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Incidence and Late Prognosis of Cushing's Syndrome: A Population-Based Study*

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ABSTRACT

The main purpose was to assess the incidence and late outcome of Cushing's syndrome, particularly in Cushing's disease. Information for all patients diagnosed with Cushing's syndrome during an 11-yr period in Denmark was retrieved. The incidence was 1.2–1.7/million·yr (Cushing's disease), 0.6/million·yr (adrenal adenoma) and 0.2/million·yr (adrenal carcinoma). Other types of Cushing's syndrome were rare. In 139 patients with nonmalignant disease, 11.1% had died during follow-up (median, 8.1 yr; range, 3.1–14.0), yielding a standard mortality ratio (SMR) of 3.68 [95% confidence interval (CI), 2.34–5.33]. The SMR was partly attributable to an increased mortality within the first year after diagnosis. Eight patients died before treatment could be undertaken. The prognosis in patients with malignant disease was very poor.

Patients in whom more than 5 yr had elapsed since initial surgery were studied separately, including a questionnaire on their perceived quality of health. In 45 patients with Cushing's disease who had been cured through transsphenoidal neurosurgery, only 1 had died (SMR, 0.31; CI, 0.01–1.72) compared with 6 of 20 patients with persistent hypercortisolism after initial neurosurgery (SMR, 5.06; CI, 1.86–11.0). In patients with adrenal adenoma, SMR was 3.95 (CI, 0.81–11.5). The perceived quality of health was significantly impaired only in patients with Cushing's disease and appeared independent of disease control or presence of hypopituitarism. It is concluded that 1) Cushing's syndrome is rare and is associated with increased mortality, in patients with no concurrent malignancy also; 2) the excess mortality was mainly observed during the first year of disease; and 3) the impaired quality of health in long-term survivors of Cushing's disease is not fully explained. (*J Clin Endocrinol Metab* **86:** 117–123, 2001)

IT IS GENERALLY recognized that Cushing's syndrome is an uncommon disorder. Few studies have attempted to estimate in detail its incidence. No population-based survey has been reported.

The outcome after various modes of treatment has been addressed in a number of papers; in particular many studies within the last years have dealt with the short-term outcome in patients with pituitary-dependent hypercorticism (Cushing's disease) after neurosurgery. Most have provided information on selected patients from geographically ill-defined areas. The long-term prognosis, including the patients' health and perceived quality of life, have received modest interest.

The purpose of this study was to analyze the incidence of and mortality in Cushing's syndrome in a population-based study and to assess the long-term outcome in initially successfully treated Cushing's disease, including the frequency of recurrences and the general health of the patients.

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Subjects and Methods

Patients

Information for patients in Denmark in whom the diagnosis of Cushing's syndrome was established during the period from January 1, 1985, through December 31, 1995, was retrieved from the National Patient Register of the Danish National Board of Health, to which all diagnoses made at Danish hospitals are reported. Additionally, every department of endocrinology and neurosurgery in Denmark searched its records for data on patients with the diagnosis of Cushing's syndrome.

With two exceptions, only patients treated for the first time for hypercorticism after January 1, 1985, were considered. One patient had successfully been operated on for an adrenal adenoma, but 12 yr later presented with a cortisol-secreting adenoma in the contralateral adrenal gland. One patient underwent bilateral adrenalectomy for florid Cushing's disease. Thirteen years later she again developed hypercorticism caused by a corticotroph pituitary adenoma.

In each case the diagnosis was made by an endocrinologist from clinical signs and symptoms and an inappropriately elevated excretion of free cortisol in the urine (UFC) (as determined by RIA). Additional investigations were performed [imaging of the pituitary and the adrenals, various dynamic tests (dexamethasone suppression and CRH tests), determination of the peripheral plasma ACTH concentration, sampling from the inferior petrosal sinus, *etc.*], but the results will not be detailed here. We assumed the patients' information on the duration of symptoms of cortisol excess not to be so concise as to allow an estimation of the duration of hypercortisolism.

One hundred and sixty-eight patients had Cushing's syndrome diagnosed during the 11-yr period. Four patients were not Danish na-

tionals. Two resided permanently in Denmark and have been included, whereas the two foreign citizens living abroad have been excluded.

