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REVIEW ARTICLE

Peri-operative steroid supplementation

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'The need for patients on long-term steroid treatment to increase their dose of glucocorticoids when under stress is a principle that rests in one of the most tranquil corners of medical dogma' [1].

Two case reports published in the early 1950s described cardiovascular collapse and death in young patients undergoing routine orthopaedic surgery. A 34-year-old man died after the withdrawal of steroids (25 mg cortisone bd) 48 h pre-operatively. Although the case was complicated by possible transfusion reactions and pre-existing cardiomegaly, the cause of death was ascribed to acute adrenal insufficiency precipitated by withdrawal of steroid therapy [2]. The second patient was a 20-year-old woman who had taken 62.5–100 mg cortisone daily for 4 months; she became hyperpyrexic and died less than 6 h after surgery [3]. Autopsy findings revealed gross bilateral adrenal haemorrhage and histological changes of complete, adrenal cortical atrophy.

These reports are considered the initial clinical recognition of iatrogenic adrenal insufficiency resulting from exogenous glucocorticoid administration. Subsequently, it has been assumed that the administration of steroids to patients frequently results in suppression and atrophy of the hypothalamic–pituitary–adrenal (HPA) axis through feedback inhibition of both hypothalamic and pituitary function. Adrenocorticotrophic hormone (ACTH) is necessary for normal adrenal gland growth and function and, in its absence, the adrenal glands become atrophic and unable to respond during periods of stress by secreting glucocorticoids. Further studies supported the contention that patients with suppression of the HPA axis required significant glucocorticoid supplementation during physiological stress. However, many of the case reports lacked conclusive biochemical evidence of adrenal insufficiency and Cope pointed out that 'the vast majority of such incidents seem to be associated with medical diagnostic and not adrenal failure' [4].

Nevertheless, the case report in 1953 concluded with a list of recommendations for peri-operative glucocorticoid treatment, which have become standard practice [3]. These recommendations amount to approximately a four-fold increase in the dose of glucocorticoid and there now appears to be an ingrained consensus that patients, currently or recently taking exogenous steroids, require additional large doses of steroids when subjected to surgery. Excessive, or prolonged, glucocorticoid administration can result in adverse clinical sequelae, including immunosuppression, delayed wound healing, decreased glucose tolerance, fluid and electrolyte imbalance and psychological effects.

In two influential studies in 1969, Plumpton, Besser and Cole attempted to clarify the issue of steroid cover in a prospective study of 100 patients undergoing surgery who had either never received steroids (40 patients), recently stopped taking steroids (40 patients) or who were currently still receiving steroids (20 patients) [5]. Of the 20 patients currently receiving long-term steroid therapy, 10 patients were receiving replacement therapy for Addison's disease, hypopituitarism or following adrenalectomy and the remaining 10 patients were receiving immunosuppressive therapy for unspecified conditions [6]. The patients treated previously had received prednisolone, or equivalent, in doses ranging from 5 to 50 mg.day^{-1} for between 6 days and 10 years; the interval since treatment varied from 3 days to 24 months. The patients currently receiving treatment had taken prednisolone, or equivalent, in doses ranging from 5 to 50 mg.day^{-1} for between 8 days and 15 years [5]. The first two groups of patients did not receive any peri-operative steroids. Steroid-treated patients were assessed pre-operatively using an insulin tolerance test;

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four patients had a normal response to insulin-induced hypoglycaemia and were operated on without steroid cover. The remaining 16 patients in this group received 20 mg prednisolone every 6 h. A normal response to surgery, defined as peak cortisol values between 800 and 1300 nmol.l^{-1} with secretion sustained for up to 72 h, depending on the magnitude of surgical stress, was observed in the first two groups and a response found in 65% of patients currently receiving steroid treatment [5]. The authors concluded that, in the majority of patients, adrenal responsiveness to stress returns very rapidly after treatment is stopped and the routine use of steroid cover is unnecessary more than a few weeks after cessation of steroid therapy. They recommended a 2-month period of safety following steroid therapy, during which recovery of the HPA may be incomplete.

Traditional views were again challenged by Kehlet in the 1970s who studied patients on glucocorticoid therapy, for unspecified reasons, undergoing surgery without supplementary steroid cover [7]. Although eight patients out of 104 developed intra-operative hypotension, only one patient showed concomitantly low corticosteroid values. He concluded that acute, stress-induced adrenocortical insufficiency in glucocorticoid-treated patients, during and after surgery, is infrequent and other factors that contribute to the occurrence of hypotension must be sought. The ability of steroids to modulate the immune response and to diminish inflammation makes them useful agents in a wide variety of medical disorders. Many glucocorticoid-treated patients are already catabolic, with anaemia and hypoproteinaemia, which may be caused partly by the glucocorticoids, if given in excess, and partly by their underlying primary disease. Kehlet proposed a simple schedule for peri-operative, glucocorticoid administration based on the principle of imitating the normal HPA response to surgery and on the magnitude of surgical stress [8]. For patients undergoing minor surgery, such as hand surgery, 25 mg cortisol at induction of anaesthesia was considered sufficient to provide the patient with adequate, intra-operative steroid cover. Postoperatively, the usual glucocorticoid therapy was given as soon as the patient was taking oral fluids. Patients undergoing major surgery, such as abdominal or thoracic surgery, were given 25 mg cortisol intravenously at induction of anaesthesia. During, or at the end of surgery, an intravenous infusion of 100 mg cortisol in 24 h was started and repeated until the return of gastrointestinal function permitted oral intake of the usual glucocorticoid therapy.

