the experience of starting school -- may also be seen. Nonetheless, it is more common that the problem becomes more evident later than sooner and that a careful history at such a time may retrospectively reveal harbingers of a child's problems in earlier behaviors whose significance was not recognized at the time. One would expect this to be especially true where an affected child is an only or oldest child and the parents are inexperienced about the bounds of "normalcy" in childhood behavior. DSM-III stipulates that when teacher and parent reports conflict, precedence is due the former because of greater familiarity with age-appropriate norms (American Psychiatric Association, 1980).

Hunt et al (1982) summarize the phenotypic expressions and natural history of ADD. Its manifestations over a child's development may include: irritability and sleeplessness as an
infant; disorganized play and unusually frayed parental patience when the child is a toddler; the appearance in elementary school of primary perceptual problems, dyslexia or other specific learning disabilities; a delay in gross and fine motor coordination as shown in handwriting, athletics and other physical activities; disciplinary conflicts in the home, peer group, school and community, and resultant depression and low self-esteem by middle childhood. Although some may outgrow their ADD completely and the motoric hyperactivity usually diminishes to a manageable level of restlessness, others will be plagued as adults by severe impulsivity, personality disorders and antisocial and legal difficulties. Some forms of major affective disorder or psychosis may have ADD as their precursor.

In a four-year followup of 62 youngsters between 10 and 16 years old initially referred for symptoms of hyperactivity, Charles & Schain (1981) found that regardless of duration of stimulant intervention (which had ranged from <6 months to 4 years) symptoms of hyperactivity lessened but remained in a higher range than in normal peers. Underachievement in school was more pervasive than behavioral or social problems. This is only the most recent study in which the authors suggest that the benefit derived from stimulants occurs early in the course of treatment and that its limited effects are not "curative" without social, psychodynamic and educational interventions.

Douglas (1972) has reviewed the studies of specific disabilities found in ADD children's performance and suggested a
useful model of the underlying cognitive deficits. In general, ADD children show unimpaired functioning on IQ, language ability, comprehension, conceptual thinking and short-term memory. Disabilities which have been reported on such functions may be attributed to the use of measures which tap complex functions dependent on poorly-defined more basic abilities in combination, with high error variances (also see [S.E. Shaywitz, 1982]). Similar caution should be exercised in interpreting findings of poor gross or fine visual-motor coordination in ADD children on tasks which require care and concentration.

The nature and centrality of the motoric hyperactivity found in these children deserves consideration. Douglas notes that classroom observation studies revealing higher activity levels have found that these behaviors were "purposive" albeit not related to the classroom agenda. In contrast, no reliable differences on "fidgeting" in this setting could be discerned in the studies which she reviews. Hyperkinesis, while present in laboratory task settings, could not be negatively related to efficiency in attending as measured by performance on a variety of tasks. On many measures, the children's best responses were as good as those of controls, but they were more erratic overall. Continuous reinforcement minimized differences from controls while striking decay occurred with its removal or under partial reinforcement schedules.

A review of the confusing data on autonomic indices of arousal was consistent with the conclusion that there were no
differences between children with ADD and controls in tonic levels of general alertness or nonspecific arousal although other authors (Satterfield et al [1972, 1974] among them) have disagreed and found baseline deficits. Douglas feels rather that the data reflects decreased autonomic and EEG responsivity to specific stimuli. All in all, she finds the evidence suggests that ADD represents a concatenation of basic defects in three related processes -- the investment of attention and effort; the inhibition of impulsive responses; and the modulation of arousal levels in response to situational demands.

Although there is good consensus that a problem of attention is central to hyperactivity, the term is not used in anything approaching a uniform manner. A review (Douglas & Peters, 1979) of eleven studies concluded that there was no good evidence that the hyperactive child has a selective attention problem, i.e. distractibility in the sense of a "stimulus-bound" or "field-dependent" quality to perceptual skills consistent with a defective "filtering" mechanism in a model of attention like that classically associated with Broadbent (1958). Hyperactive children are much less distractible by outside stimuli than often suggested, unless the stimuli are highly attractive intrinsically to the child (Douglas, 1972).

On the other hand, the evidence is consistent with an impaired capacity for concentration or sustained attention which is observable even in reduced-stimulus settings, suggesting that it is not attributable to distraction by external influences.
For example, ADD children's reaction times are similar to those of controls if the experimenter elicits the attention of the subject prior to each trial but deteriorate if the subject is left alone with an automatically programmed task. Evidence from the distractibility studies does, however, suggest an unusual need for stimulation on the part of these children, which will be discussed below in the context of arousal modulation.

Attentional demands are closely linked with the necessity for inhibitory control over impulsivity, to allow a child to take a task seriously, remain effectively involved with it over the requisite time and avoid careless responses. A review of tasks on which hyperactive children do and do not perform well (Douglas, 1980; see Table 2 adapted from tables 11.1 and 11.2, pp. 288-90, of that work) shows that such tasks make similar demands on such processes as visual discrimination, auditory memory and speed of motor responses. However, a hyperactive child cannot succeed where the nature of the task or its administration does not reduce requirements for independent or sustained effort by the child (e.g., the difference between the picture completion subtest of the Wechsler Intelligence Scale for Children on which these children do well and the Matching Familiar Figures Test [MFFT] on which their impaired performance is well-documented and which is used in the current investigation).

While not differing in basal arousal levels, phasic arousal responses to situational demands in ADD children compare unfavorably with controls, as noted above. The evidence for an
impairment of arousal modulation is also suggested by the fact that the stimulant drugs useful in the treatment of ADD may be thought of as increasing arousal, although this may be true only for routine or "low-level" tasks and they may actually impair performance on more complex tasks involving learning or memory (Rapoport et al., 1980). Furthermore, the positive effects of reinforcement may act through increasing alertness on dull and repetitive tasks, although supraoptimal arousal can decrease performance through an augmentation of impulsive responding. Arousal problems may thus represent an unusually narrow range of arousal in which the child can operate effectively, causing a relatively small shift from optimal in either direction to result in a disproportionate performance decrement.

In this light, the reported distractibility of ADD children may represent stimulus-seeking behavior to maintain arousal. Motor restlessness may be seen as compensating by the substitution of kinaesthetic stimulation in situations of relative impoverishment of external stimuli. A reasonable level of "distracting" stimuli has been seen to improve ADD subjects' efficiency on tasks (Steinkamp, 1974; Bremer & Stern, 1976). Subjects look more often at task-irrelevant stimuli but they may not show a performance impairment as a result, and there is no demonstration of a negative correlation between performance level and attention paid to distractions.

A related process may be the ADD child's tendency to respond to the most striking or salient aspects of a stimulus situation
and fail to process more subtle or less obvious but task-
important aspects since the qualities of stimulus saliency
(novelty, intensity, incongruity, etc.) act to increase arousal.
This importance of novelty to the maintenance of appropriate
arousal may explain the recent finding that 89% of a group of New
Zealand children identified as hyperactive or defective in
attention at age three were reported to no longer have a problem
after one or two years of school (Chapel et al, 1982).

The longterm sequelae of these cognitive deficits of ADD are
suggested by Douglas (1980). Because less careful examination of
the environment leads to less organized and elaborated schemas
(in terms of which future perception and experience are orga-
nized), there may be limitations on future learning. This may be
particularly crucial with regard to metacognitive development,
the level of learning which Bateson (1972) calls "learning how to
learn," the abilities necessary to gain knowledge of the sort
which is not automatically attainable but which depends on self-
conscious deliberate and strategic effort. While as noted above
ADD children are able to respond very well to appropriate rein-
forcement, their repeated experience of failure through the in-
ability to remain involved in a problem long enough to learn
about or master it may leave them with no effectance motivation,
i.e. no interest in mastering problems for their own sake. How
promptly or thoroughly in the natural history of an ADD child's
cognitive development these higher-level factors may become sig-
nificant is open to question.
Chapter 4: The Neurochemistry of ADD

The diagnosis of ADD is an elusive one, given the syndrome's protean manifestations in almost all facets of a child's life, variations over the child's maturation and development, and the lack of definitive diagnostic signs or tests (S.E. Shaywitz et al., 1978). Indeed, the disease or syndrome model of the disorder has been called into question on the basis of the assumption that its manifestations correspond to a single underlying dysfunction or the presumed uniformity in its "phenotypic expression" (Porges & Smith, 1980). Neurochemical studies may be using a heterogeneous population. Henker & Whalen (1980) review the emerging consensus that the global rubric of ADD comprises groups of multiple symptom clusters and probable etiologies and that theoretically or conceptually correlated characteristics often fail to correlate, or show only modest relationships, empirically. One reflection of this is the emerging typology of ADD in DSM-III (American Psychiatric Association, 1980) which differentiates subsets with and without hyperactivity. Another is the possibility that different populations, generally considered interconvertible in the literature, have been studied under the changing rubrics of MBD, ADD, hyperactivity and even to some extent learning disability. A failure to find definitive neurochemical features would not be unexpected in the study of a neurochemically diverse population and would in turn feed back to maintain the failure to identify definitive diagnostic signs or
tests to refine diagnosis or subgrouping, in something of a vicious circle.