The initial mode of treatment was pituitary surgery in 90, adrenal surgery in 53, thoracic surgery in 3, and radiotherapy in 2 patients. In 18 subjects, no surgical treatment was given because widespread cancer was present, the patient refused surgery, or the patient died before treatment could be started. Six patients received radiotherapy (conventional or stereotactic radiosurgery). Four had persistent hypercortisolism after repeat neurosurgery, 1 refused neurosurgery, and 1 had an empty sella (and previous hypopituitarism).

The records of all patients were searched, and the pertinent data extracted. Histological examination was performed on all tissue removed at operation; in tissue from the pituitary, additional immunohistology was carried out.

Groups

The 166 patients were divided into 4 groups (Fig. 1). The first group consisted of patients with Cushing's disease. In a subgroup (n = 73) pituitary etiology was established from the presence of a corticotroph pituitary adenoma and/or cure after pituitary surgery. [Cure was defined from 1) a subnormal plasma cortisol concentration at 30 min after iv injection of 250 μg corticotropin-(1–24) (<18 μg/dL; 500 nmol/L) and/or UFC <18 μg/24 h (50 nmol) measured 12–180 days after the operation; or 2) if the results were ambiguous postoperatively (plasma cortisol concentration at 30 min after ACTH >18 μg/dL but UFC <90 μg/24 h (250 nmol), cure was thought to have been achieved if the patient became panhypopituitary or if UFC values were <90 μg/24 h at >5 yr after the first operation. Recurrence was diagnosed if, after cure was initially achieved, UFC increased to >90 μg/24 h at any time during follow-up. Panhypopituitarism was considered present when the secretion of all anterior pituitary hormones was impaired, including TSH (hypothyroidism).] Two patients with corticotroph adenoma were nonetheless allocated to group 3. In 26 patients a pituitary cause was inferred, but could not be proven. This group included 2 patients with pituitary corticotroph hyperplasia (although no adenoma) and 9 with diffuse adrenal hyperplasia (adrenal surgery or autopsy) but no demonstrable extrasellar source of corticotropin; in the remaining patients histological examination was inconclusive or no tissue was available. The second group was made up of patients with adrenal neoplasms. The third group contained patients with concurrent Cushing's syndrome and carcinoid or cancer. Included were 2 patients who in addition to corticotroph pituitary adenoma also had bronchial carcinoma. Thus, all patients with coexistent hypercorticism and nonadrenal, malignant tumor were allocated to group 3 regardless of whether additional studies suggested or indicated this association to be causal or fortuitous. The diagnosis in groups 2 and 3 was histologically verified in all but 1, in whom ultrasonography revealed widespread liver metastases. Group 4 was made up of patients with non-ACTH-dependent hypercorticism: primary pigmented micronodular adrenocortical dysplasia and non-ACTH-dependent nonnodular macrohyperplasia (1).

Mortality

The database was "frozen" on January 4, 1999. At this time information about which patients had died was obtained from the Danish Civil Registration System. The time and cause of death were retrieved from the Danish Register of Causes of Death at the National Board of Health (2) and details from hospital records.

Long-term (>5 yr) prognosis

Patients. Those patients in whom more than 5 yr had elapsed since the first operation were considered in more detail (Fig. 2). In 68 patients with assumed Cushing's disease the first line of treatment was transsphenoidal pituitary surgery in all but 1, in whom a huge tumor expanding in all directions was approached through craniotomy. Adenomectomy was performed in 49, hemihypophysectomy in 2 hypophysectomy in 10, and exploration (no adenoma identified) in 6. In 4 patients, reoperation was performed within 90 days of the first operation. This procedure is considered 1 operation. Three neurosurgeons, all with particular experience in pituitary surgery, performed 84% of the operations.

In 45 (66.2%), all operated on transsphenoidally, cure was achieved after the first operation. Immunohistologically a corticotroph adenoma proved to be present in 32 (71.1%). In 9 patients the tissue submitted for histological examination eventually proved to be normal, in 2 the neuropathologist was unsure whether an adenoma was present, and in 2 no visible tissue was removed.

Twenty patients who underwent neurosurgery without immediate cure were also considered. Histologically, 9 patients had corticotroph adenoma in the pituitary. Eleven of the 20 patients were eventually cured, 3 after additional neurosurgery and 8 after bilateral adrenalectomy.

For comparison we included 25 patients with unilateral, adrenal adenoma. Adrenalectomy/adenomectomy was performed by laparotomy.

