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Quality of Life and Cognitive Function in Patients with Pituitary Insufficiency

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Abstract
This review is concerned with the psychosocial functioning and the quality of life in patients with pituitary insufficiency who are receiving conventional hormone replacement therapy. The possible negative effects of pituitary surgery, treatment with irradiation, and suboptimal replacement regimens with hormones other than growth hormone on mood, behaviour and cognitive functioning are discussed. The influence of growth hormone deficiency per se, and the outcome of growth hormone therapy in adult patients are addressed in detail. A possible mechanism for a direct effect of growth hormone on the brain is presented.

Introduction

Experienced clinicians have long had the impression that patients with pituitary insufficiency have a diminished overall capacity even when they are receiving adequate conventional hormone replacement therapy, i.e. thyroxine and adrenal and sex steroids. This impression is supported by reports on reduced psychosocial functioning in young adults with childhood-onset (CO) pituitary insufficiency who were treated with growth hormone (GH) until they had reached their final height [1–4]. In a study of 116 patients of ages 18–38 years, the rate of unemployment was found to be approximately 3 times higher than expected and the percentage number married less than 30% of the expected [1]. Further, a higher proportion than expected were living at home with their parents, and were lacking a driver's licence. There was no difference between patients with organic and idiopathic causes of the disease. In a recent study of 210 young adults with growth hormone deficiency (GHD) who had been treated with GH in childhood, a higher proportion of these were found to be living as singles compared with short normal controls, and on average they had less prestigious jobs and a lower income [4].

Although it seems clear that, as a group, patients with pituitary insufficiency of childhood onset are socially disadvantaged with respect to their living situation, partnership and career development, the relative impacts of inadequate hormone replacement therapy, a chronic disease during childhood and adolescence, late sexual maturation and the effects of a short stature per se remain to be clarified. The hypothesis that GH in itself may be an important determinant of psychosocial functioning is supported by the finding of similar functioning in young patients with isolated GHD and those with multiple hormone deficiencies [4].

Quality of Life and Cognitive Function in Patients with Pituitary Disease

A few studies have indicated that adult patients with pituitary insufficiency are psychologically compromised

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Table 1. Reduced quality of life in patients with pituitary insufficiency as assessed by various questionnaires

Author	Ref.	M/F n	Mean age years	Questionnaires									
				NHP				PGWB	GHQ	HSCL	POMS	STAI	Sjöberg
				total score	energy	emotions	social isolation						
McGauley, 1989	5	16/8	39	yes	yes	yes	yes	yes	yes	–	–	–	–
Degerblad et al., 1990	16	3/3	20	–				–	–	–	no[a]	–	no[a]
Whitehead et al., 1992	17	9/5	29	?				no[a]	–	–	–	–	–
Rosén et al., 1994	6	51/35	55	yes	yes	trend	yes	–	–	–	–	–	–
Burman et al., 1995	7	21/15	46	yes	yes	yes	no	yes[a]	–	yes	–	–	–
Deijen et al., 1996	8	46/0	26	–				–	–	no	yes[b]	yes[b]	–

[a] Comparisons were made with normative data in the literature.
[b] Lower vigor (POMS) and higher state anxiety (STAI) were found only in patients with multiple hormone deficiencies.

[5–8]. In most of these studies the disease in the majority of the patients had developed in adult years [5–7]. In general, information on the quality of life has been obtained from questionnaires from which the patients' perception of their well-being and ability to cope with daily life activities has been compared with that of a reference population. The two most commonly used questionnaires in this group of patients are the Nottingham Health Profile (NHP) [9] and the Psychological General Well-Being index (PGWB) [10]. Other instruments such as the Hopkins Symptom Checklist (HSCL) [11], the Profile of Mood States (POMS) [12] and the State-Trait Anxiety Inventory (STAI) [13, 14] have provided additional information. A lack of energy and emotional problems are the two most consistent findings (table 1, fig. 1). In one of the studies a tendency to a higher rate of disability pensions was observed, indicating a reduced capacity for work [6]. In another study hypopituitarism was found to be associated with an increased psychiatric morbidity, depression and dysthymia, when comparison was made with a group of patients with diabetes mellitus [15].

However, in some series of patients [16, 17], absence of negative effects on the quality of life has been reported (table 1). The lack of total conformity between study findings is not unexpected given the relatively small numbers of patients investigated in each study, the variety of instruments used and the heterogeneity of the patient materials. For instance, both gender and the duration of the disease have been found to influence the perception of the quality of life. Women with pituitary deficiency tend to report more problems than men, and patients with GHD of recent onset tend to be better off than those with disease of long-standing duration [7].

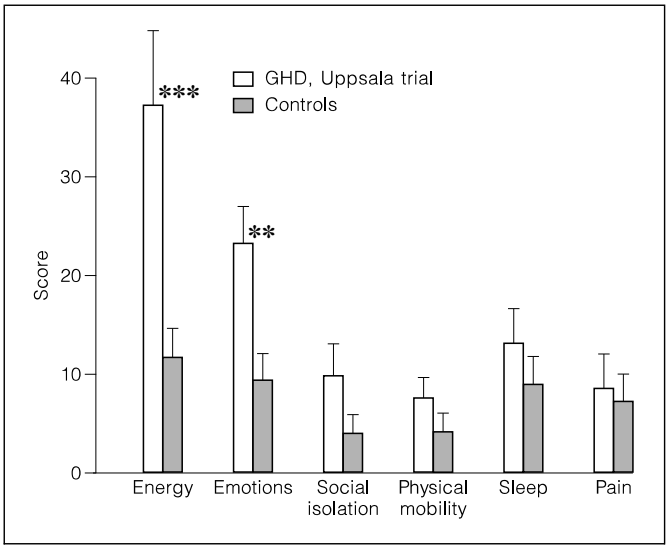

Fig. 1. Baseline data (mean ± SEM) for the six dimensions of the NHP in 36 adults with GHD. For comparison, scores of a healthy control group controlled for age and sex are given. ***$p < 0.001$; **$p < 0.01$. (Reproduced from [7] with the permission of the publisher.)

Present knowledge about the impact of pituitary insufficiency on cognitive function is limited. This is due to a lack of uniformity in the psychological tests used and to the absence of relevant control groups in some studies. In addition, the effects of treatment for pituitary tumours and the effects of the tumour growth in itself can be difficult to separate from the impact of inadequate hormone replacement.

Cognitive Function in Short-Statured Normal Children versus Children with GHD

Patients with CO pituitary insufficiency have, in the past at least, often not attained a normal height and this might be of relevance for their cognitive function. Academic underachievement and cognitive failure may be encountered in children with short stature of an idiopathic origin (ISS), despite average intelligence and unimpaired self-esteem. For instance, poor concentration, hyperactivity, lower attainment in reading and thought problems have been observed in such children [18, 19].

Several studies have found that children with idiopathic GH deficiency (IGHD), with multiple pituitary hormone deficiencies (MPHD) and with ISS showed delayed school achievements and a discrepancy between IQ and achievement scores in reading, spelling and arithmetic [20–22]. Steinhausen and Stahnke [23] found no differences in verbal comprehensiveness, reasoning, word fluency and spatial orientation in young patients with IGHD, MPHD and healthy controls with short stature. From these findings it may be concluded that GHD has no impact on psychological function and that the dysfunctioning of short-statured individuals is mainly the result of experiences associated with the small stature. However, other authors suggest that not only short stature per se, but also the neurological sequelae of long-term GHD may be responsible for the development of specific learning disabilities. This notion is based on the finding that children with MPHD and IGHD, but not those with ISS, show disturbances in visual-motor integration [24].