Further support for this physiological approach was provided by Symreng and colleagues in 1981, who assessed adrenal function in 22 patients undergoing elective surgery [9]. Three groups of patients were studied: those not receiving glucocorticoid therapy, patients receiving glucocorticoids who had a normal response to corticotrophin stimulation testing and patients with an impaired cortisol response to corticotrophin stimulation testing. The first two groups received no additional glucocorticoid treatment and the third group received only the low-dose hydrocortisone therapy regimen advocated by Kehlet (25 mg at induction + 100 mg 24 h^{-1}). There were no clinical signs of adrenal insufficiency in the three groups. Moreover, the peri-operative changes in plasma cortisol were similar in the first two groups and significantly greater for the first 2 h of surgery in the treated group. The results of this study suggested that patients receiving exogenous glucocorticoids may have preserved adrenocortical function and their response to surgery is similar to that of normal subjects. In patients with proven adrenocortical insufficiency, a low-dose physiological substitution regimen results in circulating cortisol values greater than in normal patients and is sufficient to prevent intra-operative haemodynamic instability.

The necessity for an increase in cortisol secretion in routine surgery has been questioned following the primate work of Udelsman and colleagues [10]. They found that adrenalectomised monkeys receiving subphysiological (one-tenth normal) steroid therapy and undergoing upper abdominal surgery were haemodynamically unstable before, during and after surgery and had a significantly higher mortality rate than control monkeys. However, animals who received either physiological, or supraphysiological (10 times normal), steroid replacement displayed identical haemodynamic parameters and normal wound healing. Supraphysiological glucocorticoid replacement had no apparent advantages during abdominal surgery in the primate and it can be argued that increased cortisol secretion during surgery in humans is also unnecessary. Anaesthetic techniques which obtund the catabolic hormonal response to surgery are frequently employed in high-risk patients without adverse consequences (*vide infra*).

Further clinical support for the need for only baseline steroid therapy was provided by Bromberg and colleagues in 1991 [11]. They studied renal transplant patients receiving immunosuppressive doses of glucocorticoids, who were admitted with sepsis or metabolic abnormalities, or who were undergoing surgery. They found that administering only the usual dose of prednisone was sufficient and there was no evidence of adrenal insufficiency during the clinical course of these patients. Further work was conducted on 52 recipients of renal allografts, who underwent 58 operative procedures. Again, no patient received additional steroids, but only baseline, immunosuppressive doses of glucocorticoids and there was no clinical or laboratory evidence of adrenocortical insufficiency [12].

These findings were further tested in a prospective, but

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not randomised or controlled, study by Friedman and colleagues [13]. Twenty-eight patients, who had taken on average 10 mg prednisolone daily for 7 years, underwent major orthopaedic surgery without an increase in steroid dosage. Clinical observations and laboratory measurements to assess adrenocortical function were obtained peri-operatively. There was no evidence of adrenocortical insufficiency in any patient and it was concluded that all patients had endogenous adrenocortical function which was sufficient to meet the demands of surgery.

Despite the weight of evidence afforded by these results, fears of precipitating an Addisonian crisis and the perceived innocuous nature of steroid therapy have ensured that older supraphysiological regimens are still used. Patients on maintenance steroid therapy, or who have recently received steroid therapy, continue to receive peri-operative 'stress steroids' far in excess of requirements, with the consequent risk of serious postoperative sequelae.

Normal glucocorticoid response to surgery

The onset of surgery is associated with the rapid secretion of hormones derived from the anterior and posterior pituitary gland. Corticotrophin (ACTH) is secreted by corticotroph cells in the anterior lobe of the pituitary gland. Corticotrophin contains 39 amino acids and is synthesised as part of a large precursor molecule, pro-opiomelanocortin (POMC) which undergoes considerable post-translational processing. In the human anterior pituitary, POMC is cleaved by a serine endoprotease predominantly into ACTH, ß lipotropin and an N-terminal precursor. Control of ACTH secretion is highly complex (for review see ref. [14]).

The main stimulus to secretion is corticotrophin-releasing hormone (CRH), a 41 amino acid peptide produced in the hypothalamus and secreted into the hypophyseal portal system. Corticotrophin-releasing hormone secretion in the hypothalamus is stimulated by serotonin and acetylcholine and is inhibited by noradrenaline and cortisol [15]. It acts through specific cell-surface receptors and activation results in an increase in intracellular cAMP and subsequently in ACTH secretion following increased transcription of POMC mRNA. Arginine vasopressin (AVP) plays an important role in the control of ACTH secretion during stress, by directly stimulating the release of ACTH and acting synergistically with CRH, as well as regulating pituitary CRH receptor expression.

Corticotrophin acts on the adrenal gland through a specific cell-surface receptor, a member of the G-protein-coupled receptor family. The signal is transmitted through stimulation of the activating unit of the G protein, resulting in the activation of adenyl cyclase and an increase in intracellular cAMP. Feedback inhibition by cortisol prevents any further increases in CRH or ACTH production. These processes are summarised in Table 1 [16].

Table 1 Summary of the neuroendocrine control of CRH & ACTH secretion. Adapted from [16].