Perceived health of the patients

The perceived health of the patients was measured with the Danish version (3) of the Medical Outcome Study Short Form 36 questionnaire (SF-36) (4). A questionnaire was sent to the 77 patients who were alive on January 4, 1999, with the exception of 2 patients residing on the Faroe Islands who might have linguistic problems and 1 patient who died shortly after January 4, 1999.

Statistical analyses

Standard mortality ratios (SMR) were calculated as the ratio between the observed and the expected number of deaths (5).The expected number of deaths and survival were calculated by applying age- and sex-specific mortality rates for Denmark 1991–1995 (6) to the age- and sex-distributed time of risk of the patients. Confidence intervals and *P* values for the SMR were exact (Poisson distribution) (5).

Based on the responses to the questionnaires, the relative health

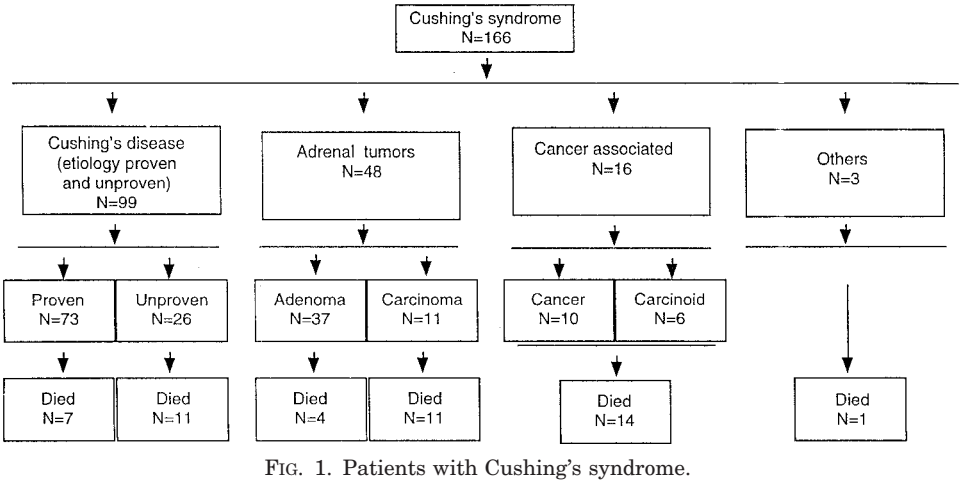

FIG. 1. Patients with Cushing's syndrome.

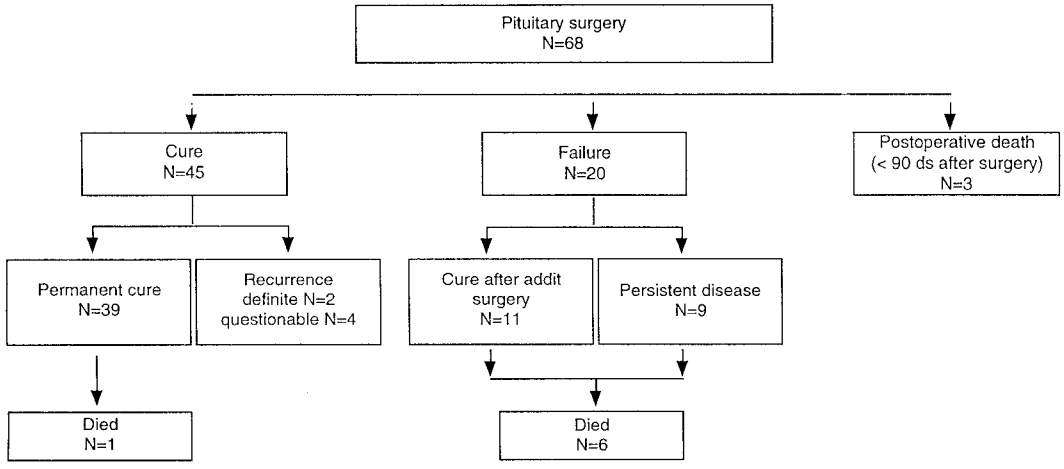

FIG. 2. Late outcome after pituitary surgery in patients with Cushing's disease and more than 5 yr of follow-up after the operation.