Cognitive Function in Adults with GHD

Patients with adult onset (AO) GHD frequently report lapses of memory, difficulty in concentrating, and forgetfulness [25–27]. However, as a group young adults with CO GHD have been found to have a normal IQ score and a good educational achievement, although differences in cognitive functions have been observed between patients with IGHD and MPHD. According to the findings by Galatzer et al. [28], the distribution of IQ scores of patients with IGHD is in the upper part of the curve, while that of patients with MPHD is skewed towards the lower part. This may indicate that a combined deficiency of pituitary hormones during the critical period of brain development may be more harmful than that due to GHD alone.

By contrast, cognitive dysfunction has been equally found in IGHD and MPHD patients with CO GHD [8]. Patients with IGHD and those with MPHD both demonstrated lower performance with respect to several memory components and showed a lower IQ score than did age-matched healthy controls (fig. 2). In addition, the IQ score and the education level in the patient group tended to be positively correlated with serum IGF-I concentration, suggesting that subnormal cognitive functioning is specifically related to GHD. Similar results have been found in a study by Burman et al. [7], in which patients with AO GHD reported significantly more problems with their cognitive function, particularly concentration ability as assessed by the HSCL, than did the healthy reference group. These studies suggest that patients with CO GHD and those with AO GHD exhibit subnormal cognitive function which may be caused by the effects of GHD on brain development or neural cell metabolism.

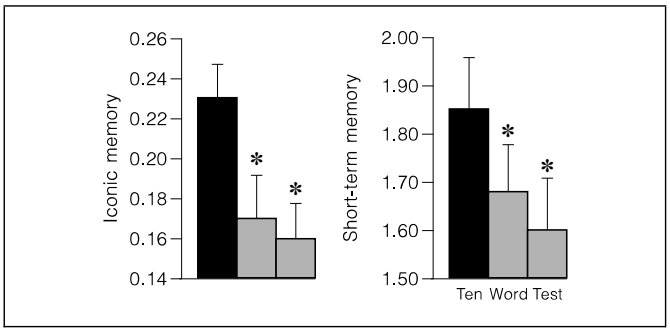

Fig. 2. Iconic and short-term memory scores (mean ± SE) in IGHD (rectangle shaded with dots) and MPHD adults (rectangle shaded with lines), compared with age- and sex-matched controls (solid rectangle); * $p < 0.05$: patients versus controls [reprinted from 8, with kind permission from Elsevier, Kidlington, UK].

Effects of Treatment for Pituitary Tumours

The aetiology of the disease and the treatment of the precipitating disorder, i.e. medication, surgery and/or radiotherapy, are likely to influence the mental performance and well-being. This issue has been addressed in two recent studies [29, 30]. In one of them the self-reported psychosocial functioning of 48 patients who had been treated with transsphenoidal surgery for nonfunctioning pituitary tumours was compared with that of 42 patients who had undergone mastoid surgery, and no differences were found [29]. A noteworthy observation was that the subgroup of hypopituitary patients who in addition to surgery had received radiotherapy reported problems with their mental health and overall quality of life. An analysis of subscores showed that this was mainly explained by an increased prevalence of depression and decreased control of emotions. The results suggest that conventional radiotherapy has a deleterious impact on

the brain function, however, but does not favour the idea of a lack of GH as a major determinant of this effect. It should be emphasized that the mean age of these patients was 59 years. The negative effects of reduced energy and vitality are likely to be less apparent in individuals who have retired from work.

Lack of energy, mild mood disturbances and decreased self-perceived social adjustment have been observed in patients treated for pituitary tumours with either medication or surgery, except in the group of patients who had been operated on with a transfrontal approach [30]. In contrast, all groups of patients were considered by a close informant to exhibit impaired social adjustment. This indicates that frontal surgery is associated with underreporting of difficulties, probably due to a lack of insight. An unrealistic self-appraisal of cognitive and behavioural impairment has previously been observed in patients with frontal brain damage following head injuries [31]. In the subgroup of patients who in addition to transsphenoidal surgery had received radiotherapy, fewer problems with depression and social adjustment were reported than in the group treated with surgery only [30].

Irradiation Effects in Children

Cousens et al. [32], who conducted a meta-analysis on 30 studies of childhood leukaemia assessing the effects of central nervous system prophylactic treatment, which includes cranial irradiation therapy (CRT), on intelligence, concluded that childhood leukaemia appears to be associated with decrements in intelligence which are a function of both psychosocial factors and the treatment.

In a more recent review on the neuropsychological effects of central nervous system prophylactic treatment in childhood leukaemia [33], 25 studies are cited that report negative effects of irradiation on cognitive measurements. Other studies indicate that children who receive CRT develop impaired visual and verbal memory, attention capacity, verbal fluency, and visual discrimination skills, verbal IQ, and reading and spelling [34, 35]. There is therefore substantial evidence that CRT may have a deleterious effect on cognitive abilities in children, the most significant cognitive decline occurring in children less than 7 years of age [36].

Irradiation Effects in Adults

A review of the neurobehavioural effects of irradiation in adults includes 18 studies of prophylactic CRT [36]. Although a large number of these studies reported behavioural changes, few made use of sensitive neuropsychological measures. One of these studies found impairments with respect to problem-solving, memory, sustained attention, complex perceptual tracking and manual dexterity [37]. A study by Lee et al. [38] showed lower scores for verbal performance, IQ, delayed visual memory, and immediate verbal memory of patients who had received CRT 2, 5–10 years previously.

A more recent study on cognitive function following CRT in adult patients made use of extensive neuropsychological measurements [39]. Transient cognitive dysfunction affecting mainly attentional processes was observed at 6 months after limited-field CRT and disappeared at 12 months after CRT. No other cognitive impairments in the entire group were found over a 48-month follow-up period.

In a study of adult patients with pituitary tumours neuropsychological assessment revealed impairment of verbal and visual memory and executive function [40]. This did not appear to be related to the size of the tumour or the effects of radiotherapy or surgery. The authors suggested that a disturbance of neurotransmission or neuromodulation at the level of the hypothalamic microenvironment could possibly explain the poor test results.

Irradiation-induced cognitive dysfunction may be due to damage to the hypothalamus, resulting in personality changes and impairment of cognitive capabilities such as reduced attention span, memory loss and reasoning ability [41]. Another possibility is that irradiation-induced vascular injury is followed by ischaemia and hypoxia in the hippocampal region in particular, which may be responsible for memory impairment [42]. Consistent with this notion is the finding that conventional CRT in rats impairs memory function, which was accompanied by a reduction in regional glucose metabolism in the frontal cortex of the radiated rats [43].

Although the underlying mechanisms of irradiation-induced neurocognitive dysfunction are not yet fully understood, present evidence indicates that CRT may induce neurocognitive dysfunction, younger children being the most susceptible to these injuries. An exact threshold dose after which negative effects occur cannot be given. Diffuse radiation-induced injury to the brain that does not result in a localized necrotizing lesion may still induce neuropsychological deficits. These deficits may be present in the absence of overt necrosis, even without identifying abnormal neural imaging [36].

Influence of Inadequate Replacement with Thyroxine, Adrenal and Sex Steroids

Psychiatric signs such as depression and anxiety are common in endocrine disorders [44]. Hormones may

affect brain function through direct effects on the course of early brain development. These effects are permanent. In addition, hormones may temporarily affect behaviour through their impact on both peripheral and neural-based processes [45]. MPHD is characterized by deficiencies in a number of hormones other than GH, such as sex steroids, ACTH/adrenal steroids and thyroxine. Patients with MPHD therefore receive hormonal replacement therapy with one or more of these hormones. However, this replacement may not be instituted in time to children with MPHD, or it may be suboptimal, with negative effects on brain function.

