Premature Mortality in Patients with Addison's Disease: A Population-Based Study

Ragnhildur Bergthorsdottir, Maria Leonsson-Zachrisson, Anders Odén, and Gudmundur Johannsson

Department of Endocrinology (R.B., M.L.-Z., G.J.), Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden; and Department of Mathematical Sciences (A.O.), Chalmers University of Technology, SE-412 96 Gothenburg, Sweden

Background: The survival rate of patients with primary adrenal insufficiency (Addison's disease) undergoing currently accepted replacement therapy is not known, although well-informed patients are considered to have a normal survival rate. In this study, we evaluated the mortality of patients with Addison's disease in Sweden.

Methods: A population-based, retrospective, observational study was performed, using the National Swedish Hospital and Cause of Death Registers, covering the period from 1987–2001. After a diagnosis of Addison's disease, each patient was followed until the end of follow-up or death. Mortality was compared with that of the Swedish background population.

Findings: We identified 1675 patients (995 women and 680 men) diagnosed with primary adrenal insufficiency. The average follow-up

from initial diagnosis was 6.5 yr. Five hundred seven patients died during the study period compared with an expected 199. The risk ratio for all-cause mortality was 2.19 (confidence interval 1.91–2.51) for men and 2.86 (confidence interval 2.54–3.20) for women. The excess mortality in both men and women was attributed to cardiovascular, malignant, and infectious diseases. Concomitant diabetes mellitus was observed in 12% of the patients, but only contributed to the increased mortality to a minor extent.

Interpretation: Compared with the background population, we observed that the risk ratio for death was more than 2-fold higher in patients with Addison's disease. Cardiovascular, malignant, and infectious diseases were responsible for the higher mortality rate. (***J Clin Endocrinol Metab* 91: 4849–4853, 2006**)

IN PRIMARY ADRENAL insufficiency, or Addison's disease, as first described by Thomas Addison in 1855 (1), the adrenal cortex produces and secretes insufficient amounts of glucocorticoids, mineralocorticoids, and androgens. Addison's disease is uncommon, having an estimated prevalence of 93–140 per million and an incidence of 4.7–6.2 per million in Caucasian populations (2). The disease has a female preponderance (3, 4), and most patients are diagnosed in their third to fifth decade of life (5–7). Tuberculosis was an important cause of the disease during the last century (8, 9). However, autoimmune disease accounts for most cases in developed countries today (6, 10), causing 80–90% of the current cases in Scandinavia, for example (11).

In the 1950s, before the availability of glucocorticoids, the 1-yr survival rate in patients with Addison's disease was 20% or less (12). However, Mason (8) studied survival after the introduction of glucocorticoid replacement therapy and estimated that mortality was similar to that of the background population, except in the case of those patients in whom the disease was undiagnosed at the time of death and in patients living under poor social conditions. Therefore, survival now is considered to be normal or comparable with that of the background population in patients receiving replacement therapy and adequate follow-up.

The dramatic improvement in survival observed after the

availability of glucocorticoid replacement therapy, the low prevalence of the disease, and the reassuring data from Dunlop (12) and Mason (8) have not prompted additional survival studies in Addison's patients. However, recent studies have demonstrated excess mortality in hypopituitary patients, a large proportion of whom are similarly dependent on life-long glucocorticoid replacement therapy (13–15). Whether these observations are the result of inadequate glucocorticoid replacement therapy (15), inadequate replacement with sex steroids (14), or untreated growth hormone deficiency (13) is not clear. To study the long-term outcome of patients with a life-long daily requirement for glucocorticoid replacement therapy, we investigated the standardized mortality rate of patients with Addison's disease between 1987–2001 in Sweden. The existence of low population diversity within Sweden, a homogenous health care system, and the Swedish National Board of Health and Welfare (SNBW) Registers all offer unique conditions under which to study the long-term outcome of this rare disease.