TABLE 1. Annual incidence per million of Cushing's disease and adrenal adenoma by age and sex (cases per yr)

Age (yr)	Cushing's disease				Adrenal adenoma	
	Pituitary etiology proven		Pituitary etiology unproven			
	M	F	M	F	M	F
0–19	0.5 [4]	0.6 [4]	0 [0]	0 [0]	0 [0]	0.1 [1]
20–39	0.9 [8]	2.2 [19]	0.2 [2]	0.4 [3]	0 [0]	2.6 [22]
40–59	1.0 [7]	3.1 [22]	0.1 [1]	1.7 [12]	0.6 [4]	1.1 [8]
≥60	0.8 [4]	0.8 [5]	0 [0]	1.2 [8]	0 [0]	0.3 [2]
Total	0.8 [23]	1.7 [50]	0.1 [3]	0.8 [23]	0.1 [4]	1.1 [33]

M, Men; F, women. The number of patients is in *brackets*.

impairment (relative to the expected for each patient's age and sex) was defined as a score below the 25th percentile for the Danish norm. Rose *et al.* (7) assumed that the expected proportion of scores below the 25th percentile is 25%, but it is actually less than 25% due to the discrete SF-36 scales. We obtained detailed information on the Danish norm distribution (3) to calculate standardized prevalence ratios. Confidence intervals (CI) for prevalence and standardized prevalence ratios were exact (binomial distribution) (5).

Results

Incidence of Cushing's syndrome

Pituitary-dependent hypercorticism was proved in 73 patients (23 men and 50 women). In an additional group of 26 patients (3 men and 23 women) the hypercorticism might have had a pituitary cause (Cushing's disease), although for various reasons this could not be finally determined. Hence, the total number was between 73 and 99 patients. Considering the population of Denmark including the Faroe Islands and Greenland (5, 3 million), these figures give an incidence of 1.2–1.7/million·yr. There was no difference between the periods 1985–1990 and 1991–1995. Consequently, Cushing's disease accounted for at most 60% of the total number of patients with hypercorticism. Thirty-seven patients (22.3%) had a benign adrenocortical adenoma (4 men and 33 women). One had previously had a contralateral adenoma, and 1 had bilateral adenomas at presentation. The incidences by age and sex are given in Table 1. Eleven (6.6%) had adrenal carcinoma (3 men and 8 women). The incidence was 0.6 and 0.2/million·yr, respectively. There were 6 patients (3.6%) with carcinoid (2 men and 4 women) of lung (n = 3), thymus (n = 1), colon (n = 1), and appendix (n = 1). The incidence was 0.1/million·yr. Ten patients (6 men and 4 women) had nonadrenal carcinoma (6.0%). Finally, 2 patients had primary pigmented micronodular adrenocortical dysplasia, and 1 had noncorticotropin-dependent, nonnodular macrohyperplasia. Thus, altogether 139 patients with Cushing's syndrome caused by nonmalignant diseases were seen during the 11-yr period, yielding an incidence of 2.3/million·yr. The median age was 41.4 yr (range, 3.6–77.7).

Mortality in Cushing's syndrome

The main data are presented in Tables 2 and 3. During the follow-up period (median, 8.1 yr; range, 3.1–14.0) from the first admission to the day the database was frozen (January 4, 1999), 7 of the 73 patients (9.6%) judged to have unequivocal Cushing's disease had died compared with 11 of the 26 patients (42.3%) in whom the etiology remained unverified. Four of the 37 patients (10.8%) with adrenal adenoma had died during a median period of 7.1 yr (range, 3.1–13.8). In neither case did the pretreatment UFC levels differ significantly between the survivors and the nonsurvivors (data not shown).

Thus, 23 of the 139 patients (16.5%) had died within the study period. The expected number was 6.24, yielding a SMR of 3.68 (95% CI, 2.34–5.33). There was no significant difference between the outcome in the patients with Cushing's disease and that in patients with adrenal adenoma. The mortality was higher during the first year after the first admission than during the following years (Table 3). It did not differ in women and men when stratified for diagnosis ($\chi^2 = 0.42$; df = 1; $P = 0.52$). Eight deaths in the 139 patients occurred before treatment could be undertaken: 1 from suicide, 1 from cardiac rupture, 1 from stroke, and 3 from severe infections (peritonitis, septicemia, and pneumonia). In 2 the cause of death could not be ascertained. Seven of the deaths occurred in patients in group 2, and 1 occurred in group 4.