	Increased secretion	Decreased secretion
Hypothalamus (CRH) Stress/circadian rhythm	Serotonin Acetylcholine Interleukin-1	Noradrenaline Opioids GABA Cortisol
Pituitary (ACTH)	Adrenaline	Cortisol

The serum half-life of corticotrophin is ≈ 10 min. Increased ACTH secretion is closely followed by increases in circulating cortisol values. Cortisol is a C^{21} corticosteroid with both glucocorticoid and mineralocorticoid activity [17]. In physiological concentrations, 90–97% of circulating cortisol is protein-bound, 89.5% is bound to transcortin or corticosteroid-binding globulin (CBG) and the rest to albumin. The level of CBG in normal plasma is about 700 nmol.l^{-1}. Its half-life in plasma is 5 days and its binding capacity limited to ≈ 690 nmol.l^{-1} of cortisol. Thus, as total cortisol rises above this value, the proportion of free cortisol increases relative to normal. Interestingly, therapeutic concentrations of prednisolone, which is the only synthetic steroid that binds to CBG, decrease the amount of CBG-bound cortisol by about 30%, resulting transiently in increased concentrations of free cortisol. Corticosteroid-binding globulin values increase 2–3 fold with administration of oestrogen to either sex, and increase during pregnancy, particularly in the third trimester. The oestrogen effect is dose-dependent, occurs within 2–4 days, reaches a maximum value at 14 days and returns to normal 7–10 days after discontinuation of therapy. Tamoxifen also causes increases in CBG. Inherited abnormalities of CBG are much less common than for thyroid binding globulin (TBG). Elevated values of CBG are also seen in thyrotoxicosis, chronic active hepatitis and during treatment with anticonvulsant drugs. Subnormal values occur in hypothyroidism, cirrhosis, multiple myeloma, obesity, the nephrotic syndrome and other protein–losing syndromes, and, rarely, on a genetic basis [18]. The endogenous cortisol production is between 25 and 30 mg.day^{-1}, circulating concentrations vary in a circadian pattern and the half-life of cortisol in the circulation is between 60 and 90 min [19].

Plasma cortisol concentrations increase rapidly in response to surgical stimulation and remain elevated for a variable time following surgery. Peak values are achieved within 4–6 h after surgery or injury and return towards

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baseline after 24 h [20]; this increase in plasma cortisol may, however, be sustained for up to 48–72 h following major surgery, such as cardiac surgery. The magnitude and duration of the cortisol response reflect the severity of surgical trauma, as well as the occurrence of postoperative complications, and values > 1500 nmol l^{-1} are not uncommon [21, 22]. Increased cortisol production is secondary to ACTH secretion, but the plasma ACTH concentration is far greater than that required to produce a maximal adrenocortical response. Furthermore, the normal pituitary adrenocortical feedback mechanism is no longer effective, as both hormones remain increased simultaneously. The administration of ACTH during surgery does not cause a further increase in cortisol secretion [20].

The amount of cortisol secreted following major surgery, such as abdominal or thoracic surgery, is between 75 and 100 mg on the first day [23–25]. Minor surgery, such as herniorrhaphy, induces less than 50 mg cortisol secretion during the first 24 h [5, 8]. However, because of changes in volume of distribution and half-life of cortisol during surgery, these calculations may be an over-estimation [26].

Cortisol has complex effects on intermediate metabolism of carbohydrate, fat and protein [27]. It causes an increase in blood glucose concentrations by stimulating protein catabolism and promoting glucose production in the liver by gluconeogenesis. Cortisol reduces peripheral glucose utilisation by an anti-insulin effect. Glucocorticoids inhibit the recruitment of neutrophils and monocyte-macrophages into the area of inflammation [28] [29] and also have well-described anti-inflammatory actions, mediated by a decrease in the production of inflammatory mediators such as leukotrienes and prostaglandins [30]. In addition, there is immunoregulatory feedback between the glucocorticoid hormones and interleukin-6 (IL-6); the production and action of IL-6 is inhibited by ACTH and cortisol [31].

Assessment of the HPA axis

Therapy with glucocorticoids results in suppression of pituitary–adrenal function. Failure of cortisol secretion is due primarily to inhibition of synthesis and secretion of corticotrophin (ACTH) [32–35], as a result of inhibited transcription of the corticotrophin gene [33, 36]. Pituitary–adrenal function in patients receiving steroid therapy can be assessed by considering the dose and duration of therapy and measurement of basal plasma cortisol concentrations, but these variables may not be reliable [37]. The rate of recovery after long-term administration of corticosteroids is also uncertain [38]. A single measurement of plasma cortisol is not an adequate appraisal of pituitary–adrenal function since it may be normal during episodic secretion [39]. Stimulation tests are usually required to identify patients with suppressed, endogenous adrenal function. The most important function of any test of HPA function is its ability to predict the patient's response to a major physiological stress such as surgery. Biochemical evaluation is based on three important principles of HPA physiology [40]:

1 cortisol exerts feedback inhibition at the pituitary and hypothalamic levels;

2 the adrenal glands depend upon ACTH as a tropic hormone so that ACTH deficiency results in a reversible inability to secrete cortisol;

3 the HPA axis can be activated by pharmacological and physiological stimuli that override the normal diurnal pattern of cortisol production.

