

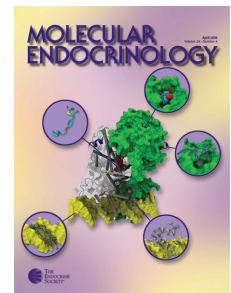
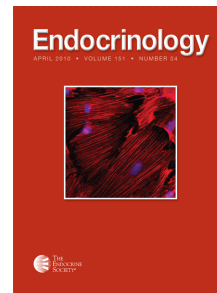
ENDOCRINE REVIEWS

Mortality in Patients with Pituitary Disease

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Mortality in Patients with Pituitary Disease

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Pituitary disease is associated with increased mortality predominantly due to vascular disease. Control of cortisol secretion and GH hypersecretion (and cardiovascular risk factor reduction) is key in the reduction of mortality in patients with Cushing's disease and acromegaly, retrospectively. For patients with acromegaly, the role of IGF-I is less clear-cut. Confounding pituitary hormone deficiencies such as gonadotropins and particularly ACTH deficiency (with higher doses of hydrocortisone replacement) may have a detrimental effect on outcome in patients with pituitary disease. Pituitary radiotherapy is a further factor that has been associated with increased mortality (particularly cerebrovascular). Although standardized mortality ratios in pituitary disease are falling due to improved treatment, mortality for many conditions are still elevated above that of the general population, and therefore further measures are needed. Craniopharyngioma patients have a particularly increased risk of mortality as a result of the tumor itself and treatment to control tumor growth; this is a key area for future research in order to optimize the outcome for these patients. (*Endocrine Reviews* 31: 301–342, 2010)

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Abbreviations: BMI, Body mass index; CI, confidence interval; CRP, C-reactive protein; CRT, conventional radiotherapy; CVA, cerebrovascular accident(s); DHEA, dehydroepiandrosterone; DI, diabetes insipidus; GTR, gross total resection; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; 11 β -HSD, 11 β -hydroxysteroid dehydrogenase; IMT, intima media thickness; LDL, low-density lipoprotein; MR, mineralocorticoid receptor; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; PR, partial removal; RR, risk ratio; SDS, sd score; SMR, standardized mortality ratio; STR, subtotal resection.

I. Mortality in Hypopituitarism

A. Introduction

The pituitary gland is the master regulator of the endocrine system, controlling adrenal, thyroid, and gonadal function, water balance, lactation, and the GH/IGF-I axis among other processes. Hypopituitarism is defined as a biochemical deficiency of one or more of the hormones of the anterior or posterior pituitary gland (1). The prevalence of hypopituitarism ranges between 290 and 455 cases per million, with a reported incidence of 42.1 cases per million (2). A recent systematic review of the prevalence of pituitary adenomas revealed a prevalence of 14.4% in postmortem studies and 22.5% in radiological studies, giving an overall prevalence of 16.7% (3). In recent years, a number of studies have revealed an increased prevalence of clinically significant pituitary adenomas in two population studies from England and Belgium ranging from one case per 1064 persons to one case per 1289 persons (4–6). Thus, many patients have pituitary adenomas without any perturbations in endocrine function of the gland. Data from the Swedish Cancer Registry have shown an increasing incidence of pituitary adenomas, with six cases per million being reported in 1958 rising to 11 cases per million in 1991 (7) (Fig. 1) (incidence in this study was from cancer registry data, the majority of these patients having pituitary adenomas that required surgery). This increase may simply reflect improvements in medical diagnostics, imaging, and clinical surveillance rather than increasing incidence *per se*.

The underlying pathology leading to hypopituitarism had not changed dramatically with time (Table 1), until the last decade when a number of other causes of hypopituitarism have been described such as traumatic brain injury (8), subarachnoid hemorrhage (8), and cranial irradiation for nonpituitary tumors (9). As a result, the incidence of hypopituitarism is likely to increase further as more patients are assessed for pituitary dysfunction with

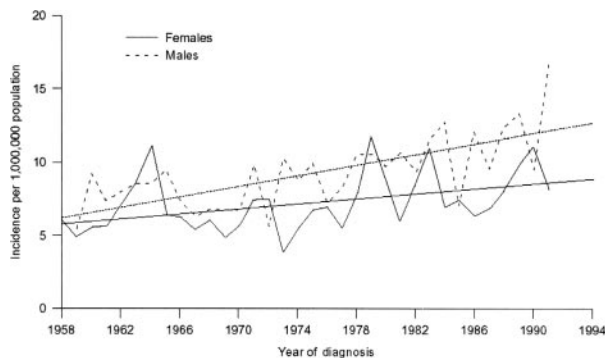


FIG. 1. Increase in incidence of pituitary adenomas in Sweden between 1958 and 1991 ($P < 0.007$). [From B. Nilsson et al.: *J Clin Endocrinol Metab* 85:1420–1425, 2000 (7). Permission granted by The Endocrine Society. © 2000, The Endocrine Society.]

TABLE 1. Causes of hypopituitarism

Underlying cause of hypopituitarism	Tomlinson et al. (12)	Regal et al. (2)	Rosén and Bengtsson (11)
Nonfunctioning adenoma	57	26	55.9
Craniopharyngioma	12	4	10.2
Prolactinoma	9	13	11.1
Idiopathic hypopituitarism	14	11	15.9
Empty sella syndrome	2	7	
Gonadotropinoma	1	NA	NA
Sheehans syndrome	<1	6	NA
TSH-secreting tumor	<1	NA	NA
Pituitary hemorrhage	<1	NA	NA
Arachnoid cyst	<1	NA	<1
Lymphocytic hypophysitis	<1	NA	NA
Parasellar lesions	3	5.2	3.9

Data represent percentage of cases. Table is based on data from the West Midlands hypopituitary cohort [Tomlinson et al. (12), $n = 1014$ patients with acromegaly and Cushing's disease excluded]; Regal et al. (2), $n = 42$ [also acromegaly, 13%; Cushing's disease, 6%; Rathkes cleft cyst, 3%; anterior communicating artery aneurysm, 1.4%; eosinophilic granuloma, 1.4%; and pituitary/choristoma, 3%]; and Rosén and Bengtsson (11), $n = 333$ [also one pinealoma, one astrocytoma, seven undifferentiated tumors, one optic nerve glioma, arachnoid cyst]. NA, Not available.

the above disorders. We will not focus on these conditions specifically with regard to mortality because data are limited, but rather we will include them as a part of the overall hypopituitarism group. Certain conditions that lead to hypopituitarism such as acromegaly, craniopharyngioma, and Cushing's disease also have increased mortality as a result of the condition itself, and these will be discussed.

Hypopituitarism remains a heterogeneous group of conditions unified by variable hormonal deficiencies (some patients will have single deficiencies, whereas others will be deficient in several axes). Indeed, in the study by Regal et al. (2), 87% had gonadotropin deficiency, 61% GH deficiency, 62% ACTH deficiency, 64% TSH deficiency, and 20% cranial (central) diabetes insipidus (DI), with 15, 23, 19, 15, and 7% of patients having two, three, four, five, and six hormone axis deficiencies, respectively. Table 2 shows the heterogeneity in incidence of individual hormonal axis deficiencies and replacement levels in studies assessing mortality in hypopituitarism (some of the patients in these studies were postmenopausal women, and therefore estrogen replacement is not always indicated). GH deficiency is the most common deficiency in pituitary disease, particularly in patients with multiple axis deficiency such as the patients reported in these studies (10). These studies did not always assess for GH deficiency systematically, nor did they replace all patients who were deficient, and this may explain the lower prevalence of GH deficiency than expected. Furthermore, within any particular underlying etiology, the severity of presentation

TABLE 2. Relative prevalence of individual pituitary axis deficiency (and replacement) in studies assessing mortality in hypopituitarism

First author (Ref.)	% ACTH deficient	% ACTH deficient treated	% TSH deficient	% TSH deficient treated	% GH deficient	% GH deficient treated	% FSH/LH deficient	% FSH/LH deficient treated	% CDI	% CDI treated
Tomlinson (12)	75.8	100	66.4	100	9.7	24	65.8	67	18.3	100
Bates (16) ^a	94	NA	79	NA	NA	NA	47	NA	20.7	NA
Lindholm (133) ^b	41	NA	40	NA	95	NA	Male, 69; female, 45	NA	4	NA
Stochholm (19) ^c	67.6	96.2	70.6	86.2	NA	49.8	39.2	83.4	17.4	92.9

The low prevalence of GH deficiency should be noted in the studies by Tomlinson *et al.*, Bates *et al.*, and Stochholm *et al.* CDI, Cranial diabetes insipidus; NA, not available/not detailed.

^a Data only available on percentage of patients treated, 56% deficient in all three axes, and 31% in two axes.

^b GH treatment greater than 75% in childhood onset and less than 25% in adult onset.

^c All patients given adequate substitution if found to be deficient.

may differ markedly between patients, and this may well impact upon morbidity and mortality.

B. Causes of hypopituitarism

The majority of cases of hypopituitarism result from tumors within the pituitary gland (Table 1) (2, 11, 12). Pituitary tumors are common, and in many cases are discovered incidentally and may have no impact upon pituitary function as shown from the relative prevalence of pituitary adenomas compared with hypopituitarism. Simply, the presence of a tumor within the pituitary gland does not equate to hypopituitarism; the diagnosis of hypopituitarism is dependent upon appropriate and often dynamic endocrine testing that is interpreted in the context of appropriate pituitary imaging. Nonfunctioning pituitary adenomas represent the commonest cause of hypopituitarism, at approximately 50% of cases (Table 1). However, the clinical presentation and natural history even within this potentially homogenous cohort may differ (2, 12). Specifically, within the elderly population (>65 yr) the incidence of craniopharyngioma is decreased (13), but nonfunctioning adenomas remain the commonest tumor within the pituitary. The diversity of the underlying diagnosis, combined with the rarity of some underlying diagnoses offers a considerable challenge in understanding and interpreting all-cause and specific mortality data that relate to hypopituitarism.

C. All-cause mortality in hypopituitarism

The standardized mortality ratio (SMR) is a measure of observed numbers of death in a study population compared with the expected numbers of deaths if the age- and sex-specific rates were the same as those of the standard population. In essence, it measures how much more (or less) likely a person is to die in the study population compared with someone of the same age and gender in the standard population, with a value of 1 meaning the patients are as equally likely to die as the normal population, a larger value meaning they are more likely to die, and a value less than 1 meaning they are less likely to die.

For internal analysis within cohorts (not compared with general population), the risk ratio (RR) is used, which allows a good indication of the strength of association between exposure and disease outcome (RR = risk in exposed group/risk in unexposed group). Poisson regression analysis allows us to compare rates between two exposures or indeed more than two exposure groups and allows us to examine the effect of an ordered or continuous exposure variable. In addition such analysis controls for the confounding effects of one or more variables and the effects of exposures that change over time (14).

TABLE 3. SMRs (observed/expected deaths) and 95% CIs (where available) for all-cause and specific-cause mortality for the published studies in hypopituitary patients

First author (Ref.)	Total (n)	Deceased (n)	% RT	Men				Women			
				SMR all-cause	SMR vascular	SMR respiratory	SMR malignancy	SMR all-cause	SMR vascular	SMR respiratory	SMR malignancy
Rosen (11)	333	104	47.4	1.47	1.7	NA	0.3	2.82	2.7	NA	0.98
Bates (16)	172	60	57	1.50 (1.02–2.13)	1.32 (0.74–2.17)	NA	0.53 (0.11–1.54)	2.29 (1.37–3.58)	1.46 (0.50–3.20)	NA	3.21 (1.46–6.11)
Bulow (18)	344	122	88.4	1.91 (1.59–2.28)	1.54 (1.16–2.03)	2.03 (0.93–3.85)	1.48 (0.95–3.85)	2.93 (2.28–3.75)	2.39 (1.60–3.52)	2.12 (0.44–6.21)	2.28 (1.25–3.82)
Bates (17)	348	83	28.5	1.2	0.9 (0.5–1.4)	NA	NA	1.3	0.5 (0.2–1.0)	NA	NA
Tomlinson (12)	1014	181	34.8	1.57 (1.19–2.06)	1.7	2.1	0.9	2.29 (1.75–3.0)	2.34	3.41	1.07
Nilsson (7)	2279	842	NA	1.88 (1.72–2.05)	1.44 (1.26–1.65)	0.98 (0.57–1.57)	1.40 (1.12–1.72)	2.28 (2.04–2.54)	1.79 (1.50–2.13)	1.90 (1.09–3.09)	1.57 (1.19–2.02)
Svensson (20)	1411	399	32	3.36 (2.93–3.83)	1.20 (0.88–1.60) ^a	NA	3.59 (2.74–4.63)	4.54 (3.89–5.26)	1.87 (1.27–2.65) ^a	NA	4.49 (3.26–6.03)
Lindholm (133)	161	41	18	0.83 (0.55–1.26)	NA	NA	NA	1.97 (1.2–3.21)	NA	NA	NA
Stochholm (19)	1794	644	19.8–30.8	1.9 (1.7–2.2) ^b	NA	NA	NA	3.4 (2.9–4.0) ^b	NA	NA	NA
Nielsen (15)	192	53	22	0.98 (0.70–1.37)	1.07 (0.59–1.93)	NA	0.69 (0.33–1.44)	2.11 (1.35–3.31)	1.09 (0.27–4.36)	NA	1.70 (0.76–3.78)

The 95% CI is derived using an error factor [EF = exp(1.96/√d)], d_i, Total observed number. 95% CI = SMR/EF to SMR × EF. RT, Patients who received pituitary irradiation; NA, data not available.

^a Data relate to myocardial infarction including fatal events outside hospital.

^b Adult-onset hypopituitary patients, all with GH deficiency.

Analysis of mortality with hypopituitary cohorts is complex and challenging due to the diversity of underlying etiologies and treatment modalities. The challenge in interpretation is further complicated by the low numbers of deaths reported in the published studies, ranging from 41 to 842 patients (Table 3). In the cohorts discussed within this section, mortality within the immediate postoperative period has been removed, as have patients with acromegaly and Cushing’s disease; these will be discussed in *Sections II and III*, respectively, because these conditions *per se* are associated with increased mortality independent of hypopituitarism.

In the vast majority of studies presented to date, all-cause mortality is increased in patients with hypopituitarism when compared with age- and sex-matched controls (Table 3 and Fig. 3). Rosén and Bengtsson (11) were the first to identify increased mortality in hypopituitary patients. In their retrospective analysis of 333 consecutive patients diagnosed with hypopituitarism, they observed a SMR in the overall group of 1.81 (observed 104/expected 57.4). When divided by gender, the SMR for males was 1.47 (observed 63/expected 42.9) and for females, 2.82 (observed 41/expected 14.5) (11) (Fig. 2). Subsequently, several other cohort studies have been published (Table 3 summarizes all studies to date assessing mortality in patients with hypopituitarism). With one exception (15), SMR is increased in men, ranging from 1.2 to 3.36 (7, 11, 12, 16–20), and is elevated in women, ranging from 1.3 to 4.54. In all cases, SMR values are higher in women than those seen in men (7, 11, 12, 15–20). A recent meta-analysis examined all published studies and concluded that the SMR associated with hypopituitarism in men is 2.06 [95% confidence interval (CI), 1.94–2.20] and in women 2.80 (95% CI, 2.59–3.02) (21) (Fig. 4), this increase in SMR in women is statistically significant ($P < 0.0001$). In clinical terms, this leads to an age of death in the entire pituitary cohort ranging between 64.5 and 72.3 yr (7, 16), in men being 56.2–65 yr (12, 16, 17) and in women 52.0–66 yr (12, 16, 17).

The impact of gender upon all-cause mortality is clear, but the underlying reasons remain obscure. However, these SMR data do not imply that the underlying condition is more severe in men than women or that men respond better to specific treatment. The higher SMR in women may simply reflect that hypopituitarism removes the natural survival advantage that women have over men in the general population. A possible explanation may be under diagnosis of hypopituitarism in women because many of the diagnostic tests are not gender specific. Indeed, in the study by Nielsen *et al.*, diagnosis of adrenal, thyroid, and gonadal deficiency and panhypopituitarism was higher in men (52, 49, 73, and 33%, respectively) than

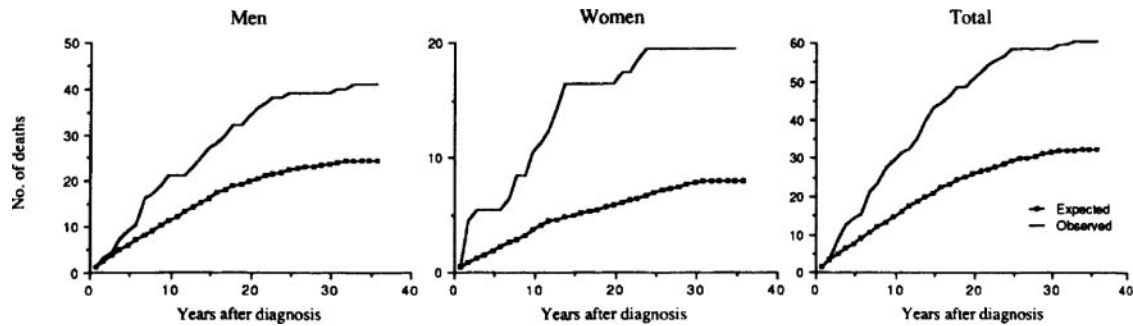


FIG. 2. Death rates from vascular disorders in patients with hypopituitarism and in age- and sex-matched controls. [Reproduced from T. Rosén and B. A. Bengtsson: *Lancet* 336:285–288, 1990 (11), with permission from Elsevier.]

women (30, 30, 46, and 17%, respectively) (15). There is evidence, however, in healthy postmenopausal women that oral estrogen replacement therapy is associated with increased mortality predominantly due to breast cancer and cardiovascular/thromboembolic diseases (22). In women who take oral estrogens, there is also evidence of GH resistance at the level of the liver to IGF-I generation (23) and elevations in total circulating cortisol as a result of elevated corticosteroid-binding globulin (24). GH itself modulates tissue glucocorticoid exposure through modulation of 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 1 (25).