In adult patients with hormone deficiencies the conventional regimens today may not be as appropriate as they were previously thought, particularly with respect to adrenal steroids and sex hormones. For instance, many patients with secondary hypoadrenalism are frequently given a standard dose of cortisone acetate of 37.5 mg or higher, even though current knowledge indicates that a lower dose is sufficient in a majority of cases. In view of the interindividual variation of the sensitivity to corticosteroids, it is probable that a proportion of the patients might experience negative emotional effects, such as anxiety and nervousness, on the too high conventional doses. On the other hand, a deficiency of ACTH and/or the concomitant cortisol deficiency may be associated with reduced energy, arousal and cognitive functioning. Adult patients with ACTH deficiency show depressive symptoms and apathy [46], coma, anorexia, weight loss, nausea, headache and seizures [47, 48]. Weakness and loss of energy in ACTH deficiency are also reported in some cases [49, 50]. Treatment with ACTH has been found to enhance arousal, vigilance, motivation and selective attention [51]. Visual attention and the associated motor responses have also been found to improve when ACTH levels were raised [52]. In MPHD patients, the observed subnormal perceptual-motor skills were attributed to ACTH deficiency on the basis of the inverse correlation between hydrocortisone replacement dose and the quality of perceptual-motor performance [8].

The present modes of administration of sex steroids are not physiological in either men or women. In addition, the views of physicians on the benefits of replacement with sex hormones in women who are past the childbearing age vary considerably. Besides affecting sexual drive and arousal, sex steroids may influence other aspects of behaviour.

With regard to testosterone, receptors are localized in the hypothalamus, amygdala, septal nucleus and hippocampus [45], regions that are involved in mood and affective behaviour. Indeed, testosterone has been found to be associated with dominance and aggression-related behaviour [53]. Higher testosterone concentrations were found to be associated with more 'masculine' attributes in females, such as enterprise, resourcefulness, uninhibitedness and impulsiveness [54]. Testosterone concentrations have also been found to be positively correlated with disinhibition, or the tendency to display high levels of sensation-seeking behaviour [55]. Men with very low concentrations of testosterone exhibit more passiveness and dependency than do those with average concentrations [56]. Administration of testosterone to hypogonadal men has been accompanied with beneficial effects on several parameters of mood and energy [57]. In patients with MPHD, state anxiety was found to be inversely related to serum testosterone. This finding was attributed to the hypogonadal appearance of these patients [8].

Concentrations of oestrogen, whether alone or in relation to other hormones such as progesterone or testosterone, may also be related to aggression. Low concentrations of oestrogen and progesterone occurring premenstrually have been associated with aggression-like behaviour such as competitiveness, irritability, tension and mood swings. Among elderly men, higher androgen/oestrogen ratios were related to higher self-ratings of irritability and aggression. From these and other observations, the general conclusion has been drawn that sex steroids (testosterone and estradiol) have activating effects on the nervous system. Oestrogens have been shown to increase the dopamine receptor density in the striatum, as well as hydroxytryptamine 2A binding sites in areas of the brain concerned with the control of mood, cognition and emotions [58]. In a recent controlled study, testosterone and oestrogen administered in physiological doses to patients with pubertal delay were found to increase self-reported aggressive behaviour in boys and girls, respectively [59]. Moderate concentrations of oestradiol have been associated with positive effects on mood and behaviour, whereas a lack of oestradiol is tied to depression and emotional lability. Overly high concentrations of sex steroids may result in negative symptoms such as anxiety and depression [45].

GHD may also be accompanied by a deficiency of thyroxine. As thyroid hyper- and hypofunction has been found to be associated with mental disturbances, suboptimal replacement with thyroxine may cause mood changes. Higher scores on obsessive-compulsive and attention-deficit symptoms have been related to lower concentrations of FT4 [60]. In addition, adjunctive treatment with T4 reduced the amplitude and frequency of manic

Table 2. Placebo-controlled studies of the quality of life in adults with GHD

Author	Ref.	n	Age	Design	Tests	Outcome
Degerblad et al., 1990	16	6	20–38	12 weeks cross-over	2 self-reported mood scales	NS
					5 psychometric tests	NS
McGauley, 1989	5	23	21–55	6 months placebo vs. drug	NHP	*
					PGWP total	NS
					mood	*
Whitehead et al., 1992	17	10	19–52	6 months cross-over	NHP	NS
					PGWB	NS
Bengtsson et al., 1993	65	9	34–58	6 months cross-over	SCL-90	NS
					CPRS	*
Mårdh et al., 1994	66	125	20–60	6 months placebo vs. drug + 6 months open	NHP total score	NS
					energy	*
					PGWB total	*
					vitality	*
Beshyah et al., 1995	67	38	19–67	6 months placebo vs. drug	GHQ	*[a]
					CPRS	NS
					Spontaneous patients reports	*
Burman et al., 1995	7	36	28–57	9 months cross-over	NHP	NS[b]
					HSCL	trend ($p = 0.06$)
					PGWP	NS
					Partner questionnaire	*
Deijen et al., 1996	8	46	19–37	26 weeks placebo vs. drug	HSCL	NS
					POMS	NS
					STAI	NS
					Cognitive function	*

* Difference between GH and placebo statistically significant. NS = not significant.

[a] The effects on the quality of life were better after treatment with placebo than after treatment with GH.

[b] $p = 0.03$ when the effects of GH were assessed only in patients with baseline scores above zero ($n = 30$).

and depressive phases in manic-depressive patients [61]. In contrast, elevated T4 levels have been found in depressed and manic patients, indicating that a higher level of thyroxine may be associated with major depressive disorders [62]. Thyroxine levels have also been correlated with psychopathology in hyperthyroid outpatients [63]. From the data available on the relation between thyroxine and mental functioning, it may be concluded that low as well as high concentrations of thyroxine may be associated with depressive illness, whereas high concentrations seem to be particularly related to manic disease. Indeed, thyroxine has been identified as belonging to a class of drugs which are probably capable of inducing mania in patients predisposed to mood disorder [64].

The above data indicate that replacement with an inadequate dose of testosterone may result in passiveness, dependency and state anxiety, whereas too high a dose may result in aggressive and dominant behaviour. Suboptimal replacement with female sex steroids may negatively affect mood and emotions. In addition, too low a dose of hydrocortisone may reduce energy, and either too low or too high a dose of thyroxine may cause depressive disturbances.

GH – Effects on Quality of Life

The finding of a suboptimal quality of life in patients with pituitary insufficiency has raised the question as to what extent this can be accounted for by lack of GH. This issue has been addressed in a few placebo-controlled studies [5, 7, 8, 16, 17, 65–67]. In general the numbers of patients included have been small, and the treatment periods have been limited (table 2). Only one of the studies [8] has included sufficient numbers of patients with IGHD vs. MPHD to allow a separate evaluation of the treatment effect.

Degerblad et al. [16] investigated young adults with CO-GHD. A positive effect of GH therapy was experienced by some of the patients, but was not confirmed in

two mood scales and five psychometric tests. In two studies on small numbers of patients, 6 months of GH therapy was compared with placebo treatment in a cross-over design, with variable results [17, 65]. In one of the studies, 7 of 9 patients showed improvement when assessed by an interviewer with use of the Comprehensive Psychological Rating Scale, but no positive effects were found with use of the Symptom Checklist-90 inventory [65]. In another two studies where the quality of life of adult GHD patients was found to be poorer than that of reference populations, a beneficial effect of GH was found after 6 [5] and 9 months [7], respectively. McGauley et al. [5] reported that treatment with GH was associated with a positive effect on the overall score of NHP, and on a subscale assessing mood in the PGWB index. In the Uppsala trial [7] the effects on the quality of life were documented by the use of three validated self-rating tests and by a partner questionnaire. The most pronounced improvements after GH therapy consistently occurred in areas that were particularly problematic at baseline, i.e. energy, emotions and cognitive functions. The difference between drug and placebo was close to being statistically significant when assessed with the HSCL ($p = 0.06$) and the NHP ($p = 0.08$).