Laboratory assessment of HPA axis

Single measurements of serum cortisol and urinary-free cortisol excretion

In the past, single measurements of serum cortisol and urinary-free cortisol excretion have been used to assess adrenal function [41–44]. However, serum cortisol concentrations in the healthy resting state overlap with those in adrenal insufficiency and in cortisol excess syndromes [45]. Similarly, urinary-free cortisol (UFC) estimation on a timed 24-h specimen is not usually specific enough to distinguish adrenal insufficiency from the lower limit of normal. Stimulation tests are therefore required to distinguish, with confidence, patients suffering from adrenal insufficiency.

Random cortisol estimation

A random cortisol value is sometimes helpful in evaluating adrenal function in the clinical setting of severe stress, when endogenous HPA activity should be at a maximum. Its use therefore is limited to the peri-operative period. In an acutely ill patient in whom adrenal insufficiency is suspected, a sample of blood can be taken for cortisol estimation, steroids administered and formal testing carried out at a later date.

The best dynamic test for the assessment of the HPA axis, and the interpretation of cortisol values obtained, remains a matter of controversy. The insulin stress test is accepted by many as the 'gold standard' for overall assessment of the entire HPA axis, but is unpleasant and not without risk. The short synacthen test is an effective alternative and easier to perform, as well as more acceptable for patients. A consistent finding has been the high degree of correlation between the two tests, but discrepancies have also been reported.

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The short synacthen test (SST)

The corticotrophin test has been used since the 1950s to measure adrenal function. Earlier tests of adrenal function depended on the fall in eosinophil count or changes in the sodium/potassium ratio in response to corticotrophin. These tests were simple to perform but lacked specificity and were superceded by investigations of the effect of an intravenous infusion of corticotrophin on urinary steroid excretion, or on plasma 17-hydroxysteroids. These developments, however, were not widely adopted because of the difficulties in analysis, inconvenience of administering corticotrophin infusions and the risks of allergic reactions to natural corticotrophin. The introduction of the synthetic polypeptide-β^{1-24} (Synacthen® Ciba) in the 1960s and the use of fluorometric assays enabled rapid determination of plasma cortisol concentrations without risk of allergic reactions

In 1965 the application of a test using synthetic corticotrophin (the short synacthen test [SST]) was reported in 66 normal subjects and has been widely adopted as an estimate of adrenocortical function [46]. In this test the plasma cortisol response after 30 min to a single injection of 250 μg synthetic polypeptide-β^{1-24} (Synacthen® Ciba) intramuscularly was measured. The adrenocortical stimulatory activity was found to be equivalent to that of natural corticotrophin, but with a shorter duration of response. Peak cortisol values were noted minutes after injection and the concentrations achieved after 30 min taken to reflect the maximal response. After 60 min cortisol decreased and had reached baseline values after 4 h. The test was found to be reliable, reproducible and equally practical for both in-patients and out-patients and has remained one of the standard tests for evaluating adrenocortical function. Although the test measures directly only the functional integrity of the adrenal glands, it also provides an indirect assessment of hypothalamic and pituitary function because the adrenal glands depend on endogenous ACTH for its tropic effect. When ACTH production is impaired by pituitary or hypothalamic disease, or by administration of exogenous steroids, the adrenal glands lose their capacity to respond to exogenous stimulation. In the present form of the SST 250 μg synthetic ACTH is administered intavenously and serum cortisol is measured at 0, 30 and 60 min. Two aspects continue to generate discussion – selection of the best test criterion, peak cortisol response vs. incremental cortisol response, and the definition of adequate cortisol secretion. Although both the incremental increase in cortisol and the absolute values achieved have been considered as important, the use of an incremental rise as the sole index of adrenal function has been criticised. In one study a third of normal subjects failed to demonstrate an increase greater than 200 nmol.l^{-1} [47]. Furthermore, the cortisol increment is inversely proportional to the basal cortisol value and hence smaller increases are obtained in the morning when endogenous concentrations are already high [48, 49]. It has been suggested that calculation of the incremental increase in serum cortisol has no value [50]. Peak cortisol concentrations ranging from 420 to 700 nmol.l^{-1} have been proposed as criteria for establishing adequate adrenal function based on the SST and values of 500–560 nmol.l^{-1} are well supported in the literature. In one retrospective series, cortisol responses were examined in a heterogeneous population of 399 patients [48]. In 95% of the tests, the peak cortisol was greater than 530 nmol.l^{-1}, although no data were provided regarding the actual incidence of adrenal insufficiency and other tests of adrenal function were not used. Hurel and colleagues assessed 57 healthy volunteers to establish normal parameters for both the SST and the insulin tolerance test (ITT) [51]. The mean (minus 2SD) 30 min value during the SST was 390 nmol.l^{-1} and the 60 min value was 500 nmol.l^{-1}; the mean maximal cortisol response (minus 2SD) during the ITT was 520 nmol.l^{-1}.