Subjects and Methods

National survey

The National Hospital and Cause of Death Registers at the SNBW were used to identify and track patients. We evaluated all patients hospitalized in Swedish hospitals for primary adrenal insufficiency between 1987–2001 using a technique similar to that described previously (16, 17). Patients with primary adrenal insufficiency who were coded 255.4 according to the International Classification of Diseases, ninth revision (ICD 9) and E27.1 or E27.2 (adrenal crisis) according to the International Classification of Diseases, tenth revision (ICD 10), were identified. Patients who were, at any time, diagnosed with Cushing's syndrome or any pituitary disease were excluded from the analysis. We also looked for the presence of diabetes mellitus (DM) at the time of the initial diagnosis of primary adrenal insufficiency. By making use of

---

TABLE 1. The number of men and women with Addison's disease obtained from The National Hospital and Cause of Death Registers at the SNBW during the period 1987–2001

| | n | Subjects with DM | | No. of deaths |
		No.	Percentage of total	
Men	680	86	12.6	208
Women	995	113	11.4	299
Total	1675	199	12.0	507

The number and percentage of patients with concomitant DM at the time of detection is also shown.

unique, personal identification codes, each individual was counted once only. The patient's county of residence and date of hospitalization were recorded. After the registered hospitalization during which the diagnosis of primary adrenal failure first occurred, each patient was tracked until the end of follow-up or death. Cause of death was identified using the Swedish Cause of Death Register. The mortality rate after hospitalization for primary adrenal failure was compared with that of the general Swedish population.

More than 99% of deaths are reported in the Cause of Death Register and the frequency of miscoding is between 1.2–6.3%, as has been shown by repeated quality control tests (18). The National Hospital Register covers more than 99% of all hospital admissions, and the rate of miscoding reported during quality control checks is less than 8.3% (19).

Local study

To validate the selection criteria used in the national survey, a similar search was performed using a local hospital register. Patients with primary adrenal insufficiency, adrenal crises, drug-induced adrenal insufficiency and other unspecified adrenal insufficiencies (ICD 10 codes E27.1–4), and receiving inpatient or outpatient medical care between 1999 and 2003 were identified and their medical records reviewed. A broader search strategy was performed in the local register to estimate the proportion of patients with Addison's disease who were not identified in the National Survey, as well as the proportion classified with adrenal crises or primary adrenal insufficiency who did not have Addison's disease.

Statistical analysis

The expected numbers of deaths, if the risk coincided with that of the general population, were calculated for men and women separately, taking age and calendar time into account. Comparisons between observed and expected numbers were performed using Poisson distributions, which were also applied to the calculation of 95% confidence intervals (CI) of risk ratios (RR). A Poisson model (16, 20) was used to estimate the risk of Addison's disease with respect to latitude. Poisson regression was also used to estimate the hazard function of death as a continuous function of time from the initial Addison's diagnosis and depending on the presence of DM at the time of diagnosis. We have used the term "hazard ratio" for the quotient between two hazard functions and RR for the quotient between observed and expected number of deaths. The two terms essentially reflect the same function. The χ^2 test was used to assess the difference between regions with respect to the risk of Addison's. All tests were two-tailed.
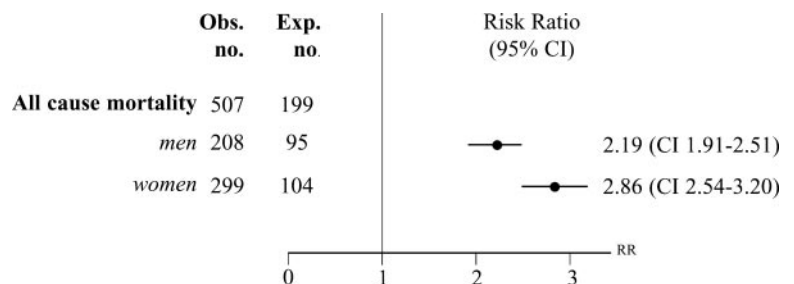
Results

National survey

The search in the National Hospital Register identified 1675 patients with Addison's disease between 1987–2001 (Table 1). The mean age at initial identification was 52.8 yr (SD 22.0), and the average follow-up period was 6.5 yr; 3.4 yr for those patients who died and were found in the National Cause of Death Register and 7.9 yr for those who survived the period of observation.