Cardinal symptoms, which as we have seen occur in combination with varying relative weights in different individual ADD cases, may arise from a single pathogenetic process or alternatively coincide as unrelated symptoms or perturbations in different NT systems which are not independent but whose interrelations are not subject to simple characterization. Furthermore, the nature of the relationship between observed behavioral and neurochemical dysfunctions is problematic — they may be coincident without a direct causal link or may be parallel in only a subset of children with such difficulties, or they may be indirectly linked through the mediation of other cognitive, emotional or environmental reactions. CNS defects may place a child "at risk" for etiological influence by specific situations, without themselves "causing" the deficits. As Shaywitz & Shaywitz note (in press, p. 19):

Scientific methodology itself tends to foster an oversimplified view of behavior...in which behavioral regularities are abstracted as general principles of behavior while any apparent aberration in expected outcome is ignored. Furthermore it is obvious that behavior has multiple determinants, thus necessitating a cautious approach when predicting or generalizing about the effects of a particular treatment or lesion on behavior.

As Henker & Whalen (1980) observe, the evidence that children with ADD have behavioral and physiological defects must be combined with a consideration of parental behaviors, social
system responses and other environmental factors to make "person-by-situation matrices" the prime research targets. Interactions of ADD children's behavior with the experimental or observational setting in which it is assessed are to be expected; indeed, as noted above in characterizing the syndrome, increased inconsistency of response within and between settings is the rule rather than the exception in ADD. Some investigators believe that a differentiation between "situational" and "true" or "transsituational" ADD is possible (Henker & Whalen, 1980).

Nonetheless, various lines of evidence converge on a delineation of the biological substrate of this syndrome. Shaywitz & Shaywitz (in press) have reviewed the studies that show that an increased incidence of perinatal diagnosis of minor congenital anomalies is associated prognostically with ADD-type difficulties at various ages, indicating an early prenatal insult or genetically altered embryogenesis. Congenital anomalies in neonates have also been associated with parental hyperactivity, and associated findings relate attention-related learning disabilities in school-age children with heavy maternal alcohol consumption during pregnancy. Fetal alcohol syndrome (FAS) is associated with minor congenital anomalies and growth deficiency; S.E. Shaywitz et al (1980) on this basis suggest an expansion of the scope of FAS to include behavioral and learning disabilities as manifestations of CNS involvement.

So-called "soft neurological signs" and nonspecific EEG abnormalities found in ADD also suggest a physiological substrate
(Hunt et al, 1982), although Lerer & Lerer (1976) showed that post-MPH improvements in these neurological indicators did not always parallel attentional and behavioral changes after the treatment. Of course the development of new neuroimaging technology including NMR and PET scanning renews hopes for the identification of CNS morphological correlates to ADD which have been sought so far unsuccessfully since the days of the "brain-damage" conceptualization of the condition.

Diverse familial studies reviewed by S.E. Shaywitz et al (1978) contribute to a biochemical hypothesis. A higher prevalence of childhood hyperactivity and increased prevalence of psychiatric disorders (sociopathy, alcoholism, hysteria, e.g.) in the parents of hyperactive children than of controls; increased prevalence of MBD in the biological but not adoptive families of adopted-away MBD children; increased incidence of both hyperactivity and subclinical increases in activity levels in the monozygotic (MZ) but not the dizygotic (DZ) twins of hyperactive children; and correlations between ADD children and their siblings when foster-reared apart, have been shown.

Satterfield et al (1972) review studies which suggest that the increased prevalence of psychopathology in the first-degree relatives of hyperactive children may be largely accounted for by a subset of the children and, intriguingly, that this subset may be equivalent to the clinical subset of stimulant-nonresponders (averaging about 30% in most series of hyperactives) and that of children who go on to antisocial disorders in adulthood. In
other studies (Satterfield et al, 1974) they distinguished hyperactives who were MPH responders and nonresponders on a variety of arousal measures such as skin conductance, cortical evoked response amplitudes, EEG slowing and nonspecific EEG abnormalities. These measures were predictors of treatment-responsiveness and also sensitive to MPH effects, supporting a model of MPH-responsive ADD associated with CNS underarousal and suggesting that the heterogeneity of the syndrome of ADD may ramify widely through genetic nature, outcome measures, treatment response and psychophysiology.

The evidence for many neuropsychiatric disorders suggests a relationship with abnormalities of biogenic amines, viz. serotonin (5-HT), dopamine (DA) and norepinephrine (NE). At least in the initial phases of the study of the relationship between a behavioral complex and the amine systems, most investigators tend to focus on absolute levels of function of individual NT systems, and studies of ADD are no exception. However, as Young et al (1982) indicate, if different NT systems subserve differing functions in the overall organization and ultimate integration of behavior, it may be the ratios of their metabolites rather than their absolute levels which relate most closely to aspects of behavioral disorganization. With this caveat in mind, one can look at the clinical studies in ADD children.

Urinary 5-hydroxyindoleacetic acid (5-HIAA; the major metabolite of 5-HT) was not different in groups of ADD children.
and controls (Wender et al., 1971); however, MBD children did show lower blood 5-HIAA levels in two studies (Wender, 1969; Coleman, 1971) and reduced platelet 5-HT relative to controls (Bhagavan et al., 1975). However, Rapoport et al. (1974) found similar platelet 5-HT levels in hyperactives and controls and no correlation between level of hyperactivity and platelet 5-HT level within the hyperactive group. Imipramine decreased 5-HT but had no behavioral effects while MPH did not alter 5-HT while ameliorating hyperactive behavior.

Less than 2% of the total body pool of 5-HT originates in the CNS (S.E. Shaywitz et al., 1978), confounding any efforts to assess brain 5-HT activity from peripheral observations, although some observers have justified looking at platelet 5-HT in light of demonstrated pharmacokinetic similarities with neuronal 5-HT. In any case, assessment of CSF amine metabolite levels should derive preferable information. The methodological problems with investigations of CSF metabolites, reviewed in Young et al. (1982), include the need for lumbar puncture(s), possible differences between ventricular and lumbar CSF composition, possible moment-to-moment variability in CSF constituent concentrations and differences in the contributions to CSF arising from different brain areas. Nonetheless, there is ample evidence supporting the notion that CSF metabolite levels reflect brain turnover of parent amines (reviewed in B.A. Shaywitz et al. (1980). The existence of a blood-brain barrier for amines should prevent peripheral contamination, and animal studies show that
pharmacological manipulations of brain levels alter CSF levels accordingly.

Two studies showed no abnormalities in CSF 5-HIAA levels of MBD children in comparison with controls (B.A. Shaywitz et al., 1977; Shetty & Chase, 1976), and in their review S.E. Shaywitz et al. (1978) conclude that the majority of investigations do not convincingly implicate 5-HT metabolism in ADD. Recent advances, however, such as improved platelet preparations and HPLC plasma assays (Hunt et al., 1982) may provide renewed impetus for further investigation of the relevance of 5-HT to ADD, especially in light of its presumed contribution to attentional processes through the midbrain Raphe nucleus' modulation or gating of sensory input (Young et al., 1982).

Initial interest in an association between the catecholamines (CAs) and ADD arose from the abundant evidence of the ameliorating effects of stimulant medications on ADD in light of the knowledge that their CNS effects were mediated predominantly by their actions on CA systems (stimulation of release; depression of reuptake; and inhibition of degradation by monoamine oxidase, MAO) (Wender, 1971, 1976). However, S.E. Shaywitz et al. (1978) caution that while stimulants affect parameters like activity level, attention, and distractibility, it is unclear if they improve learning. And Shaywitz & Shaywitz (in press) further observe the methodological difficulty of arguing for a CA-based pathogenesis of ADD on the basis of the effectiveness of stimulants known to work via CAs, likening it to the error of arguing
for an aspirin-deficiency theory of rheumatic fever on the basis of the effectiveness of aspirin in treating the disease. Furthermore, Rapoport & Ferguson (1981) note that some hyperactive children respond to DA antagonists rather than agonists. And Henker & Whalen (1980) review the evidence that the calming effects of stimulants on hyperactive children, if they are interpreted as secondary effects of increasing focal attention, may not be a "paradoxical" effect at all in light of a growing consensus that psychostimulants have similar effects (enhanced focusing and sustaining of attention, inhibition of extraneous responses, and increased ability to modulate behavior in accordance with situational cues) on normals.

For example, Rapoport et al (1980) compared normal and hyperactive boys and normal adult males in a double-blind crossover study of the effects of dextroamphetamine. Measures of motor activity, vigilance, autonomic indices of reaction time and performance on a learning task (all target symptoms in the treatment of ADD) were affected similarly in all groups, and differences between hyperactive and normal boys (a control group usually lacking in the studies which support drug-response-based speculations on the pathophysiology of ADD) were less striking than between hyperactive boys and adults. Thus they may represent age-specific rather than disorder-specific alterations in the responses of some CNS systems to the drugs, supporting the notion that there may be little justification for reasoning backward from treatment effects to etiological speculations.
While Parkinsonism was produced in adult victims as a sequela to the worldwide epidemic of von Economo’s encephalitis in 1917-18, childhood victims developed an ADD-like syndrome, suggesting the implication of a central DA disturbance in ADD. However, most clinical studies have been inconclusive with respect to a CA-ADD association when taken alone (S.E. Shaywitz et al, 1978) -- e.g. comparisons of urinary HVA or MHPG (respectively the DA and NE metabolites) or plasma DBH (the enzyme catalyzing the conversion of DA to NE which is extruded from presynaptic neurons proportionally with NE) with controls. These represent combined activity levels of CAs in CNS, peripheral, autonomic and adrenal systems and, as argued above in the consideration of 5-HT, should be less preferable than CSF assessments. However, concentrations of CSF metabolites are low in relation to assay sensitivities. The resulting range of error may be responsible for some findings in CSF metabolite studies after stimulant treatment for ADD which are difficult to reconcile with the known modes of action of these stimulants (S.E. Shaywitz et al, 1978). Some investigations have turned to the use of probenecid loading to prevent carrier-mediated efflux of acid metabolites (HVA and 5-HIAA) from the CSF, putting them into ranges which more accurately reflect brain turnover and which are more accurately assayable (B.A. Shaywitz et al, 1980; Hunt et al, 1982).