The time since diagnosis does not seem to impact upon mortality (12, 18), but age itself is an important factor. SMRs are highest in the youngest patients, with mortality in elderly patients in some cohorts no different from age- and sex-matched controls (Fig. 5). Again this may not reflect differing degrees of severity of the underlying condition with age but may simply reflect age-related mor-

tality rates within the control population. The year of diagnosis is important, as judged by historical databases showing higher SMR in patients who were diagnosed in the more distant past, with a negative correlation between the first year of inclusion in study and SMR ($r = -0.65$; $P = 0.017$) (21). However, when data were analyzed according to gender, the negative correlation was significant for men only (men, $r = -0.65$, $P = 0.03$; women, $r = 0.58$, $P = 0.18$) (Fig. 6).

D. Specific cause mortality in hypopituitarism

This has been an important step in enhancing our understanding of factors that contribute to increased mortality in patients with hypopituitarism. Furthermore, an appreciation of specific cause mortality can help to target appropriate therapy in an attempt to modify risk. However, several important limitations need to be realized. First, much of the reported data are based on death certification and not on postmortem findings, and therefore complete accuracy of cause mortality cannot be ascertained. Indeed, several studies have reported the potential inaccuracies of death certificate data compared with autopsy data (26–28). This is particularly the case for cardiovascular (29, 30), respiratory, and gastrointestinal death (26); however, recording of cancer death is usually concordant (26). Second, in many cases, subgroup analysis is based upon very small numbers of observed deaths, and therefore a very small number of excess deaths can seemingly translate to dramatic changes in SMR (Table 3).

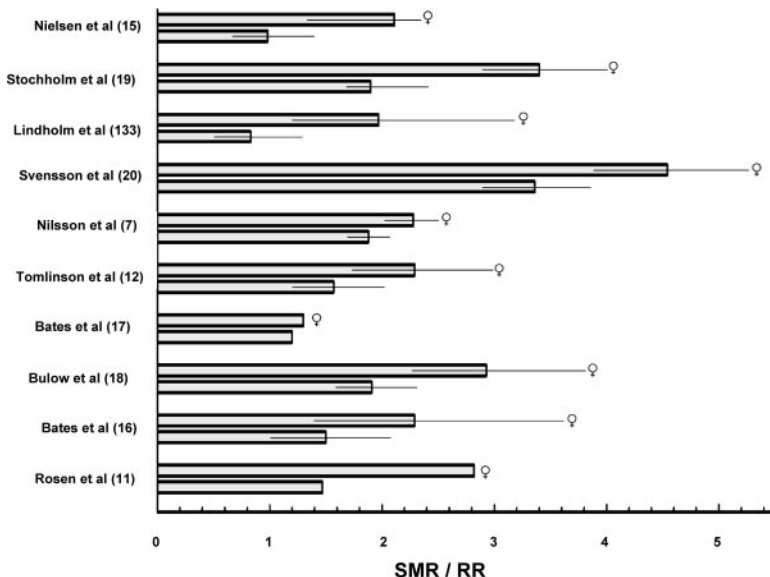


FIG. 3. SMRs (observed/expected deaths) and 95% CIs (where available) for all-cause and specific-cause mortality in men and women for the published studies in hypopituitary patients. The line in the bars equates to the 95% CI when available. ♀, Female patients.

1. Vascular death

In most studies (11, 12, 18, 20), but not all (15, 16, 31), vascular and cardiovascular mortality is increased, with SMRs up to 18.4 in the youngest female patients with adult onset hypopituitarism (however, it should be highlighted that this increased SMR was based on four deaths) (19). The main cause of mortality

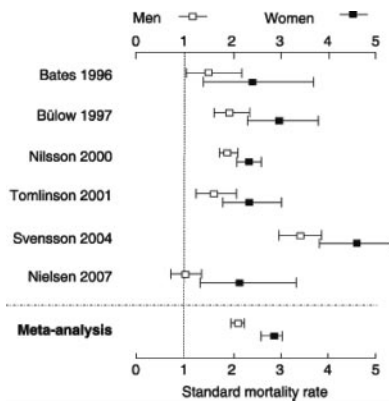


FIG. 4. SMR and 95% CI in patients with nonmalignant pituitary diseases (Cushing’s disease and acromegaly excluded). Weighted meta-analysis (bottom line). Results are shown for men (open boxes) and women (black boxes) separately. Weighted SMR values for men (SMR, 2.06; 95% CI, 1.94–2.2) and women (SMR, 2.8; 95% CI, 2.59–3.02) were calculated using inverse variance method. The widely separate 95% CIs of weighted SMR values illustrate the statistically significant difference between calculated overall SMR values in men and women. [From E. H. Nielsen et al.: *Clin Endocrinol (Oxf)* 67:693–697, 2007 (21). Permission granted from Wiley-Blackwell.]

in the study by Rosén and Bengtsson (11) was vascular disease with SMR in the overall group of 1.95 (observed 60/expected 30.8), and in males SMR 1.7 compared with 2.7 in females; however, the risk quotient was not significantly higher in women than men. Similarly, the main causes of the increased mortality in the study of Tomlinson et al. (12) were cardiovascular deaths (SMR = 1.62; $P < 0.0001$), but cerebrovascular (SMR = 2.55; $P < 0.0001$) and respiratory (SMR = 2.03; $P = 0.002$) deaths were also increased.

The finding that in some studies vascular mortality was not increased is interesting. Within 391 patients diagnosed with hypopituitarism (patients with Cushing’s disease and acromegaly excluded) who all underwent autopsy (although not formal dissection in all cases), cerebrovascular death was increased in both males [odds ratio (OR), 2.02]

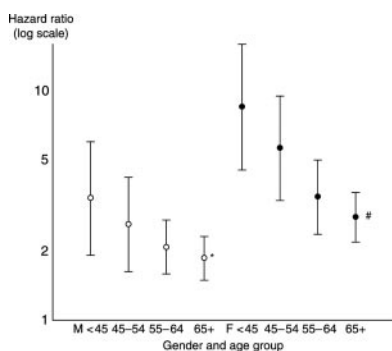


FIG. 5. Hazard ratios of total mortality in adult-onset GH deficiency (1980–2004), subdivided into four age groups according to age at entry and gender. Open circles, Males; black circles, females. Mortality is decreased with increasing age at entry. *, $P < 0.05$; #, $P < 0.001$. [Reproduced from K. Stochholm et al.: *Eur J Endocrinol* 157:9–18, 2007 (19). © 2007 Society of the European Journal of Endocrinology. Reproduced with permission.]

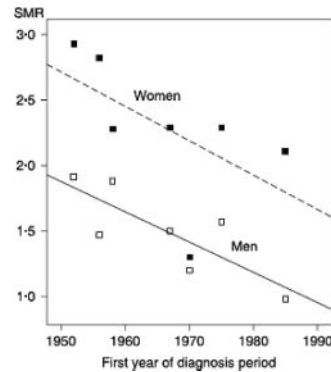


FIG. 6. Association between SMR and first year of diagnosis in patients with hypopituitarism. When all SMR values were included in a partial correlation analysis controlling for the effect of sex, a statistically significant negative correlation was found between SMR and first year of diagnosis. When data were analyzed separately for each sex, the correlation was statistically significant in men only. Computed regression lines are shown for men and women separately. [From E. H. Nielsen et al.: *Clin Endocrinol (Oxf)* 67:693–697, 2007 (21). Permission granted from Wiley-Blackwell.]

and females (OR, 1.73) with a particular increase in cerebral hemorrhage (male OR, 4.6; female OR, 4.8) but no difference from the general population for cerebral infarction (31). Data relating to the exposure to radiotherapy in this group were not reported. However, deaths related to ischemic heart disease were lower (notably in women) than those in age- and sex-matched controls (male SMR, 0.44; female SMR, 0.27) (31). In the two studies by Bates et al. (16, 17), vascular mortality was not increased. In the first unselected hypopituitary cohort, whereas the vascular SMR was increased (1.35; 95% CI, 0.84–2.07; $P = 0.11$), this failed to reach statistical significance, perhaps due to the relatively small size of the cohort ($n = 172$) (16). In the subsequent study, mortality was assessed in a cohort of patients who had all undergone pituitary surgery. SMR for vascular mortality was significantly lower than controls at 0.7 (95% CI, 0.5–1.1; $P = 0.03$) (17). The SMR for cardiovascular death was 0.5 (95% CI, 0.2–1.0; $P < 0.01$) in women and 0.9 (95% CI, 0.5–1.4; $P = 0.26$) in men (17). The discrepancies between studies could perhaps reflect overreporting of cardiovascular disease-related deaths on death certification in the absence of autopsy, as well as the selection of patients who are suitable for surgical intervention.

The mechanisms that underpin the increase in cardiovascular mortality are not fully understood. The role of GH deficiency has been widely speculated and is dealt with in Section 1.F. Importantly, most of the large cohort studies that have examined mortality in hypopituitary patients have been in patients with either documented or presumed GH deficiency (patients were not on GH replacement in the vast majority of cases). It is important to note that to date there are no data reporting normalization of mortality after GH replacement. Indeed, the number of patients

required to adequately power such a study suggests that such data will not be forthcoming in the near future.

Not all studies have had sufficient numbers to allow the analysis specifically of cerebrovascular mortality. However, where data are presented, cerebrovascular disease-specific SMRs range between 1.73 and 4.9 (7, 12, 18–20, 31) (Table 3). Furthermore, there is evidence to suggest that those patients diagnosed at a younger age have increased cerebrovascular mortality (18). Interpretation of the published data is challenging and in many situations is complicated by the use of radiotherapy and its effects (some studies report radiotherapy rates ranging from 25–88.4% (12, 18–20) (Table 3), whereas others do not (7, 31). The contribution of radiotherapy to mortality in pituitary disease is discussed in *Section V*. Other possible contributing factors to explain the increased vascular mortality are outlined below.

a. Insulin sensitivity. The studies of cardiovascular risk in hypopituitarism have been either cross-sectional studies comparing patients on conventional replacement to control subjects or interventional studies primarily examining the impact of GH replacement therapy. Patients on conventional replacement therapy exhibit abnormalities of protein, fat, and carbohydrate metabolism that contribute to the abnormal body composition observed. Lean mass is reduced, and fat mass is increased. There is a propensity to central obesity, and intraabdominal or visceral fat deposition is significantly increased compared with control subjects with similar body mass index (BMI) (32, 33). In the general population, increased visceral adiposity is associated with the metabolic syndrome: insulin resistance or diabetes mellitus, hypercholesterolemia, and hypertension (34, 35).

Although blood glucose and plasma insulin levels are similar to those seen in controls, patients treated for pituitary disease have been shown to be insulin resistant. Johansson *et al.* (36) used the euglycemic clamp to assess insulin sensitivity in 15 patients and 15 controls matched for age, gender, and BMI. The glucose infusion rate required to maintain normal glucose levels was significantly lower in the patients than in controls (3.9 ± 0.5 vs. 9.9 ± 0.7 mg/kg body weight/min; $P = 0.001$). When corrected to account for the differences in body composition, the difference was more profound (5.8 ± 0.8 vs. 13.9 ± 0.9 mg/kg lean body mass/min; $P < 0.001$).

b. Lipid abnormalities. In some hypopituitary cohorts, patients have adverse fasting lipid profiles, including low high-density lipoprotein (HDL) cholesterol, increased triglycerides, and decreased low-density lipoprotein (LDL) particle size; increased BMI (up to 32% being clin-

ically obese BMI >30 kg/m²), and waist circumference (37–41). Importantly, in the large cohort studies characterizing metabolic phenotype, interpretation of the data is hampered by lack of age-, sex-, and demographically matched controls. The serum lipid profile is abnormal in patients on conventional pituitary hormone replacement, with elevated total and LDL cholesterol and triglyceride levels (37, 42–47). Serum levels of HDL cholesterol have been reported as either unchanged (44, 47) or decreased (43, 45, 46) in hypopituitarism. In the largest study to date, a centralized laboratory was employed to examine the fasting lipid profile in 2589 patients (48.8% female; age, 44.2 ± 14.6 yr) before commencing GH replacement (38). The mean (\pm SD) total, HDL and LDL cholesterol were 6.1 ± 1.3 , 3.7 ± 1.1 , and 1.2 ± 0.4 mmol/liter respectively. The total cholesterol was above the target level of 5.2 mmol/liter in 71% of patients (66% of males and 75% of females); HDL was below the target level of 1.2 mmol/liter in 49% (46% of men, 49% of premenopausal women, and 57% of postmenopausal women). The ratio of total cholesterol to HDL was increased above 4.5 in 59% of patients (69% of men, 44% of premenopausal women, and 55% of postmenopausal women). Triglycerides were above the target value in 57% of men, 49% of premenopausal women, and 60% of postmenopausal women. The frequency of an abnormal lipid profile increased with age in both sexes. Total cholesterol was also increased in the presence of smoking, diabetes mellitus, and epilepsy and in patients taking lipid-lowering drugs. The HDL concentration decreased with increasing BMI, waist:hip ratio, and waist circumference and was also lower in patients who smoke, had diabetes mellitus, or took lipid-lowering agents.

c. Blood pressure. The data regarding the prevalence of hypertension in patients with hypopituitarism compared with the general population are conflicting. Rosén *et al.* (45) described an increased prevalence of hypertension in patients with hypopituitarism, but a number of other studies have found no difference (48–50), and some studies have found that patients with hypopituitarism have lower blood pressure than controls (51–54). The majority of data would suggest that hypertension is not a major feature of hypopituitarism and is unlikely to play a major role in the associated vascular morbidity.

d. Vascular structure and function. The development of atherosclerotic disease is a gradual process that has been studied using a variety of structural and functional measures and serological markers. The earliest detectable change is in the intima media thickness (IMT), which increases as lipids are deposited in the intima of large arteries. Carotid

IMT can be measured using ultrasound and is a predictor of myocardial infarction and cerebrovascular accident (CVA) in adults over 65 yr of age (55). The carotid IMT is significantly increased in adults with hypopituitarism compared with age-matched controls (40, 56, 57); however, this is not the case in adolescents with untreated GH deficiency (58). Major blood vessels dilate to accommodate the pulse pressure generated by the heart to smooth the flow of blood through the arterial system. As vascular disease develops, these vessels become stiffer and are less likely to dilate in response to the pressure wave or to stimuli such as acetylcholine. This is dependent upon nitric oxide generation by nitric oxide synthase. Impaired vascular reactivity is thought to promote further endothelial damage facilitating the atherogenic process. Patients with hypopituitarism on conventional replacement therapy have impaired large vessel reactivity and evidence of impaired nitric oxide generation (59).

Impaired endothelial function promotes adhesion of leukocytes to the endothelium that migrate through it and produce an inflammatory response (60). This is mediated via adhesion molecules that are expressed on the luminal surface of the endothelium. Serum levels of C-reactive protein (CRP), IL-6, and TNF- α are increased in patients with hypopituitarism (61–63). Adhesion molecules such as intercellular adhesion molecule-1, E-selectin, and P-selectin are reported to be elevated in patients with panhypopituitarism, although these findings appear to be variable. Furthermore, *in vitro* studies demonstrate that monocytes collected from these patients show increased adhesion to bovine endothelial cells (64).

Fibrinolytic activity is an important contributor to cardiovascular risk; reduced activity is associated with venous thromboembolic disease, stroke, and ischemic heart disease. One of the major regulators of the fibrinolytic system is plasminogen activator inhibitor-1 (PAI-1), which regulates tissue plasminogen activator through inhibition (65). PAI-1 levels are elevated in patients with hypopituitarism (66–69). Devin *et al.* (66) demonstrated that the 24-h fibrinolytic profile was abnormal in hypopituitarism, reporting a 62% increase in PAI-1 antigen levels ($P < 0.05$) and a 24% reduction in tissue plasminogen activator levels ($P = 0.003$). In addition, the normal circadian rhythm of PAI-1 was lost. Thus, hypopituitarism treated with conventional replacement therapy (but not GH) is a prothrombotic state that may contribute to the increased cardiovascular mortality observed in patients, and this has been shown to be improved by GH replacement in some studies (68, 69). Circulating levels of AMDA (asymmetrical dimethylarginine), an endogenous nitric oxide synthase antagonist, are elevated in hypopituitary patients independent of GH deficiency (70). In addition, in

hypopituitary women, inflammatory cytokines that have been implicated in the pathogenesis of cardiovascular disease including IL-6 and CRP and remain elevated in women after correcting for BMI (71).

2. Malignancy

Where data have been reported, malignant causes of death have included tumors within the gastrointestinal tract, pancreas, liver, bone, central nervous system, lungs, skin, breast, urogenital tract, and lymphohemopoietic system (7, 31). The data have been somewhat conflicting as to whether mortality secondary to malignancy is different in patients with hypopituitarism compared with the general population. In the earliest reports (11, 16), deaths related to malignancy were lower than expected, notably in men, although the actual number of deaths was very small [three male deaths in each of those studies with 10.1 (11) and 5.7 (16) expected, respectively]. Larger studies have reported either no increase in malignant deaths (12, 18, 21, 31) or a significant increase (7, 16, 19, 20) with SMRs up to 12.2 in the youngest patients, reflecting the rarity of malignant diagnoses in the control cohort (19). Differences in control populations may be important, bearing in mind the prevalence of specific cancer types within certain populations. Also, patients with a pituitary adenoma may have an inherent increased risk of malignancy. Overall, the lack of consensus within the literature may reflect differences in the specific populations (and control cohorts) that have been studied as well as differences in treatment modalities and power of studies to assess this outcome. The effects of radiotherapy on future development of secondary intracranial malignancy are discussed in *Section V*.