All patients with adrenal carcinoma succumbed soon after admission (median survival time, 7 months; range, 0.9–46.7). Fourteen of the 16 patients with concurrent extraadrenal malignancy (cancer or carcinoid) had died. Both patients

TABLE 2. Standard mortality ratios (SMR) in patients with Cushing's syndrome

Diagnosis	No. of patients	Age[a] (yr), median, range	No. of deaths	Time at risk (yr)	Expected no. deaths	SMR (95% CI)	P^b
Cushing's disease (etiology proven)	73	41.1, 7.6–69.7	7	560.0	4.12	1.70 (0.68–3.50)	0.14
Cushing's disease (etiology unproven)	26	51.1, 24.9–74.1	11	153.1	0.96	11.48 (5.73–20.5)	<0.001
Adrenal adenoma	37	38.3, 3.6–77.7	4	255.2	1.15	3.48 (0.95–8.90)	0.04

CI, Confidence interval.
[a] Age at first admission.
[b] Compared to the expected from national mortality rates.

TABLE 3. Mortality as a function of time after first admission for Cushing's syndrome

Time after 1st admission	No. of patients	No. of deaths	Time at risk (yr)	Expected no. of deaths	SMR (95% CI)	*P*
First yr	139	13	130.3	0.64	20.27 (10.8–34.7)	<0.001
Following yr	126	10	863.6	5.60	1.79 (0.86–3.28)	0.08

SMR, Standard mortality ratio; CI, confidence interval.

TABLE 4. Main results in 90 patients with Cushing's syndrome

Group	n	M/F ratio	Age (yr), median, range at operation	Follow-up (yr), median, range	Time at risk (yr)	No. of deaths	Cause of death	Expected no. of deaths	SMR (95% CI)	*P*
A	45	14/31	38.5, 15.0–69.5	9.1, 5.1–13.7	410.3	1	Ruptured aortic aneurysm (6.3 yr)	3.24	0.31 (0.01–1.72)	>0.05
B	25	3/22	35.8, 3.7–77.7	8.3, 5.6–13.8	208.8	3	Myocardial infarction (0.7 yr) Mesothelioma (5.5 yr) Breast cancer (4.2 yr)	0.76	3.95 (0.81–11.5)	>0.05
C	20	7/13	46.4, 25.2–63.6	10.0, 5.0–13.6	158.0	6	Stroke (n = 2; 5.8; 6.7 yr) Malignant tumor (n = 2; 0.2; 0.9 yr) Septicemia (5.6 yr) Surgical complication (0.5 yr)	1.19	5.06 (1.86–11.0)	<0.05

Group A: Cured after initial transsphenoidal neurosurgery; group B: unilateral adrenalectomy because of a benign adenoma; group C: not cured at initial pituitary surgery. In brackets: time at death (yrs after 1. operation). SMR, Standard mortality ratio; CI, confidence interval.

with micronodular dysplasia were alive, but the patient with non-ACTH-dependent macrohyperplasia had died.

Long-term (>5-yr) outcome

The main data are presented in Tables 4 and 5 and Fig. 3.

Cure achieved. During the follow-up period, 1 of the 45 patients (2.2%) had died. The SMR was not significantly different from that in the control population. Twelve patients (26%) became panhypopituitary (as defined in *Materials and Methods*), of whom none had died. In 2 patients a recurrence (as defined in *Materials and Methods*) was proven and reoperation performed, and in 4 reoccurrence of the hypercorticism might be suspected. Thirty-seven of 43 patients (86.0%) returned a completed questionnaire. The prevalence of health impairment was significantly increased on several scales (Table 5).

Persistent hypercorticism after initial neurosurgery. The mortality was significantly higher than that in the background population. Ten of 12 questionnaires (83%) were returned. Considerable impairment of health, on both the physical and mental scales, was evident (Table 5).

Adrenal adenoma. Three patients (12%) had died. The SMR was similar to that in the general population. Twenty of 22 questionnaires were returned (91%). The prevalence of health impairment did not significantly differ from the population norm (Table 5).

Discussion

Our search for patients was exhaustive and included several sources of information. It was facilitated by the fact that few departments in Denmark treat patients with hypercorticism. We are very confident that all patients with Cushing's syndrome operated on in a neurosurgical department and all patients treated for an adrenal tumor in Denmark have been included. We accepted the diagnosis as reported, meaning that the clinical presentation was pertinent, and elevated urinary cortisol excretion was present. In most patients additional studies were performed.