There was an equal distribution of Addison's disease within Sweden with no significant difference in the number of cases reported between regions or with respect to latitude (*i.e.* a North-to-South gradient).

Mortality

Within the time period of 1987–2001, 507 deaths were noted compared with the expected 199 deaths (Fig. 1). The overall RR was 2.19 (CI 1.91–2.51) for men and 2.86 (CI 2.54–3.20) for women. The greatest number of deaths occurred from cardiovascular (n = 239), malignant (n = 73), endocrine (n = 64), respiratory (n = 45), and infectious diseases (n = 12). The relative death rate from cardiovascular and malignant diseases was increased in both men and women (Fig. 2). Ischemic heart disease was the most common cardiovascular cause of death (n = 133) followed by cerebrovascular disease (n = 46). No clustering of cancer type or cancer from a specific organ system was observed (Table 2).

An increased risk of death from infectious disease was found in both men and women and from respiratory disorders in women only (Fig. 3). If patients who died from infectious disease from all disease categories were counted together, a total of 35 patients died from infection, the majority (66%) from pneumonia. One death was related to tuberculosis.

Thirty-six patients were reported to have died from adrenal insufficiency, five of those died within 2 d and five within 3 wk of hospitalization. No patient was reported to have died from adrenal crisis according to ICD 10. The ICD 9 classification does not allow for a differentiation between primary adrenal insufficiency and adrenal crisis.

Impact of concurrent DM

At the time of the initial identification in the register, 12.6% of the men and 11.4% of the women had a concomitant diagnosis of DM (Table 1). The RR for death was 1.82 (CI 1.29–2.06) for men and 1.52 (CI 1.11–2.07) for women with Addison's disease and DM compared with those patients

FIG. 1. The RR and 95% CI for all-cause mortality in patients with Addison's disease in Sweden from 1987–2001. This was calculated for men and women separately, taking age and calendar time into account. Obs. no., Observed number; Exp. no., expected number.

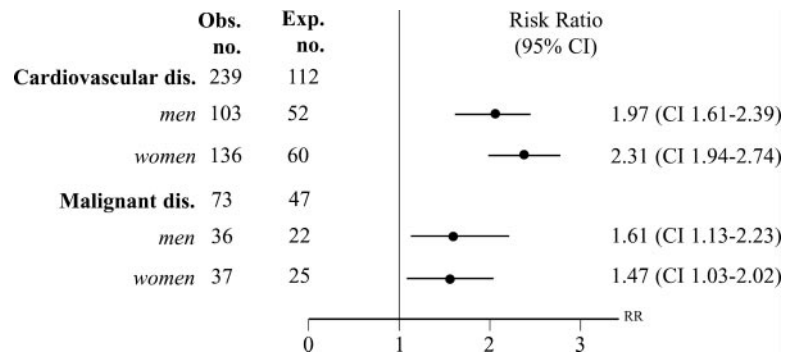|	Obs. no.	Exp. no.	Risk Ratio (95% CI)
All cause mortality	507	199	
men	208	95	2.19 (CI 1.91-2.51)
women	299	104	2.86 (CI 2.54-3.20)

FIG. 2. The RR and 95% CI for cardiovascular mortality and mortality from neoplastic disorders in patients with Addison's disease in Sweden from 1987–2001. This was calculated for men and women separately, taking age and calendar time into account. Obs. no., Observed number; Exp. no., expected number.

with Addison's disease without DM. Therefore, DM had a significant influence on total mortality in both men and women.