3. Respiratory and respiratory tract infections

Respiratory mortality remains a poorly defined area in most studies. Only three studies have quoted specific respiratory mortality, and the data are contradictory. Mortality was increased in both males and females in one study (overall SMR, 2.55; $P < 0.0001$) (12); increased in males but not females in another study (SMR, 1.48, and 95% CI, 1.02–2.14; *vs.* SMR, 0.818, and 95% CI, 0.53–1.3) (31); and increased in females but not males in another study (SMR, 1.9, and 95% CI, 0.57–1.57; *vs.* SMR, 0.98, and 95% CI, 0.57–1.57) (7). Although there are theoretical reasons as to why hypopituitary patients may be more vulnerable to respiratory tract infections, including the role of glucocorticoid replacement and potential defects in immune function, there is still little evidence to suggest that this translates to increased respiratory mortality. There is some evidence within the literature to suggest that hypopituitary patients may be more susceptible to life-

threatening infection (72). In a retrospective case note series, severe infections including those affecting the respiratory tract were more common in neurosurgically treated hypopituitary patients compared with control-treated patients without pituitary hormone deficiencies. This was a small retrospective study, and the control group may not be entirely appropriate, but the results do provide an indication of increased susceptibility to infection (72). Mukherjee *et al.* (73) found that the immune response to pneumococcal vaccine and other markers of humoral immunity was abnormal, particularly in patients with low prolactin and IGF-I. This impaired immune function may contribute to the mortality attributed to respiratory disease, particularly in patients with craniopharyngioma who are likely to have severe hypopituitarism including prolactin deficiency. Replacement of dehydroepiandrosterone (DHEA), which is frequently deficient in patients with hypopituitarism, may have a positive effect on immune function in patients with Addison's disease (74), and there is much *in vitro* work suggesting that DHEA may have an immunomodulatory role (75) (it must be noted that many of these studies have used supraphysiological DHEA levels), but to date the evidence for this effect in patients with hypopituitarism is lacking. The hypothalamic pituitary gonadal axis has also been shown to be a key regulator of immune function in both experimental and clinical studies. Both GnRH and sex steroids appear to be important modulators of both B and T cell function; however, it should be highlighted that there are conflicting results in some clinical studies. This area has been reviewed in detail by Tanriverdi *et al.* (76).

E. Role of ACTH deficiency and glucocorticoid replacement

1. Dosage of glucocorticoid replacement

Patients with primary adrenal failure in addition to those with hypopituitarism have an increased risk of premature mortality compared with the general population (77, 78). This increased mortality is predominantly due to cardiovascular, respiratory, and cancer mortality (77, 78). However, the association between mortality and secondary adrenal insufficiency is not as robust. Sherlock *et al.* (79) have recently shown that in a cohort of patients with acromegaly, the RR for mortality in the ACTH-deficient group [RR, 1.7 (95% CI, 1.2, 2.5); $P = 0.004$] was significantly greater than the ACTH-replete group. Increasing doses of hydrocortisone were associated with an increasing SMR (P for linear trend, <0.001). On internal analysis, having adjusted for age, sex, calendar period, period of follow-up, and radiotherapy, there was a significant increase in RR of mortality in patients receiving daily hydrocortisone doses between 25 and 30 mg [RR, 1.6

(95% CI, 1.1, 2.4); $P = 0.014$] and daily hydrocortisone doses greater than 30 mg [RR, 2.9 (95% CI, 1.4, 5.9); $P = 0.003$] (79). The rate of cardiovascular death was also increased with increasing doses of hydrocortisone therapy. In the group of patients who were ACTH replete, 26.2% of deaths were due to cardiovascular causes. In the overall group of ACTH-deficient patients, 31.6% of patients died from cardiovascular causes, and there was an increase in cardiovascular death with increasing hydrocortisone dose (hydrocortisone dose >0 and ≤ 20 mg/d, 10% cardiovascular mortality; hydrocortisone dose >20 and ≤ 25 mg/d, 33.3% cardiovascular mortality; hydrocortisone dose >25 and ≤ 30 mg/d, 38.5% cardiovascular mortality; and hydrocortisone dose >30 mg/d, 44.4% cardiovascular mortality) (79). Similarly, within the general population, the use of glucocorticoids was associated with a relative risk for a cardiovascular event in patients receiving high-dose glucocorticoids of 2.56 (95% CI, 2.18 to 2.99) (80).

Traditionally, the daily dose of hydrocortisone was 30 mg/d split into two doses (two thirds in the morning and one third in the evening). In recent years, it has been reported that the cortisol production rate in normal subjects is less than was previously thought. Esteban *et al.* (81) (using stable isotope dilution chemospray liquid chromatography/mass spectrometry) showed that the normal cortisol production rate in young adults can be estimated to be 27.3 $\mu\text{mol/d}$ (equivalent to 5.7 mg/m²/d or approximately 9.9 mg/d). This was supported by deconvolution analysis data from young males who on average had a total daily cortisol production rate of 5.7 ± 0.3 mg/m²/d (82). In recent years, endocrinologists have tried to decrease glucocorticoid replacement doses in patients to levels that remain safe but do not lead to overtreatment. Nevertheless, it is possible that subtle increased glucocorticoid exposure over time might contribute to morbidity and increased mortality as observed in patients with Cushing's syndrome.

Cortisol day curves reveal that median doses of hydrocortisone of $29.5 + 1.2$ mg lead to peak cortisol and mean daily cortisol concentrations above the normal range, which in one study led to a change in therapy in 88% of patients (75% of patients received a dose reduction) (83). Agha *et al.* (84) have shown that patients with "partial ACTH deficiency" (basal 0900 h cortisol >200 nmol/liter but a peak cortisol on insulin tolerance test of <500 nmol/liter) have similar day curves to healthy controls, suggesting that these patients may be overtreated by conventional steroid replacement therapy. Filipsson *et al.* (85) have described an adverse metabolic profile in a cohort of GH-deficient hypopituitary patients on higher doses of glucocorticoid replacement. They found that patients on hydrocortisone replacement had increased total cholest-

terol, triglycerides, waist circumference, and glycosylated hemoglobin (HbA1c) compared with the ACTH-sufficient patients. Importantly, subjects who had hydrocortisone equivalent doses of less than 20 mg/d did not differ in metabolic endpoints compared with the ACTH-sufficient patients. However, when a hydrocortisone equivalent dose of at least 20 mg/d was administered, patients had an adverse metabolic profile (85) (Fig. 7). Filipsson *et al.* (85) reported that cortisone acetate may be associated with a lower HbA1c than seen in patients with hydrocortisone therapy or who were ACTH sufficient [however, it must be noted that patients receiving cortisone acetate

were also the ones with the lowest IGF-I SD score (SDS) at baseline]. However, Dunne *et al.* (51) reported no changes in weight, glucose, or HbA1c in patients after decreasing their hydrocortisone dose from 30 to 15 mg/d for 3 months.

2. Mode of glucocorticoid delivery

Twice or thrice daily doses of glucocorticoids are recommended to mimic the normal circadian rhythm and changes to circulating cortisol, but this is rarely achieved. The bioavailability of orally administered hydrocortisone is approximately 95% (86, 87), and its half-life is 60–90 min. A single morning dose of 15 mg hydrocortisone leads

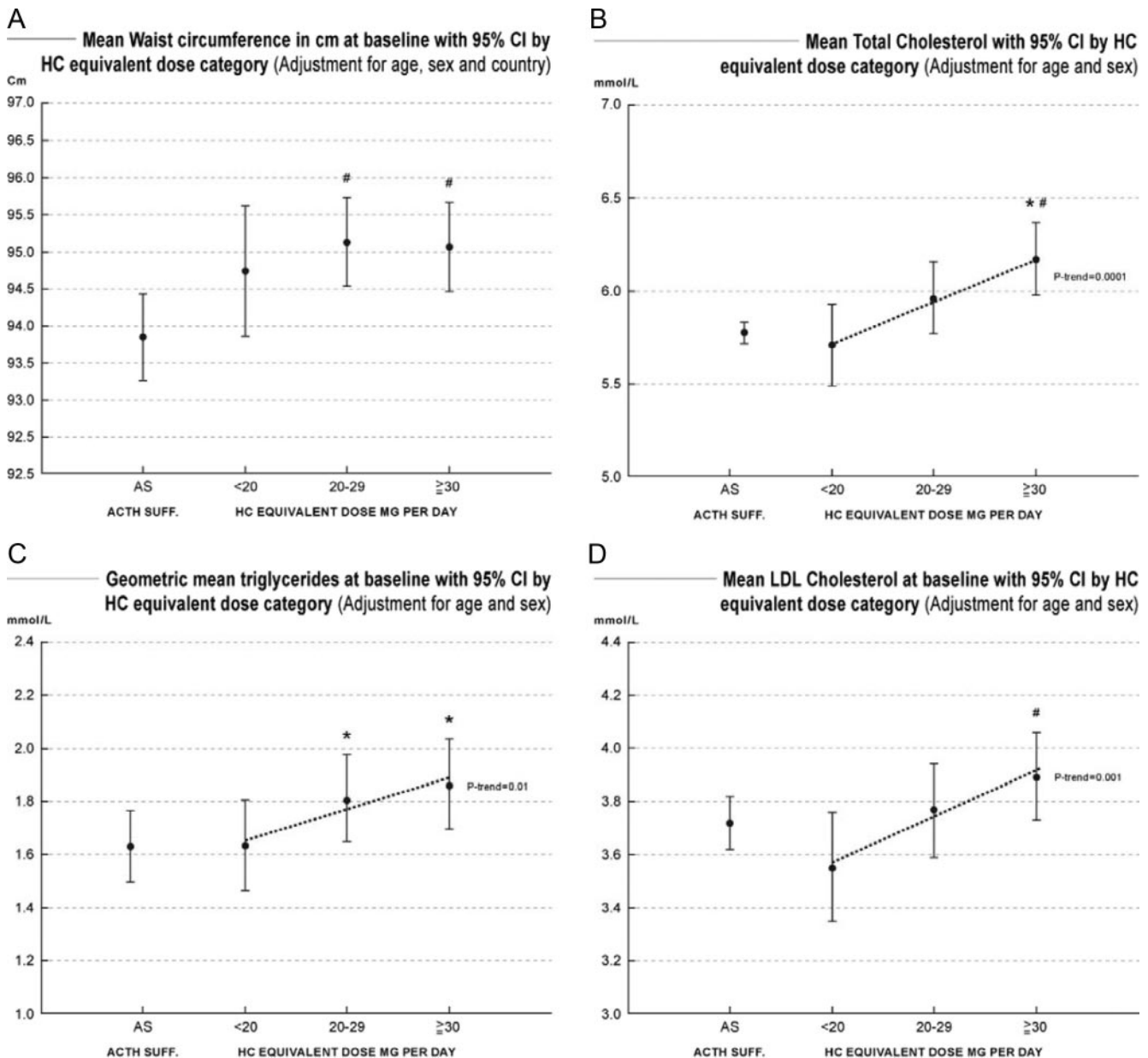


FIG. 7. Hydrocortisone equivalent doses in ACTH-deficient patients with GH deficiency before GH replacement. The broken line represents a dose response analysis within the glucocorticoid-treated groups. A, Waist circumference. #, $P < 0.001$ vs. AS. B, Total cholesterol. #, $P < 0.0001$ vs. AS. C, Triglycerides. #, $P < 0.001$ vs. AS. D, LDL cholesterol. #, $P < 0.05$ vs. less than 20 mg/d. HC, Hydrocortisone; AS, ACTH sufficient. [From H. Filipsson *et al.*: *J Clin Endocrinol Metab* 91:3954–3961, 2006 (85). Permission granted by The Endocrine Society. © 2006, The Endocrine Society.]

to supraphysiological serum cortisol concentrations 1–2 h after oral administration and a return to subphysiological or undetectable levels 6–8 h later (86, 88, 89). There is evidence that continuous, prolonged, compared with intermittent short exposure to glucocorticoids may have different effects on a number of steroid responsive enzymes (90). Pulsatility is also important because it has significant effects on the occupancy of the glucocorticoid receptor (90). Circadian iv infusions of hydrocortisone can mimic the normal cortisol rhythm via a programmable pump resulting in beneficial effects in patients with Addison's disease and congenital adrenal hyperplasia (91); using sc fusions, it was also possible to reduce the daily dose of hydrocortisone (92). These infusions are obviously cumbersome and not practical; however, over the last few years there has been a push to design orally active delayed or sustained release formulations of hydrocortisone to reproduce "physiological replacement" (93). Johannsson *et al.* (94) recently showed that a novel modified release once daily oral hydrocortisone preparation (Duocort) produced a diurnal plasma cortisol profile that mimicked the physiological serum cortisol profile. Similar results are reported with a preparation originating from Sheffield, UK (Chronocort) (95, 96).

The metabolic fuel profile of 10 patients who were treated with conventional doses of glucocorticoid therapy (median, 22 mg; range, 10–30 mg/24 h) were assessed compared with 13 age-, gender-, and BMI-matched controls. In the patient group, there was decreased glucose, nonesterified fatty acid, and 3-hydroxybutyrate overnight, and this was associated with decreased integrated levels of total and free plasma cortisol and 24-h urine cortisol excretion. Indeed, the decreased glucose and nonesterified fatty acid continued throughout the 24-h period of testing (97). In a further study, morning replacement doses of glucocorticoid resulted in higher glucose levels, which were correlated with the maximal plasma cortisol levels (98).

In a further study, Howlett (89) assessed the glucocorticoid replacement in 130 patients requiring hydrocortisone replacement therapy for ACTH deficiency (in total 174 day curves were performed: 65 on twice daily and 109 on thrice daily glucocorticoid replacement). Optimum replacement was defined as achieving a 0900 h cortisol within the reference range (after taking morning hydrocortisone on awakening), and 1230 h and 1730 h cortisol above 50 nmol/liter and ideally above 100 nmol/liter. Fifteen percent of patients on twice daily hydrocortisone replacement regimens achieved optimal replacement, compared with 60% on thrice daily regimens. When regimens were compared, the patients who received 10/5/5 mg achieved optimal replacement in 66% (mean quality

score, 3.62), 10/10/5 mg in 50% (mean quality score, 3.32), and 20/10 mg in 10% (mean quality score, 2.48) (89). Dunne *et al.* (51) assessed whether lowering the dose of hydrocortisone replacement from 30 to 15 mg/d in a hypopituitary cohort was associated with improvements in blood pressure and other markers of cardiovascular function. After 3 months on the lower dose of hydrocortisone, there was no change in blood pressure, glucose, or HbA1c; however, there was a significant improvement in forearm blood flow (51).

3. Tissue metabolism of glucocorticoids

At the tissue level, glucocorticoid action is modulated by isozymes of 11 β -HSD, types 1 and 2. 11 β -HSD 2 is a nicotinamide adenine dinucleotide-dependent enzyme predominantly located in tissues that express the mineralocorticoid receptor (MR); it acts as a dehydrogenase [*i.e.*, converting active (cortisol) to inactive (cortisone) glucocorticoids]. This action protects the MR from illicit binding of cortisol, which has similar affinity for the MR as for the glucocorticoid receptor (99). 11 β -HSD 1 is a bidirectional enzyme; however, *in vivo* it acts predominantly as an oxoreductase enzyme (due to reduced nicotinamide adenine dinucleotide phosphate cofactor supply from the endoplasmic reticulum located enzyme hexose-6-phosphate dehydrogenase) (100). Thus, it converts inactive (cortisone) to active (cortisol) glucocorticoids within tissues. 11 β -HSD 1 is modulated by many factors, including GH/IGF-I, thyroid hormone, insulin, glucocorticoids, and sex steroids (101). Thus, in patients with hypopituitarism, there may be alterations in tissue-specific exposure to glucocorticoids independent of circulating values. This is particularly relevant in patients with GH deficiency (see *Section I.F.*).

F. Role of GH deficiency and replacement

The majority of studies to evaluate a role for GH have been performed in patients with hypopituitarism who are also receiving replacement with sex steroids, glucocorticoids, T₄, and desmopressin where appropriate. However, abnormal findings of these studies have been attributed in many cases to untreated GH deficiency leading to the supposition that patients should receive GH replacement therapy to correct these abnormalities and potentially reduce cardiovascular mortality to normal.

There is now a substantial body of evidence that indicates that GH replacement therapy has a beneficial effect upon many of the parameters outlined above. Body composition improves consistently with GH replacement. Lean mass increases, and fat mass decreases significantly. Studies utilizing computed tomography (33), waist:hip ratio (38, 102, 103), or simply waist circumference (38) have

demonstrated a significant reduction in central adiposity. The fasting lipid profile improves with reductions in total and LDL cholesterol and an improvement in the total: HDL cholesterol ratio (38, 43, 44, 104, 105). A study of 1206 patients who received GH treatment for 2 yr demonstrated an average reduction in total and LDL cholesterol levels of 0.4 mmol/liter (95% CI, -0.4 to -0.3 ; $P < 0.0001$) and 0.4 mmol/liter (95% CI, -0.4 to -0.3 ; $P < 0.0001$), respectively, with a further reduction reported after 2 yr of treatment (38). Although there was a small but significant reduction in HDL cholesterol, the ratio of total: HDL cholesterol improved by 0.3 (95% CI, -0.1 to -0.2 ; $P < 0.0001$). Serum triglyceride levels were not affected by GH treatment.

GH treatment in hypopituitary adults also impacts upon endothelial function, the inflammatory process, and fibrinolytic profile. GH replacement results in increased excretion of nitric oxide metabolites in the urine; however, it is not clear whether this reflects greater production or decreased inactivation of nitrous oxide (59). The markers of inflammation, CRP, IL-6, and TNF- α also fall during GH replacement therapy (64, 106). Perhaps as a consequence of the reduction in inflammation and improvement in nitric oxide metabolism, the reactivity of the blood vessels also improves (56, 107). Measurement of the carotid IMT also demonstrates a significant improvement during therapy (56, 57, 108). Although these studies have been of relatively short duration, one study compared the outcome of patients after 10 yr of treatment and demonstrated that the beneficial changes in lipid profile, body composition, and carotid IMT were sustained over that period (109).

These changes all reflect beneficial effects on recognized markers of cardiovascular risk. However, GH replacement produces changes in some parameters that may have an adverse effect upon cardiovascular outcome. Although GH replacement therapy results in a reduction of central fat mass, insulin resistance is increased. In one study of 90 patients, there was an increase in HbA1c levels from 4.9 ± 0.05 to $5.07 \pm 0.06\%$ ($P < 0.001$). Plasma glucose levels rose from 4.72 ± 0.06 to 5.15 ± 0.07 mmol/liter ($P < 0.001$). These changes were evident after 6 months of treatment and were sustained for 2 yr (110). Lipoprotein (a) is an independent marker of cardiovascular risk that increases significantly during GH replacement (111–113). Despite these changes, which in isolation would suggest a negative effect on cardiovascular risk, the balance of the effect of GH on overall cardiovascular risk appears to be positive, as is evident from the beneficial effects upon vascular structure and function.

The beneficial effects upon the cardiovascular risk profile provided by GH replacement therapy in GH-deficient adults would imply a reduction in expected cardiovascular

mortality in that population, but there are currently no data demonstrating directly that GH replacement therapy reduces cardiovascular mortality in hypopituitary adults. Long-term, postmarketing surveillance studies supported by the pharmaceutical industry are in place that may answer this important question in the future.