TABLE 5. The perceived health of the patients as measured with the Medical Outcome Study Short Form 36 questionnaire

SF-36 scale	Cushing's disease (cured)		Persistent hypercorticism		Adrenal adenoma	
	Prevalence (%)	Standardized prevalence ratio (95% CI)	Prevalence (%)	Standardized prevalence ratio (95% CI)	Prevalence (%)	Standardized prevalence ratio (95% CI)
Physical functioning	37	1.7[a] (1.0–2.6)	73	3.2[a] (1.7–4.1)	30	1.5 (0.6–2.6)
Role physical	44	2.2[a] (1.3–3.1)	45	2.2 (0.8–3.8)	35	1.6 (0.7–2.7)
Bodily pain	20	1.0 (0.4–1.8)	45	2.1 (0.8–3.6)	10	0.50 (0.1–1.6)
General health	50	2.3[a] (1.5–3.1)	82	3.6[a] (2.2–4.4)	25	1.1 (0.4–2.2)
Vitality	46	2.2[a] (1.4–3.0)	73	3.5[a] (1.9–4.5)	25	1.2 (0.4–2.2)
Social functioning	37	1.7[a] (1.0–2.6)	64	2.9[a] (1.4–4.0)	20	1.0 (0.3–2.0)
Role emotional	45	2.3[a] (1.4–3.2)	27	1.5 (0.3–3.3)	10	0.5 (0.1–1.5)
Mental health	32	1.5 (0.8–2.3)	64	2.9[a] (1.4–4.0)	15	0.7 (0.1–1.7)

Prevalence is the proportion of patients scoring less than the 25th percentile for age and sex. CI, Confidence interval.
[a] $P < 0.05$ compared to controls.

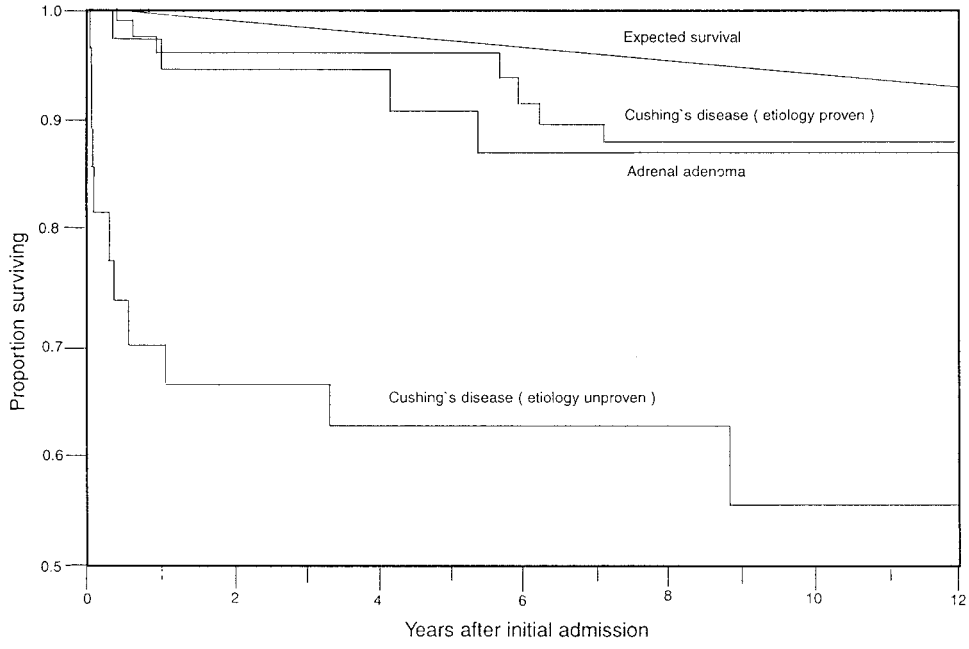

FIG. 3. Survival in patients with Cushing's disease (proven and unproven) and with adrenocortical adenoma.

It is possible that the number of patients with malignant tumor causing hypercorticism has been underestimated. Such patients may present with a clinical picture not typical of classical Cushing's syndrome and are not seen by an endocrinologist, and the diagnosis may be overlooked.

An ACTH-positive adenoma was identified in 54 of the 73 patients with definite Cushing's disease, which may be present with no accompanying corticotroph adenoma (8, 9). Our criteria for cure included measurements of cortisol in both plasma and urine. The timing of the short ACTH test relative to operation and the normal limits applied seem appropriate (10). Our cut-off value for the urinary excretion of cortisol (18 μg/24 h; 50 nmol) is more arbitrary. Admittedly, adrenal insufficiency is somewhat poorly reflected in the amount of cortisol excreted in the urine. There is, however, little doubt that in this setting a urinary cortisol excretion of less than 18 μg/24 h strongly suggests adrenocortical failure.