A limitation with the NHP is that the scores tend to be skewed towards low values both in general populations [68] and in patients with diseases [69]. In the Uppsala trial 6 of 36 patients had a baseline problem score of zero, leaving no room for improvement. When the effect was evaluated after exclusion of these 6 patients, so that the comparison was made only in patients with problems at baseline, the difference between GH and placebo became statistically significant ($p = 0.03$). We speculated that a family member would be less likely to be subject to a placebo effect and would be more objective than the patients in evaluating effects on behaviour. Indeed the partners observed marked effects after treatment with GH but not after placebo (table 3).

Table 3. Responses to the partner's questionnaire completed at the end of the 21-month cross-over trial with human recombinant GH and placebo in 36 adult patients with GHD

	Placebo %	GH %	p<
More alert	0.0	69.0	0.0001
More active	3.7	51.8	0.001
Higher endurance	3.6	60.7	0.0001
Less easily annoyed	7.1	28.6	0.10
Less worried	6.9	37.9	0.05
More extrovert	3.4	37.9	0.01
More industrious	3.3	46.7	0.001
More happy	11.1	48.1	0.01
Better looks	10.3	51.7	0.01
More satisfied with his/her occupation	7.7	34.6	0.05
Fewer family conflicts	3.4	24.1	0.10
Better personal relationships	3.4	34.5	0.01

The values indicate the percentages of yes responses to the different short questions. Significance was evaluated by the χ^2 test.

With permission [7].

In a large European multicentre trial beneficial effects of GH on vitality, energy and overall well-being were clearly documented by Mårdh et al. [66]. These effects were sustained after 12 months (table 2). Inconsistent effects were reported in a study by Beshyah et al. [67]. A major problem with their study was the uneven match of patients at baseline. The patients allocated to the placebo group had significantly more health-related problems than the other group, making comparisons difficult. In the Amsterdam trial of men with childhood onset disease [8], only patients with MPHD showed reduced vigour and an increased state of anxiety, attributed to low self-esteem, before treatment. This could indicate that hormones other than GH are of major importance for mood and behaviour. As a group these patients had a hypogonadal appearance and reduced testosterone levels. However, since the severity of the GHD, as assessed by serum insulin-like growth factor (IGF)-I, was less pronounced in the patients with isolated GHD than in those with MPHD, direct comparisons between the two groups can be difficult. In the same series of patients the presence of abnormal lipid levels was found to be inversely related to serum IGF-I [70]. However, it is worthy of note that the observed deviations in vigour and anxiety were not corrected by GH [8], which could indicate either that inadequately treated hormone deficiencies other than GHD, or structural brain damage, or a combination of the two was of relatively greater importance in this group of patients than GH per se.

In an open study with two different doses of GH, similar effects were obtained with respect to quality of life after 6 months of therapy, despite a difference in IGF-I response [71]. Both regimens were associated with beneficial effects as assessed by the NHP and the PGWB.

In summary, although the results of the different trials have shown some inconsistencies, taken together a positive effect of GH in addition to the beneficial effects of placebo has been observed, at least in patients with AO disease. To clarify the full potential of GH replacement therapy further controlled studies with a longer duration

are desirable. Also, improved instruments for assessing the quality of life in GHD have recently been developed and validated [72, 73]. Ideally, the patients selected for future studies should be those with psychosocial problems, and patients with a detectable structural brain damage should be evaluated separately.

GH Replacement and Cognitive Function

There is only one report on the cognitive effects of GH replacement in GHD children. In an open study, the intellectual capabilities of 11 children aged between 4 and 18 years were assessed before and after 1 year of GH treatment. At the start of treatment the group's verbal, nonverbal, and overall abilities fell within the low average range, and their visual-motor skills were below average. No improvements from pretest to posttest were found [24].

In GHD adults the effects of GH replacement on cognitive function have been evaluated in several studies (table 4). In one of the first, patients with CO GHD received native human GH or biosynthetic GH for two separate 4-week periods [74]. Before and at the end of each treatment period, five cognitive tests were performed. GH administration was found to improve face recognition, a test that assesses memory. Degerblad et al. [16] performed a double-blind cross-over study using synthetic GH and a placebo for 12 weeks each in a small number of patients. GH replacement did not result in any improvements in memory and attention. In an open study in adults with CO GHD, 6 months of GH treatment was associated with an improvement in the symbol-number association subtest of the Wechsler Adult Intelligence Scale (WAIS) [75]. In patients with AO GHD (table 4), the effects of GH supplementation on psychological parameters, including cognition as assessed by a subscale of the HSCL, were studied by Burman et al. [7]. Compared to placebo, GH treatment was found to significantly improve cognitive ability, memory in particular. In another long-term GH substitution study, the effects of 2 years of GH replacement therapy on cognitive performance were evaluated in male patients with CO GHD [76]. Patients who were initially given placebo were switched to GH therapy after 6 months. After the placebo-controlled phase of the study, short-term and long-term memory were improved. However, when a distinction was made between patients who had a normalization of serum IGF-I and patients receiving supraphysiological GH treatment, it appeared that only the group receiving supraphysiological GH treatment demonstrated beneficial treatment effects. Patients receiving physiological GH treatment required a year of treatment before demonstrating significant improvement in memory function. As the differences between the two treatment groups disappeared after 1 year of treatment, it would appear that supraphysiological treatment merely serves to speed up the recovery of memory performance. After 1 year of treatment, patients and age-matched controls showed similar scores on these memory parameters (fig. 3). This study demonstrates that the improvement in memory function after short-term GH replacement continues with long-term GH replacement.

From the studies cited, it may be concluded that cognitive dysfunction is observed both in patients with IGHD and those with MPHD. In addition, GH replacement therapy improves cognitive function irrespective of the age at onset of disease. This could indicate that the cognitive impairment may, at least partly, be associated with a disturbance in neural cell metabolism.

GH and the Brain – Possible Mechanisms of Action

Binding sites specific for GH have been demonstrated in several areas of the central nervous system in various species, including man [77, 78]. The binding sites are particularly abundant in the choroid plexus, but a high density of GH binding has also been found in the pituitary, the hypothalamus and the hippocampus [77]. The last-mentioned structure is considered to have a central role in learning and memory, and is a part of the limbic system, which is involved in affective behaviour [79].

GH binding in the choroid plexus has been found to be mainly attributable to the presence of a binding protein rather than the full length receptor [80]. It has been suggested that these binding sites may indicate transport of GH over the blood-brain barrier into the brain [77]. Indeed, subcutaneous administration of physiological doses of GH to GHD patients has been found to be associated with an increase in GH in the cerebrospinal fluid (CSF) [81, 82]. A positive relation between the given dose and the increase in GH in the CSF was observed, indicating passage of GH into the central nervous system [81] (fig. 4).