There is evidence that GH increases the clearance of cortisol by inhibition of 11 β -HSD1 (thus preventing conversion of inactive cortisone to active cortisol) (114). There are *in vitro* data to indicate that this is through the direct action of IGF-I, not GH (115). Clinically, patients starting on GH may need a slight increase in glucocorticoid replacement dose, or patients who are ACTH replete before GH replacement may need retesting once they are on GH treatment (116). However, in GH-deficient patients, cortisol bioavailability is increased in key tissue such as liver, fat, and muscle. This might explain some of the reported deleterious effects of GH deficiency (abnormal lipid profile, increased fat mass, low muscle mass, and increased BMI/waist:hip ratio).

G. Role of TSH deficiency and replacement

Adequacy of thyroid hormone replacement in patients with hypopituitarism is difficult to assess because the normal negative feedback mechanisms are disrupted and serum TSH levels cannot be used as a marker to determine the correct dose of T₄. Instead, one has to rely upon measures of the serum T₄ level. There is no true consensus about which level of T₄ a patient with pituitary disease should be diagnosed with secondary hypothyroidism. Classically, secondary hypothyroidism was diagnosed in the setting of a low T₄ level with an inappropriately low TSH in a patient with pituitary disease. However, there is increasing evidence that, although the population may show a spectrum of TSH and T₄ values, within any individual levels of TSH/T₄ remain remarkably constant over a year (117). Therefore, if a patient has set their “thyrostat” to a high T₄ and pituitary surgery decreases this significantly but still is within the normal range, does this mean they are at the same risk of central hypothyroidism as someone who has a low T₄ that does not change after pituitary surgery? Further work is needed to ascertain the best diagnostic criteria for secondary hypothyroidism, and there is urgent need for tissue measures of T₄ action other than TSH. Lower limits of reference ranges are used, suggesting that many patients may have secondary hypothyroidism and not be adequately replaced. In the normal population, a suppressed TSH level (a marker of thyroid hormone excess) is associated with an increased risk of atrial fibrillation (118), placing the individual at increased risk of embolic events, such as stroke. Furthermore, in a population study, deaths from cardiovascular disease were significantly increased in subjects who had a sup-

pressed TSH level but a normal free T₄ concentration (119). Thus, mild overtreatment with T₄ in patients with hypopituitarism may contribute to the increased cardiovascular mortality observed. This risk may be augmented by the prothrombotic state of patients with hypopituitarism (67). It should be highlighted that in the general population there is still debate regarding increased mortality in patients with thyroid dysfunction (120), and there are little data regarding this in patients with pituitary disease.

H. Role of sex steroid deficiency and replacement

Data regarding the role of estrogen and testosterone replacement therapy on mortality in patients with hypopituitarism are weak, and as such we extrapolate findings from studies in the general population, with the caveat that there may be several confounders such as GH therapy/deficiency and altered body composition in patients with hypopituitarism. For many years the use of sex-steroid replacement in normal, postmenopausal women was advocated for the amelioration of menopausal symptoms and the prevention of bone loss and cardiovascular disease. This practice was thrown into doubt by two large, randomized, placebo-controlled studies that reported increased cerebrovascular and cardiovascular events and an increased risk of developing breast cancer after prolonged hormone replacement therapy in postmenopausal women (121, 122). This area is beyond the scope of this review; however, increasingly, the literature regarding randomized control trials in this area shows an increase in overall incidence of breast cancer, stroke, coronary heart disease, pulmonary embolism, and, in women older than 65 yr of age, an increase in dementia rates, with a significant decrease in the incidence of colorectal cancer and fractured neck of femur (123, 124). There does not appear to be a change in endometrial cancer incidence (123). A recent study has also reported an increase in death from non-small cell lung cancer in women on estrogen and progestin therapy (125). Hormone replacement therapy appears to be safer in young women than older cohorts, but more data are needed to fully assess this (124, 126). These findings raised concern in young women of premenopausal age who require sex steroid replacement to manage hypopituitarism or other conditions that result in ovarian failure. Tomlinson *et al.* (12) demonstrated that mortality was increased in subjects with gonadotropin deficiency that were not receiving sex steroid replacement, whereas mortality in those on sex steroid replacement was similar to patients with an intact axis (Fig. 8). Further reassurance is provided by the low frequency of malignant disease reported in patients with hypopituitarism; one study reported a 50% reduction in deaths from this cause (11).

The role of androgens and, in particular, testosterone in cardiovascular disease has been increasingly reported over

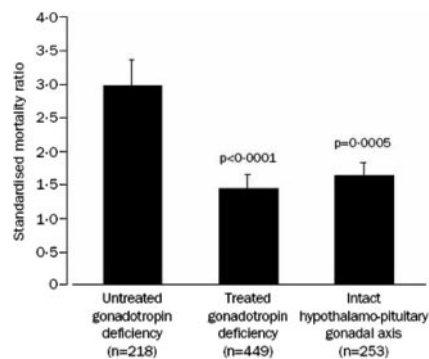


FIG. 8. Effect of gonadotropin deficiency and sex-steroid replacement on SMR in patients with hypopituitarism (*P* values refer to comparison with untreated deficiency). [Reprinted from J. W. Tomlinson *et al.*: *Lancet* 357:425–431, 2001 (12), with permission from Elsevier.]

the last decade both in the general population and in patients receiving therapy for prostatic carcinoma. In the general population above the age of 40, lower testosterone levels have been associated with increased risk of cardiovascular disease (127); however, this is not the case in all studies (128). The role of androgens and testosterone in the development of cardiovascular disease and coronary artery disease has been extensively reviewed by Liu *et al.* (129) and by Wu and von Eckardstein (130), respectively. However, it should be noted that the vast majority of studies in this area do not include a hypopituitary cohort. Another controversial area regarding androgen replacement therapy in men is the role of testosterone in the development of prostatic carcinoma. The Endocrine Society has recently published clinical practice guidelines for adult men with androgen deficiency syndromes that include recommendations for monitoring of prostate, hematocrit, and bone mineral density in patients on testosterone therapy (131). However, the role of testosterone replacement therapy in hypogonadal men in the development of prostatic carcinoma above and beyond that seen in the age-matched general population is controversial (132) because the goal of testosterone replacement is to return testosterone to the normal age-related range.

More detailed studies of sex-steroid replacement strategies and their long-term effect on cardiovascular risk factors, malignancy, and outcome in men and women with hypopituitarism are required to ensure that current practice is optimal.

I. Role of underlying etiology on mortality in hypopituitarism

Hypopituitarism encompasses a number of diverse conditions. The mortality associated with acromegaly, Cushing's disease, and the underlying diagnosis of craniopharyngioma is discussed in *Sections II, III, and IV*, respectively. In the majority of cases, studies have not been able to analyze data with respect to specific etiology due to insuffi-

cient patient numbers and power. However, in two studies, nonfunctioning pituitary adenomas have been analyzed in separate cohort analyses (12, 133). In the study by Lindholm *et al.* (133), all patients had undergone surgical intervention, and overall mortality was not significantly different from that of the control population. However, 30% had normal pituitary function postoperatively, and even once they had been excluded from the analysis, mortality was not different from control subjects (SMR, 1.21; 95% CI, 0.86–1.70). Importantly, however, this study only included a total of 109 patients. In the study by Tomlinson *et al.* (12), 573 patients were identified with an underlying diagnosis of nonfunctioning pituitary adenoma. SMR remained significantly elevated compared with an age- and sex-matched population (SMR, 1.70; 95% CI, 1.34–2.15) and deaths were increased in women and were predominantly due to vascular and respiratory causes. When compared against other causes of hypopituitarism (which included craniopharyngiomas in this study), mortality outcome was improved when nonfunctioning adenoma was the underlying diagnosis (SMR, 1.70 *vs.* 2.34). Although nonfunctioning pituitary adenomas appear to be associated with improved mortality outcome, it is very hard to generalize. Not all nonfunctioning pituitary adenomas behave in the same way, and, as described above, tumor characteristics may have an impact upon mortality outcome (134).

J. Other factors contributing to mortality in hypopituitarism

Tumor characteristics may influence mortality. In a series of 281 patients who underwent operative procedures (transcranial surgery in 96% of cases) and radiotherapy (98% of cases within 6 months of operation), all-cause mortality was increased significantly in those patients that had tumor regrowth compared with those with no tumor regrowth (SMR, 3.74 *vs.* 1.71). However, hypopituitarism was only diagnosed in 89% of patients within 5 yr of diagnosis, and mortality was increased in the cohort with and without tumor regrowth. Cerebrovascular deaths were increased in both the regrowth and non-regrowth groups, although this only reached statistical significance in the non-regrowth group compared with age- and sex-matched controls, principally due to the total numbers of observed deaths (134).

II. Mortality in Acromegaly

A. Introduction

Acromegaly is caused almost invariably by a GH-secreting pituitary adenoma, although rarely it may be due to a hypothalamic tumor secreting GHRH or ectopic GHRH secretion from a carcinoid tumor. It is a rare condition with an estimated prevalence of around 60 per million and an annual incidence of three or four per million (135).

The clinical features of acromegaly are due to the somatic and metabolic effects of prolonged excess GH/IGF-I exposure or to local effects of an expanding pituitary mass (136). Clinical symptoms include headaches, sweating, symptoms of carpal tunnel syndrome and arthralgia, visual symptoms, and symptoms of pituitary hormone deficiencies. Typical clinical signs include coarse facial features; large, spade-shaped hands; and enlarged feet resulting from soft tissue swelling and bony enlargement. Growth of the mandible results in prognathism and malocclusion, and widened interdental spaces are also common clinical features. Other common features include enlargement of the tongue (macroglossia), swelling of the nasopharyngeal tissue, sleep apnea, lethargy, skin tags, goiter, and colonic polyps. The expanding pituitary mass may cause hypopituitarism, reproductive disorders, and visual symptoms. GH hypersecretion occurring before the epiphyses have fused results in excess linear bone growth and gigantism. Long-term complications include arthropathy, cardiomyopathy, hypertension, and impaired glucose tolerance, and these have been extensively evaluated in a recent review by Colao *et al.* (137).

B. Studies of mortality in acromegaly

It is now well established that untreated acromegaly is associated with reduced life expectancy. Several retrospective studies have demonstrated a 2- to 3-fold increased mortality in acromegalic patients compared with age- and sex-matched controls. Death is due predominantly to cardio/cerebrovascular disease, respiratory disease, and, in some studies, malignancy (Table 4 and Fig. 9) (138–147). Results from the more recent studies also demonstrated that the high mortality rates associated with acromegaly can be reversed if treatment is successful in reducing GH levels to less than 2–2.5 $\mu\text{g/liter}$ (139–142, 144, 145, 148) (Fig. 10) and in some studies the normalization of IGF-I levels into age-specific reference ranges (142, 148–150) (Table 5).

As far back as the 1920s, patients with acromegaly were thought to have reduced life expectancy. In a series of 100 patients with acromegaly studied and reported on in 1966, 50% had died before the age of 50 yr and 89% by the age of 60 yr (151). The causes of death in these early series included diabetic coma, vascular disease, sepsis, and extension of the pituitary tumor.

The excess mortality associated with acromegaly was first accurately qualified and quantified in the series by Wright *et al.* (146), published in 1970; cause of death in a cohort of 194 subjects with acromegaly was analyzed and compared with those of the general population of England and Wales (Table 4). Fifty-four deaths were observed, compared with 28.5 expected, giving a SMR of 1.9. The increased number of deaths was predominantly due to cardiovascular disease in males, cerebrovascular disease in

TABLE 4. Studies assessing disease-specific mortality rates in patients with acromegaly

First author, year (Ref.)	No. of patients	No. of deaths	Mortality cause
Before 2000			
Wright, 1970 (146)	194	55	Total group SMR, 1.8; cause-specific: vascular, 38.5%; respiratory, 18%; malignant, 18%
Alexander, 1980 (138)	164	45	Total group SMR, 3.3 (male 24/5, SMR = 4.8; female 21/8.1, SMR = 2.6); cause-specific: vascular, 60%; respiratory, 15.5%; malignant, 15.5%
Nabarro, 1987 (143)	256	47	Total group SMR, 1.3 (<55 yr, 10/5.3, SMR = 1.9; female 23/13.7, SMR = 1.7); cause-specific: cardio/cerebrovascular 47/37.2, SMR = 1.3 N/S; vascular, 55%; respiratory, 6%; malignant, 23%
Bengtsson, 1988 (152)	166	62	Total group SMR, 3.2; cause-specific: vascular deaths 32/9, SMR = 3.6; cancer deaths 15/5.6, SMR = 2.7
Rajasoorya, 1994 (145)	151	32	Total group SMR, 3.0; cause-specific: cardiovascular SMR 3; cerebrovascular SMR 3; malignancy SMR 1
Extabe, 1993 (153)	74	10	Total group SMR, 3.2 (1.55–5.93) [male, SMR 7 (2.81–14.4), female, SMR 1.4 (0.29–4.17)]; cause-specific: vascular, 10 (0.25–55.7); malignancy, 7.1 (2.31–16.6)
Bates, 1993 (140)	79	28	Total group SMR, 2.63 (1.8–3.9); cause-specific: vascular, 57%; respiratory, 25%; malignant, 11%
Orme, 1998 (144)	1362	366	Total group SMR, 1.60 (1.44–1.77); cause-specific: vascular, SMR 1.76 (1.47–2.07), $P < 0.001$; cerebrovascular, SMR 2.06 (1.5–2.76), $P < 0.001$; respiratory, SMR 1.85 (0.92–1.44), $P < 0.001$; malignant, SMR 1.16 (0.92–1.44), $P = 0.1$
Swearingen, 1998 (149)	149	12	Total group SMR, 1.16 (0.66–2.0); cause-specific: vascular, 5/12; respiratory, 1/12; malignant, 4/12
Abosch, 1998 (154)	254	29	Total group SMR, 1.28; cause-specific, not available in majority of 20 deaths
After 2000			
Beauregard, 2003 (141)	103	18	Total group SMR, 2.14; cause-specific: vascular, 5/18; malignant, 9/18
Arita, 2003 (344)	154	11	Total group SMR, 1.17 (0.54–2.38); cause-specific: vascular, 4/11; respiratory, 2/11; malignant, 2/11
Biermasz, 2004 (150)	164	28	Total group SMR, 1.33 (0.87, 1.87); cause-specific: vascular, 7/28; malignant, 13/28
Holdaway, 2004 (142)	208	72	Total group SMR, 1.22; cause-specific: vascular, 36/72 (50%); respiratory, 2/76; malignant, 17/72 (24%)
Ayuk, 2004 (139)	419	95	Total group SMR, 1.26 (1.03–1.54), $P = 0.045$; cause-specific: cardiovascular, SMR 1.37 (0.98–1.9), $P = 0.111$; cerebrovascular, SMR 2.68 (1.73–4.15), $P = 0.007$; respiratory, SMR 1.52 (0.88–2.61), $P = 0.219$; malignant, SMR 0.91 (0.59–1.39), $P = 0.65$
Mestron, 2004 (148)	1219	56	Total group SMR, not available; SMR 1.3 (0.52–2.67) for remission group and 1.38 (0.51–3.0) in persistent disease group; cause-specific: cardiovascular, 26.8%; cerebrovascular, 8.9%; respiratory, 5.4%; malignant, 16.1%
Kauppinen-Makelin, 2005 (155)	334	56	Total group SMR, 1.16 (0.85–1.54); cause-specific: cardiovascular, 23.2% (coronary artery disease); other cardiovascular diseases, (16.1%); cerebrovascular, 14.3%; malignant, 21.4%
Trepp, 2005 (162)	94	13	Total group SMR, 1.34 (0.71–2.29); cause-specific: cardiovascular, 6/13; malignant, 4/13
Sherlock, 2009 (79)	501	162	Total group SMR, 1.7 (1.4–2.0), $P < 0.001$; cause-specific: cardiovascular, SMR 1.9 (1.6–2.4), $P > 0.001$; cerebrovascular, SMR 2.7 (1.9–4.1), $P < 0.001$; respiratory, SMR 1.8 (1.1–2.8), $P = 0.01$; malignant, SMR 1.2 (0.9, 1.7), $P = 0.26$

females, and respiratory disease in both. There was no increased mortality from malignancies. Factors associated with increased mortality included the presence of hypertension and diabetes mellitus. Even in this early study, it was evident that control or improvement in GH levels could lead to a decrease in mortality rates [deaths: no treatment group, 27 of 55 (49.1%), compared with 28 of 139 (20.1%) in treated group of which five of 11 had surgery, 15 of 81 had radiotherapy, and eight of 47 had multiple treatment modalities]. These findings were confirmed in a number of subsequent series over the following two decades (138, 140, 143, 145, 147, 152, 153). The excess deaths were predominantly due to vascular disease, respiratory disease, and in some studies, malignancy (Table 4).

In recent years, significant advances have been made in the management of acromegaly, resulting in a change in overall mortality rates seen in acromegaly. In epidemiological studies performed over the last decade (139, 141, 142, 144, 149, 150, 154, 155), although mortality in acromegalic patients remains elevated compared with the general population in several studies, the mortality increase is generally less than 2-fold, compared with the 2- to 3-fold mortality rates seen in earlier series (Table 4), and indeed some studies report no increase in mortality. In a recent meta-analysis pooling 16 studies, SMR ranged from 1.16 to 3.31, with a mean weighted SMR of 1.72 (95% CI, 1.62–1.83) (156). A metaregression pointed toward improved survival in more recent studies (SMR of 1.62 in papers published in 1995 onward compared with SMR of

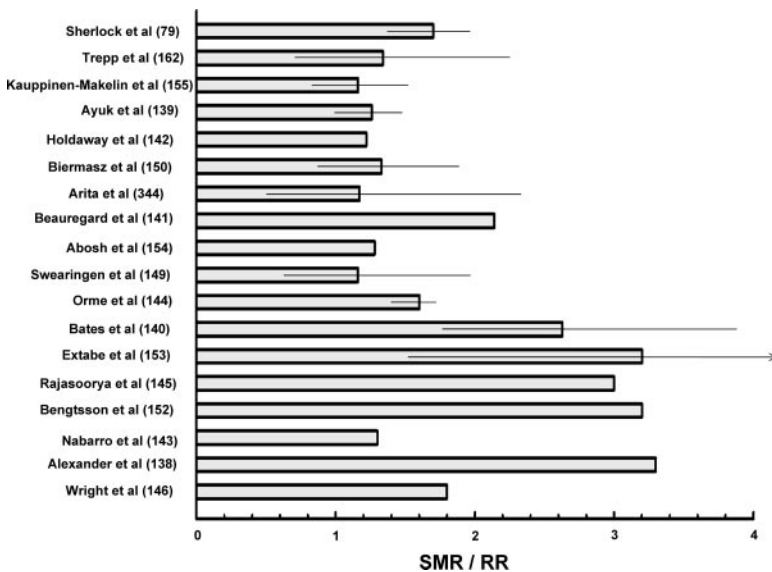


FIG. 9. Summary of studies assessing mortality rates in patients with acromegaly. Bars = 95% CI (when available), see Table 4 for more information.