The SST has been used to determine the ability of glucocorticoid-treated patients to respond to surgical stress and the data confirmed the close correlation between the results obtained with ACTH testing and insulin stress testing [52]. In a study of 100 adult subjects, 90 with proven or suspected hypothalamic–pituitary–adrenal hypofunction and 10 normal subjects, an excellent correlation ($r = 0.92$) was achieved between the results of the two tests [53]. Almost 10 years later, in the largest study yet reported, 200 consecutive patients with proven or suspected hypothalamic–pituitary disorder were assessed using the SST and ITT and, again, an excellent correlation ($r = 0.83$) was found between the results of the two tests [54]. In eight patients discordant results were found and ascribed to testing shortly after documented pituitary necrosis (two patients), an inadequate hypoglycaemic stimulus (two patients) and marginal discrepancies between the two tests (four patients). The authors concluded that the SST is reliable for assessing integrated HPA function, except shortly after acute ACTH deprivation.

Kane and colleagues also compared the SST with the ITT in patients on long-term corticosteroid treatment [55]. Both tests were performed on 22 patients on long-term, stable doses of prednisolone (< 10 mg.day^{-1}). A pass was defined as a 30-min plasma cortisol > 550 nmol.l^{-1} for the SST and a maximal cortisol > 500 nmol.l^{-1} for the ITT. Using these criteria five patients passed both tests, nine failed both and eight had discrepant results; all passed the insulin tolerance test, but failed the SST. There was a significant correlation between the maximal cortisol concentration achieved during the ITT and the 30-min SST value, as well as the incremental rise. There was, also, an

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inverse correlation between the dose and duration of use of steroids and the cortisol response in both tests. From these results, the authors inferred that the SST is a reliable, safe and easily performed initial assessment of the HPA axis in patients on long-term corticosteroids, with the ITT remaining as a valuable test for those who fail the SST. These views received further support from Hurel's study in which 166 patients, including 83 on long-term steroid therapy which had been reduced and stopped 2 days before testing, were evaluated using both the SST and the ITT [51]. Using a 30-min cortisol value $> 600\,\text{nmol.l}^{-1}$ as a cut off, the short synacthen test proved a suitable substitute for the insulin stress test. This unit evaluated the cost of an ITT at approximately £150 and that of an SST at only £18.

The SST has been criticised [56, 57] and a number of case reports have documented instances in which the short synacthen test failed to diagnose unequivocally symptomatic secondary hypoadrenalism [58, 59]. The SST may be less reliable in assessing the HPA axis in patients withdrawing from steroids [60, 61], those with pituitary disease [62] and in the first 14 days following pituitary surgery [63]. There is also considerable discrepancy over the criteria to determine a 'pass' result with the SST. In a survey of 191 clinical laboratories undertaking biochemical measurements, there was no consensus regarding the protocol for synacthen testing, the interpretation of the cortisol responses, the source of those values or the analytical method for cortisol measurement [64]

Differences of opinion also exist between clinicians regarding the peak cortisol value accepted in determining a 'pass' test, with concentrations ranging from 400 to $700\,\text{nmol.l}^{-1}$ [44]. A further criticism of the SST concerns the dose of synacthen used. The 250 μg dose is grossly supraphysiological and may induce false positive cortisol responses in some patients. The use of 1 μg ACTH and measurement of the 30-min cortisol value is a more sensitive test of adrenal function and identified a small subgroup of patients on long-term steroids, who responded normally to the regular 250-μg test, but had a reduced response to 1 μg [65]. It has been suggested that the 1-μg ACTH test follows the ITT more closely and may be more sensitive than the standard SST in detecting subtle deficiencies in the hypothalamic–pituitary–adrenal axis [66].

It is clear that, after a period of relative certainty, the value of the SST in assessing HPA function has undergone reappraisal recently. Most of the concerns expressed relate to the fear of under-diagnosing adrenal insufficiency, although Bromberg has argued the opposite – that the SST is an over-sensitive laboratory investigation that is not mirrored by any clinical deficit [11]. Clayton has suggested that by taking a 30-min cortisol value $> 600\,\text{nmol.l}^{-1}$ as a pass in the SST, the sensitivity of the test could be increased, the number of false positive 'pass' results reduced to 3.5% and the number of ITTs undertaken reduced by 25% [67]. Preliminary data suggest that a low 1-μg dose of ACTH may further improve sensitivity.

The insulin tolerance test (ITT)

The insulin tolerance test has been used as the reference standard for assessing the function of the HPA axis since its inception in the 1960s [68, 69]. In this test, the intravenous administration of soluble insulin ($0.10–0.15\,\text{U kg}^{-1}$) to patients who have been fasted overnight results in a rapid (10–20 min) lowering of blood glucose concentration. The dose of insulin may be increased in insulin-resistant states, such as acromegaly or obesity. A lower dose of insulin may prevent prolonged glucose suppression in those with hypopituitarism, but doses $< 0.10\,\text{U kg}^{-1}$ do not reliably achieve adequate hypoglycaemia. Neuroglycopenia occurs when blood glucose is less than $2.2\,\text{mmol.l}^{-1}$ resulting in the release of both ACTH and GH from the pituitary, following hypothalamic stimulation, and subsequently cortisol from the adrenal glands, thus allowing assessment of the entire HPA axis [70]. Venous blood samples are collected over 90 min for measurement of glucose and cortisol concentrations.