With our definition of Cushing's disease (either the presence of corticotroph adenoma or cure after neurosurgery), we found an incidence of 1.2/million·yr. Including patients in whom diagnosis was possible (although not proven), the incidence increased to 1.7/million·yr. We elected to allocate all patients with concurrent malignant disease to one group regardless of the results of additional, diagnostic studies to clarify the mechanism of this relationship.

There are few data on the incidence of Cushing's syndrome. However, some epidemiological studies on Cushing's disease have recently been published. Ambrosi *et al.* (11) found an incidence of 0.7/million·yr in northern Italy. It is not clear which patients were included or how the diagnosis was verified. Etxabe and Vasquez (12) found a much higher figure of 2.4/million·yr in a province of Spain. The way the researchers defined Cushing's disease may not be entirely adequate.

In an overview of three large series comprising 298 patients with Cushing's syndrome, Huff (13) concluded that benign adrenal adenoma was the cause in 9%, and adrenal carcinoma in 8%. We found that adenomas occurred more than twice as often and much more frequently than carcinomas. Racial differences seem to exist (14).

In 1952 Plotz *et al.* (15) published a study on the natural

history of Cushing's syndrome. Actually, several patients had an adrenal tumor removed or received pituitary or adrenal irradiation. Slightly more than half the patients had died within 5 yr. Refinement in pituitary surgery [first performed for Cushing's disease in 1933 (16)], better diagnostic tools, and the availability of adequate hormonal substitution almost certainly have improved the outcome.

Our data show that the survival in Cushing's syndrome associated with malignancies including adrenocortical carcinomas remains extremely poor. If patients with these diseases are excluded, the remaining 139 patients can be considered potentially curable. During follow-up 23 patients had died (16.5%). For several reasons (*e.g.* failure to identify a corticotroph adenoma or to achieve cure after neurosurgery, or the patient dying before a full investigation could be performed) the etiology was ambiguous in 26 patients. Hence, it was not possible to precisely delineate the survival in patients with Cushing's disease. The SMR can, however, be estimated to be between 1.70 (in patients with proven Cushing's disease) and 3.68 (in patients with either proven or suspect Cushing's disease). This discrepancy is not surprising, as achievement of cure was part of our definition of unequivocal Cushing's disease. So was the presence of a corticotroph adenoma, which specifically seems to be associated with a favorable outcome (17). In this group all patients were operated on, whereas only 66% of the patients with presumed Cushing's disease underwent surgery.

There was no significant difference between the prognosis in patients with proven Cushing's disease and those with adrenal adenoma. In both groups an excess mortality was noted within the first year after the initial admission for hypercorticism. Later, in both groups, the mortality was not significantly higher than that in the background population.

Seven patients died before treatment could be begun. This might connote poor professional skills in managing the patients. As no patient with definite Cushing's disease died before treatment, it might also reflect a certain delay in deciding upon a therapeutic strategy in patients in whom the etiology cannot swiftly be established.

Previously, total adrenalectomy was the preferred treatment in Cushing's disease. The late outcome after this operation is not completely known. Few recent studies have included unselected patients only, undergoing no other mode of treatment and followed for an extended period of time. Some studies have found a long-term survival not markedly different from that in the background population if immediate postoperative deaths were excluded (18, 19). In contrast, Ross and Lynch (20) reported a substantially elevated mortality. However, many of their patients were treated with pituitary radiation, and only 16 of 57 were treated with adrenalectomy. Welbourn also found long-term decreased survival in patients after total adrenalectomy (21). Scant information is available on the long-term outcome after surgery for unilateral, adrenal adenoma. Recurrences seem to be rare, and the mortality low (22, 23).

A considerable number of investigations have addressed the immediate prognosis after neurosurgical treatment. Few have considered the long-term course. Furthermore, there are problems in interpreting some of these reports: the length of the follow-up period either has not clearly been stated (24, 25) or was relatively short (26), results of various treatment modalities have been grouped together (14), the patients were recruited over an extended period of time (>30 yr) (27), or only children and adolescents were reviewed (28, 29). Recently, an Italian study demonstrated that even late in the course after cure of Cushing's disease, atherosclerosis, hypertension, and diabetes mellitus occurred significantly more frequently than in controls (30).