However, the impact of DM on the excess mortality of the whole group of Addison's patients was limited. The RR of death for patients with Addison's disease without DM was 2.04 (CI 1.74–2.37) for men and 2.68 (CI 2.36–3.04) for women as compared with the background population, *i.e.* 7% less for men and women than the ratios obtained for the whole cohort. The excess mortality among patients with Addison's disease with and without concomitant DM was most pronounced in the time period close to the initial detection (Fig. 4).

Local study

Using wider search criteria than in the national study, we identified 122 patients; of these, 105 were included in the analysis. The remaining 17 patients were excluded due to secondary adrenal insufficiency (two), tertiary adrenal insufficiency (three), Waterhouse-Friedrichsen syndrome (one), adrenalectomy due to Cushing's disease (four) or due to malignant disease (two), miscoded diagnosis (two), and insufficient medical records (three). Therefore, depending on whether using ICD 9 or ICD 10 coding, seven (6%) or six (5%) patients, respectively, who did not have Addison's disease could have been included in our national cohort.

Only one patient was diagnosed with certainty in the outpatient clinic. Eighty-two percent of the patients (86 of 105) were hospitalized when the diagnosis of Addison's disease was confirmed. In 18 cases, information on whether patients were diagnosed in an outpatient unit or during hospitalization was unavailable.

The mean age at diagnosis was 37.3 yr (SD 15.5); 42.1 (14.7)

TABLE 2. The number of deaths from the various forms of malignant diseases among the patients with Addison's disease in Sweden between 1987–2001

Type of malignancy	No. of deaths
Prostate	6
Breast	3
Pancreas	8
Colorectal (including anus)	2
Trachea, bronchus, lung	9
Urinary organs (including kidney)	7
Corpus uteri and cervix	6
Malignant lymphoma	7
Leukemia	3
Other and/or unspecified sites	22
Total number of deaths	73

in women and 31.1 (14.3) in men. Fifty-two percent (55 of 105) had other endocrine disorders. Forty-one percent (43 of 105) had primary hypothyroidism and 11% (12 of 105) had DM (four type 1, five type 2, and three unknown type). One hundred and two patients received cortisone acetate and three patients received hydrocortisone as replacement therapy. The median daily cortisone acetate dose was 50 mg (range, 18.8–75 mg) administered twice daily in 85% (89 of 105) of the patients. Ninety-four percent (99 of 105) of the patients also received fludrocortisone with a median daily dose of 0.1 mg (range, 0.025–0.2 mg).

Discussion

This study shows that patients with primary adrenal insufficiency identified by the use of the National Hospital Register in Sweden have a mortality rate which is 2-fold greater than that of the background population. The excess mortality was greatest close to the time of hospitalization and was mainly attributed to cancer and cardiovascular and infectious disease.

A possible explanation for an increased mortality rate in Addison's patients is inappropriate glucocorticoid replacement therapy in the case of both excess and inadequate glucocorticoid exposure in response to stress and concurrent illnesses. Excess glucocorticoid exposure can induce hypertension, obesity with abdominal fat distribution, and DM; all strong independent risk factors for cardiovascular disease (21, 22). In addition, an attenuated diurnal variation in the serum cortisol profile has been associated with abdominal obesity and the metabolic syndrome supporting the importance of the diurnal profile (23). Finally, a thorough reevaluation of patients undergoing glucocorticoid replacement therapy revealed that doses were too high and could be reduced in the case of more than half of the patients (24). Therefore, it is likely that many patients in the national cohort were receiving overly high doses of glucocorticoids delivered in a nonphysiological pattern, as indicated by the local study.