Caution is indicated in the interpretation of probenecid loading studies (B.A. Shaywitz et al, 1980) because a dose
completely inhibiting metabolite efflux causes nausea and vomiting in children and the clinically-indicated lower dosage may not have complete effects; and because of the possible intersubject variability of probenecid pharmacokinetics. Therefore, metabolite concentrations are generally expressed as a ratio with probenecid concentrations. More fundamental limitations include the possibility that probenecid itself has behavioral effects, e.g. via effects on brain as well as CSF egress of amine substances. Motor retardation in rats has been demonstrated although this may represent a toxic effect. Probenecid may affect metabolite levels differently in health and disease and may affect the mature and developing CNS differently.

Nevertheless, B.A. Shaywitz et al (1977), using the probenecid loading technique in a clinically homogeneous group of MBD children, found a significant reduction in MVA concentrations in the CSF, suggesting reduced CNS DA turnover.

With regard to NE, Shekin and Dekirmenjian (1978) found increased urinary MHPG in hyperactive children and in non-hyperactive learning-disabled children, implicating NE and suggesting a biochemical relationship between ADD-H and learning disability without hyperactivity. Hunt et al (1982) review several studies which indicated that the central alpha-adrenergic agonist clonidine produces clinical improvement in ADD in measures of hyperactivity, attention, impulsivity and learning. In one study compliance and frustration tolerance ratings improved and, while distractibility continued, task completion
was nonetheless better. This is interesting in light of the
dissociation between distractibility and performance suggested by
Douglas' (1980) model discussed above.

It is clear that more study and methodological refinements
must proceed if the evidence from clinical studies is to be
considered conclusive. Hunt et al (1982) propose a model for the
study of ADD employing single doses of "neurochemical probes"
like MPH and clonidine followed by correlations of sequential
levels of drugs and NTs and their metabolites (as well as other
indicators of the responsivity of aminergic mechanisms such as
observations of the responses of hormones known to be under
neurological control, as discussed above). This might be thera¬
peutically useful as well, to identify failure to achieve
adequate drug levels in stimulant-nonresponders as discussed
above. The authors further suggest that the concurrent study of
multiple neurochemicals both within and across NT systems can
refine conclusions about the function of a particular system in a
disorder. As well as the currently-available characterization of
overall high or low level in a NT's activity one could presumably
localize alterations in sensitivity and modulation in: presynap-
tic functioning (synthesizing enzyme levels and effects of
inhibiting them; dietary loading or precursor administration or
depletion); turnover (metabolite levels, especially after
probenecid loading); and postsynaptic receptor functioning (e.g.
examination of sensitivity of second messengers like cAMP to
receptor stimulation).
Another body of evidence converges on the catecholaminergic hypothesis of ADD from research strategies based on animal models of the disorder. Reviewing the relevancy of such models, Shaywitz & Shaywitz (in press) mention the shorter time frame of the maturational cycle of an experimental animal as well as their simpler behaviors more accurately measurable under better controlled conditions of observation than are possible with human investigations. Animal studies may be particularly apt in pediatrics because, since ontogenetic development progressively separates species through maturational differentiation, immature non-human neurobehavioral features may more closely approximate those of immature humans than their mature counterparts. Nevertheless, generalizing anthropomorphic interpretations may represent reductionistic simplification even though, to paraphrase Shaywitz & Shaywitz (in press) no thoughtful investigator really thinks that rat pups are simply small furry children with tails.

To have heuristic value, the most that can be claimed for it, an animal model for ADD should meet specific criteria which S.E. Shaywitz et al (1978) stipulate in a review of attempts at such models. Specific clinical features, which should recapitulate those of ADD in children (hyperactivity, cognitive difficulties, attention deficits, poor habituation to new environments) should occur in the developing animal after the application of toxic, traumatic, infectious or metabolic insults similar to those presumed or epidemiologically demonstrated to be
associated with human ADD. Medication responses of animals with the deficits should parallel human clinical response and the disorder should attenuate as the animal matures.

By such standards, many attempts to simulate human ADD with laboratory animals are inadequate. Models based on lead poisoning in weanling rats persist into adulthood and show inconsistent brain CA alterations and stimulant effects. Encephalitis induced in rats by neonatal virus inoculation produces effects which are either sustained into the animal's adulthood or difficult to replicate. Carbon monoxide exposure inducing perinatal anoxia leads to hyperactivity only when the rats reach maturity.

However, experimental animal models utilizing pharmacological manipulations of brain neurochemistry reproduce many cardinal features of ADD (B.A. Shaywitz et al, 1977). The selective ablation of brain DA systems in neonatal rats by the administration of desmethyliimipramine (DMI) and 6-OHDA leads to persistent selective reduction of DA activity and results in increased motor activity in comparison with unlesioned littermate controls. This is ameliorated in response to stimulant administration and accompanied by persistent cognitive difficulties represented in appetitive, escape and avoidance tasks and the failure to habituate. The disorder abates with maturity (B.A. Shaywitz et al, 1976a, 1976b; Shaywitz & Shaywitz, in press).

The DA-depletion rat ADD model primarily demonstrates hyperactivity and some cognitive deficits rather than the
Attentional deficits which may be central to human ADD. Selective NE perturbations, in contrast, have no effect on activity levels; more ambiguous effects on cognitive functions; but, in experiments on adult animals, important effects on functions equated with selective attention (Mason & Iversen, 1978; Mason, 1980).

Mason & Iversen (1978), lesioning the dorsal NE bundle (connecting the locus coeruleus to forebrain areas including parts of the limbic system traditionally associated with extinction and attention [and also implicated in the neural control of GH secretion as discussed above]) in adult animals, showed little effect on motor activity or avoidance-learning acquisition but demonstrated what the investigators have come to call the dorsal bundle extinction effect (DBEE), a decreased ability to extinguish previously-learned responses after the withdrawal of the associated reinforcement. Speculation on the neural correlates of "attention" is rife and a thorough review would lead far afield from the present specific concern with the neurochemistry of ADD; but several excellent reviews discuss the relevance of the NE-based DBEE to attention (Mason, 1980; Mason & Iversen, 1979). They conclude that the effect may be explained by a failure to ignore stimuli irrelevant to a reinforcement in favor of relevant stimuli, which leads to a generalized increased sampling of environmental stimuli and a decreased habituation to novelty by lesioned rats. This model presents a clear analogy to the interpretation of distractibility in the service of arousal.
modulation in Douglas' (1980) model of the cognitive deficits in human ADD.

Caution is indicated in the acceptance of the DBEE model in light of reported inability to replicate Mason & Iversen's findings (Tombaugh et al., 1983). And similar effects have not been seen in a study with NE-ablated young animals by Raskin and associates (Dr. Lisa Raskin, personal communication). If the DBEE model were to be established, Shaywitz & Shaywitz (in press) find it intriguing to speculate that the neurochemical defect in ADD might by analogy be inferred to include DA involvement in deficits of activity level and some cognitive functions in combination with NE involvement in deficits of attentional functions. It is tempting to see variations in the proportion of dysfunction in these two CA systems as the basis for some of the heterogeneity in the symptom complex and perhaps for some of the differences between ADD-H and other ADD. The emerging appreciation of the complex interactions between these two amine systems may in this light be seen as indicative of the complex interplay of functions subsumed by our notions of arousal, attention (selective and sustained), alertness, vigilance, awareness, etc. Of course, the progress of investigations in this area can only be expected to deepen our appreciation of the complexity of the interplay of these NT systems and the modulatory effects of other NTs which undoubtedly impinge upon these central processes.
Subjects

Subjects were six native-speaking American males from around Connecticut whose ages when tested ranged from 8 years 8 months to 13 years 3 months, with a mean of 11 years 4 months (see Table 3). All subjects were referred to the study from the pediatric endocrinology clinic and Children's Clinical Research Center (CCRC) outpatient unit at Yale-New Haven Hospital (YNHH), where they were under treatment for either simple or combined GH deficiency. All subjects were significantly below the third percentile of height for age at the time of commencement of their GH therapy, which ranged from 2 years 1 month to 6 years 4 months (mean 4 years 8 months) prior to selection to participate in our study. At the time of inclusion in the study, although the slopes of their growth curves indicated that over the course of their treatment they were catching up to their age norms, only one had reached the fifth percentile. When our study began, subjects were on thrice-weekly doses of GH ranging from 2.5 to 4 units (mean 3.2) with dosage levels determined on the combined basis of body weight and empirical response. Four of the subjects also received thyroid supplements. None had received stimulant treatment for ADD or any other disorder and none were receiving special learning disabilities attention in school.

Patients and their families were initially approached by Dr.
Joseph Gertner in their course of their treatment by him for their GH deficiency. Informed consent was obtained from both subjects and parents in accordance with a protocol approved by the Human Investigations Committee at the Yale University School of Medicine and YNHH.