For this reason, part of this study was a long-term (>5 yr) follow-up of patients assumed, by rather strict criteria, to have been cured of Cushing's disease. In some of these patients the operation caused endocrine deficits that might influence the outcome. Hence, for comparison, we also studied patients operated on for benign adrenal adenoma. In neither group did the mortality differ significantly from that in the background population matched for sex and age. In contrast, the prognosis in patients not cured initially after pituitary surgery was considerably worse, as six (30%) had died, and four remained uncured at the time of death.

During follow-up, evidence of a recurrence developed in six patients with unambiguous Cushing's disease. In two, this appeared indisputable, as UFC values were high, and the clinical picture was diagnostic. In the remaining four, UFC values remained below 140 μg/24 h (390 nmol), and concurrent diseases were present that might explain the modest increase in UFC. In none of the patients did clinical signs support the suspicion of recurrent hypercorticism. Hence, from a practical and clinical point of view it can be argued that only two patients (4.4%) suffered a relapse. Whether this reasoning is correct can be settled only after an even longer follow-up period. A survey of recurrence rates in the literature has recently been published (31). A comparison between these results is not relevant, as a definition of neither cure nor relapse has been agreed upon. This may at least partly explain the widely differing results (0–20.6%).

Swearingen *et al.* published a clinic-based audit of the long-term outcome of patients with Cushing's disease after transsphenoidal surgery (32). Their analysis is not immediately comparable to our population-based study. No information was provided on the total number of patients with Cushing's disease seen and how they were selected for neurosurgery. The definition of cure was different from ours, and evaluation was performed within 10 days after surgery. A corticotroph adenoma was confirmed in all their patients *vs.* in only 74% of our patients. The ages of the patients were similar in the 2 studies. Our cure rate pertains only to the first operation and patients with definite Cushing's disease followed for more than 5 yr; it was 66.2% and contrasts with the 87% reported by Swearingen *et al.* The mortality differed between the 2 studies: 6 deaths in 159 (3.8%) patients (median follow-up, 8.0 yr) *vs.* 7 of 73 (9.6%) patients (median follow-up, 8.1 yr). The difference was not statistically significant (by Fisher's exact test, $P = 0.14$). If all of our patients who underwent neurosurgery were included, the difference would be greater. The 2 studies agree that the long-term mortality after curative transsphenoidal surgery is not significantly different from that in the general population.

For the appraisal of quality of life we used the SF-36, which is among the best validated instruments for measuring health-related qualities. A validated Danish version with

published norms made it possible to compare scores from the patients with those of the Danish general population. However, the distribution of most SF-36 scales is far from normal, and the preconditions for *t* tests and related statistics are not fulfilled. Hence, we followed the suggestion of Rose *et al.* (7) to express the occurrence of relative health impairment in patients as the prevalence of scores below the 25th percentile for the appropriate age group and sex in the population norm. However, due to the discrete nature of the SF-36 scales, the population prevalence below the 25th percentile most often is less than 25%. We used as yet unpublished data on the Danish norm to calculate standardized prevalence ratios for the relative health impairment. Although the quality of life in the patients with an adrenal adenoma was quite satisfactory, the prevalence of health impairment was increased in patients successfully operated on for Cushing's disease. It was even higher in patients in whom cure was not achieved initially. The cause of the poor quality of life in these patients cannot be exactly determined. Seven patients were panhypopituitary, seven had undergone bilateral adrenalectomy, and four had persistent hypercorticism.

A Finnish study (33) has analyzed the well-being of patients after treatment for hypercortisolemia. Unfortunately, the data were not analyzed separately for patients with pituitary and adrenal disease.

Twelve of the 45 patients (27%) were classified as having panhypopituitarism. More than the 12 patients had partial insufficiency. Six of the patients with unequivocal Cushing's disease received GH substitution postoperatively. This represents an underestimation of the true prevalence, as hyposomatotropinism occurs very frequently after pituitary surgery. The degree to which unsubstituted GH deficiency influenced the perceived health is, however, unknown. None of the patients with panhypopituitarism died during the follow-up period. From the questionnaires it seems that their health was not significantly different from that of subjects who were not panhypopituitary. The number of patients is clearly too small for any valid assessment.

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