As in the SST, the peak cortisol response to insulin-induced hypoglycaemia is a more reliable criterion for confirming HPA axis function than the incremental rise in cortisol [71]. Adequate adrenal function is shown by a peak cortisol value $> 500\,\text{nmol.l}^{-1}$ at any time during the test, a cut-off that reliably separates normal controls from patients with adrenal insufficiency [72]. Hypoadrenalism is demonstrated by a peak cortisol value of $< 500\,\text{nmol.l}^{-1}$ associated with symptomatic hypoglycaemia (glucose $< 2.2\,\text{mmol.l}^{-1}$). Rarely, patients will pass the ITT although displaying clinical evidence of hypoadrenalism. In a small study of six patients, who passed the ITT, frequent blood sampling uncovered hypocortisolaemia and symptoms were alleviated by administration of glucocorticoids. Partial deficiency of CRH was postulated to explain these results [73].

Plumpton and Besser compared the adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects [74]. Twenty control patients and 20 corticosteroid-treated patients were studied during both insulin-induced hypoglycaemia and while undergoing major surgery including hip osteotomy, hysterectomy or surgery on the gastro-intestinal tract. The corticosteroid-treated group included nine patients currently receiving steroids at doses up to 50 mg prednisolone, or equivalent, and 11 patients who had discontinued steroid therapy. It was noticeable that surgery provided a more intense stimulus to corticosteroid

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secretion than insulin-induced hypoglycaemia, producing higher and more sustained cortisol concentrations. A normal response to the ITT was (i) plasma cortisol increment $>140\,\text{nmol.l}^{-1}$ and (ii) maximum value $>560\,\text{nmol.l}^{-1}$. All 11 patients who had stopped corticosteroid treatment (with a mean interval since treatment of 10 months) had a normal response to insulin-induced hypoglycaemia and underwent surgery without any steroid cover. None of these patients developed any signs of adrenal insufficiency. Of the nine patients who were currently taking corticosteroids, only two had a normal response to insulin stress testing and underwent surgery without steroid cover and without incident. The remaining seven patients were given prednisolone during surgery, although five of the seven showed some increase in plasma cortisol during surgery. The authors concluded that a normal response to the ITT indicated that a patient would respond satisfactorily to surgery, while a subnormal response did not preclude an increase in plasma cortisol during surgery. The insulin stress test therefore erred on the side of safety. The close relationship between the plasma cortisol response to hypoglycaemia and surgery was confirmed in a small study of eight normal patients undergoing major abdominal surgery, inferring that the ITT is predictive of the HPA response to surgical trauma [75].

The main criticisms of the ITT are that it is unpleasant and not without risk [76, 77]. Loss of consciousness, seizures, resistant hypoglycaemia, myocardial infarction and even death are recognised complications. However, when performed in an experienced endocrine unit with adequate supervision, the ITT was deemed a safe procedure [78]. Patients with a baseline cortisol of $>500\,\text{nmol.l}^{-1}$ were uniformly shown to have a normal cortisol response to ITT. Fish and colleagues reviewed 6580 ITTs and found only six cases with untoward side-effects (two comas, two episodes of angina and two impending seizures) [79]. All were reversed with glucose administration intravenously.

CRH testing

Circulating CRH concentrations may be useful in the diagnosis of adrenal insufficiency; CRH concentrations should increase during the ITT, but discrepant results have been reported [80]. These may be caused by CRH binding protein, extrahypothalamic sources of CRH, assay variability or the presence of other secretagogues. For these reasons, random, stimulated or suppressed plasma CRH values have no part currently in the assessment of adrenal insufficiency [40]

Stimulation testing with CRH is useful in both diagnosis and localisation of adrenal insufficiency. Human or ovine CRH may be given in a dose of $1\,\mu\text{g.kg}^{-1}$ (or $100\,\mu$g bolus); $1\,\mu\text{g.kg}^{-1}$ provides near-maximal stimulation with minimal side-effects and is equally effective in all ages. Ovine CRH has a prolonged action, possibly due to its longer half-life, but may cause side-effects such as flushing (20% patients) or, rarely, tachypnoea. Human CRH causes shorter periods of ACTH and cortisol secretion similar to the physiological response of these hormones [81]. Nevertheless, ovine CRH has been preferred to human CRH because of its longer duration of action and because many of the initial studies were performed with oCRH before hCRH became available [82]. Following injection of CRH, ACTH and cortisol concentrations are evaluated over the succeeding 2 h. In secondary adrenal insufficiency, baseline ACTH values are low and do not respond to CRH [40].

The responses to CRH and ITT were compared in 61 patients who had received chronic glucocorticoid therapy, taking an arbitrarily defined 'pass' value of $550\,\text{nmol.l}^{-1}$ for both tests [37]. The peak plasma ACTH and cortisol concentrations were higher after insulin-induced hypoglycaemia, but 85% results were in agreement and the correlation between the peak plasma cortisol responses to the two stimuli was significant. Only six patients who had normal responses to hypoglycaemia had blunted responses to CRH and three patients with blunted responses to hypoglycaemia had no response to CRH. The close correlation between the two tests is surprising, since evaluation criteria based on the ITT were used for both tests and peak plasma ACTH and cortisol responses after maximal CRH stimulation are not as high as those after hypoglycaemia [83, 84]. The responses to hypoglycaemia are greater, as this activates not only endogenous CRH but also other stimuli of corticotrophin secretion such as vasopressin [85].