The increased frequency of other endocrine disorders in patients with autoimmune primary adrenal insufficiency such as mineralocorticoid insufficiency, primary hypothyroidism, and type 1 DM may also compromise survival in these patients. Overly high doses of fludrocortisone, which result in an increase in the activity of the mineralocorticoid receptor, may have deleterious effects on the heart and vascular system (25). Also, untreated hypothyroidism is associated with an increased risk of atherosclerotic disease (26),

FIG. 3. The RR and 95% CI for mortality from infectious and respiratory disorders in patients with Addison's disease in Sweden from 1987–2001. This was calculated for men and women separately, taking age and calendar time into account. Obs. no., Observed number; Exp. no., expected number.
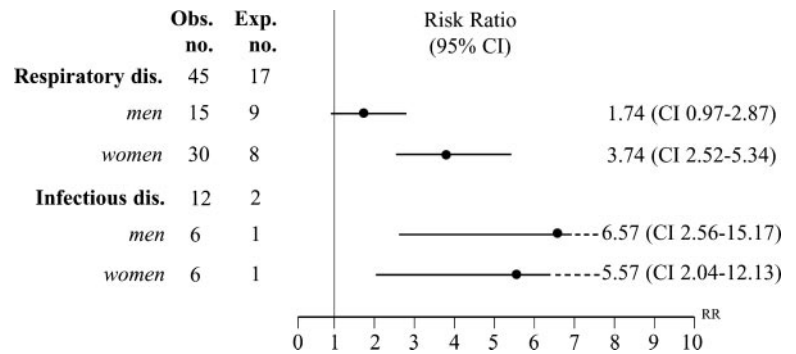
which may have contributed to increased cardiovascular mortality in our patient cohort if the thyroid status was inadequately monitored and treated. Untreated dehydroepiandrosterone deficiency could also be a contributing factor to the poor outcome in patients with Addison's disease as indicated in recent dehydroepiandrosterone replacement trials (27–29).

In the national cohort, the frequency of DM among patients with primary adrenal failure was 12.0%, which is similar to that found in a recent survey (3). This is three to four times higher than the expected prevalence of 2.7–4.3% reported in the Swedish population (30, 31). We were not able to determine the proportion of type 1 and 2 DM in the national cohort, but others have demonstrated an increased frequency of type 1 DM among patients with Addison's disease (3). The relative risk of death for patients with DM is 3.8 in Sweden (31). Having DM and primary adrenal insufficiency significantly increased the risk of death when compared with having adrenal insufficiency alone. However, the overall impact of concomitant DM on the total mortality was minor. By excluding patients with DM, the overall mortality rate reduced only by 7% in men and women, demonstrating the independent influence of Addison's disease on the increased relative risk of death.

The relative risk of death from cancer was increased in both men and women. The increased cancer mortality may be an effect of obesity associated with an inadequate replacement therapy or it may be due to the underlying autoimmune disorder. However, the absence of clustering of cancer types such as colon, rectum, breast, endometrial, and kidney cancer, which are associated with obesity (32), or non-Hodgkin's lymphoma, which is associated with autoimmunity (33), does not support such a notion.

The mortality rate resulting from infectious diseases was more than five times that expected. This is an uncommon cause of death in the age-adjusted background population, and, therefore, the numbers are small. The goal should be to prevent these cases through continuous education of patients and a constant awareness of this risk in the overall care of patients with adrenal insufficiency(15). Tuberculosis did not contribute to the increased mortality rate because only one case was identified.

Published mortality data in patients with hypopituitarism where the majority have secondary adrenal insufficiency have demonstrated increased relative risk of death of approximately 1.8 (13). This increased risk has not been associated statistically with the presence of secondary adrenal insufficiency (14). However, as the excess mortality is of similar magnitude as demonstrated in this study, it might therefore be speculated that adrenal insufficiency is a contributing factor to the increased mortality rate also in hypopituitarism.