Treatment with GH has been found to result in a significant decrease in the dopamine metabolite homovanillic acid in the CSF, but no change in the metabolites of serotonin and noradrenaline (HMPG), or in the concentration of β-endorphin [81]. As a group the patients also showed an increase in the concentration of aspartate, whereas no effects were found on two other neurotrans-

Table 4. Summary of studies investigating the effect of GH treatment on cognitive function

Study	Ref.	Subjects	Treatment	Test	Outcome
Abbott et al. 1982 open	24	n = 11 (4 girls, 7 boys) MPHD: 4 IGHD: 7 Age: 4–18 years	0.15 U/kg/week for 1 year	Intelligence draw-a-person visual-motor skill	No effects
Almqvist et al. 1986 open	74	n = 5 (2 females, 3 males) MPHD: 5 Age: 22–36 years CO	Treatment for 4 weeks with pituitary-derived or biosynthetic GH, 8 IU 3 times weekly	Face recognition letter identification simple additions letter rotation letter substitution	↑Recognition memory (face recognition)
Degerblad et al. 1990 controlled	16	n = 6 (3 females, 3 males) MPHD: 5 IGHD: 1 Age: 20–38 years CO	Cross-over Duration: 12 weeks 0.5–0.6 IU/kg/week	Verbal learning non-verbal learning reaction time symbol-digit substitution	No effects
Sartorio et al. 1995 open	75	n = 8 (males) MPHD: 5 IGHD: 3 Age: 25–34 years CO	6 months of GH treatment 0.5 IU/kg/week	Intelligence draw-a-person	↑Intellectual capacity
Burman et al. 1995 controlled	7	n = 36 (15 females, 21 males) MPHD: all Age: 28–57 years AO	1.25 U/m^2/day for 9 months cross-over	HSCL: subscale cognitive complaints	↑Cognitive ability
Deijen et al. in press controlled	76	n = 45 (all male) MPHD: 29 IGHD: 16 Age: 19–37 years CO	Four parallel groups (random assignment) Duration: 104 weeks 1, 2 or 3 IU/m^2/day	Iconic memory short-term memory long-term memory	↑Memory

↑ = More or better; ↓ = less.

mitter amino acids, glutamate and glycine. In this study lumbar puncture was performed after 9 months of treatment with GH or placebo in a cross-over design. In another study, where the CSF was assessed in GHD patients after 1 month on either GH or placebo, the reduction of the dopamine metabolite after treatment with GH was confirmed [82]. In addition, β-endorphin was found to be increased by GH. The discrepant results may be explained by the design of the studies or reflect methodological differences. For instance in the last-mentioned study a steady-state situation with respect to side-effects such as arthralgia and muscle stiffness is not likely to have been attained in the short period of the study. In patients with fibromyalgia, increased CSF levels of β-endorphin have been reported [83].

The monoamine system is considered to be involved in mood disorders. The dopamine neurones of the midbrain project to many parts of the limbic system, including areas known to be associated with alterations in mood and cognitive functioning. This could indicate an important role of dopamine in the CNS. Release of dopamine in the area of the nucleus accumbens generates positive reinforcing feelings [84]. A reduction of the CSF level of the dopamine metabolite homovanillic acid, similar to that observed after treatment with GH, has been found after treatment with tricyclic antidepressants and monoamine oxidase inhibitors [85]. Such drugs generally affect the turnover of more than one monoamine metabolite, but the effect of GH seems to be more restricted.

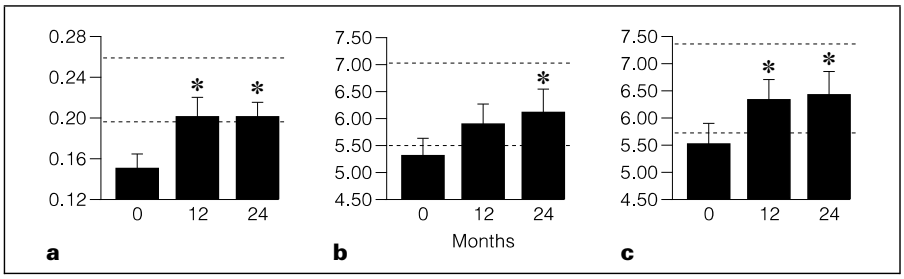

Fig. 3. Mean scores ± SE for iconic (**a**), short-term (**b**; associate learning) and long-term (**c**; associate recognition) memory tasks at baseline (n = 45), after 12 (n = 45), and after 24 months (n = 43) of GH treatment. Dotted lines indicate a 95% confidence interval of the mean for the control group (n = 41); * $p < 0.05$ compared to baseline [reprinted from 76, with kind permission from Elsevier, Kidlington, UK].

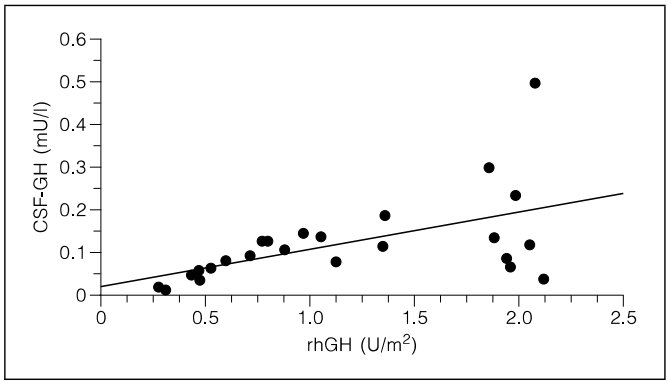

Fig. 4. Correlation between the CSF concentration of GH and the administered dose of rhGH in 24 adults with GH deficiency. (Reproduced from [81] with the permission of the publisher.)

The elevated CSF level of aspartate may be of particular relevance for cognitive functions, since aspartate is a ligand for the N-methyl-*D*-aspartate (NMDA) receptor [86, 87]. This receptor has been implicated in long-term potentiation of synaptic efficacy, a potential mechanism of memory in the hippocampus [87]. Interestingly, injection of an NMDA receptor antagonist has been reported to influence the activity of the central dopamine system [88]. It might thus be speculated that an effect of GH on the dopamine turnover could be mediated through the NMDA receptor.

Other observations of possible significance for emotions and behaviour are the effects of GH on thyroid hormone metabolism. A decrease in the serum concentration of thyroxine (T_4) and an increase in serum triiodothyronine (T_3) are generally found after treatment with GH [89] and are thought to be mediated by enhanced T_4 to T_3 conversion. In the brain, minor changes in the local thyroid homeostasis have been considered to be of clinical relevance for mood [90]. The addition of T_3 to tricyclic antidepressants may be beneficial for resolution of a depressive state [91, 92], and was formerly used in patients refractory to conventional antidepressive therapy. During treatment with GH not only serum levels but also CSF levels of free T_4 have been found to be decreased [81], indicating an increase of T_3 to T_4 ratio in the brain. The T_3 levels in the CSF were, however, too low to be adequately assessed, a finding supported by others [93]. A link between well-being and thyroid homeostasis in the brain is corroborated by a decrease in free thyroxine in the CSF after successful treatment with electroconvulsive therapy (ECT) in patients with depression [94].

In summary, treatment with GH affects the thyroxine concentration and turnover of some important neurotransmitters in the brain. These effects are in some respects similar to those reported after treatment with antidepressive drugs and ECT. The possible relation between these changes and the positive effects on psychological functioning remains to be clarified.

Conclusions

Patients with pituitary insufficiency receiving conventional hormone replacement therapy are found to have a suboptimal quality of life and reduced cognitive functions. Psychosocially the patients are disadvantaged with respect to their family situation and career development, at least if the disease has been acquired during childhood. In patients with AO disease a tendency towards a higher rate of disability pensions has been reported, indicating a reduced capacity for work.

Several factors may be partly responsible for this poor outcome. Surgical treatment and/or irradiation of the precipitating disorder, may cause irreversible brain damage. Inadequate replacement regimens with adrenal and sex steroids or thyroxine may contribute to negative changes in emotions, mood and behaviour. In patients with pituitary insufficiency acquired in childhood, the effects of a chronic disease during an important period of life, as well as the influence of a short stature per se, may be of significance.