2.11 in papers published before 1995), presumably due to modern treatment modalities and more strictly defined cure criteria.

In the West Midlands Acromegaly Study, we reported on the outcome in 419 patients with acromegaly, of whom 324 were alive and 95 deceased (139). Compared with the general population, all-cause mortality was significantly increased with an SMR of 1.26 (95% CI, 1.03–1.54). The excess mortality was due predominantly to cerebrovascular disease, with small but nonsignificant increases due to cardiovascular and respiratory disease (Table 4). There was no increase in deaths from malignancy. No significant increase in mortality was identified in patients with a posttreatment GH less than 4 mU/liter (2 µg/liter), but survival was reduced in the cohort failing to

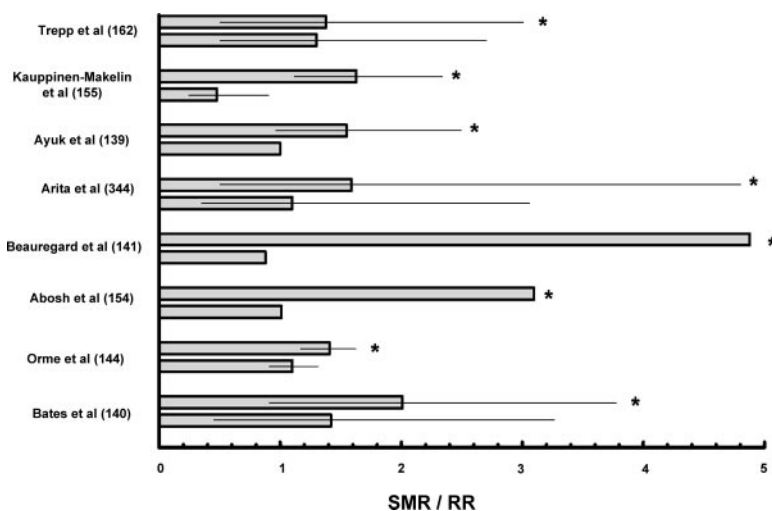


FIG. 10. Studies assessing the role of GH on mortality in acromegaly related to SMR, OR, or RR. *, Patients who were above the GH cutoff in the study (see Table 5 for more details).

achieve this target, with a RR of 1.55 (95% CI, 0.97–2.5; $P = 0.068$). IGF-I data were available in 360 patients, representing 86% of the cohort. No effect of IGF-I on outcome could be demonstrated, with the RR for those patients achieving serum IGF-I within the normal age-related range similar to those who did not [elevated IGF-I RR, 1.2 (0.71–2.020); $P = 0.5$].

C. Impact of GH levels on mortality in acromegaly

However, results from two of these studies also demonstrated that the increased mortality associated with acromegaly can be diminished if treatment is successful in reducing GH hypersecretion to less than 5 mU/liter (2.5 µg/liter), whether this is measured as the mean of a GH day profile or as a random GH level (140, 145). In the first of these studies by Bates *et al.* (140), in a cohort of 79 patients with acromegaly, the SMR fell from 2.6 to 2.0 if treatment reduced GH levels to under 10 mU/liter (5 µg/liter). Even more significant was the fact that mortality was reduced to normal if posttreatment GH levels of less than 5 mU/liter (2.5 µg/liter) were achieved (Table 5). The second study by Rajasoorya *et al.* (145) in a cohort of 151 patients with acromegaly showed both on univariate and multivariate analysis that higher GH levels were associated with reduced survival.

The studies discussed above reached a consensus in showing that posttreatment GH values of less than 2.5 µg/liter restore SMR to normal (Table 5), providing an evidence base for targeted reduction of GH concentrations (157–159). However, cutoff points of 2.5 µg/liter and less than 1 µg/liter to define an adequate response to treatment have been arbitrarily adopted, with little scientific basis for this selection (140). In the West Midlands Acromegaly Study, comparison of crude death rates per 1000 population suggested that a GH of 2 µg/liter may be a more appropriate treatment target, with a step-up in the death rate once GH exceeded 2 µg/liter (Fig. 11) (139). Data from Holdaway *et al.* (142) suggest a further improvement in outcome if GH can be lowered to under 1 µg/liter as opposed to 2.5 µg/liter (Fig. 12). The Finnish Nationwide Survey of Mortality in Acromegaly reported similar findings (155). In a cohort of 334 acromegalic patients with 56 deaths, excess mortality was seen in those with posttreatment GH levels greater than 2.5 µg/liter (SMR, 1.63 (1.1–2.35); $P < 0.001$).

In a recent meta-analysis focusing on the relationship between biochemical measurements

TABLE 5. Studies assessing the role of GH and IGF-I on mortality in acromegaly

First author, year (Ref.)	Study period	No. of patients	No. of deaths	Total group SMR	SMR if GH above cutoff	SMR if IGF-I above cutoff
Bates, 1993 (140)	1967–91	79	28	2.63 (1.8–3.9)	GH <2.5 ng/ml, SMR 1.42 (0.46–3.31); GH <5 ng/ml, SMR 2.01 (0.9–3.8)	NA
Orme, 1998 (144)	NA	1362	366	1.60 (1.44–1.77)	GH <2.5 ng/ml, SMR 1.1 (0.89–1.35); GH 2.5–9.9 ng/ml, SMR 1.41 (1.16–1.68); GH ≥10 ng/ml, SMR 2.12 (1.7–2.62)	NA
Swearingen, 1998 (149)	1978–96	149	12	1.16 (0.66–2.0)	NA; 39 patients used GH and 133 used IGF-I for criteria of cure	Mortality risk if active disease 3.5-fold (1.0–12) (multivariate analysis)
Abosch, 1998 (154)	1974–92	254	29	1.28	Remission = GH ≤5 ng/ml, remission SMR = 1.01, persistent SMR = 3.1	NA
Beauregard, 2003 (141)	1970–99	103	18	2.14	Remission SMR = 0.88, persistent SMR = 4.8	Remission SMR = 0.88; persistent SMR = 4.8
Arita, 2003 (344)	1977–2000	154	11	1.17 (0.54–2.38)	GH <2.5 ng/ml, SMR 1.1 (0.34–3.07); GH 2.5–5 ng/ml, SMR 1.59 (0.47–4.79); GH >5 ng/ml, SMR 0.6 (0.09–2.53)	NA
Biermasz, 2004 (150)	1977–2002	164	28	1.33 (0.87–1.87)	GH <5 mU/liter, RR 1.77 (0.8–3.94); GH suppressed OGTT, RR 1.32 (0.57–3.03)	Elevated age-related IGF-I, RR 4.78 (1.01–22.7)
Holdaway, 2004 (142)	1964–2000	208	72	1.22	GH <1 ng/ml, 18% deceased; GH 1–2 ng/ml, 21% deceased; GH 2–5 ng/ml, 39% deceased; GH >5 ng/ml, 52% deceased	Multivariate analysis IGF-I not independent variable, but SMR 3.5 (2.8–4.2) when IGF-I SDS >2
Ayuk, 2004 (139)	Pre 2001	419	95	1.26 (1.03–1.54)	GH >2 ng/ml vs. <2 ng/ml, rate ratio 1.55 (0.97–2.5)	IGF-I not predictive; internal comparison of normal vs. elevated IGF-I RR = 1.2 (0.71–2.02)
Mestron, 2004 (148)	NA	1219	56	NA	GH <2 ng/ml OGTT (8 deaths); GH >2 ng/ml (48 deaths); <i>P</i> < 0.001	IGF-I never normal, 41 compared with 15 deaths (<i>P</i> = 0.001)
Kauppinen-Makelin, 2005 (155)	1980–99	334	56	1.16 (0.85–1.54)	GH <2.5 ng/ml, SMR 0.48 (0.23–0.88); GH >2.5 ng/ml, SMR 1.63 (1.1–2.35); multivariate >2.5 ng/ml; OR 3.21 (1.37–7.52)	IGF-I not predictive; OR 0.46 (0.17–1.26)
Trepp, 2005 (162)	1971–2003	94	13	1.34 (0.71–2.29)	Remission criteria: normal age-related IGF-I and either OGTT GH <1 ng/ml or random GH <2.5 ng/ml. Remission SMR, 1.3 (0.52–2.67); persistent SMR, 1.38 (0.51–3.0)	

NA, Not available.

and mortality during follow-up after treatment for acromegaly (160), mortality was close to the expected level when last available GH was under 2.5 μg/liter (SMR, 1.1; 95% CI, 0.9–1.4), but was significantly elevated in those with last available GH above 2.5 μg/liter (SMR, 1.9; 95% CI, 1.5–2.4). The RR for a serum GH greater than 2.5 μg/liter was 1.7 (*P* < 0.05) (Fig. 13).

Therefore, the fundamental aim of treatment in acromegaly should be reduction of GH values to less than 2.5 μg/liter and possibly even lower to less than 1 μg/liter, although care must be taken that this is not at the expense of inducing GH deficiency and hypopituitarism (which in itself is associated with an adverse outcome; see *Section I*).

In addition, it must be noted that GH cannot be used to monitor treatment in patients treated with the GH antagonist pegvisomant.

D. Impact of IGF-I levels on mortality in acromegaly

IGF-I is now widely used as a first-line investigation for the diagnosis and therapeutic monitoring of patients with acromegaly (157, 161). Indeed, the introduction of GH antagonists as medical treatment for acromegaly necessitates the use of IGF-I in the biochemical monitoring of patients treated with these agents. However, the relationship between outcome and latest IGF-I levels is not as clear-cut as with latest GH (139, 141, 142, 149, 155)

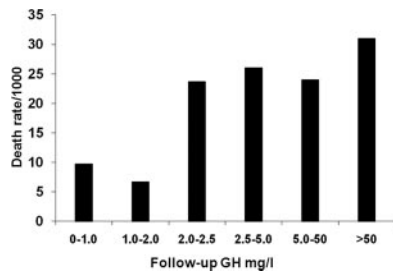


FIG. 11. Crude death rates per 1000 in patients with acromegaly related to posttreatment GH levels. [Adapted from J. Ayuk *et al.*: *J Clin Endocrinol Metab* 89:1613–1617, 2004 (139). Permission granted by The Endocrine Society. © 2004, The Endocrine Society.]

(Table 5). In the first of these studies (162 patients, 12 deaths) (149), those patients who were surgically cured, defined by a normal IGF-I, had mortality similar to that of the general population of the United States, whereas those with active disease as defined by a persistently elevated IGF-I had reduced life expectancy for the period that the IGF-I was elevated. A further study also concluded that IGF-I normalization reduced mortality to expected levels (142); however, serum IGF-I was not an independent predictor of mortality when both GH and IGF-I measurements were included in the multivariate analysis (142) and was only significant when looking at SDS above 2 for IGF-I compared with normal IGF-I levels. Further issues raised included the use of different IGF-I assays over the study period and a relatively small number of deaths.

In the recent meta-analysis by Holdaway *et al.* (160), those with normal IGF-I had mortality close to the expected values for the general population (SMR, 1.1; 95% CI, 0.9–1.4), whereas the SMR for those with elevated IGF-I at last follow-up remained significantly increased (SMR, 2.5; 95% CI, 1.6–4.0) (Fig. 14). The RR for an elevated serum IGF-I was 2.3 ($P < 0.05$). However, it

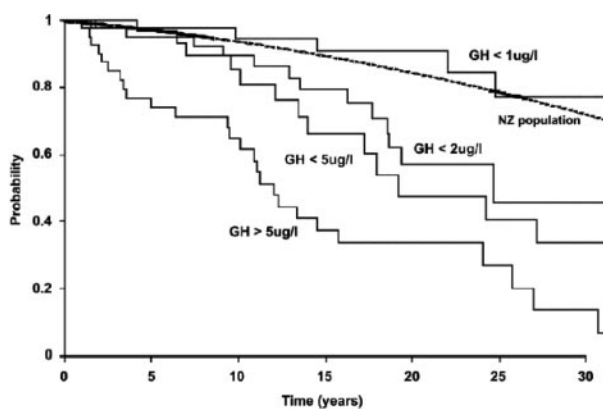


FIG. 12. Probability of survival in acromegaly according to serum GH concentrations at last review after treatment (curves different at $P < 0.0001$, by log rank). The dotted line represents the probability of survival for the New Zealand population (142). [From I. M. Holdaway *et al.*: *J Clin Endocrinol Metab* 89:667–674, 2004 (142). Permission granted by The Endocrine Society. © 2004, The Endocrine Society.]

should be noted that two of the largest studies, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between posttreatment IGF-I levels and mortality [RR, 1.2; 95% CI, 0.71–2.02; $P = 0.5$ (139) and RR, 0.46, 95% CI, 0.17–1.26; $P = 0.13$ (155)] (Table 5), suggesting that last available serum IGF-I may not be as reliable a marker of mortality in acromegaly as last available GH.

E. Assay variability

There are also methodological problems with using the last available GH/IGF-I in the analysis for mortality because this value is inherently biased and does not take into account prior GH/IGF-I levels. Many studies were also performed using older assays that may not be used in clinical practice today; however, it may take many years to get meaningful data on survival using newer more sensitive assays, and these older studies have to be interpreted with this in mind. Many studies have used multiple assays during the duration of study (142, 150, 155, 162) or multiple assays in different centers in multicenter studies both for GH and IGF-I (155). Some studies do not describe the assays used (144, 148, 149, 154). Both IGF-I and GH assays, even those in use today, are prone to large variability that will impact on the result of the studies (163). Other difficulties include normal age- and gender-matched reference ranges for IGF-I and different GH standards during time (142, 150, 155). For example, in the Finnish national acromegaly study during the years 1980 to 1999, GH measurements were performed in five laboratories using seven assays (these assays were not all calibrated to the same International Reference Preparation) (155). When the assays changed between 1995 and 2000, four laboratories changed to an immunofluorometric assay (measures only 22-kDa forms), and one laboratory changed to a chemiluminescent assay (measures 22- and 20-kDa forms, leading to a 1.4- to 1.5-fold higher value than the immunofluorometric assay). Serum IGF-I was measured by RIA or immunoradiometric assay and various centers used different cutoffs.

In recent years, the use of higher sensitivity immunofluorometric, chemiluminescent, and immunoradiometric assays has been associated with significantly lower nadir GH during oral glucose tolerance test (OGTT) in healthy controls than was previously thought [ranging from 0.029–0.25 mg/liter (164–168), there was also a gender difference noted in some studies]. Therefore, with the use of more sensitive assays, the target for GH may decrease over time because they can detect much lower levels of GH compared with older RIA and have redefined normality during an OGTT. There has also been discussion as to whether targets for GH need to be altered as a result of these newer assays; however, it must be noted that it may

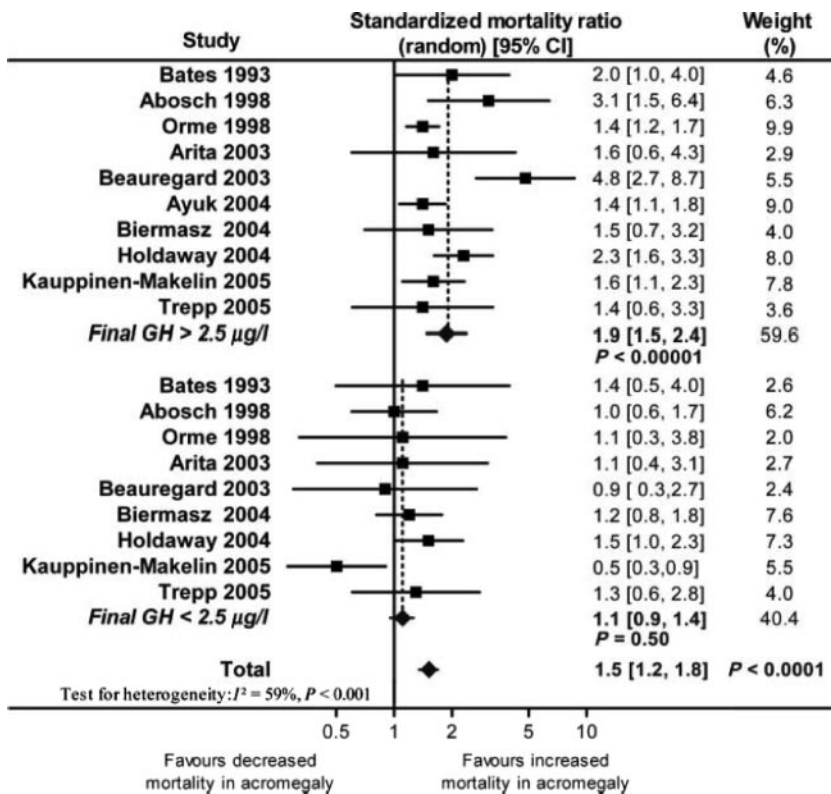


FIG. 13. Pooled SMRs in studies of acromegaly grouped according to GH level at final follow-up. Data are SMR (95% CI). [From I. M. Holdaway et al.: Eur J Endocrinol 159:89–95, 2008 (160). © 2008 Society of the European Journal of Endocrinology. Reproduced with permission.]

be some time before we have adequate follow-up data to assess GH cutoffs to normalize mortality using these newer assays.