In contrast, a study of 43 patients with hypothalamic, pituitary or adrenal disease found that six patients who were ACTH deficient in response to insulin-induced hypoglycaemia responded normally to CRF-41 (ovine CRH) [86]. However, these patients had suffered either hypothalamic or pituitary lesions and the data suggested a functional defect of ACTH secretion due to the failure of CRF to reach the corticotroph. No patient was receiving chronic glucocorticoid therapy, so the CRH test may play a role under these circumstances. The utility of the CRH test as an initial diagnostic test for adrenal insufficiency has not yet been fully evaluated and additional studies are needed. A further application of the CRH test has been its use in combination with desmopressin in the differential diagnosis of Cushing's syndrome [87].

Anaesthetic implications

Despite intensive investigation during the past 30 years there is little consensus over what constitutes the best

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overall test of adrenal function and reserve. The SST continues to be criticised over the lack of established 'pass' criteria and doubts have been raised about its accuracy. The accuracy of the ITT has rarely been questioned, but it is an expensive, time-consuming and subjectively unpleasant test. During surgery, the situation is further complicated by the fact that the results of the test chosen should provide an unequivocal 'final answer' about the patient's adrenal reserve. At present, the conventional SST may not meet this need, but anaesthetists rarely have access to an ITT.

No single test appears to satisfy all the criteria of efficacy, safety, simplicity and cost, although most of the work assessing the HPA axis in patients undergoing surgery has used the SST. The optimal means of assessing a patient with suspected secondary adrenal insufficiency may be to employ a hierarchy of tests. Patients who satisfy clearly defined end-points at each stage, for example random serum cortisol $>500\,\text{nmol.l}^{-1}$ [78], or basal cortisol $<100\,\text{nmol.l}^{-1}$ [88] need not proceed to further testing. The ITT may then be reserved for patients who display equivocal results with other tests, including the SST. The use of CRH testing appears promising, but its accuracy and predictive ability have yet to be confirmed. Within the peri-operative period, various anaesthetic agents and techniques are used which can ablate, or obtund, the cortisol response to surgery.

Intravenous induction agents

Etomidate, an imidazole derivative, is a potent inhibitor of adrenal steroidogenesis and acts on the mitochondrial 11β-hydroxylase step and cholesterol cleavage part of the biosynthetic pathway. Fragen and colleagues found that a single induction dose of etomidate inhibited cortisol and aldosterone production for up to 8 h after pelvic surgery [89]. Etomidate is often used in sick patients with limited cardiovascular reserve without adverse effects, thereby raising the question of how much circulating cortisol is required in routine surgery for cardiovascular stability. The primate work by Udelsman [10] inferred that only resting circulating values were necessary to maintain homeostasis. Both diazepam and midazolam have also been shown to inhibit cortisol production from isolated bovine adrenocortical cells *in vitro* [90]. Midazolam, which has an imidazole ring in addition to its benzodiazepine structure, was found to decrease the cortisol response to peripheral surgery [91] and major upper abdominal surgery [92] and may also have a direct effect on ACTH secretion [91].

Volatile anaesthetic agents

Volatile anaesthetic agents probably have little effect on the HPA axis when used at low concentrations. No difference was found between 2.1 and 1.2 MAC halothane in obtunding the pituitary hormone and sympathoadrenal responses to pelvic surgery [93]. It is likely that other volatile anaesthetic agents behave similarly at clinical concentrations

High-dose opioid anaesthesia

The ability of morphine to inhibit the HPA axis has been known for many years [94], but it was only in the 1970s that the use of morphine to modify the metabolic and endocrine responses to surgery was first investigated [95]. Large doses of morphine, however, resulted in unacceptably prolonged recovery times. Fentanyl $50\,\mu\text{g.kg}^{-1}$ given intravenously abolished the cortisol response to pelvic surgery [96] but $100\,\mu\text{g.kg}^{-1}$ was required in upper abdominal surgery [97]. The inhibitory effect of fentanyl on surgically induced secretion of pituitary hormones is mediated via the hypothalamus [98]. The inevitable penalty of this technique is profound respiratory depression for several hours postoperatively. Many studies have examined the effects of high-dose fentanyl and its congener, sufentanil, on the HPA axis during cardiac surgery [99]. In general, the majority of studies have shown that cortisol secretion is attenuated only until the start of cardiopulmonary bypass.

Regional anaesthesia

It is well recognised that complete afferent blockade, both somatic and autonomic, is necessary to prevent stimulation of the HPA axis. Thus an extensive T4–S5 block is necessary for pelvic surgery [100] and it has been known for over 25 years that it is very difficult in upper abdominal surgery to prevent cortisol secretion with regional anaesthesia [101]. Other operations which are amenable to complete afferent blockade are limb and eye surgery [102].

Side-effects of steroids

The side-effects of long-term steroid administration are well known. Growth retardation, osteoporosis and osteonecrosis, myopathy, ocular reactions, hypertension, peptic ulceration, pancreatitis and rarely intestinal perforation, immunosuppression and neuropsychiatric effects, as well as HPA axis suppression have all been documented in the literature [103, 104].

Special concerns regarding the use of corticosteroids in surgical patients include adverse effects on wound healing [105], immunosuppression [106–108], interaction with nondepolarising neuromuscular blocking drugs [109,110] and myopathy, particularly in intensive care patients [111]. Other acute side-effects which have been reported with use of high doses of steroids include glucose intolerance [112], adverse cardiovascular effects, including arrhythmias and myocardial infarction [113, 114], bowel perforation

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[115], pancreatitis [116] and peptic ulceration [117] as well as neuropsychiatric disorders [118]. One author has seen all these complications following the use of large doses of steroids in the peri-operative period.