During recent years the importance of GH for maintaining normal body composition and physical performance in adult patients has been increasingly recognized. The combined data from hitherto published studies on the relative impact of GH therapy per se on the psychosocial capacity indicate beneficial effects. In particular energy, vitality and memory have been found to be improved by GH. Whether the reported effects of GH on brain dopamine and thyroxine are of relevance for these improvements remains to be established. Future studies of longer duration, with improved instruments, and with homogeneous groups of patients without significant structural brain damage, should clarify the full potential of GH replacement therapy on the capacity for work and the quality of life.

Patient Account

This report is based on the patient's own written report of how she describes herself, how she experienced her pituitary disease and the medication she was given, in particular GH.

The patient is a previously healthy nurse, born in 1947, who at the beginning of the seventies gradually developed headache, irregular bleedings, loss of weight, marked tiredness, thinning of the scalp hair and intermittent bouts of fainting. She was given medication for migraine without effect. Her fainting fits became more frequent and she seeked medical care several times at the local hospital. Lumbar puncture and brain scintigraphy were reported to be normal. After approximately 4 years since the onset of the first symptoms she was admitted for a thyroid scan which revealed a low iodine uptake. Laboratory tests showed low levels of serum cortisol. A diagnosis of hypopituitarism was made, and an empty sella was found on X-ray investigations. During this period she had undergone further training in intensive care. She was on sick-leave for short periods. After the start of replacement therapy with thyroxine, corticosteroids and oestrogen, she worked 65% and felt well.

As she and her husband wanted to have children, ovulation was induced by gonadotrophins. The treatment was successful regarding ovulation, but was associated with severe headache, and was stopped at the request of the patient after three courses of gonadotrophins that did not result in pregnancy. The couple then decided to adopt children and received 2 boys in 1979 and 1981, respectively.

In 1987, at the age of 40, the patient started to work 75% as a nurse in a renal dialysis unit. The new tasks were perceived as stressful and demanding and she lost weight. Her oestrogen medication dose was reduced in 1988. During the same time period she started to experience anxiety and nervousness.

In the following years she became increasingly more tired, and her social life was reduced to a minimum. She had problems in concentrating but continued with her work although she was constantly worried about making a serious mistake, as her attention was poor. After work she felt exhausted and often went to bed after preparing dinner for her family. Her work took all her strength and she finally changed, after much hesitation and considerable grief, to a less demanding position as a nurse in a municipal nursing home for the elderly. During these difficult years she discussed her situation with her district medical officer, and an antidepressant drug was tried but without any positive effects.

In 1990 2 of her 4 sisters passed away. This was a serious blow and worsened her condition. She was now convinced that she had acquired some unusual mental disorder and reduced her working time from 75 to 50%. In the same year she was asked if she would take part in a placebo-controlled study of GH. Placebo and GH would be given in random order for 9 months each. This offer was experienced as 'a light in the tunnel', although no promises of an improved situation were made.

After a few weeks on the first 'drug' (which was later found to be GH), she and her family and her colleagues noticed a change for the better. Slowly but steadily she began to return to her former self, i.e. a creative, happy and extroverted person. At her new job she had previously been perceived as shy and quiet, a person who did her job and then returned home. With time she regained her physical capacity and she took up her previous interest in swimming and long walks. 'I felt like a machine that finally had been given the right kind of petrol', the patient told us.

She has now been on treatment with GH for 6 years. She worked full time for a year without problems, but has now returned to 75% and is studying at the university in parallel with her work at the nursing home, which she is now quite content with.

The patient summarises her story with the following statements: For me treatment with GH gave me my personality back. It gave my husband his wife back. It gave my 2 boys a mother they need and are entitled to. It gave my friends once more a person who takes the time to listen to them and support them if needed. I live a normal life and most people around me are not aware of my disorder, which must be considered a good sign.