**Apparatus**

The attentional battery was composed of measures chosen on the basis of demonstrated sensitivity to ADD (Douglas, 1980; Young et al, 1982; Hunt et al, 1982) and to drug-related improvements in ADD children's clinical status (S.E. Shaywitz et al, in press). These were:

1. The Matching Familiar Figures Test (MFFT), consisting of a book of line drawings;
2. The Porteus Maze Test, a series of pencil-and-paper mazes with a standardized scoring sheet;
3. The Children's Checking Test (CCT), consisting of a tape recorder, an audio tape and a booklet of numbers plus correcting overlays for the pages of the booklet;
4. a computerized attentional battery using an Apple II microcomputer with CRT monitor and a joystick control;
5. a sentence-copying task on paper;
6. a variety of printed surveys -- the Yale Children's Inventory, Child Behavior Rating Scale (CBRS) for teachers, Conners Parent's Rating Scale and children's mood questionnaire.

All testing sessions were carried out in soundproof rooms.
and each subject was in the same room each time he was tested.

**Procedure**

Prior to each child's commencement of the protocol but after consent for their participation was obtained, a letter describing the study in detail was sent to parents by the investigators. Appointments were made by phone for three visits to YNNH at two-week intervals, with confirmation by letters and follow-up phone calls prior to each visit.

The protocol, a double-blind crossover study of within-subject design, was identical for all subjects. After $3\frac{1}{2}$ weeks off their usual dosage of GH, a baseline testing session occurred. At this first visit, parents handed in any remaining GH in their possession at home (to be held and returned at the end of the study). Patients were assigned in a random fashion to either placebo or hormone treatment condition of two weeks' duration. Investigators, subjects and their parents were all blind to the nature of the treatment being administered to each subject, the code being kept only by the research coordinator of the CCRC and the pharmacist who prepared the colorless solutions of identical appearance for injection.

Randomized assignment to treatment order was felt to be better than alternating order so that the accidental revelation of one subject's treatment order would not invalidate double blind conditions overall. Because of the paucity of appropriate subjects, when the study was begun we did not know the rate at
which we would obtain referrals and therefore how many subjects would have been included over the timespan available to the investigators to complete the study. Thus, while random fluctuations in randomization might imbalance for order with a very small n, we felt it was preferable to the risks of alternating order.

During the study, GH (or placebo) was administered by intramuscular injections three times a week in a manner identical to the child's usual receipt of his GH (in most cases by his mother, although at least one of the boys customarily administered his own injections). The protocol medications were given in the child's usual volume of injection.

At the conclusion of this first treatment condition, subjects were tested again in a manner identical to the baseline testing. They again handed in any residual supplies of the medication they had been taking and each one crossed over to a two-week period of the other treatment condition (either from hormone to placebo or from placebo to hormone, respectively treatment designs AB or BA). A third identical testing session was undertaken at the end of this second and last treatment period. At the conclusion of each subject's participation in the study with this third visit, any GH they had placed in the custody of the CCEC was returned.

Human GH for the study was supplied by the National Pituitary Agency, which coordinates the collection and
distribution of cadaveric GH in the United States. This hormone was identical in all respects to that which the patients receive normally in the course of their usual treatment for GH deficiency. Because the effects of GH on growth deficiency are cumulative and because there are normally discontinuities in these children's receipt of hormone supplementation as a result of temporary national shortfalls in GH supplies, it was felt that the gaps represented by the washout to baseline and the placebo treatment periods did not represent appreciable compromises to the subjects' treatment regimens.

At the time of testing, subjects came to the CCRC for fasting blood levels of GH and prolactin, having been instructed to refrain from eating that morning until after blood sampling. The total amount of blood removed at each visit to the CCRC prior to a testing session was approximately 30 milliliters. Parents also collected 12-hour urine samples from the subjects twice a week for each treatment period. These were analyzed for MHPG levels after the parents returned them to the CCRC at each visit.

After blood sampling, each child was given a full breakfast and accompanied one of the two investigators to the testing room. Each child was tested by the same experimenter at each of his sessions, and the order of administration of components of the test battery was consistent from session to session and from subject to subject. The duration of the sessions was approximately 1 ½ hours and a rest period was taken before starting the CCT (about halfway through the morning).
The attentional battery on which each subject was tested at each session consisted of the following measures presented in the order indicated:

*Children's Mood Questionnaire:* This self-rating scale is a modification (Table 4) suggested by Rapoport et al (1980) of the van Kammen-Murphy Mood Scale (van Kammen & Murphy, 1975). The scale, completed by all subjects for the hormone and placebo sessions, consists of 28 items (see Table 8) to which a subject must check "not at all," "a little," "some" or "a lot." These responses are given scoring weights of 0, 1, 2 and 3 respectively. Subjects were instructed to use the scale to describe their mood over the week previous to the testing day, i.e. the second week of each treatment protocol.

*Sentence copying task:* The subject was given a sheet of paper with five sentences on it and instructed to copy them; they were told to print rather than write in "cursive" or "script." The following were the sentences used:

A boy had a dog.

A dog saw a bird.

My name is [filled in with the subject's given name].

Please come quickly.

The question is about the Constitution.

The children's products were scored for time to completion of task and number of copying errors, erasures and reworking, all
of which (as well as others reflecting overall organization and legibility, size, spacing and placement, which we did not rate) are handwriting problems shown to be associated with MDD (Lerer et al, 1977).

Matching Familiar Figures Test (MFFT) (Kagan et al, 1964): This task consists of two practice items followed by twelve test trials. In each trial of the adolescent version which was used in the present study, the subject is shown a page on which is a line drawing of a familiar object (soldier, lion, flower, house, etc.) and, on the facing page, eight drawings of the same item which differ from the index drawing in small details except for one which is completely identical to it. In each trial, a subject must discover and indicate which of the items is exactly the same as the index drawing. The subject is given immediate feedback about the correctness of each response and continues the trial until the correct figure is indicated. Trials are scored for latency to first response and total number of errors. Multiple versions of the MFFT, with the same drawings but in different orders on the page, exist to eliminate practice effects with repeated measures on the same subject. Children's performance on the MFFT is taken to reflect the degree of active reflection on the validity of solution hypotheses the child pursues in problems containing response uncertainty (i.e., where there would be an inverse correlation between latency and error scores). In such cases, the quotient of latency over error
scores (which we have called the MFFT-Q) operationalizes the concept of reflection-impulsivity by defining a continuum from [slow, accurate] to [fast, inaccurate] (Kagan & Kogan, 1970). Although its relationship to the everyday notions of reflectiveness and impulsivity has been called into question (Block et al, 1974), studies of the generality of error and latency tendencies across analogous measures and of visual scanning strategies in the MFFT situation support the construct, and it has been shown to be sensitive to such attributes of ADD as hyperactivity, attentional deficit, distractibility and lack of persistence on intellectual tasks (Ault et al, 1972; Kagan et al, 1964; Keogh & Margolis, 1976).

A complementary way of presenting MFFT data is in terms of the product of latency and errors (to which we have referred as the MFFT-P score), one way of operationalizing a concept of "efficiency" by defining the continuum from [slow, inaccurate] to [fast, accurate] (Salkind & Wright, 1977). Together with the reflection-impulsivity coordinate, an efficiency axis (orthogonal to it) allows the location of any subject's test result in a space which serves to define whether accuracy or rapidity is the major contributor to the subject's impulsivity rating.

**Porteus Maze Test** (Porteus, 1959): This test, used for over 65 years, consists of a series of graded mazes of increasing difficulty. The task is introduced to subjects with a standardized script of directions. Subjects are instructed to
take as much time as necessary to complete each maze without turning into any blind alleys, instances of which are scored as unsuccessful trials. Subjects may not lift their pencil once they begin to trace the continuous path through the maze but may pause to plan at any time. The task is not timed. A score, labelled test age (TA), reflects ability to execute the mazes and is calculated on the basis of the level, in years, assigned to the highest maze a subject passes in the permitted number of trials or less, minus a half-year deduction for each unsuccessful trial at or below that level. The TA may be converted into an age-appropriate test quotient (TQ) on the analogy of the relationship of mental age (MA) and IQ. The TA and TQ have been thought of by Porteus (1965) and others (Riddle & Roberts, 1977, 1978; Spitz & deRisi, 1978) as tapping aspects of intellectual functioning involving foresight, planning ability, control of impulsivity and capacity for restricting attention to appropriate information (as Porteus [1965] described it, a "focusing of attention on the goal to be reached while at the same time allowing perceptions to range over alternative courses in order to select the relevant responses"). Douglas (1980) has reviewed the evidence showing that Porteus maze performance is sensitive to ADD. A qualitative (Q) score relatively independent of both IQ and TQ may also be derived in a standardized fashion from a subject's maze performance, and may be thought of as a measure of neatness of execution; we did not score the mazes in this manner in the present study. Distinct
series of mazes exist for the first (original, or Vineland revision), second (Extension series) and third (Supplement series) administrations to the same subject, to minimize practice effects in repeated-measures designs such as our investigation.