Patients receiving steroid therapy often show evidence of the side-effects of chronic steroid use. The use of additional large doses of steroids within the peri-operative period may contribute significantly to peri-operative morbidity, prolong convalescence and delay overall recovery. With physiological replacement regimens, side-effects can be minimised and postoperative recovery may be expedited.

Steroid treatment regimens

The increase in circulating cortisol, in response to surgical trauma, is one component of the 'stress response' to surgery. This response evolved to aid survival in a more primitive environment, when fluid retention together with glucose, lipid and protein mobilisation would be beneficial to the animal. However, in modern surgical and anaesthetic practice, where such physiological disturbances may be easily prevented or rapidly corrected, the benefits of the stress response are tenuous. Anaesthetic and surgical techniques, which are associated with a decreased stress response, may improve patient outcome [119, 120]. Logic dictates that using the minimal amount of steroid replacement, rather than supraphysiological dosing regimens, will optimise postoperative recovery and avoid deleterious side-effects.

Evaluation of the status of the HPA axis and adrenal reserve of patients on long-term steroids should be based on biochemical testing, if available. The magnitude of the surgical stress as well as pre-operative steroid dose must be considered. Adequate replacement therapy is essential to avoid peri-operative haemodynamic instability. Patients receiving 10 mg or less of prednisolone daily have been shown to have a normal response to HPA testing [13, 38] and do not require formal HPA testing or peri-operative steroids greater than their usual requirements. For other patients we recommend a physiological substitution regimen based on those described by Kehlet, Symreng and colleagues and Salem and colleagues [8, 9, 121].

Only 25 mg hydrocortisone intravenously, or equivalent, at induction of anaesthesia has been shown to provide adequate, intra-operative, plasma cortisol concentrations [5, 9]. Patients undergoing minor surgery, such as herniorrhaphy, should take their routine dose of glucocorticoids pre-operatively, or receive 25 mg hydrocortisone at induction, and resume oral replacement therapy postoperatively.

For moderate surgery, such as total abdominal hysterectomy, patients should receive the normal glucocorticoid dose pre-operatively, 25 mg hydrocortisone intravenously at induction and an infusion of 100 mg hydrocortisone intravenously in the first 24 h postoperatively. If the postoperative course is uncomplicated, normal oral therapy can be restarted by day 2 postoperatively

For patients undergoing major surgery, such as cardiac surgery, in which a delay will be experienced before oral intake is resumed, the glucocorticoid target should be 100–125 mg hydrocortisone 24 h^{-1}. Patients should receive their routine glucocorticoid therapy pre-operatively, 25 mg hydrocortisone intravenously at induction and an infusion of 100 mg hydrocortisone 24 h^{-1} for the first 48–72 h following surgery. Oral glucocorticoid therapy is resumed when gastrointestinal function returns. This regimen will provide adequate peri-operative plasma cortisol concentrations, whilst avoiding both the enormous increases in plasma cortisol caused by intermittent bolus doses [9] and the harmful side-effects of supraphysiological dosing schedules.

The time to HPA recovery after discontinuation of

Table 2 Steroid treatment regimens.

Patients currently taking steroids	< 10 mg day^{-1}	Assume normal HPA response	Additional steroid cover *not* required
	> 10 mg day^{-1}	Minor surgery	25 mg hydrocortisone @ induction
		Moderate surgery	Usual pre-operative steroids + 25 mg hydrocortisone @ induction + 100 mg day^{-1} for 24 h
		Major surgery	Usual pre-operative steroids + 25 mg hydrocortisone @ induction + 100 mg day^{-1} for 48–72 h
	High-dose immunosuppression	Give usual immunosuppressive doses during peri-operative period	
Patients stopped taking steroids	< 3 months	Treat as if on steroids	
	> 3 months	No peri-operative steroids necessary	

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steroid therapy is controversial, with reports varying from 2–5 days [122, 123] to 9 months [124, 125]. These studies, however, cover an 18-year period, dating from before the use of the SST. Differences in the methods of assessment of the HPA axis probably account for the huge variability in reported recovery times. Plumpton and Besser suggested 2 months as the maximum interval following treatment during which recovery of the HPA may be incomplete [6], while La Rochelle and colleagues found that the duration of therapy, total steroid dose and highest steroid dose administered did not affect HPA recovery [38]. Based on this evidence, we suggest that patients who have taken steroids in excess of 10 mg prednisolone, or equivalent, within 3 months of surgery, should be considered to have some degree of HPA suppression and receive a low-dose replacement regimen according to the magnitude of surgery. Patients who have not received steroids for more than 3 months are considered to have full recovery of the HPA axis [5].

A final group of patients are those taking high doses of steroids for acute immunosuppression at the time of surgery. It is imperative that such patients have the dose of steroids maintained during the peri-operative period. For example, a patient who is taking 60 mg prednisolone $24\,h^{-1}$ requires 250 mg hydrocortisone infusion $24\,h^{-1}$ during the peri-operative period. Additional steroid cover is not required since immunosuppressive doses are more than sufficient to maintain cardiovascular stability. Failure to maintain immunosuppression will cause deterioration in organ function, for example renal function in nephritis, and is a 'hanging offence'. The steroid regimens are summarised in Table 2.

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