References

1 Dean HJ, McTaggart TL, Fish DG, Friesen HG: The educational, vocational and marital status of growth hormone deficient adults treated with growth hormone during childhood. Am Dis Child 1985;139:1105–1110.
2 Björk S, Jönsson B, Westphal O, Levin J-E: Quality of life in adults with growth-hormone deficiency: A controlled study. Acta Paediatr Scand 1989;356(suppl):55–59.
3 Takano K, Tanaka T, Saito T, and the Committee for the Study Group of Adult GH Deficiency: Psychosocial adjustment in a large cohort of adults with growth hormone deficiency treated with growth hormone in childhood: Summary of a questionnaire survey. Acta Paediatr Scand 1994;399(suppl):16–19.
4 Rikken B, van Bussbacht J, le Cessie S, Manten W, Spermon T, Grobbee R, Wit J-M, and the Dutch Growth Hormone Working Group: Impaired social status of growth hormone deficient adults as compared to controls with short or normal stature. Clin Endocrinol 1995;43:205–211.
5 McGauley GA: Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand 1989;356(suppl):70–72.
6 Rosén T, Wirén L, Wilhelmsen L, Wiklund I, Bengtsson B-Å: Decreased psychological well-being in adult patients with growth hormone deficiency. Clin Endocrinol 1994;40:111–116.
7 Burman P, Broman JE, Wiklund I, Erfurth EM, Hägg E, Karlsson FA: Quality of life in adults with growth hormone (GH) deficiency: Response to treatment with recombinant human GH in a placebo-controlled 21-month trial. J Clin Endocrinol Metab 1995;80:3585–3590.
8 Deijen JB, de Boer H, Blok GJ, van der Veen EA: Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 1996;21:313–322.
9 McEwen J: The Nottingham Health Profile; in Walker SR, Rosser RM (eds): Quality of Life, Assessment and Application. Lancaster, MTP Press, 1987, pp 95–111.
10 Dupuy HJ: The Psychological General Well-Being (PGWB) Index; in Wenger NK, Mattson ME, Furberg CF, Elinson J (eds): Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies. New York, Le Jacq, 1984, pp 170–183.
11 Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L: The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. Behav Sci 1974;19:1–15.
12 Shacham S: A shortened version of the Profile of Mood States. J Pers Assess 1983;47:305–306.
13 Ploeg HM van der, Defares PB, Spielberger CD: Handledning bij de Zelf-Beoordelings vragenlijst ZBV. Een nederlandstalige bewerking van de Spielberger State-Trait Anxiety Inventory. Swets and Zeitlinger, Lisse, 1980.
14 Spielberger CD: Test manual of the State-Trait Anxiety Inventory – STAI Form Y. Palo Alto, Consulting Psychologists Press, 1980.
15 Lynch S, Merson S, Beshyah SA, Skinner E, Sharp P, Priest RG, Johnston DG: Psychiatric morbidity in adults with hypopituitarism. J R Soc Med 1994;87:445–447.
16 Degerblad M, Almkvist O, Grunditz R, Hall K, Kaiser L, Knutsson E, Ringertz H, Thorén M: Physical and physiological capabilities during substitution therapy with recombinant growth hormone in adults with growth hormone deficiency. Acta Endocrinol (Copenh) 1990;123:185–193.
17 Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, Hadden DR: Growth hormone treatment of adults with growth hormone deficiency: Results of a 13-month placebo controlled cross-over study. Clin Endocrinol 1992;36:45–52.
18 Skuse D, Gilmour J, Tian CS, Hindmarsh P: Psychosocial assessment of children with short stature: A preliminary report. Acta Paediatr Suppl 1994;406:11–17.
19 Voss LD, Baily BJR, Mulligan J, Wilkin TJ, Betts PR: Short stature and school performance – The Wessex growth study. Acta Paediatr Scand 1991;377(suppl):29–31.
20 Fletcher A, Gore S, Jones D, Fitzpatrick R, Spiegelhalter D, Cox D: Quality of life measures in health care. II: Design, analysis, and interpretation. Br Med J 1992;305:1145–1148.
21 Holmes CS, Thompson RG, Hayford JT: Factors related to grade retention in children with short stature. Child Care Health Dev 1984;10:199–210.
22 Stabler B, Clopper RR, Siegel PT, Stoppani C, Compton PG, Underwood LE: Academic achievement and psychological adjustment in short children. J Dev Behav Pediatr 1994;15:1–6.
23 Steinhausen HC, Stahnke N: Negative impact of growth-hormone deficiency on psychological functioning in dwarfed children and adolescents. Eur J Pediatr 1977;126:263–270.
24 Abbot D, Rotnem D, Genel M, Cohen DJ: Cognitive and emotional functioning in hypopituitary short statured children. Schizophr Bull 1982;8:310–319.
25 Hunt SM, McKenna SP, Doward LC: Preliminary report on the development of a disease-specific instrument for assessing quality of life of adults with growth hormone deficiency. Acta Endocrinol 1993;128(suppl 2):37–40.
26 McGauley GA, Cuneo RC, Salomon F, Sönksen PH: Growth hormone deficiency and quality of life. Horm Res 1996;45(1-2):34–37.
27 Rosén T, Johansson G, Bengtsson B-Å: Consequences of growth hormone deficiency in adults, and effects of growth hormone replacement therapy. Acta Paediatr Suppl 1994;399:21–24.
28 Galatzer A, Wasserman N, Neuhaus H, Laron Z: Psychological well-being of young adults with growth deficiency before and after hGH treatment; in Laron Z, Butenandt O (eds): Growth Hormone Replacement Therapy in Adults: Pros and Cons. London, Freund, 1993, pp 115–122.
29 Page R, Hammersley MS, Burke CW, Wass JAH: An account of quality of life of patients after treatment for non-functioning pituitary tumours. Clin Endocrinol 1997;46:401–406.
30 Peace KA, Orme SM, Sebastian JP, Thompson AR, Barnes S, Ellis A, Belchetz PE: The effect of treatment variables on mood and social adjustment in adult patients with pituitary disease. Clin Endocrinol 1997;46:445–450.
31 Godfrey HPD, Partridge FM, Knight RG: Course of insight disorder and emotional dysfunction following closed head injury: A controlled cross-sectional follow-up study. J Clin Exp Neuropsychol 1993;15:503–515.
32 Cousens P, Waters B, Said J, Stevens M: Cognitive effects of cranial irradiation in leukemia. A survey and metanalysis. J Child Psychol Psychiatry 1988;29:839–852.
33 Butler RW, Copeland DR: Neuropsychological effects of central nervous system prophylactic treatment in childhood leukemia: Methodological considerations. J Pediatr Psychol 1993;18:319–338.
34 Garcia-Pérez A, Sierrasesumaga L, Narbona-Garcia J, Calvo-Manuel F, Aguirre-Ventallo M: Neuropsychological evaluation of children with intracranial tumors: Impact of treatment modalities. Med Pediatr Oncol 1994;23:116–123.
35 Smibert E, Anderson V, Godber T, Ekert H: Risk factors for intellectual and educational sequelae of cranial irradiation in childhood acute lymphoblastic leukaemia. Br J Cancer 1996;73:825–830.
36 Crossen JR, Garwood D, Glatstein E, Neuwelt EA: Neurobehavioral sequelae of cranial irradiation in adults: A review of radiation-induced encephalopathy. J Clin Oncol 1994;12:627–642.
37 Hochberg FH, Slotnick B: Neuropsychologic impairment in astrocytoma survivors. Neurology 1980;30:172–177.
38 Lee PWH, Hung BKM, Woo EKW, Tai PTH, Choi DT: Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma. J Neurol Neurosurg Psychiatry 1989;52:488–492.
39 Vigliani MC, Sichez N, Poisson M, Delattre JY: A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults. Int J Radiat Oncol Biol Phys 1996;35:527–533.
40 Grattan-Smith PJ, Morris JGL, Shores EA, Batchelor J, Sparks RS: Neuropsychological abnormalities in patients with pituitary tumours. Acta Neurol Scand 1992;86:626–631.