Although the study is based on official registers that have a very high yield, there are some limitations to be considered. Patients enter the study when being hospitalized, and this may occur when the diagnosis is first made; however, a patient in whom Addison's disease has previously been diagnosed can also enter the study because of a concurrent illness. Selection of subjects by this means may explain the higher average age in the national cohort as compared with the mean age at the time of diagnosis in the local survey and in previous cross-sectional studies (3). Very rare causes of primary adrenal failure are likely to be represented within the national cohort, but the contribution to overall mortality is probably small. Furthermore, the study does not allow the detection of patients dying from adrenal insufficiency before diagnosis, which would increase the relative risk of death further. In addition, an unavoidable aspect of the study is that a small proportion of cases may have been incorrectly
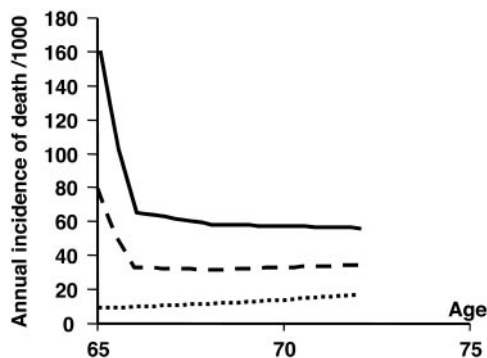

FIG. 4. The figure demonstrates an example of the annual incidence of death for female patients at the age of 65 yr during the calendar year of 1997 with Addison's disease with and without concomitant DM. The *dotted line* depicts the risk of death in the background population, the *banded line* depicts women with primary adrenal failure, and the *solid line* represents the risk of death for patients with both DM and primary adrenal failure. The Poisson regression model demonstrated an excess mortality compared with the general population most pronounced during the first time after detection of Addison's disease. However, substantial excess remained for many years. An example of men demonstrated similar results.

coded, which is more likely to have occurred in ICD 9 than in ICD 10.

The strength of this study is its size: it is the largest cohort of primary adrenal insufficiency reported in the literature. Moreover, the analysis included a longitudinal follow-up from initial detection to either death or to the end of the study period. Finally, because the majority of new cases were diagnosed during hospitalization in the local study, detection of cases in the national study was evenly distributed within the country and throughout the study period and suggests a high yield of all newly diagnosed cases during the 14-yr study period.

This study has demonstrated that the relative risk of death is more than 2-fold greater in patients with primary adrenal failure. The excess mortality was highest in the period immediately after detection and hospitalization. The excess mortality from infectious diseases may be prevented by adequately educating patients and health care workers and through other safety measures. An unexpected finding was the excess mortality observed as a result of cardiovascular disease and cancer. This could be due to overly high doses of glucocorticoids and a nonphysiological serum cortisol profile associated with the currently available replacement therapy. Concomitant endocrine disorders may have a significant impact on the outcome of this patient group, although our analysis of the impact of DM only explained the increased death rate to a minor extent. The results of this study should pave the way for improvements in the overall care of patients with adrenal insufficiency.