Children's Checking Test (CCT) of Margolis (Keogh & Margolis, 1976): This test depends on a subject's maintenance of vigilance or sustained attention over a prolonged monotonous task. The child is asked to detect discrepancies which have been set up between a 20-minute audio tape on which a voice reads a random series of digits at a constant rate of one per second, and a printed sequence of the digits in a booklet. Each of the lines of the booklet is labelled with a letter (in alphabetical order) and each page with a color to which is referred on the tape when the beginning of each new line or page is reached, so that a subject who loses her/his place can be periodically reoriented. The subject's performance on each page can be measured by counting errors of omission (failures to detect discrepancies present) and of commission ("false alarms" where a subject reports a discrepancy when none is in fact present). Because the pages of the test have been standardized for difficulty, have an equivalent number (seven) of discrepancies and take the same amount of time to complete, the comparison of a subject's omission errors over pages of a single test administration may be taken as a measure of the decline over time in attending efficiency which is physiologically characteristic of vigilance.
performance. This decrement can be compared over repeated administrations of the test which, while using the same tape, utilize separate test booklets each of which embodies different errors, to avoid practice effects.

Numerous investigators including Keogh & Margolis (1976) and Charles et al (1979) have shown that both absolute performance level and degree of vigilance decrement are sensitive to ADD and to stimulant-induced improvements in ADD. As the latter investigators note, vigilance performance has been thought to be free from the confounding effects of learning and memory.

Relatively few commission errors are made and experimenters have generally felt that these are attributable to a psychological state rather than reflecting the physiology of attention. Moreover, Charles et al (1979) have demonstrated that commission errors are highly subject to practice effects. While some investigators analyze and explain commission data, they are usually ignored on vigilance tasks (Davis & Tune, 1969) as we do herein.

**Computerized attentional battery:** This consists of three tasks, developed in the laboratory of Drs. B.A. Shaywitz and S.E. Shaywitz, each of which utilizes feedback in the form of tones to inform a subject at once if his/her response was correct. (a) CONPREP is a continuous performance task in which a subject's attention is directed to a computer screen on which pairs of large-format X's and C's are flashed with varying delays between
the first and second letter of the pair. Children must indicate by the direction of deflection of the joystick control whether the two letters are the same or different. The computer records correctness of response and latency of response for each trial. The test consists of 80 stimuli pairs with delays within pairs ranging from 0 to 900 milliseconds. (b) SELATT is a selective attention task where the stimuli flashed on the screen consist of either horizontal or vertical lines embedded in either squares or triangles. In each of six subtests of 20 trials each, a subject is instructed to respond to only one of the stimulus modalities (i.e. either line direction or figure shape alone) with appropriate joystick motions. After four subtests which have held the nonsalient stimulus characteristic invariant (i.e. lines in only triangles; lines in only squares; figures with only horizontal lines; and figures with only vertical lines), the last two subtests vary the background stimulus too (i.e. lines of both directions [criterion] embedded in both squares and triangles [background]; and figures of both types [criterion] with embedded lines of both directions [background]). The computer records response correctness and latency for each trial. (c) MAINTR is a vigilance task where small squares of colors red, green and blue are flashed one at a time at random positions on the monitor screen, with stimulus durations of 0.1 second and delay of 1.0 second between subject's response and the presentation of the next stimulus. The subject is instructed to indicate blue and green stimuli by the appropriate joystick movements and not
respond to red stimuli. Omission errors, comission errors, discrimination errors and latencies are recorded for each trial in the 5-minute test.

In addition to collecting data from each subject, additional questionnaires were given to their teachers and parents. These were the following:

The Child Behavior Rating Scale (S.E. Shaywitz, 1980) was sent to a teacher selected by the subject and parent as knowing the child well (usually the homeroom teacher) at the end of baseline, placebo and hormone treatment periods. For each subject, the same teacher completed the rating form all three times. Teachers were directed to fill out the form with reference to the previous week (the last week of each protocol period) and a stamped addressed envelope accompanied each form so that the teacher could return it directly to the investigators when completed. The scale consists of 25 items (see Table 10) which describe child behaviors and are rated on a four-point scale whose criteria are descriptive rather than inferential (S.E. Shaywitz, 1982). Sleator and von Neumann (1974) founds teacher ratings to be more sensitive to level of attentional function than parent ratings. Charles et al (1979) have shown that teacher ratings of attentional factors correlate with objective measures of attentional performance such as the CCT. Conners (1969) showed that a similar teacher's rating scale was sensitive to medication-
induced changes in the behavior of children with learning and/or behavior disorders, and Satterfield et al (1974) have demonstrated its sensitivity to stimulant-induced improvement in ADD children's behavior in a number of studies.

The Conners Parent's Rating Scale (Conners, 1970): This survey consists of 95 items representing symptoms grouped under general headings such as "problems of eating," "problems of sleep," etc. (see Table 4) which are checked as "not at all" present, "just a little," "pretty much," or "very much" present. These are given scoring weights of 0, 1, 2 and 3 respectively. The parent or guardian accompanying each child at each session (in each case the mother except for one child raised by his aunt and accompanied by her) completed the form and was instructed to rate the presence of these symptoms with reference to the previous week (i.e. the last week of washout or the second week of each treatment period). Conners (1970) has shown that factor-analytically defined symptom clusters from the parent's rating scale can discriminate neurotic, psychiatric outpatient and hyperactive children from normal controls.

The Yale Children's Inventory (S.E. Shaywitz, 1979): This form of 800 items is filled out once by the parent(s) of each subject and encompasses environmental and demographic information; genetic background and family history; pre- and perinatal events; medical, developmental and social history; symptom and treatment
survey; educational experiences; and current areas of difficulty. It incorporates questions obtaining DSM-III (American Psychiatric Association, 1980) criteria to allow diagnostic use of the historical information obtained (S.E. Shaywitz, 1982).

Statistical analyses were used cautiously in view of the small number of subjects. However, in cases where they were used, analysis of variance and multiple regressions on test data were performed on the ANOVA and STATS-PLUS software packages of the Apple II microcomputer. Small-sample t-tests using a matched pairs design compared item-by-item responses across treatment conditions on questionnaire-type measures.
All subjects completed the protocol with no difficulty. However, as a result of equipment failures and procedural errors, every measure was not obtained on all subjects, and this is reflected in the reported results.

With such a small sample size, most results will of necessity be presented as trends rather than in terms of their statistical significance. In many cases it seemed useful to split the sample in terms of the level of pretreatment performance on a measure and examine those whose baseline levels were low and high separately to ascertain the source of an observed overall trend.

An attempt was made to control for order by counterbalancing the number of subjects receiving hormone first and placebo first by random assignment to protocol. (Our reasons for preferring this approach to counterbalancing by strict alternation are discussed in Chapter 5 above.) However, because deadlines forced the study to be terminated after such a small number of subjects, this unfortunately resulted in a disparity whereby four of our six subjects received placebo first (protocol BA) while only two received hormone first (protocol AB). Thus, a careful examination of the data was done to see if trends which we observed on the basis of treatment could be better explained by the confounding effect of order. No such influence was seen.

CII and prolactin concentrations which were derived from
fasting blood samples on test mornings on all subjects were inspected after the study was over and the code had been broken. These revealed that in all cases hormone levels appropriately reflected the treatment that the subject was receiving at the time of each test.

In the sentence copying task (see Table 5), a trend toward faster copying from baseline to placebo to hormone sessions was observed. This was accompanied by a consistent downward trend in numbers of the kinds of errors we analyzed on this task. The decreasing time on task was mostly a difference between baseline and the other two sessions and was mostly accounted for by an acceleration in the performance of the three subjects who were slowest to begin with. They stayed slower than the other three but the disparity lessened with treatment. [In fact, the faster group worsened slightly on GH.]

On the MFPT (Table 5), no important change in overall response latencies could be observed. However, there was a decrease in errors of response from baseline to placebo to GH, largely between baseline and the other two conditions. MFPT-Q, or the quotient of latency over errors, a measure of "reflection-impulsivity," showed a clear trend toward more reflectivity with treatment, again largely a difference between baseline and the other two tests. This trend was largely attributable to increasing reflectivity of the three subjects who were most reflective to begin with; the three more impulsive subjects became more impulsive with treatment. Analysis of the MFPT-P, or
product score, revealed a significant trend toward "efficiency" (greater after placebo than baseline, greatest after hormone treatment), $F(2) = 3.401, p = .074$. This difference arose largely between baseline and treatments.

There was no overall tendency toward treatment effects on the Porteus Maze test performance (Table 5), but when subjects with $TQ < 100$ and $TQ > 100$ were examined separately, it was observed that poorer performers improved substantially on GH while better performers stayed in the same range.

The CCT (Table 6) showed a clearcut trend approaching significance of more omission errors after GH than in placebo or baseline periods, $F(2,4) = 2.511, p = .130$. This is largely accounted for by poorer performance on the early pages of the test after GH treatment, rather than an enhanced deterioration with time on task. Those subjects who initially performed most poorly on this test accounted for the major part of the worsening on GH, and these three were the only subjects who consistently demonstrated a noticeable vigilance decrement over time within sessions.

On the computerized attentional battery (Table 7), the smaller sample sizes indicate various equipment failures which precluded testing some subjects on all measures. On COMPREP (continuous performance), 5 subjects showed significant differences between mean response times on placebo (107.2 msec) and GH (116.9 msec), $F(1) = 5.911, p = .071$. There was no discernable trend with regard to errors. Three subjects who
completed all three sessions of MAINTR (the vigilance task) demonstrated markedly slower response times after GH than on the other two test occasions. No trend in errors was seen. On SELATT (selective attention) (n = 4) as well, response times were noticeably slower on GH than other conditions. An upward trend in errors from baseline to placebo to GH was also apparent and readily attributable to differences between GH and the other two conditions, mostly on the last two subtests (where background varies as well as figure) of the test. Overall, though, there was no discernable trend to worsen from subtest to subtest as a test proceeded, i.e. no decrement characteristic of vigilance performance.