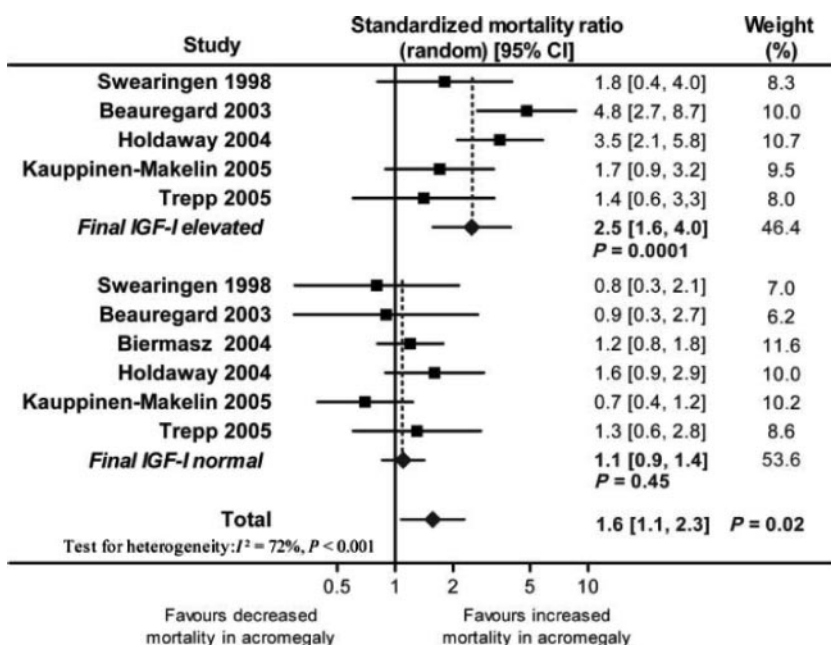


FIG. 14. Pooled SMRs in studies of acromegaly grouped according to IGF-I level at final follow-up. Data are SMR (95% CI). [From I. M. Holdaway et al.: Eur J Endocrinol 159:89–95, 2008 (160). © 2008 Society of the European Journal of Endocrinology. Reproduced with permission.]

F. Role of pituitary radiotherapy on mortality in acromegaly

In the West Midlands study, compared with the general population, the use of external radiotherapy was associated with increased mortality, with an SMR of 1.58 (95% CI, 1.22–2.04; $P = 0.005$), and when assessed on internal analysis within the acromegaly cohort resulted in a RR of 1.67 (95% CI, 1.1–2.56; $P = 0.02$) (139). In the Finnish survey, mortality was also increased in patients who had been treated with radiotherapy [SMR, 1.69 (95% CI, 1.05–2.58); $P < 0.001$] (155). In the Spanish acromegaly registry, patients who died had a twice greater probability of having been treated with radiotherapy than those who had survived (hazard ratio, 2.29; 95% CI, 1.03–5.08; $P = 0.026$) (148) (Table 6). The role of radiotherapy is further discussed in Section V.

G. Role of pituitary dysfunction on mortality in acromegaly

Although hypopituitarism is associated with increased mortality (see Section I), there are little data on the role of hypopituitarism in patients with acromegaly *per se*. In the West Midlands study, there was a trend ($P = 0.07$) toward reduced survival in patients with acromegaly who had a greater number of deficient hypothalamic-pituitary axes compared with those without evidence of hypopituitarism (139). In the recent study by Sherlock et al. (79), neither TSH deficiency nor gonadotropin deficiency was associated with increased mortality in acromegaly on internal analysis (gonadotropin deficiency was associated with increased SMR compared with the general population); however, ACTH deficiency was associated with increased mortality [RR, 1.7 (95% CI, 1.2–2.5); $P = 0.004$]. The cause of death was predominantly cardiovascular, and higher doses of hydrocortisone therapy were associated with increased mortality (see Section I.E).

H. Cancer mortality in acromegaly

Both IGF-I and GH have well-described mitogenic properties *in vitro*, and case-controlled studies have found in-

TABLE 6. Studies assessing the role of pituitary radiotherapy in mortality in patients with acromegaly

First author, year (Ref.)	No. of patients	RR	SMR	RR	Comments
Biermasz, 2004 (150)	164	57 CRT	NA	1.73 (0.77–3.86); age and sex adjusted, 1.169 (0.52–2.65)	Cause of death not known
Holdaway, 2004 (142)	208	143 CRT, 35 Yttrium	NA	NA	No increase in stroke mortality
Ayuk, 2004 (139)	419	211 CRT	DXT group, 1.58 (1.22–2.04); $P = 0.005$	1.67 (1.1–2.56); $P = 0.02$	Cerebrovascular SMR = 4.42
Kauppinen-Makelin, 2005 (155)	334	116 CRT	DXT group, 1.69 (1.05–2.58); non-DXT, 0.94 (0.62–1.37); $P < 0.001$	2.27 ($P = 0.08$)	6/8 stroke deaths
Mestron, 2005 (148)	1219	504 CRT, 27 stereotactic radiotherapy, 9 radiosurgery	HR 2.29 (1.03–5.08)	NA	Cerebrovascular mortality data NA
Sherlock, 2009 (79)	501	220 CRT, 17 Yttrium/ radiosurgery	2.1 vs. 1.4 for non-DXT ($P = 0.006$)	1.8 ($P = 0.008$)	Cerebrovascular SMR 4.1

RT, Radiotherapy treatment; HR, hazard ratio.

creased serum levels of IGF-I in subjects who had or eventually developed prostate cancer or premenopausal breast cancer (169); therefore, one might anticipate excess malignancies in acromegaly. However, epidemiological studies exploring the link between acromegaly, cancer incidence, and cancer mortality have given rise to conflicting data. Early studies suggested an increased incidence of neoplasia overall, particularly of the breast (143) and colon (170), in patients with acromegaly. More recent studies, however, have failed to confirm these findings and suggest that overall cancer incidence is not increased in acromegaly (144, 171). Orme *et al.* (144) retrospectively examined the cancer incidence and mortality in a UK cohort of 1362 patients with acromegaly; overall cancer mortality rate was not increased (indeed, if anything it was lower: SMR, 0.76; 95% CI, 0.6–0.95), but there was a significant increase in the colon cancer mortality rate (SMR, 2.47; 95% CI, 1.31–4.22) and a nonsignificant increase in female breast cancer mortality (SMR, 1.60; 95% CI, 0.85–2.74; $P = 0.07$). An important finding was that the overall mortality rate increased significantly if GH levels were elevated [GH <2.5 ng/ml, SMR, 1.1 (95% CI, 0.89–1.35); GH 2.5–9.9 ng/ml, SMR, 1.41 (95% CI, 1.16–1.68); GH >10 ng/ml, SMR, 2.12 (95% CI, 1.7–2.62); P for trend < 0.0001]. This was also true for cardiovascular death [GH <2.5 ng/ml, SMR, 1.2 (95% CI, 0.83–1.68); GH 2.5–9.9 ng/ml, SMR, 1.59 (95% CI, 1.15–2.15); GH >10 ng/ml, SMR, 2.11 (95% CI, 1.42–3.01); P for trend 0.02] and cancer death [GH <2.5 ng/ml, SMR, 0.96 (95% CI, 0.63–1.41); GH 2.5–9.9 ng/ml, SMR, 0.81 (95% CI, 0.5–1.24); GH >10 ng/ml, SMR, 1.81 (95% CI, 1.13–2.74); P for trend 0.05]. Most recent studies have found cancer death rates in patients with acromegaly to be similar to those in the general population, suggesting that malignancy is not a significant cause of mortality in patients with acromegaly with modern treat-

ment modalities and strict targets (139, 142, 148, 155). Although the data regarding cancer mortality in patients with well-controlled acromegaly in recent years does not show a significant increase, there is an increasing body of evidence that the incidence of malignant disease may be greater in patients with acromegaly than the general population; however, several confounding factors must be appreciated while interpreting these data. This area has been extensively reviewed by Renehan and Brennan (172) and by Loeper and Ezzat (173).

The exact magnitude of the risk of colon cancer and the role of screening programs remain the subject of much debate (174–177). Full colonoscopy is important because up to two thirds of lesions were right-sided in one study (178). A significant amount of data in the general population suggest that the majority of colorectal carcinomas arise from adenomas, and as such detection and removal of adenomatous polyps should reduce colorectal cancer incidence and mortality (179). Ron *et al.* (170) assessed the risk of gastrointestinal cancer in 1041 patients with acromegaly reviewed between 1969 and 1985 from all Veterans Affairs (VA) hospitals in the United States and compared them to more than 37,000 veterans discharged from VA hospitals during the same follow-up time. Patients with acromegaly had a standardized incidence ratio for cancer of 1.6 (1.3–1.9) (116 observed cancers compared with 72.8 expected), with a standardized incidence ratio of 2.0 (95% CI, 1.3–2.9) for digestive organ or peritoneal cancers [in particular, esophageal 3.1 (95% CI, 1.3–6.0) and colonic 3.1 (95% CI, 1.7–5.1) neoplasia] (170). However, other large studies of mortality in patients with acromegaly have not reported raised risk of neoplastic deaths. It is likely that the increased risk of colorectal cancer in acromegaly is modest (176). Renehan *et al.* (176) have suggested that over a 10-yr period, 556 colonosco-

pies would need to be performed to prevent one death. Therefore, the issue of colonoscopy screening in acromegaly remains a contentious one, and further large-scale prospective studies are required.

There has also been interest in recent years with regard to increased thyroid cancer incidence in patients with acromegaly. However, it should be highlighted that the numbers in these studies are very small (and any changes in incidence may lead to a dramatic change in relative risk). Tita *et al.* (180) assessed thyroid disease in 125 patients in a single center over 25 yr and reported that the prevalence of thyroid cancer is 5.6% (seven of 125) patients compared with the estimated prevalence in the general population (0.093%). However, there are a number of caveats to this study, including the length of study that leads to inherent bias because the criteria for diagnosis of thyroid cancer may have changed. Also, all patients had thyroid ultrasound at diagnosis. This would not be the screening protocol for the normal population, and there was no matched control group. It is known that many patients in the general population have asymptomatic thyroid malignancy. There is a need for further larger studies with matched control populations to assess the risk of thyroid cancer in patients with acromegaly.

I. Other factors influencing mortality in acromegaly

Analysis of the determinants for mortality in acromegaly indicates that approximately 60% of patients die from cardiovascular/cerebrovascular disease and 25% from respiratory disease, and in 15% of patients, the cause of death is attributed to malignancy (171). From published retrospective studies, the major negative determinants for survival are high GH levels and the presence of hypertension, cardiac disease, and diabetes mellitus (171). Other variables found to influence outcome included hypertension, duration of the disorder before treatment, and age. Hypertension and glucose intolerance are important contributory factors to the vascular morbidity associated with acromegaly (181). However, there are few published reports on their impact on mortality in acromegaly and how this correlates with GH and IGF-I levels. Hypertension occurs in approximately one third of all patients with acromegaly, ranging in some series up to 60% (182, 183). The pathogenesis of hypertension in acromegaly is thought to be multifactorial, with an increase in extracellular sodium, a decrease in atrial natriuretic peptide, insulin resistance, and the direct effects of GH/IGF-I on vascular endothelial cells all playing a role (183). Hypertension is considered one of the most relevant negative prognostic factors for mortality in acromegaly (145, 146, 171, 184).

The presence of diabetes mellitus has been demonstrated to be a significant predictor of mortality in some studies (145, 146), but not in others (140, 152). Further studies are required to examine this association and to determine whether diabetes mellitus is primarily responsible for poor outcome or whether glucose intolerance is a surrogate marker for patients with higher GH levels, who are known to have a poor prognosis independently of any other factors.

III. Mortality in Cushing's Disease

A. Introduction

In Harvey Cushing's original series published in 1932, the median survival in untreated Cushing's disease was just 4.6 yr (185). Plotz *et al.* (186) endorsed these data some 20 yr later, reporting a 5-yr survival of just 50%. Undoubtedly, these reports reflected severe cases of hypercortisolism at a time when surgical and medical management were not as advanced as they are today but were sufficient to label Cushing's as the "killing disease" with premature mortality from infection and cardiovascular/cerebrovascular disease (187). Cushing's disease is rare, with an incidence of 2.4 cases per million (4.7 females and 0.3 males) and prevalence of 29.1 per million (188). The incidence appears to be increasing with time (from 1.5 to 3.9 million per year), and this is most likely explained through greater awareness and improved diagnostic techniques that detect patients with less florid clinical features.

B. Mortality studies in Cushing's disease

Several series have evaluated long-term outcome in treated patients (Table 7) (186, 188–198). Many such series also contain patients with Cushing's syndrome secondary to autonomous adrenal lesions (adenomas, carcinomas), but most reports separately identify and report on patients with Cushing's disease. It should also be highlighted that the treatment algorithms and techniques used in many of these historic studies would not be in keeping with modern clinical practice.

Pikkarainen *et al.* (196) reported six deaths in 48 Cushing's disease patients followed for a mean of 7.4 yr after treatment. Twenty-five cases were cured after surgery, and 16 also received radiotherapy. SMR was 2.67 (95% CI, 0.89–5.25) in this cohort. SMR was 3.8 (95% CI, 2.5–17.9; $P < 0.03$) in a Spanish series comprising 49 patients, with vascular mortality (SMR, 5) being the principal cause (188). Dekkers *et al.* (190) compared outcome in 248 consecutive cases of transsphenoidal surgery, 174 of whom had nonfunctioning pituitary adenomas and 74 of whom had Cushing's disease. Cushing's patients fared significantly worse with an overall SMR of 2.39 (95% CI, 1.22–

TABLE 7. Studies assessing mortality in patients with Cushing’s disease

First author, year (Ref.)	Patients	Follow-up years	Type of surgery	Initial remission rates	Long-term mortality numbers	SMR	Surgical mortality	RT	F:M
Plotz, 1952 (186)	33 CD patients and 189 cases from literature	1932–51	18 pituitary RT, 10 adrenal surgery, 2 adrenal RT	5/33	17 died within 5 yr of onset of symptoms	NA	5	18/33	4.3:1
Webbourn, 1985 (198)	79 CD	1953–80	B/L adrenalectomy	NA	Total 20; 55% cardio/cerebrovascular	SMR NA; actuarial mortality: 1 yr, 87.3%; 5 yr, 79.2%; 10 yr, 71.9%; 20 yr, 61.6%	3/79	16 (20.3%)	2:1
Guilhaume, 1988 (192)	64 CD	1978–85	TSS	42 (70%)	NA	NA	1 meningitis	NA	NA
Burke, 1990 (189)	57 CD, 8 Nelsons	NA	TSS	83%	NA	NA	NA	2 (3.1%)	NA
Grabner, 1991 (191)	109 CD	1950–87	B/L adrenalectomy	All but 5	Total 29; >50% CVS	NA	8 (7%), 3 MI, 2 PE, 1 CNS bleed, 1 Addisonian crisis, 1 sepsis	17 (15.6%)	3:1
Etxabe, 1994 (188)	49 CD	1975–92	46 TSS	87.5%	5 Total, 3 CVS, 1 infection, 1 post op	All 3.8 (2.5–17.9), women 4.5 (2.94–21), CVS 5 (3.4–48.6)	1 post op	16 (32.7%)	15:1
O’Riordain, 1994 (195)	Total = 50; 25 CD, 18 ectopic, 7 adrenal hyperplasia	1980–91	B/L adrenalectomy	All	Total 15	SMR NA; actuarial mortality in CD: 1 yr, 96%; 3 yr, 96%; 5 yr, 86%	All = 2; 1 Addisonian crisis, 1 extensive metastases	NA	NA
Pikkarainen, 1999 (196)	Total = 74; 43 CD, 4 ectopic, 26 ACTH independent	1981–94	TSS or adrenalectomy	33.8%	Total 10	1.68 (0.81–3.09) in all; CD 2.67 (0.89–5.25)	NA	CD 16 (37.2%)	6.4:1
Swearingen, 1999 (197)	161 CD	1978–96	TSS	90% of micro, 65% macro	6 Total, 2 CVS, 2 CVA	0.98 (0.44–2.2); actuarial survival: 5 yr, 99%; 10 yr, 93%	Nil	NA	2.5:1
Lindholm, 2001 (194)	Total = 166; CD 99, adrenal tumors 48, cancer associated 16, others 3	1985–95	90/99 had TSS and 5 yr follow-up data	Permanent cure 45/68, failure 20/68 (11 cure after additional surgery, 9 persistent disease)	Overall group, 23/139	Overall 3.68 (2.3–5.3); CD proven, 1.7 (0.68–3.5); CD unproven, 11.5 (5.7–20.5); adrenal adenoma, 3.5 (0.95–8.9)	3 post op	8	NA
Hammer, 2004 (193)	289 CD	1975–98	TSS	82%	29	Actuarial survival: remission 5 yr, 99%; 10 yr, 96%; 15 yr, 85%; persistent disease: 5 yr, 95%; 10 yr, 95%; 15 yr, 84%	3 MI	30	4.8:1
Dekkers, 2007 (190)	74 CD	1977–2005	TSS	80%	12 Total, 5 CVS	2.39 (1.22–3.9); remission 1.8 (0.71–3.37); persistent 4.38 (1.38–9.07)	NA	14 (18.9%)	3:1:1

CD, Cushing’s disease; ectopic, ectopic ACTH secretion; TSS, transsphenoidal surgery; B/L adrenalectomy, bilateral adrenalectomy; F:M, female:male ratio; NA, not available; CVS, cardiovascular; RT, radiotherapy; MI, myocardial infarct; PE, pulmonary embolism; CNS, central nervous system; micro, microadenomas; macro, macroadenomas; Nelsons, Nelsons syndrome.

3.9) compared with 1.24 (95% CI, 0.85–1.74) in the non-functioning adenoma group. In terms of therapy, a Danish study reported just one death in 45 patients with Cushing's disease who were cured after surgery, compared with six deaths in 20 patients with persistent hypercortisolemia (SMR, 0.31 vs. 5.06) (194). Similar conclusions were published from Swearingen *et al.* (197) in Boston who reported normal 5- and 10-yr survival rates in 161 patients after transsphenoidal surgery; 90% of the cohort were apparently cured after surgery. Normal long-term survival was also documented in a large series (n = 248) from Ann Arbor, Michigan (193). However, increased mortality was observed in a small number of patients who had recurrent/persistent disease. The overall conclusion from the published literature is that mortality is increased in patients with Cushing's disease, but with effective therapy long-term survival is no different from the background population. By contrast, persistent/recurrent disease is associated with poor outcome, data which collectively provide an evidence base for early and aggressive intervention. It is important to remember that these conclusions are drawn from relatively small series with small numbers of deaths (therefore, even high SMR values often have very wide CIs). It remains to be seen whether the reported ongoing and deleterious cardiovascular risk factors (IMT, metabolic abnormalities) many years after "cure" in these patients translate into poor outcome in larger multicenter/national series (199). In the interim, aggressive treatment of cardiovascular risk abnormalities (hypertension, hyperlipidemia, insulin resistance) with conventional therapies is warranted if these are present.