41 Mechanick JI, Hochberg FH, LaRocque A: Hypothalamic dysfunction following whole-brain irradiation. J Neurosurg 1986;65:490–494.
42 Abayomi OK: Pathogenesis of irradiation-induced cognitive dysfunction. Acta Oncol 1996; 35:659–663.
43 Lamproglou I, Chen QM, Boisserie G, Mazeron JJ, Poisson M, Baillet F, Le Poncin M, Delattre JY: Radiation-induced cognitive dysfunction: An experimental model in the old rat. Int J Radiat Oncol Biol Phys 1995;31:65–70.
44 Brambilla F: Psychopathological aspects of neuroendocrine disease: Possible parallels with the psychoendocrine aspects of normal aging. Psychoneuroendocrinology 1992;17:283–291.
45 Buchanan C, Eccles JS, Becker JB: Are adolescents the victims of raging hormones: Evidence for activational effects of hormones on moods and behavior at adolescence. Psychol Bull 1992; 111:62–107.
46 Donovan BT: Humours, Hormones and the Mind. An Approach to the Understanding of Behavior. Hampshire/London, Macmillan, 1988.
47 Stacpoole PW, Interlandi JW, Nicholson WE, Rabin D: Isolated ACTH deficiency: A heterogeneous disorder, clinical review and report of four new cases. Medicine 1982;61:13–24.
48 Sauter NP, Mclaughlin CD, Dyess EM, Kritzman J, Lechan RM: Isolated adrenocorticotropin deficiency associated with an antibody to a corticotroph antigen that is not adrenocorticotropin or other proopiomelanocortin-derived peptides. J Clin Endocrinol Metab 1990;70: 1391–1397.
49 Gonzalez-Clemente JM, Halperin I, Navarro MP, Conget JI, Martinez-Osaba MJ, Vilardell E: Déficit aislado de ACTH. Med Clin 1994; 102:220–224.
50 Kawai K, Tamai H, Nishikata H, Kobayashi N, Matsubayashi S: Severe depression associated with ACTH, PRL, and GH deficiency: A case report. Endocr J 1994;41:275–279.
51 Wolkowitz OM, Tinklenberg JR, Weingartner H: A psychopharmaco-logical perspective of cognitive functions. II. Specific pharmacologic agents. Neuropsychobiology 1985;14:133–156.
52 Veith JL, Sandman CA, George JM, Kendall JW: The relationship of endogenous ACTH levels to visual attentional functioning in patients with congenital adrenal hyperplasia. Psychoneuroendocrinology 1985;10:33–48.
53 Hoyenga K, Hoyenga KT: Gender-related differences. Origins and Outcomes. Needham Heights, Allyn & Bacon, 1993.
54 Baucom DH, Besch PK, Callahan S: Relations between testosterone concentration, sex role identity, and personality among females. J Pers Soc Psychol 1985;48:1218–1226.
55 Daitzman R, Zuckerman M: Disinhibitory sensation seeking, personality and gonadal hormones. Pers Individ Diff 1980;1:103–110.
56 Rubin RT, Reinisch JM, Hasker RF: Postnatal gonadal steroid effects on human behavior. Science 1981;211:1318–1324.
57 Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, Steiner B, Hull L, Callegari C, Swerdloff RS: Testosterone replacement therapy improves mood in hypogonadal men – a clinical research center study. J Clin Endocrinol Metab 1996;81:3578–3583.
58 Fink G, Sumner BE, Rosie R, Grace O, Quinn JP: Estrogen control of central monoamission: Effect on mood, mental state and memory. Cell Mol Neurobiol 1996;16:325–344.
59 Finkelstein JW, Susman EJ, Chinchilli VM, Kunselman SJ, Dárcangelo MR, Schwab J, Demers LM, Liben LS, Lookingbill G, Kulin HE: Estrogen and testosterone increases self-reported aggressive behaviour in hypogonadal adolescents. J Clin Endocrinol Metab 1997;82: 2433–2438.
60 Dorn LD, Burgess ES, Dichek HL, Putnam FW, Chrousos GP, Gold PW: Thyroid hormone concentrations in depressed and nondepressed adolescents: Group differences and behavioral relations. J Am Acad Child Adolesc Psychiatry 1996;35:299–306.
61 Whybrow PC: The therapeutic use of triidothyronine and high dose thyroxine in psychiatric disorder. Acta Med Austriaca 1994;21(2):47–52.
62 Sokolov ST, Kutcher SP, Joffe RT: Basal thyroid indices in adolescent depression and bipolar disorder. J Am Acad Child Adolesc Psychiatry 1994;33:469–475.
63 Zeitlhofer J, Saletu B, Stary J, Ahmadi R: Cerebral function in hyperthyroid patients. Psychopathology, psychometric variables, central arousal and time perception before and after thyreostatic therapy. Neuropsychobiology 1984; 11:89–93.
64 Peet M, Peters S: Drug-induced mania. Drug Safety 1995;12:146–153.
65 Bengtsson B-Å, Edén S, Lönn LJ, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tölli J, Sjöström L, Isaksson OGP: Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab 1993;76:309–317.
66 Mårdh G, Lundin K, Borg G, Jonsson B, Lindeberg A on behalf of the investigators: Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: Combined data from 12 European placebo-controlled clinical trials. Endocrinol Metab 1994;1(suppl A):43–49.
67 Beshyah SA, Freemantie C, Shahi M, Anyaoku V, Merson S, Lynch S, Skinner E, Sharp P, Foale R, Johnston DG: Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. Clin Endocrinol 1995;42:73–84.
68 Kind P, Gudex M: Measuring health status in the community: A comparison of methods. J Epidemiol Community Health 1994;48:86–91.
69 Bardsley MJ, Astell S, McCallum A, Home PD: The performance of three measures of health status in an outpatient diabetes population. Diabetic Med 1993;10:619–626.
70 De Boer H, Blok GJ, Voerman B, Phillips M, Schouten J: Serum lipid levels in growth hormone deficient men. Metabolism 1994;43:199–203.
71 Carrol PV, Littlewood R, Weissberger AJ, Bogalho P, McGauley G, Sönksen PH, Russel-Jones DL: The effects of two doses of replacement growth hormone on the biochemical, body composition and psychological profiles of growth hormone-deficient adults. Eur J Endocrinol 1997;137:146–153.
72 Holmes SJ, McKenna SP, Doward LC, Hunt SM, Shalet SM: Development of a questionnaire to assess the quality of life of adults with growth hormone deficiency. Endocrinol Metab 1995;2:63–69.
73 Wallymahmed ME, Baker GA, Humphris G, Dewey M, MacFarlane IA: The development, reliability and validity of a disease specific quality of life model for adults with growth hormone deficiency. Clin Endocrinol 1996;44:403–411.
74 Almqvist O, Thorén M, Sääf M, Eriksson O: Effects of growth hormone substitution on mental performance in adults with growth hormone deficiency: A pilot study. Psychoneuroendocrinology 1986;11:347–352.
75 Sartorio A, Molinari E, Riva G, Conti A, Morabito F, Faglia G: Growth hormone treatment in adults with childhood onset growth hormone deficiency: Effects on psychological capabilities. Horm Res 1995;44:6–11.
76 Deijen JB, de Boer H, van der Veen EA: Cognitive changes during GH replacement in adult men. Psychoneuroendocrinology, in press.
77 Lai Z, Emtner M, Roos P, Nyberg F: Characterization of putative growth hormone receptors in human choroid plexus. Brain Res 1991;546: 222–226.
78 Lobie PE, Garcia Arragon J, Lincoln D, Barnard R, Wilcox JN, Waters MJ: Localization and ontogeny of growth hormone receptor gene expression in central nervous system. Dev Brain Res 1993;74:225–233.
79 Wyss JM, Van Groen T: The limbic system; in Conn PM (ed): Neuro-science in Medicine. Philadelphia, Lippincott, 1995, pp 321–342.
80 Thörnwall M, Chhajlani V, Le Greves P, Nyberg F: Detection of growth hormone receptor mRNA in ovine choroid plexus epithelium cell line. Biochem Biophys Res Commun 1995;217: 349–353.
81 Burman P, Hetta J, Wide L, Månsson J-E, Ekman R, Karlsson FA: Growth hormone treatment affects brain neurotransmittors and thyroxine. Clin Endocrinol 1996;44:319–324.
82 Johansson J-O, Larsson G, Elmgren A, Hynsjö L, Lindahl A, Lundberg P-A, Isaksson O, Lindstedt S, Bengtsson B-Å: Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmittors. Neuroendocrinology 1995;61:57–66.
83 Vaerøy H, Nyberg F: Endogenous opoid peptides, substance P, calcitonin gene-related peptide and their relation to fibromyalgia; in Vaerøy H, Merskey H (eds): Progress in Fibromyalgia and Myofascial Pain. Amsterdam, Elsevier, 1993, pp 75–91.
84 Sundberg DK: Chemical messenger systems; in Conn PM (ed): Neuroscience in Medicine. Philadelphia, Lippincott, 1995, pp 403–426.

85 Risby ED, Hsiao JK, Sunderland T, Ågren H, Rudorfer MV, Potter WZ: The effects of antidepressants on the cerebrospinal fluid homovanillic acid/5-hydroxyindoleacetic acid ratio. Clin Pharmacol Ther 1987;42:547–554.
86 Hyman SE, Nestler EJ: The Molecular Foundations of Psychiatry. Washington, American Psychiatric Press, 1993, pp 56–135.
87 Gardner D: Synaptic transmission; in Conn PM (ed): Neuroscience in Medicine. Philadelphia, Lippincott, 1995, pp 75–114.
88 Svensson A, Pileblad E, Carlsson M: A comparison between the noncompetitive NMDA antagonist dizocilpine (MK-801) and the competitive NMDA antagonist D-CCPene with regard to dopamine turnover and locomotor stimulatory properties in mice. J Neural Transm Gen Sect 1991;85:117–129.
89 Laurberg P, Jakobsen PE, Hoeck HC, Vestergaard P: Growth hormone thyroid function: Is secondary thyroid failure underdiagnosed in growth hormone deficient patients? Thyroidology 1994;6:73–79.
90 Whybrow PC: Behavioral and psychiatric aspects of hypothyroidism; in Braverman LE, Utiger RD (eds): Werner and Ingbar's the Thyroid. A Fundamental and Clinical Text. Philadelphia, Lippincott, 1991, pp 1078–1083.
91 Wilson IC, Prange AJ, McClane TK, Rabon AM, Lipton MA: Thyroid-hormone enhancement of imipramine in nonretarded depressions. N Engl J Med 1970;282:1063–1067.
92 Goodwin FK, Prange AJ, Post RM, Muscettola G, Lipton MA: Potentiation of antidepressant effects by triiodotyronine in tricyclic nonresponders. Am J Psychiatry 1982;139:34–38.
93 Thompson P, Burman KD, Wright FD, Potter MW, Wartofsky L: Iodothyronine levels in human cerebrospinal fluid. J Clin Endocrinol Metab 1982;54:653–655.
94 Kierkegaard C, Faber J: Free thyroxine and 3,3′,5′-triidothyronine levels in cerebrospinal fluid in patients with endogenous depression. Acta Endocrinol (Copenh) 1991;124:166–172.