Differences between placebo and GH on the children's self-reports of mood were analyzed on an item-by-item basis. Trends toward significance could be seen on six of the 28 items (Table 9). Subjects on GH rated themselves higher than on placebo on the following three: #3 ("I have trouble keeping my mind on things"), #6 ("I feel unhappy"), and #22 ("I have trouble doing things"). On the following three, subjects rated themselves lower on GH than on placebo: #16 ("I feel like my thoughts are going fast"), #25 ("I feel friendly") and #14 ("I feel 'funny,' not like myself"). No important differences between GH and placebo treatments were seen on the other 22 items of this survey.

In the CBRS, trends in teachers' ratings of subjects over the treatment conditions were apparent on 11 of the 25 items
(Table 11). Children on GH, in comparison to the other two test periods, were rated more poorly on their ability to follow verbal commands (#12); monitoring or self-correcting of work (#15); ability to 'catch on,' i.e. adaptive learning (#18); distractibility (#20); ability to relate to adults (#24) and ability to relate to other children (#25). Ratings worsened between baseline and the other two treatments on motor-inhibition, as measured by ability to refrain from touching people and objects within reach (#3); rapidity of performance of schoolroom tasks (#6); and ability to "focus in" or pay attention (#21). Children were rated as better on treatment than baseline on one item, relating to reaction to or tolerance for frustration (#10). Other items did not show overall trends across experimental conditions.

Analysis of urinary MHPG levels will be examined and reported subsequently. Meaningful interpretation of the data from the Conners Parent's Rating Scale and the Yale Children's Inventory await factor analyses which are still pending.
Chapter 7: Conclusions

It should be emphasized once again that all results must be considered tentative in view of the small sample size of the study and the even smaller sample size for some measures. The present investigation should be seen as a pilot study suggesting a methodology for the examination of this problem over sufficient time to obtain an adequate number of subjects.

Results of this study suggest that short-statured subjects do not function as efficiently or accurately on attentional tasks while receiving GH as without, their difficulties being most dramatic on the CCT and the computerized attentional battery, all three of the component tests of which showed a consistent trend to longer latencies to response after GH.

To the extent that the data from these six subjects can be taken as representative, the attentional problems observed in GH patients in at least some respects do not duplicate those found in ADD children with or without hyperactivity. Our subjects' performance on the MPFT and the Porteus Maze test did not reveal a clearcut trend. These two tests in a sense measure similar and complementary abilities to use foresight in reflecting on the validity of solution hypotheses in situations with (MPFT) and without (maze) response uncertainty, and both have been shown to be sensitive to an ADD-type deficit (Porteus, 1959; Kagan et al., 1964; Keogh & Margolis, 1976; Douglas, 1980) which presumably affects such a skill. Our secondary supposition that GH might
have an overall effect to worsen the performance only of those who perform poorly at baseline and thus widen the disparity between good and poor baseline performers was not borne out either. On the MFPT, the reflectives become more reflective and the impulsives more impulsive, but in the sentence copying task and the Porteus Maze test the opposite is true and discrepancies are narrowed on GH. In fact, the best explanation for the improvements noted on sentence copying time and errors and MFPT errors (and the associated findings in MFPT-Q [impulsivity] and -P [efficiency] scores which partially depend on errors) is that they represent practice effects in light of the fact that the major differences observed are between the baseline and post-treatment levels rather than between placebo and GH treatments. This makes sense too in terms of the nature of these tasks. While the order of pictures in each trial of the MFPT is altered from test to test to prevent a memorized response, the altered details on each of the pictures remain the same and it is likely that subjects would learn to key in to these better with repetitive exposure. This might decrease errors without having much effect on overall latency to response if the latter were more a function of search strategy and style. Keogh & Margolis (1976) have similarly found that the differences in MFPT performance between "educationally handicapped" and control youngsters were largely in terms of errors rather than differences in response latencies. There is however controversy over the relative contributions of the cognitive underlays of these two dimensions to
the reflection-impulsivity construct which the test is designed to measure (Kagan & Messor, 1975; Block et al, 1974). It is equally plausible that a sentence copying task which for purposes of standardization uses the same sentences on each retesting is also prone to a practice effect from the subjects' growing familiarity with the sentences from test to test. A more multidimensional analysis of the handwriting samples for reliable ratings of qualitative changes, as in the study of the effects of MPH treatment on the handwriting of ADD children of Lerer et al (1977), might make more thorough and meaningful use of the samples. There would also seem to be an indication for the creation of multiple sentence copying tasks of comparable difficulty for repeated measures on the same subjects.

In other respects, the performance of our subjects does closely parallel that of ADD children. The CCT was designed specifically to measure the ability to maintain attention over time; along with coming to attention (focusing, perceptual organization, determination of saliency and suppression of distraction) and decision-making, one of Keogh & Margolis' (1976) three components of attentional ability and/or task demands. The investigators found that these three aspects of attention may be considered relatively independent of one another when measured fairly specifically. The CCT, a monotonous task which was uniformly the least enjoyable aspect of the test battery for the subjects, in many ways taps pure vigilance through an assay of its decrement with time on task, unconfounded by demands on
analytic processes or memory. Keogh & Margolis found that enhancement of decrement formed an adequate basis for discriminating their educationally handicapped sample from controls. But they were using a 30-minute seven-page variant of the test which might enhance vigilance-decay. On the current five-page version, Charles et al (1979) found that deterioration with time on task was not a primary index of attentional deficit (in a group of forty-five hyperactive children in a crossover study of KPH) but rather that errors on the early pages are significantly greater for those with poor attention than the normal attention group. The authors suggest that the administration of the first two pages of the CCT, while not reflecting a true vigilance paradigm, may be adequate for clinically diagnosing attentional deficits and monitoring treatment or remediation. The implication in terms of the Keogh & Margolis attentional paradigm is that the ADD child's problem with sustained attention is compounded by inefficient or inaccurate performance \textit{per se} and that these dimensions of attention are only partially independent. The similar pattern of our subjects' performance when tested on GII -- not so much an accelerated vigilance decrement over task as poorer performance from early on in the test -- suggests that they have an attentional impairment of a structure similar to at least this component of the ADD child's problem.

Longer latencies to response on the computerized attentional battery, which the authors interpreted in terms of impaired
reaction times (Dr. B.A. Shayvitz, personal communication) were a demonstrated correlate of ADD in a study of 13 boys (S.E. Shaywitz et al., 1982) in which this measure of attention was found to improve, in response to MPH, in parallel with amelioration of hyperactivity. The clearcut trend to longer response latency throughout all three of the component tests of this battery in our study of GH-treated children thus suggests another parallel to ADD-type deficits. Slower reaction times might represent a motor problem similar to that suggested in ADD (Abbott et al., 1982) -- especially in terms of the contrasting invariance of error performance -- or a cognitive deficit, on a task success on which demands the synergistic application of capacities in both these areas. Many authors have seen the pathophysiology of ADD in terms of CNS underarousal as defined by a variety of measures (reviewed in Satterfield et al., 1974) which would lead to reaction time decrements. A related interpretation in terms of the failure of situationally appropriate modulatory control of arousal, which is a central feature of Douglas' (1980) model of ADD, is also consistent with the data.

Regardless of the pathophysiology, the results on the computer battery are akin to those on the CCT in a basic way. If the longer latency performance were cut off with a lower ceiling, many of the subjects' slower responses on GH would cross the threshold to be counted as an increase in errors of omission analogous to that observed on the CCT in subjects on GH. A major dimension of the skills tapped by the computerized battery, like
the CCT, is sustained attention or vigilance (although the simple fact that these are "computer games" made them motivationally far more interesting to our subjects than the CCT was). Douglas' (1980) model of ADD proposes that this is the aspect of "attention" with which ADD children really have difficulty. It is interesting that a salient difference between the two kinds of tasks, the presence of immediate feedback to the subject about the correctness of each response on the computer battery, which has been posited to make an important difference to the performance of the ADD child (Douglas, 1980), was not distinctive in our study.

Charles et al (1979) demonstrated correlations between CCT performance and teacher ratings of hyperactive children both initially and over the course of their study of response to MPH treatment. Our study shows parallel trends on CBRS teacher ratings on items relating to distractibility; organization of and approach to schoolwork; adaptive learning; and social interactions (including classroom obedience). In contrast, items relating to motor activity (fidgeting, restlessness, fatiguability, slowed, rushed or pressured performance) were not perceived by the teachers to be affected by GH. This is again consistent with an ADD-type deficit centrally involving attentional processes and, if at all, only secondarily motor disinhibition that is not purposive (Douglas, 1980). Charles et al (1979) indicate that teachers are better than parents at rating attention, presumably because of its greater saliency in
the school situation than at home and the teacher's greater familiarity with the behavioral norms. It would be interesting to compare teacher and parent ratings, especially on the same scale, e.g. the Conners or the abbreviated (10-item) Conners used by those authors.

Our subjects' mood self-reports seem to reflect psychic changes which echo the observations of their teachers. The children feel more distractible ("I have trouble keeping my mind on things"), inefficient in their work ("I have trouble doing things") and have greater difficulties with peer relations (they feel less friendly and more unhappy) when taking GH. Interestingly, children rated themselves lower when on GH on the statement, "I feel funny, not like myself." Rapoport et al (1980) demonstrated that hyperactive boys rated themselves lower than normal boys on this item although both groups' ratings on the item increased with the administration of stimulants. This rise in their study may represent a direct side effect of the drug rather than a mood effect; but perhaps attentional deficits of the type examined here include a component of impaired self-attention. Not "feeling funny" may not mean not having such feelings but merely not attending to or noticing them, in comparison with either normal controls or the alleviation effected by psychostimulants.