C. Factors influencing mortality in Cushing's disease

1. Hypertension

Hypertension is present in approximately 80% of patients with endogenous Cushing's syndrome and rises to 95% in patients with ectopic ACTH secretion (187, 200, 201). In keeping with the loss of cortisol circadian rhythm, there is also a loss of blood pressure circadian rhythm such that hypertension due to Cushing's syndrome is associated with a loss of the nocturnal fall in blood pressure (202). Faced with the known actions of glucocorticoids, it is relatively easy to link hypercortisolism to premature vascular mortality. Glucocorticoids increase blood pressure through several mechanisms (203), including the mineralocorticoid action of cortisol, activation of the renin-angiotensin system, potentiation of vasoconstriction through increased β -adrenergic receptor sensitivity to catecholamines, and suppression of vasodilatory actions (203). The resultant effect of these changes is an increase in peripheral vascular resistance, plasma volume, cardiac output, and renovascular resistance (203). Sleep apnea and insulin resistance

in patients with Cushing's syndrome have also been reported as playing a role in the development of hypertension (204, 205).

In one study assessing the underlying pathophysiology of elevated blood pressure in 12 patients with Cushing's syndrome secondary to an adrenal adenoma compared with six control subjects, patients with Cushing's syndrome had increased angiotensinogen levels and decreased plasma renin concentration, but no difference in plasma renin activity or plasma aldosterone (despite this, the angiotensin-converting enzyme inhibitor captopril, but not an angiotensin II antagonist, was effective in decreasing blood pressure). The study also described decreased urinary prostaglandin E2 and kallikrein in patients with Cushing's syndrome, which are known to be depressor systems and therefore may have a role to play in increased blood pressure seen in Cushing's syndrome. Pressor responses to norepinephrine and angiotensin II were significantly enhanced in this study. All 12 patients had normal blood pressure 1 yr after adrenal adenectomy (206).

In Cushing's disease, the highest cortisol secretion rates are associated with the greatest sodium retaining "mineralocorticoid" effects through saturation of the renal protective enzyme 11 β -HSD type 2, which normally inactivates cortisol to cortisone within the renal tubule, protecting the MR from cortisol excess (201). Persistence of hypertension after treatment of hypercortisolemia is associated with increased mortality (188). Blood pressure was shown to fall significantly in a childhood/adolescent study, with normalization of diastolic and mean blood pressure 3 months after effective therapy (207); interestingly, there was no correlation between blood pressure pretreatment and cortisol concentrations. As outlined in recent clinical guidelines statements, further outcome studies are urgently required to inform an evidence base for treating patients with Cushing's disease, particularly when hypercortisolism and/or clinical symptoms/signs are mild (208).

2. Other cardiovascular risk factors

This increase in blood pressure along with other factors may play a key role in the altered left ventricular characteristics and function of patients with Cushing's syndrome. Muiesan *et al.* (209) recently described decreased left ventricular end-diastolic diameter and left ventricular end-systolic diameter, but increased left ventricular inter-ventricular septum diameter, left ventricular posterior wall diameter, relative wall thickness, and left ventricular mass index in patients with Cushing's syndrome compared with age-, gender-, and blood pressure-matched controls, leading to reduced systolic performance and diastolic dysfunction. Baykan *et al.* (210) have also reported left ventricular diastolic dysfunction in patients with Cushing's syndrome; serum cortisol was positively correlated with Tei index (a measure of global cardiac dysfunction).

tion) and negatively with ejection fraction. These cardiovascular changes may not revert to normal after remission of Cushing's syndrome. Faggiano *et al.* (211) showed that 1 yr after remission of Cushing's disease, patients still had abnormal LDL cholesterol, IMT, systolic lumen diameter, and distensibility coefficient than the age- and gender-matched control group, but not BMI-matched controls (albeit with improvement in all these values compared to when the patients had active Cushing's disease). Colao *et al.* (199) assessed cardiovascular risk in patients with Cushing's disease who had been in remission for 5 yr and compared them to an age- and gender-matched population. Patients who were in remission from Cushing's disease still had higher BMI, waist:hip ratio, systolic and diastolic blood pressure, fasting glucose and insulin, total and LDL cholesterol, fibrinogen, and lipoprotein (a) than controls. This was associated with an increased carotid IMT and diastolic peak velocity and a decreased systolic/diastolic lumen diameter and distensibility coefficient (199). When the groups were matched for BMI, Cushing's disease patients still had higher waist:hip ratios, diastolic blood pressure, fibrinogen levels, HDL cholesterol, common carotid artery IMT, and diastolic peak velocity and decreased diastolic lumen diameter and distensibility coefficient.

Hypercoagulability has been associated with a hypercoagulable state, and several studies have described an increased risk of thromboembolic disorder in patients with Cushing's syndrome. Van Zaane *et al.* (212) have recently performed a systematic review in this area, and although much of the data are based on small numbers, it is clear that glucocorticoid-induced hypercoagulability leads to venous thrombosis in patients with Cushing's syndrome, particularly in postoperative patients. Hypercoagulability was suggested by high levels of factor VIII, factor IX, and von Willebrand factor and evidence of enhanced thrombin generation (212). A risk of 1.9–2.5% was reported for venous thromboembolism not provoked by surgery, with an increased risk in the postoperative period (212).

Hypercortisolism leads to hyperglycemia and insulin resistance and stimulates hepatic gluconeogenesis and glycogenolysis. *In vivo* glucocorticoids reduce glucose uptake by reducing glucose transporter 4 translocation and increasing lipolysis (213). Assessment of lipid status in clinical studies of patients with Cushing's disease is not well defined, but patients have a low HDL cholesterol and elevated total and LDL cholesterol (199). The above abnormalities also contribute to hepatic steatosis, which occurs in 20% of patients with Cushing's syndrome (214).

3. Infection risk

With the actions of glucocorticoids known, it is relatively easy to link hypercortisolism to premature mortality

secondary to infection. In terms of infection risk, glucocorticoids suppress the inflammatory response and are immunosuppressive, and Cushing's syndrome has been suggested to be a transitory immune deficiency state (215). Indeed, there are many case reports and studies reporting opportunistic infection in Cushing's syndrome with infections such as pneumocystis (216, 217), aspergillus (218), other invasive fungal infections (219), mycobacterium (220), cytomegalovirus (221), cryptococcal (222), and nocardial infections (223). Glucocorticoids influence the traffic of circulating leukocytes and inhibit many functions of leukocytes and immune accessory cells (224). They suppress the immune activation of these cells and inhibit the production of cytokines and other mediators of inflammation (224). They particularly suppress type I helper T cells and stimulate apoptosis of eosinophils, and they inhibit the expression of adhesion molecules and their corresponding receptors (224).

With the exception of the association between cortisol secretion rate and renal mineralocorticoid action (201), there are no data linking vascular risk factors or immune markers to absolute levels of cortisol *per se*. Nevertheless, the assumption is made that the severity of Cushing's (as translated to the daily cortisol secretion rate) is positively correlated with the mortality risk. This is an important concept when considering the evidence base for therapy in any given patient; the more severe the disease, the greater the potential benefit after therapy (225). However, in terms of underlying etiology of increased mortality, other factors need to be considered.

4. Hypopituitarism

Although pituitary dysfunction has been associated with increased mortality (*Section I*), it should be highlighted here that all of these studies excluded Cushing's patients from analysis. Although the majority of pituitary tumors in Cushing's disease patients are microadenomas, hypercortisolism *per se* rather than any mass effects from a tumor, surgical intervention, and/or radiotherapy can result in GH, T₄, and sex steroid deficiencies, all of which may be confounders (12). In the study by Lindholm *et al.* (194), seven of 47 (14.9%) patients had TSH deficiency, seven of 12 (58.3%) men had low testosterone levels, and 10 of 23 (43.5%) premenopausal women had estradiol concentrations below 100 pmol/liter before treatment of Cushing's disease. However, after treatment 17 patients (49%) were hypogonadal, with 15 having panhypopituitarism (33.3%) (194). Burke *et al.* (189) reported DI in 25% of patients, gonadotropin deficiency in 48%, TSH deficiency in 28%, and recovery of ACTH function in 47%.

IV. Mortality in Craniopharyngioma

A. Introduction

Craniopharyngiomas are rare epithelial tumors that arise along the path of the craniopharyngeal duct from squamous epithelial remnants of Rathke's pouch. The pathophysiology and complications that arise from craniopharyngiomas and their treatment has been extensively addressed previously in this journal by Karavitaki *et al.* (226). Although craniopharyngiomas may arise anywhere along the craniopharyngeal path, the majority of them are located in the sellar/suprasellar region (226) and have a suprasellar component (only 4–6% are intrasellar) (226, 227). Craniopharyngiomas have an incidence of 0.13 per 100,000 person-years that does not vary by gender or race (228) and constitutes 2–5% of adult and 5.3–15% of childhood intracranial tumors (226, 229). They may occur at any age, although a bimodal distribution has been described, with peak incidence rates in children (ages 5–14) and among older adults (ages 65–74) (228). These tumors can be primarily solid, primarily cystic, or more commonly, a combination of both consistencies (227). There are two major histological variants, the commonest being the adamantinomatous type, which is commonly calcified and predominantly affects children, and the papillary or squamous epithelial type, which is rarely calcified and predominantly affects adults (226). Craniopharyngiomas are histologically benign, with only nine cases of malignant craniopharyngiomas reported (230). However, they tend to be locally aggressive, with finger-like attachments that invade adjacent critical structures such as the pituitary, hypothalamus, optic nerves, third ventricle, and blood vessels (231, 232). In fact, craniopharyngiomas are associated with greater tumor-related morbidity than other central nervous system tumors, and most patients present with a combination of neurological, endocrine, and somatic effects that may be permanent or may be exacerbated by treatment (233).

B. Mortality studies in craniopharyngioma

Craniopharyngiomas are associated with significant mortality, with reported overall mortality rates three to five times higher than those of the general population (234, 235). When assessing mortality in patients with craniopharyngioma, it may be important to consider adults and children separately. The overall survival rates (which reflect the effect of multiple treatments) described in exclusive children series range from 83–96% at 5 yr (236–241) and 65–100% at 10 yr (237–248) and average 62% at 20 yr (249). In adults or a mixed-age range population (adults and children) series, the overall survival rates range from 54–96% at 5 yr (228, 232, 235, 239, 240, 250, 251),

from 40–93% at 10 yr (232, 234, 235, 239, 240, 250–255), and from 66–85% at 20 yr (235, 254, 255) (Table 8). The lower limits of survival rates usually reflect data from earlier series, before modern advances in microsurgery, neuroimaging, neuroendocrinology, and radiotherapy. It is not clear whether the age at diagnosis represents a survival prognostic factor because some studies have shown that the youngest patients have better survival rates (228, 234, 239, 240, 253); others have found better outcome in older patients (255, 256), whereas still other studies report no difference between pediatric and adult populations (232, 250, 254, 257, 258).

C. Factors influencing mortality in craniopharyngioma

1. Hypopituitarism

Craniopharyngioma patients have evidence of endocrine dysfunction at presentation and preoperatively in 39–87% of children series (237, 238, 246, 259–261) and 23–95% of mixed adult and children series (232, 235, 240, 250, 251, 254, 262, 263). GH deficiency is reported in 35–100% of patients, FSH/LH deficiency in 10–91%, ACTH deficiency in 21–68%, TSH deficiency in 13–46%, and cranial DI in 6–38% (226, 235, 238, 259, 264–266). Although hypopituitarism is associated with increased mortality, patients with craniopharyngiomas have mortality rates nearly 10 times higher than for other causes of hypopituitarism (12). This highlights the contribution of other factors associated with these tumors to the increased mortality over and above that documented for hypopituitarism *per se*. Particularly in children, hypoadrenalism and associated hypoglycemia, as well as DI, can lead to significant morbidity and mortality (232, 267, 268).

Hypopituitarism may also result from therapeutic interventions, notably surgery with some degree of hormone deficiency in 73–100% (236, 242, 247, 251, 256, 261, 264, 265, 268, 269) and panhypopituitarism in 44–100% (235, 241, 244, 251, 262, 263, 270, 271). Moreover, previous endocrine insufficiencies do not reverse after surgery (232, 235, 250, 263), except in rare occasions (262, 269, 272). The exact incidence of postradiation endocrine deficiency is difficult to define because the majority of the patients have undergone surgery before irradiation (244). A dose-effect relationship is found, with a significant increase in endocrine dysfunction when maximum doses of radiotherapy exceeded 61 Gy (249). Posttreatment pituitary dysfunction in radiotherapy series (reflecting data from patients receiving surgery plus radiotherapy and radiotherapy only) ranges from 91 to 100% (232, 233, 237, 246, 254, 273) and panhypopituitarism from 80 to 100% (232, 235, 237, 254, 260). The incidence of endocrine complications may be higher in those patients receiving

TABLE 8. Studies reporting overall survival rates in craniopharyngioma patients

First author (Ref.)	No. of patients (% children at diagnosis) ^a	Follow-up period	Overall survival rates (%) ^b		
			5 yr	10 yr	20 yr
Bunin (228)	285 (29) ^c	1985–1988 and 1990–1992	80	NA	NA
Stripp (232)	75 ^d	1974–2001	96	85	NA
Bulow (234)	60 (43%) ^c	1951–1988	NA	68	NA
Pereira (235)	54 (25%)	1965–2002 (median 10 yr)	95	85	85
Muller (238)	385 (100) ^e	1980–2001	91	87	NA
Regine (239)	58 (33)	1958–1982	54/84 ^f	51/72 ^f	NA
Tomita (241)	54 (100)	1984–2003	93	90	NA
Sung (240)	109 (40) ^g	1950–1977	67 ^h	53 ^h	NA
Fisher (236)	30 (100) ^e	1980–1996	95	NA	NA
Habrand (237)	37 (100) ^g	1969–1992	91	65	NA
Lin (246)	31 (100) ⁱ	1970–2002 (median 6.5 yr)	NA	96	NA
Kalapurakal (244)	25 (100) ^g	1983–1996 (median 10 yr)	NA	100	NA
Poretti (247)	25 (100)	1980–2002 (median 11 yr)	NA	92	NA
Scott (248)	61 (100) ⁱ	1970–1990	NA	91	NA
Hetelekidis (243)	61 (100) ⁱ	1970–1990 (median 10 yr)	NA	91	NA
Khafaga (245)	56 (100) ^e	1975–1996	NA	65	NA
Devile (242)	75 (100)	1973–1994 (median 5 yr)	NA	88	NA
Regine (249)	19 (100)	1961–1981 (median 21 yr)	NA	NA	62
Karavitaki (250)	121	1964–2003 (median 8.6 yr)	91	90	NA
Van Effenterre (251)	122	1975–2000	92	85	NA
Fahlbusch (253)	148	1983–1997	NA	93	NA
Rajan (255)	173	1950–1986 (median 12 yr)	NA	77	66
Bartlett (252)	85	1938–1970	NA	43	NA
Pemberton (254)	87	1976–2002	NA	86	70

^a Children considered as <16 yr unless otherwise specified.

^b Survival rates from diagnosis or initial operation/radiotherapy treatment depending on the study.

^c Children considered as ≤20 yr.

^d Percentage of children not reported, but patients' age at diagnosis ranged from 1.5–24.8 yr, with a median of 8.5 yr.

^e Children considered as ≤18 yr.

^f Survival rates of 54 and 51% in adults and 84 and 72% in children at 5 and 10 yr, respectively.

^g Children considered as ≤15 yr.

^h Survival rates of 55 and 40% in adults and 83 and 72% in children at 5 and 10 yr, respectively.

ⁱ Patients' age at diagnosis ranged from 1.1–20 yr with a median of 8.1 yr.

^j Children considered as ≤21 yr.

surgery only (aggressive surgery) *vs.* those receiving a less extensive surgery and radiotherapy (233), although other studies have shown similar endocrine dysfunction irrespective of the extent of initial surgical resection (236, 250, 269) or type of tumor therapy (226).

Posterior pituitary dysfunction is more frequently induced by surgery, especially radical surgery (232, 233, 246). The frequency of individual hormone deficiencies after treatment of craniopharyngioma (including exclusive surgical series as well as series with different therapeutic options) ranges from 47–100% for GH (226, 235, 236, 264, 273, 274), 12–100% for gonadotropins (226, 235, 236, 259, 261, 264, 275), 49–91% for ACTH (226, 235, 236, 259, 261, 264, 275), 39–95% for TSH (226, 235, 236, 259, 261, 264, 275), and 25–87% cranial DI (226, 232, 235–237, 241, 246, 251, 259, 261, 264).

2. Therapy

The different therapeutic modalities may also contribute to decreased survival in craniopharyngioma patients.

Treatment options include surgery [gross total resection (GTR), subtotal resection (STR), cyst drainage, intracystic bleomycin, or partial removal (PR) with observation], radiotherapy [postoperative conventional external beam radiotherapy, stereotactic radiosurgery, or radiotherapy and intracystic irradiation], or a combination of the above. The two most widely practiced approaches are primary GTR or STR followed by radiation therapy. However, it is difficult to discern which treatment is associated with a better survival rate because there is much heterogeneity among reported groups. Also, there may have been selection bias in the choice of treatment depending on center expertise. Moreover, most studies are retrospective, nonrandomized, and descriptive, with many lacking robust statistical evaluation. The rarity of this tumor limits controlled studies and the experience of any single group or individual in its treatment (233). The variable and extensive nature of its pretreatment morbidity and the competing side effects

of surgery and radiotherapy make it difficult to evaluate or standardize treatment.

The 10-yr survival rates range from 62–100% after GTR (240, 250, 251), 27–86% after STR/PR (240, 250, 251, 276, 277), 74–100% after STR/PR and radiotherapy (232, 240, 250, 276–278), and 81–100% after radiotherapy alone (243, 248, 255). Regarding surgical intervention, perioperative mortality was as high as 33–41% in earlier series before 1950 (279, 280). The introduction of cortisone after 1950 caused prompt improvement in the outcome of surgery, although in a review of a larger series of patients surgically treated after 1950, mortality still varied between 10 and 40% (281). Thanks to the advances of microsurgery, supportive care, and the multidisciplinary management of patients with craniopharyngiomas, the surgical mortality for primary operations reported in studies with mixed age range populations published in the last decade has decreased to 1.1–4.9% (250, 251, 253, 282).