Acknowledgments

References

1. **Addison T** 1855 On the constitutional and local effects of disease of the suprarenal capsules. London: Highley
2. **Arlt W, Allolio B** 2003 Adrenal insufficiency. Lancet 361:1881–1893
3. **Lovas K, Husebye ES** 2002 High prevalence and increasing incidence of Addison's disease in western Norway. Clin Endocrinol (Oxf) 56:787–791
4. **Laureti S, Vecchi L, Santeusanio F, Falorni A** 1999 Is the prevalence of Addison's disease underestimated? J Clin Endocrinol Metab 84:1762
5. **Willis AC, Vince FP** 1997 The prevalence of Addison's disease in Coventry, UK. Postgrad Med J 73:286–288
6. **Kong MF, Jeffcoate W** 1994 Eighty-six cases of Addison's disease. Clin Endocrinol (Oxf) 41:757–761
7. **Oelkers W** 1996 Adrenal insufficiency. N Engl J Med 335:1206–1212
8. **Mason AS** 1968 Epidemiological and clinical picture of Addison's disease. Lancet 2:744–747
9. **Nerup J** 1974 Addison's disease—a review of some clinical, pathological and immunological features. Dan Med Bull 21:201–217
10. **Betterle C** 2002 Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev 23:327–364
11. **Myhre AG, Undlien DE, Lovas K, Uhlving S, Nedrebo BG, Fougner KJ, Trovik T, Sorheim JI, Husebye ES** 2002 Autoimmune adrenocortical failure in Norway autoantibodies and human leukocyte antigen class II associations related to clinical features. J Clin Endocrinol Metab 87:618–623
12. **Dunlop D** 1963 Eighty-six cases of Addison's disease. Br Med J 5362:887–891
13. **Rosen T, Bengtsson BA** 1990 Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 336:285–288
14. **Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart PM** 2001 Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet 357:425–431
15. **Mills JL, Schonberger LB, Wysowski DK, Brown P, Durako SJ, Cox C, Kong F, Fradkin JE** 2004 Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients. J Pediatr 144:430–436
16. **Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK** 2003 The components of excess mortality after hip fracture. Bone 32:468–473
17. **Svensson J, Bengtsson BA, Rosen T, Oden A, Johannsson G** 2004 Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab 89:3306–3312
18. 2002 The Swedish National Board of Health and Welfare (Social styrelsen). Dödsorsaker 2002 (in Swedish).
19. 2003 The Swedish National Board of Health and Welfare (Social styrelsen). Patient registret 1964–2003 (in Swedish).
20. **Breslow NE, Day NE** 1987 Statistical methods in cancer research. Volume II—The design and analysis of cohort studies. IARC Sci Publ 82:1–406
21. **Andrews RC, Walker BR** 1999 Glucocorticoids and insulin resistance: old hormones, new targets. Clin Sci (Lond) 96:513–523
22. **Plotz CM, Knowlton AI, Ragan C** 1952 The natural history of Cushing's syndrome. Am J Med 13:597–614
23. **Bjorntorp P** 1993 Visceral obesity: a civilisation syndrome. Obes Res 1:206–222
24. **Peacey SR, Guo CY, Robinson AM, Price A, Giles MA, Eastell R, Weetman AP** 1997 Glucocorticoid replacement therapy: are patients over treated and does it matter? Clin Endocrinol (Oxf) 46:255–261
25. **McFarlane SI, Sowers JR** 2003 Cardiovascular endocrinology 1: aldosterone function in diabetes mellitus: effects on cardiovascular and renal disease. J Clin Endocrinol Metab 88:516–523
26. **Becker C** 1985 Hypothyroidism and atherosclerotic heart disease: pathogenesis, medical management, and the role of coronary artery bypass surgery. Endocr Rev 6:432–440
27. **Williams MR, Dawood T, Ling S, Dai A, Lew R, Myles K, Funder JW, Sudhir K, Komesaroff PA** 2004 Dehydroepiandrosterone increases endothelial cell proliferation in vitro and improves endothelial function in vivo by mechanisms independent of androgen and estrogen receptors. J Clin Endocrinol Metab 89:4708–4715
28. **Arlt W, Allolio B** 2003 DHEA replacement in adrenal insufficiency. J Clin Endocrinol Metab 88:4001; author reply 4001–4002
29. **Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, Herbert J, Chatterjee VK** 2000 Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. J Clin Endocrinol Metab 85:4650–4656
30. **Andersson DK, Svardsudd K, Tibblin G** 1991 Prevalence and incidence of diabetes in a Swedish community 1972–1987. Diabet Med 8:428–434
31. **Berger B, Stenstrom G, Sundkvist G** 1999 Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. Diabetes Care 22:773–778
32. **Key TJ, Allen NE, Spencer EA, Travis RC** 2002 The effect of diet on risk of cancer. Lancet 360:861–868
33. **Bjornadal L, Lofstrom B, Yin L, Lundberg IE, Ekbom A** 2002 Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol 31:66–71