Changes in GH secretory activity in ADD, in other behavioral disorders, in DMI administration and other therapeutic psychopharmacological interventions in response to problems, are
likely to be dependent measures secondary to primary processes whose effects lie in altering the operation of various CNS NT systems (as the possible uses of GH monitoring in the investigation and treatment of these disorders, suggested by Young et al (1982) among others, recognize). In contrast, the administration of exogenously-derived GH to deficient patients represents a primary alteration likely to have any putative CNS effects through the feedback processes which are now beginning to be elucidated. Although circulating GH might directly affect pituitary somatotrophs in such a situation, without the mediation of any NT system, most feedback schemes propose a role for GH or tissue-generated somatomedins which cross the blood-brain barrier to act at hypothalamic or higher levels and affect the NT-mediated higher influences on the pituitary (Tannenbaum, 1980). Even though there is no primary GH secretion to be "fed back upon" when GH is administered to a GH deficient child, these higher mechanisms are presumably still altered and extra-pituitary manifestations of these alterations should still appear. Thus patients with a GH-associated attentional deficit (GH-AD) such as that which we suggest in the present study might be expected to show alterations in NT function that could be demonstrated with the increasingly sophisticated techniques being applied to the investigation of the pathophysiology of ADD. Of course, humanitarian concerns arising from the stringent requirements for the justification of investigative lumbar punctures would preclude such studies as the examination of CSF NT metabo-
lites after probenecid loading in a GH treatment protocol.

The heuristic value of taking a tack in examining GH-AD suggested by its analogy with ADD in a broad range of senses seems clear. The emerging consensus that the relationship between the biochemical lesion(s) in ADD and the person-specific and situation-specific "phenotypic expressions" of the disorder is far from simple, e.g., suggests that a GH-AD might show analogous variability over time and situation. Studies might have to elicit specific conditions, if these can be ascertained, in which a fluctuating deficit might most likely be manifest.

This need to study GH-AD in terms of "person-by-situation matrices" (Henker & Whalen, 1980) also contributes to our inconclusiveness on the question posed early in this paper of whether the deficits emerge de novo under the influence of GH or represent an elicitation of an underlying deficit. Our study clearly showed baseline heterogeneity in various aspects of attentional performance from subject to subject; a larger series might allow a meaningful characterization of baseline performance in comparison with population norms for the measures, something not even attempted with the small sample size, skew of ages and lack of standardization on such parameters as IQ in the present study. [Of course, our within-subjects design has a great toleration for such heterogeneity to the extent that we are interested in inrasubject changes across treatments.]

In fact, a question arises concerning the extent to which alterations evoked by CNS effects of exogenous GH administration
are unphysiological at all in comparison to the effects a normal child's native GH would have on her/his CNS through negative feedback autoregulation mechanisms. Might the episodic GH secretory pattern engender ultimately detectable alterations in attentional processes over the course of a day in a normal subject? As an alternative, are the differences between the pharmacokinetics of exogenous GH administration and physiological secretion crucial ones from a neurophysiological perspective? Or are the two situations different because of longterm alterations to the CNS which might be engendered by the underlying disease in hypopituitary patients; i.e. might GH affect the CNS differently in the presence and absence of disease? It does not seem feasible to administer GH to normal children to obtain such a comparison group. The distinction mentioned above between classical GH-responsive GH deficiency and the GH-responsive subset of normal-variant short stature (NVSS) might provide at least partial opportunities (to the extent that the secretory impairments and any lesions underlying them are sufficiently distinct in the two conditions).

Furthermore, might GH affect the CNS differently in the presence and absence of a history of prolonged GH use? The 3\(\frac{1}{2}\) week washout to baseline in the current study, which it would be no exaggeration to call quite adequate in terms of GH pharmacokinetics, might not take into account the presence of such chronic changes the characterization of whose nature may have to await further elucidation of the mechanisms of

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autoregulation. Moreover, in an interactive "biopsychosocial" model of the person, possible personality changes engendered by short stature, IM injections and/or the sense of "treatment failure" relative to expectation which plagues these patients (Rotnem et al, 1979) might even have neurophysiological correlates that could act as substrates, contributors or precipitants for a GH-AD. A within-subjects design controls for as much of such personality effect can be controlled for, and such was the major rationale for employing such a protocol in this study. However, it is conceivable that it might be only under the acute influence of GH that some effects might be elicited from an altered nervous system, making them impossible to distinguish investigationally from GH effects. Eric Kandel's provocative but highly speculative recent work on the possibility that experience may alter gene expression in the nervous system (personal communication) is not irrelevant to this question, a central one in psychiatry regarding the locus of changes induced by experiences which have ongoing behavioral consequences.

It is hoped that these and other interesting questions will be elucidated through both further investigation of attentional processes in children receiving GH for the treatment of hypopituitary short stature; and implications of ongoing research in the associated areas of the biology of ADD and the neural regulation of GH secretion between which GH-AD serves as a nexus. It is hoped that this study and this discussion herein suggest useful directions to pursue for the widening of this nexus.
Table 1: Factors Affecting Growth Hormone Secretion  
(adapted from Table 7-4, p. 170, Frohman [1981])

<table>
<thead>
<tr>
<th>Stimulate</th>
<th>Suppress*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiologic</strong></td>
<td><strong>Physiologic</strong></td>
</tr>
<tr>
<td>sleep</td>
<td>postprandial hyperglycemia</td>
</tr>
<tr>
<td>exercise</td>
<td>elevated free fatty acids</td>
</tr>
<tr>
<td>postprandial:</td>
<td></td>
</tr>
<tr>
<td>hyperaminoacidemia</td>
<td></td>
</tr>
<tr>
<td>hypoglycemia</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacologic</strong></td>
<td><strong>Pharmacologic</strong></td>
</tr>
<tr>
<td>hypoglycemia:</td>
<td>hormones:</td>
</tr>
<tr>
<td>absolute: insulin</td>
<td>somatostatin</td>
</tr>
<tr>
<td>2-DG</td>
<td>growth hormone</td>
</tr>
<tr>
<td>relative: post-</td>
<td>progesterone</td>
</tr>
<tr>
<td>glucagon</td>
<td>glucocorticoids</td>
</tr>
<tr>
<td>hormones:</td>
<td></td>
</tr>
<tr>
<td>peptides (ACTH, MSH, VP)</td>
<td></td>
</tr>
<tr>
<td>estrogen</td>
<td></td>
</tr>
<tr>
<td>NTs etc.:</td>
<td>NTs etc.:</td>
</tr>
<tr>
<td>alpha-agonists</td>
<td>alpha-antagonists</td>
</tr>
<tr>
<td>beta-blockers</td>
<td>beta-agonists</td>
</tr>
<tr>
<td>serotonin agonists</td>
<td>serotonin antagonists</td>
</tr>
<tr>
<td>dopaminergic agonists</td>
<td>dopamine blockers</td>
</tr>
<tr>
<td>GABA agonists</td>
<td></td>
</tr>
<tr>
<td>endorphins</td>
<td></td>
</tr>
<tr>
<td>pyrogens (Pro. endotoxin)</td>
<td></td>
</tr>
<tr>
<td><strong>Pathologic</strong></td>
<td><strong>Pathologic</strong></td>
</tr>
<tr>
<td>protein depletion &amp;</td>
<td>obesity</td>
</tr>
<tr>
<td>starvation</td>
<td>hyperthyroidism</td>
</tr>
<tr>
<td>chronic renal failure</td>
<td>hypothyroidism</td>
</tr>
<tr>
<td>acromegaly:</td>
<td>acromegaly:</td>
</tr>
<tr>
<td>TRH</td>
<td>dopamine agonists</td>
</tr>
<tr>
<td>LHRH</td>
<td></td>
</tr>
</tbody>
</table>

*Suppressive effects of some factors can be demonstrated only in the presence of a stimulus.*
### Table 2: Performance Characteristics of ADD Children

#### a. Tasks on Which Hyperactive Children Perform Relatively Well

<table>
<thead>
<tr>
<th>Task:</th>
<th>Task requirements:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple reaction time task</td>
<td>Concentrate on reaction signal</td>
</tr>
<tr>
<td>continuous reinforcement&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Concentrate on reacting quickly</td>
</tr>
<tr>
<td>Choice reaction time task</td>
<td>Concentrate on pushing buttons, corresponding to geometric figures on screen</td>
</tr>
<tr>
<td>Serial reaction time task</td>
<td>Concentrate on responding quickly</td>
</tr>
<tr>
<td></td>
<td>Concentrate on pushing buttons corresponding to particular lights as lights appear</td>
</tr>
<tr>
<td>Picture Completion Subtest:</td>
<td>Concentrate on reacting quickly</td>
</tr>
<tr>
<td>Wechsler Intelligence Scale</td>
<td>Conduct visual search of picture for missing part</td>
</tr>
<tr>
<td>for Children&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Concept identification task:</td>
<td>Concentrate on discovery of &quot;correct&quot; concept from series of visual stimuli presented in pairs</td>
</tr>
<tr>
<td>continuous reinforcement&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Abstract stimulus dimensions from task stimuli &amp; categorize stimuli by class</td>
</tr>
<tr>
<td></td>
<td>Modify response strategies on basis of information feedback</td>
</tr>
</tbody>
</table>

#### b. Tasks on Which Hyperactive Children Perform Relatively Poorly

- Continuous performance: vigilance tasks
- Reaction time tasks with preparatory interval
- Kagan's Matching Familiar Figures Test (MFFT)
- Embedded figures test: field-dependence
- Porteus Maze test
- Tests with multiple choice format
- Card sorting subtest: Wechsler Intelligence Scale for Children
- Matrix solution tasks
- Rule learning tasks
- Memory for paired associates: arbitrary associations
- Story-completion task: frustrating stories

<sup>1</sup>(Significant ADD-normal differences do occur on partial reinforcement schedule.)