Although it has been suggested that radical excision may cause substantial perioperative morbidity and mortality (226), some studies have reported that the immediate postoperative mortality is not influenced by the extent of surgery excision (234, 250). Tumor recurrence increases the perioperative mortality, but it also increases overall mortality after different therapeutic interventions (234, 240, 249, 250), with overall survival rates ranging between 29 and 86% at 10 yr (240, 250, 270, 283), and 25% at 20 yr (249). The perioperative mortality for surgery after tumor recurrence remains high at 10.5–24% (250, 253, 282). This may be related to the adhesion of the tumor capsule to local structures secondary to previous surgery or radiotherapy, which makes subsequent surgery a higher risk procedure (282, 284). In pediatric series, perioperative mortality in studies published in modern series range between 0 and 3.8% (241, 259–261, 285). In combined children and adult/children series, lower surgical mortality rates may be obtained in some (253), but not all (250, 259) transsphenoidal surgery procedures when directly compared with the transcranial approach. However, it is questionable whether the tumors treated using the transsphenoidal and transcranial approach can be compared due to differences in size, extension, and adherence to intracranial structures (251, 253).

3. Hypothalamic damage

Morbidity due to hypothalamic damage includes obesity, cognitive impairment (defective short-term memory and limited concentration span), behavioral abnormalities, defective thirst sensation, sleep disturbances, and thermoregulatory disorders (244, 286). Hypothalamic damage can be due to the tumor itself, surgery, and after radiotherapy (231, 285).

TABLE 9. Contributing mechanisms and risk factors linked to the development of obesity in craniopharyngioma patients

- Lesion/infiltration of hypothalamus (by the tumor and/or its treatment)
- Lesion of ventromedial nucleus (regulator of eating behavior)
- Insensitiveness of hypothalamic structures to leptin
- Hypothalamic disinhibition of vagal output with consequent increased vagal activity, hyperinsulinemia, and adipogenesis
- Impaired hypothalamic regulation of melatonin rhythmicity, with decreased melatonin levels
- Extensive surgery
- Hypothalamic radiotherapy >51 Gy
- High BMI SDS before and at the time of diagnosis of craniopharyngioma
- Early and rapid postoperative weight gain
- Recurrence
- Reoperation
- High rate of hydrocephalus requiring a shunt
- High tumor volume (not associated in all studies)
- Reduced physical activity
- Reduced sympathetic tone
- Neurological and visual deficits
- Increased daytime sleepiness and disturbances of the day-night rhythm, in relation to impaired melatonin regulation
- Familial disposition for obesity

Obesity in the general population is associated with increased risk of death (287), and in craniopharyngioma patients, those with severe obesity have reduced survival compared with those with moderate obesity and normal weight (288). Obesity rates vary from 6–30% of craniopharyngioma patients at presentation (232, 237, 247, 250, 256, 259–261, 265, 289), and its incidence increases to 17–62% after surgery (with or without radiotherapy) (232, 235, 237, 241, 244, 246, 247, 259–261, 265, 273, 275, 289, 290). Obesity in patients with craniopharyngioma is multifactorial (Table 9). One of the major causes is the disruption of hypothalamic mechanisms that control satiety, hunger, and energy balance (291). Craniopharyngiomas can be intimately attached to the hypothalamic ventromedial nucleus (241), which regulates eating behavior (292). Lesion of ventromedial areas by aggressive tumors or their treatments can therefore create hyperphagia and obesity (238, 241). Hypothalamic involvement has been associated with the development of obesity in children with craniopharyngioma (288, 292–294). de Vile *et al.* (295) reported that childhood patients with severe postoperative obesity showed evidence of significant disruption of the normal hypothalamic anatomy assessed by magnetic resonance imaging, with either complete deficiency or extensive destruction of the floor of the third ventricle. Moreover, the extent of surgery and hypothalamic irradiation exceeding 51 Gy have been identified as risk factors for the development of obesity (296). Children with craniopharyngioma who have a higher BMI SDS at the time of diagnosis, as well as those with early and rapid postoperative weight gain, are at highest risk of future

obesity (293, 294, 297). Recurrence (285), reoperation (285, 288), higher rate of a hydrocephalus requiring a shunt (293), and higher tumor volume (288, 293) have also been shown to be linked to the development of obesity, although tumor volume has not been associated with obesity in all studies (289) (Table 9). Other mechanisms may be involved, such as insensitivity of hypothalamic structures to endogenous leptin (298). However, it has also been shown that reduced physical activity, rather than hyperphagia, could be the major factor accounting for obesity in craniopharyngioma patients because the caloric intake in these patients has been found to be similar to that of BMI- and age-matched controls (299). The decreased physical activity and severe obesity could be related to reduced sympathetic tone (300). Other factors such as neurological and visual deficits (299), increased daytime sleepiness, and disturbances of the day-night rhythm may be involved (301).

Decreased melatonin levels are associated with increased daytime sleepiness, BMI, and hypothalamic tumor (301), suggesting an impaired hypothalamic regulation of melatonin rhythmicity in patients with suprasellar craniopharyngioma (238). A further contributing factor may be increased vagal activity, which leads to hyperinsulinemia and adipogenesis, secondary to hypothalamic disinhibition of vagal output (302). Finally, familial predisposition for obesity could also be a risk factor for the development of severe obesity in craniopharyngioma subjects (293).

The metabolic syndrome is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increase for incident type 2 diabetes mellitus (303). Compared with age-, sex-, BMI-, and pubertal stage-matched healthy controls, craniopharyngioma patients have significantly higher abdominal fat and adverse lipid profile (higher fasting triglycerides and lower HDL cholesterol to total cholesterol ratio), although insulin sensitivity is equally reduced for patients and controls (273). In a Dutch study with both adult and children subjects with craniopharyngioma, a high prevalence of features of the metabolic syndrome such as dyslipidemia, obesity (four times more common), and type 2 diabetes mellitus (twice as common) were also found (235). General obesity and specifically abdominal obesity, together with the adverse lipid profile, and type 2 diabetes could contribute to the increased risk of cardio- and cerebrovascular mortality risk found in craniopharyngioma patients (234, 235).

4. Other factors

“Nontraditional” cardiac risk factors have also been described in patients with craniopharyngioma. A small retrospective study of 12 craniopharyngioma patients found that half of them had at least one abnormality of

cardiac structure, function, or rhythm, specifically prolonged QT in 25% of the cohort (304). Besides cardio- and cerebrovascular mortality, other main underlying causes of death in patients with craniopharyngioma are respiratory (12) and infections (235). Finally, it is not clear which other factors may impact on the survival of craniopharyngioma subjects. As already described, it is controversial whether the age at diagnosis has an influence on survival. Similarly, the role of gender as a prognostic factor is not established; some authors report a higher mortality among females (234, 235), but others have not found any gender differences (232, 241, 250, 258). One of the two studies reporting higher mortality rates in females suggested a possible role of estrogen deficiency (235), but the other did not consider that unsubstituted gonadal insufficiency had a significant impact on enhanced mortality (234). Tumor size could be a prognostic factor because increased survival rates have been shown in tumors under 3 cm (257), and the larger the tumor, the greater will be the damage, both pre-operatively and intra-operatively to vital intracranial structures (256). The histological type as a prognostic factor is also controversial; better 5-yr survival rates have been found in the squamous epithelial type *vs.* the adamantinous and combined histological types (305), and higher perioperative deaths have also been reported in adult adamantinous tumors (306), but other authors have not found significant differences between the two histological types (307, 308). Several studies have described a more favorable prognosis when tumors lack calcification, especially in adults (257, 306), although no specific pathological feature predicted survival in children (236). In other studies, neither consistency of the tumor (250, 257) nor its location (241, 250) had prognostic importance. In children, the use of modern imaging as well as a good initial performance status (measured according to a functional classification that includes the presence of visual deficits, neurological impairment, and hypopituitarism) have been correlated with enhanced overall survival at 10 yr (237). Finally, it is not clear whether the presence of hydrocephalus constitutes a prognostic factor because increased mortality (256) and lack of association with mortality have been reported (232, 236, 241, 250).

V. Pituitary Radiotherapy and Mortality in Pituitary Patients

A. Introduction

Conventional radiotherapy (CRT) is the most frequently used method of radiation therapy for pituitary tumors. It is most commonly used in patients who have large remnants of pituitary adenomas with evidence of progression after surgery or if surgery does not lead to

normalization of hormone excess. Surgery remains the primary therapy of choice for all pituitary tumors, with the exception of prolactinomas. However, radiotherapy has been shown to be efficacious adjuvant treatment for both tumor (309–317) and endocrine control (318–325). Because stereotactic radiosurgery is only a relatively new therapy, the majority of data regarding efficacy, potential adverse effects of radiotherapy, and in particular effect of radiotherapy on mortality are derived from studies where CRT was used; this review will focus predominantly on studies that used CRT.

B. Cerebrovascular morbidity and mortality following pituitary radiotherapy

Increased cerebrovascular disease and death have been reported in a number of studies after pituitary irradiation. In a series of 156 patients with nonfunctioning pituitary adenoma, increased cerebral infarction rates were found in patients administered higher doses of radiotherapy (326). In a study assessing the role of pituitary radiotherapy in the development of CVA in 331 patients who received pituitary radiotherapy for a number of underlying diagnoses, it was reported that patients who received radiotherapy had a relative risk of CVA of 4.1 (95% CI, 3.6–4.7) compared with the general population (327). On multivariate analysis, the authors reported that the main predictors of CVA were older age at diagnosis, prior extensive surgery compared with biopsy or no operation, higher doses of radiotherapy, and an underlying diagnosis of acromegaly (327). In a further study, Brada *et al.* (328) assessed cerebrovascular mortality in 344 patients who had received radiotherapy (79% also had transcranial or transsphenoidal surgery); cerebrovascular disease accounted for 26% of all deaths [33 deaths compared with eight deaths expected (RR, 4.11; 95% CI, 2.84–5.75)], with an even further increase in female patients [RR, 6.9 (95% CI, 4.29–10.6)] compared with males [RR, 2.4 (95% CI, 1.24–4.2); $P = 0.002$]. Surgery also plays a role in the increased cerebrovascular mortality reported in this study because patients with prior surgery had an increase RR compared with those with no surgery or biopsy alone [RR, 5.19 (95% CI, 3.5–7.42) *vs.* RR, 1.33 (95% CI, 0.27–3.88); $P = 0.02$], but there may be several confounders that led to this increase (328).

C. Hypopituitarism following pituitary radiotherapy

More than 50% of patients who receive pituitary radiotherapy will develop one or more anterior pituitary hormone deficiencies within the following decade (315, 318, 329). The classic pattern of pituitary hormone deficiency to radiotherapy of GH deficiency (100% at 5 yr), gonadotropin deficiency (91% at 5 yr), ACTH deficiency (77% at 5 yr), and TSH deficiency (42% at 5 yr) (329) is

not always seen, and deficiencies may occur in any order. Because deficiencies can occur at any time point, even up to 20 yr later, long-term testing is required (309, 315, 330). With CRT, the speed of onset of hypopituitarism is related to the total and fractional doses of radiotherapy (315), and the rate of hypopituitarism increases from time of irradiation.

A number of studies have described an increased mortality in patients with hypopituitarism compared with age- and sex-matched controls, which is covered in *Section I* (11, 12, 16, 18). In these studies, the increased mortality was predominantly due to cardiovascular and cerebrovascular mortality. In total, nearly 1900 patients have been included in these studies, and approximately 50% had radiotherapy; in two studies, radiotherapy was not associated with increased mortality (11, 16), and in the third study, it was not possible to investigate the link because nearly all patients had radiotherapy [304 of 344 (88.4%) received radiotherapy with an overall cerebrovascular mortality RR of 3.39 (95% CI, 2.27, 4.99); men, 2.64 (95% CI, 1.44–4.42); and women, 4.91 (95% CI, 2.62–8.4)] (18). In the largest series in the literature, Tomlinson *et al.* (12) reported that radiotherapy significantly increased mortality with an SMR of 2.32 (95% CI, 1.7–3.14; $P = 0.004$) in the radiotherapy group compared with 1.87 (95% CI, 1.62–2.16) in the general cohort of patients with hypopituitarism. In particular, patients who had received radiotherapy had an elevated cerebrovascular risk [SMR, 4.36 (95% CI, 2.48–7.68); $P = 0.001$] (Fig. 15). Erfurth *et al.* (331) compared radiation regimens and duration of symptoms of hypopituitarism in 342 patients treated with surgery and radiotherapy. They compared 32 patients who had died from cerebrovascular disease to 62 matched patients from the cohort who had not died from CVA. They found no significant difference between the

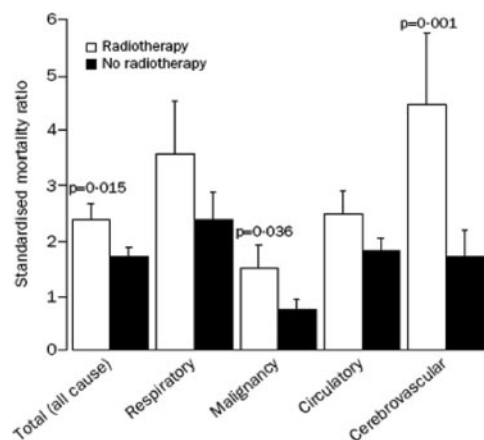


FIG. 15. Effect of pituitary radiotherapy on total and specific-cause mortality in patients with hypopituitarism. [Reprinted from J. W. Tomlinson *et al.*: *Lancet* 357:425–431, 2001 (12), with permission from Elsevier.]

two groups for a number of irradiation parameters such as maximum absorbed dose, maximum biological equivalent dose, field size, and number of fractions. The only difference found was a longer duration of symptoms of hypopituitarism in the cerebrovascular mortality group. They concluded that untreated hormone deficiency may be more directly implicated in cerebrovascular mortality than radiotherapy *per se*. The increase in cerebrovascular mortality after radiotherapy has also been described in patients with acromegaly (*Section II*).

D. Mechanisms of radiation injury

Radiation injury to the vasculature was first described more than 100 yr ago (332) and has subsequently been reported to be one of the commonest adverse effects of therapeutic radiotherapy. Radiotherapy leads to damage of both large and small vessels, with a predilection to smaller vessels (333) because endothelial cells are radiosensitive (334). In capillaries and sinusoids, irradiation can lead to focal cytoplasmic degeneration, vacuolation, and irregular projections of the cytoplasm to the vessel lumen. In the early stages, this leads to increased capillary permeability and intracellular edema. This may be followed by platelet and fibrin thromboses leading to the detachment of endothelial cells from their basement membrane (332), which may ultimately lead to necrosis of the endothelial cell and wall rupture with resulting loss of a segment of microvessel (335). Less severe damage often results in permanent dilatation and teleangiectasia; there may also be compensatory endothelial cell proliferation, which, if the insult is not significant, can reestablish microvascular segments (335). Arteriolar lesions can also occur. This is most commonly in the form of myointimal proliferation that leads to narrowing of the lumen, and foamy macrophage plaques may also develop (particularly likely to be due to radiation if they occur in arterioles measuring less than 100 μM in diameter). Fibrin may accumulate in the media or intima of arteriole, leading to fibrinoid necrosis, or the media may be replaced by dense collagen-rich tissues leading to hyalinization of the media (332). Also, some studies have shown an acute lymphocytic vasculitis affecting the media, intima, and adventitia of medium-sized arteries localized to the radiation field leading to fibrinous exudate and occasionally thrombosis (333). In arteries measuring more than 100 μM , lesions are observed less frequently than in smaller vessels, and these lesions are similar to those seen in atherosclerosis. However, because the patients are often young and the plaques are limited to the radiation field, one can assume that they may be secondary to the radiation therapy.

These changes may be clinically important, as seen in patients with pituitary radiotherapy who have increased risks of cerebrovascular death but also in other patient

groups who receive radiotherapy. A recent retrospective analysis of 4665 Hodgkin's disease patients who had irradiation to the heart followed up for 7 yr revealed a RR of 2.56 (95% CI, 1.11–5.93) for myocardial infarct, whereas those treated with chemotherapy alone had no increase (336). Another study assessing 2232 Hodgkin's patients (79% >40 Gy) followed for 9.5 yr, the RR for myocardial infarct in patients treated with radiotherapy alone was 3.8 (95% CI, 2.8–4.8). This RR increased with the latency period and was highest in patients who had been treated with radiotherapy before the age of 20 (337).

E. Secondary oncogenesis following pituitary radiotherapy

Secondary oncogenesis after pituitary radiotherapy is a controversial area. It is impossible to calculate the true incidence of tumors arising after pituitary radiotherapy because most of the literature covers case reports or cross-sectional studies. Another factor to take into account is that patients with pituitary disease receive disproportionately frequent imaging, which historically took the form of recurrent computed tomography scans and, in more recent years, magnetic resonance imaging; a more appropriate control group might be patients treated with surgery alone rather than normal population controls (338) because they also undergo regular surveillance imaging. In some studies, the incidence of secondary neoplasm is as high as 1–2%, occurring with a latency of 8–15 yr (339–341). One study has estimated an incidence of extracranial tumors in non functioning adenoma patients to be 3.9-fold that of the general population, irrespective of whether or not the patient had radiotherapy (342); therefore, having a pituitary adenoma may lead to some underlying increased susceptibility to tumorigenesis. Secondary intracranial tumors (most commonly gliomas or meningioma) due to pituitary irradiation are now rarer due to newer techniques that expose a smaller volume of cranial tissue to radiation (343).

VI. Summary

Pituitary disease is associated with increased mortality predominantly due to vascular disease. Control of cortisol secretion and GH hypersecretion (and cardiovascular risk factor reduction) are key in the reduction of mortality in patients with Cushing's disease and acromegaly, retrospectively. For patients with acromegaly, the role of IGF-I is less clear-cut. Confounding pituitary hormone deficiencies such as gonadotropins and particularly ACTH deficiency (with higher doses of hydrocortisone replacement) may have a detrimental effect on outcome in patients with pituitary disease. Pituitary radiotherapy is an additional fac-

tor that has been associated with increased mortality (particularly cerebrovascular). Although SMRs in pituitary disease are falling due to improved treatment, SMRs for many conditions are still elevated above that of the general population, and as such further measures are needed. Craniopharyngioma patients have a particularly increased risk of mortality as a result of the tumor itself and treatment to control tumor growth; this is a key area for future research to optimize the outcome for these patients.

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