<sup>2</sup>(ADD children performed very poorly on the same task with partial reinforcement.)

<sup>3</sup>(In the continuous reinforcement condition, ADD children showed excellent transfer to a second concept. They were also able to reverse concepts when feedback changed -- no evidence of perseveration.)
### Table 3: Characteristics of Subjects

<table>
<thead>
<tr>
<th></th>
<th>JL</th>
<th>GW</th>
<th>EW</th>
<th>RG(^1)</th>
<th>EG(^1)</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D.O.B.</strong></td>
<td>9-28-69</td>
<td>12-26-70</td>
<td>8-28-70</td>
<td>6-10-74</td>
<td>6-5-72</td>
<td>10-8-71</td>
</tr>
<tr>
<td><strong>ht. beginning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH Rx (cm)</td>
<td>101.7</td>
<td>107.5</td>
<td>102.7</td>
<td>78</td>
<td>81</td>
<td>110.4</td>
</tr>
<tr>
<td><strong>present ht</strong></td>
<td>144.5</td>
<td>129.4</td>
<td>136.2</td>
<td>114.5</td>
<td>125.5</td>
<td>124.0</td>
</tr>
<tr>
<td><strong>age beginning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH Rx (yr-mo)</td>
<td>7-4</td>
<td>8-5</td>
<td>7-5</td>
<td>3-5</td>
<td>4-4</td>
<td>9-1</td>
</tr>
<tr>
<td><strong>present age</strong></td>
<td>13-3</td>
<td>11-11</td>
<td>12-5</td>
<td>8-8</td>
<td>10-6</td>
<td>11-2</td>
</tr>
<tr>
<td><strong>time on GH</strong></td>
<td>5-11</td>
<td>3-6</td>
<td>5-0</td>
<td>5-3</td>
<td>6-4</td>
<td>2-1</td>
</tr>
<tr>
<td>GH dose(^2)</td>
<td>4</td>
<td>2.8</td>
<td>3</td>
<td>2.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>synthroid qd</td>
<td>150</td>
<td>100</td>
<td>50 mcg</td>
<td>75 microgm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thyroxin qd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GH protocol(^3)</strong></td>
<td>BA</td>
<td>AB</td>
<td>BA</td>
<td>BA</td>
<td>AB</td>
<td>BA</td>
</tr>
</tbody>
</table>

\(^1\)(these two subjects are brothers)

\(^2\)(units of growth hormone, three times per week IM)

\(^3\)(BA = placebo first; AB = hormone first)
Listed below are items concerning children's behavior or the problems they sometimes have. Read each item carefully and decide how much you think your child has been bothered by this problem during the last week: NOT AT ALL, JUST A LITTLE, PRETTY MUCH, or VERY MUCH. Indicate your choice by checking the appropriate box for each item.

<table>
<thead>
<tr>
<th>ID</th>
<th>1-4</th>
<th>5-8</th>
<th>9-10</th>
<th>11-16</th>
<th>17-22</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORM</td>
<td>T050</td>
<td>01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATE</td>
<td>/ /</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOB</td>
<td>/ /</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Problems of Eating
- **1.** Picky and finicky
- **2.** Will not eat enough
- **3.** Overweight

### Problems of Sleep
- **4.** Restless
- **5.** Nightmares
- **6.** Awakens at night
- **7.** Cannot fall asleep

### Fear and Worries
- **8.** Afraid of new situations
- **9.** Afraid of people
- **10.** Afraid of being alone
- **11.** Worries about illness and death

### Muscular Tension
- **12.** Gets stiff and rigid
- **13.** Twitches, jerks, etc.
- **14.** Shakes

### Speech Problems
- **15.** Stuttering
- **16.** Hard to understand

### Wetting
- **17.** Bed wetting
- **18.** Runs to bathroom

### Bowel Problems
- **19.** Soiling self
- **20.** Holds back bowel movements

### Complains of Following Symptoms Even Though Doctor Can Find Nothing Wrong
- **21.** Headaches
- **22.** Stomachaches
- **23.** Vomiting
- **24.** Aches and pains
- **25.** Loose bowels
<table>
<thead>
<tr>
<th>PROBLEMS OF SUCKING, CHEWING OR PICKING:</th>
<th>Not at all</th>
<th>Just a little</th>
<th>Pretty much</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>26. Sucks thumb</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>27. Bites or picks nails</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>28. Chews on clothes, blankets, or other</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>29. Picks at things such as hair, clothing, etc.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>30. Does not act his age</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>31. Cries</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>32. Wants help doing things he should do alone</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>33. Clings to parents or other adults</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>34. Baby talk</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>35. Keeps anger to himself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>36. Lets himself get pushed around by other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>37. Unhappy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>38. Carries a chip on his shoulder</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>39. Bullying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>40. Bragging and boasting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>41. Sassy to grown-ups</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>42. Shy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>43. Afraid they do not like him</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>44. Feelings easily hurt</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>45. Has no friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>46. Feels cheated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>47. Mean</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>48. Fights</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>49. Disturbs other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>50. Wants to run things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>51. Picks on other children</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Section</td>
<td>Item</td>
<td>Not at all</td>
<td>Just a little</td>
<td>Pretty much</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------</td>
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<td>56. Throws himself around</td>
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<td>60. Involved in sex play with others</td>
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<td>65. Daydreams</td>
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<td>66. Truancy</td>
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<td>67. Will not obey school rules</td>
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<td>69. Blames others for his mistakes</td>
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<td>70. Tells stories which did not happen</td>
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<td>77. Things must be done same way every time</td>
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<td>78. Sets goals too high</td>
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95. How serious a problem do you think your child has at this time?

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<td>82. Climbing, gets into things</td>
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<td>86. Cannot stand too much excitement</td>
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<td>87. Laces and zippers are open</td>
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<td>89. Unable to stop a repetitive activity</td>
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<td>90. Acts as if driven by a motor</td>
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<td>91. Mood changes quickly</td>
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<td>92. Poorly aware of surroundings or time of day</td>
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<td>93. Clumsy</td>
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## Table 5: Test Results: Porteus Maze, MFFT, Sentence Copying

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1 "quotient" score; high = "reflective"; low = "impulsive"
2 "product" score; high = "inefficient"; low = "efficient"

(products have been divided by 100)
Table 6: Children's Checking Test
Mean Omission Errors

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overall | .22| .61| .78| 1.56| .94|

Table 7: Computerized Attentional Tests: Results

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1These numbers refer to the six subtests of SELATT.
Table 8: Children's Mood Self-Report Items

1. Feel sad
2. Feel cranky or tired
3. Have trouble keeping my mind on things
4. Feel like something bad might happen
5. Feel restless -- like moving around
6. Feel unhappy
7. Feel like I don't want to play with anyone
8. Feel mad
9. Feel in a good mood
10. Feel like no one wants to help me
11. Feel worried
12. Feel like talking more than usual
13. Feel in a bad mood
14. Feel "funny," not like myself
15. Feel like things may get messed up today
16. Feel like my thoughts are going fast
17. Have thoughts I don't usually have
18. Feel I'm not much good at things
19. Feel like I have a lot of energy
20. Feel tired and slow
21. Feel scared
22. Have trouble doing things
23. Feel like I'm doing a pretty good job
24. Feel like I could cry
25. Feel friendly
26. Feel weird, sort of "freaky"
27. Feel happy
28. Feel like something good is going to happen

Subject is to check off whether the item applies to him/her not at all (0), a little (1), some (2) or a lot (3) over the past two weeks.

(Adapted from van Kammen and Murphy, 1976)
Table 9: Children's Mood Self-Report Ratings by Items

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*(these items approach significance [p < 0.1])
Table 10: Child Behavior Rating Scale (for teachers)

1. impulsivity; acts or thinks without first speaking  
2. fidgeting  
3. motor inhibitions; touches people or objects within reach  
4. motor activity; restlessness  
5. fatiguability  
6. slow performance  
7. pressured or rushed performance  
8. social awareness  
9. cooperation  
10. reaction to or tolerance for frustration  
11. ability to work independently  
12. follows verbal directions  
13. knowledge and application of rules in academic work  
14. ability to listen  
15. monitoring; checks over his/her work  
16. ability to "get started"  
17. performance during any one assignment  
18. adaptive learning; ability to "catch on"  
19. persistence in approach to a difficult task  
20. distractibility  
21. ability to focus in  
22. lapses in performance  
23. expressive language ability  
24. ability to relate to adults  
25. ability to relate to other children

[All items are rated on a 0-3 scale; every level has a substantive descriptor rather than just the number.]
Table 11: Mean Teachers' Ratings of Subjects on CERS Items

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'Items 14-25 were analyzed on the basis of five subjects only because the second half of one questionnaire was not returned.'
References


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DATE

24 March 1954