calcipotriol has been used in higher concentrations than calcitriol. Long and Marks seem unaware of controlled studies showing that calcipotriol ointment 50 μg/g is better than vehicle control.[4] Now that calcipotriol has been shown to compare favourably with betamethasone 17-valerate, it may be possible to replace topical corticosteroids with calcipotriol in many patients with psoriasis. We should soon know how calcipotriol compares with dithranol: more than 400 patients have entered a multicentre trial designed to compare the efficacy and tolerability of the two agents.

Calcipotriol is by far the best studied vitamin KD_3 analogue. The results obtained in more than 3000 patients with psoriasis have shown calcipotriol to be both effective and well-tolerated. It represents a breakthrough in the topical treatment of psoriasis.

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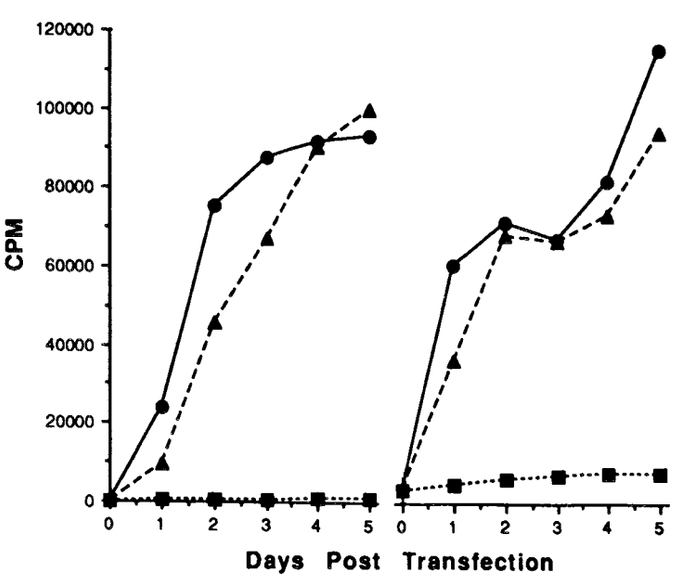
Inhibition of hepatitis B virus by antisense oligodeoxynucleotides

SIR,—Hepatitis B virus (HBV) infection is a major cause of chronic liver disease and hepatocellular carcinoma world wide.[1] Although interferon alpha is effective in about one-third of patients,[2] other therapeutic strategies need to be explored.

We analysed the effect of antisense oligodeoxynucleotides on HBV gene expression and replication. Transfection of human hepatoma cells with HBV-DNA[3] (control) results in the synthesis and secretion of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). Cotransfection of HBV-DNA with an oligodeoxynucleotide of antisense polarity (ATC-40) completely blocked HBsAg and HBeAg synthesis as well as HBV replication (figure). The same oligodeoxynucleotide of sense polarity (GAT-40) had no effect on viral antigen production or replication.



Inhibition of viral antigen synthesis by HBV-specific antisense oligodeoxynucleotide.

Detection of HBsAg (left) and HBeAg (right) in cell culture medium after transfection of human hepatoma cells (HuH-7) with HBV-DNA alone (——●—— control), HBV-DNA plus an antisense oligodeoxynucleotide (···■··· ATC-40), or HBV-DNA plus a sense oligodeoxynucleotide (---▲--- GAT-40). Analyses were completed with commercially available radioimmunoassays (Centocor, Malvern, and Abbott, Chicago, USA).

These data show that HBV-specific antisense oligodeoxynucleotides can block viral gene expression and replication. Inhibition of both human immunodeficiency virus infection[4] and lymphoma growth[5] will have to await a clearer definition of the role of antisense oligodeoxynucleotides, either alone or in combination with other strategies.

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Cortisol response to corticotropin and survival in septic shock

SIR,—Dr Rothwell and colleagues (March 9, p 582) show a poor response to corticotropin in 13 patients with septic shock, all of whom died. They state that "the cause of this apparent adrenal impairment is unclear". We offer a possible explanation.

Cortisol plasma concentrations are usually raised in severe sepsis. Interleukin-1 and tumour necrosis factor are lymphokines that play an important part in endotoxin-mediated septic shock. It has been suggested that these cytokines stimulate the ACTH-cortisol axis.[1,2] The degree of rise in blood cortisol tends to reflect the severity of sepsis. In Rothwell and colleagues' report, total blood cortisol after stimulation shows no significant difference between survivors and non-survivors (1174 and 963 nmol/l, respectively). In our experience, the stimulation from already stimulated adrenal glands may result in a smaller difference between the basal concentration and the 30–60-minute concentration than expected for the short corticotropin stimulation test. In addition, we do not agree that a trial of steroid replacement in severe sepsis with physiological doses of cortisol might be of value because cortisol plasma concentrations are already high in severe sepsis, as Rothwell et al recognise.

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1. Michie HR, Manogue KR, Spriggs DR, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988; **318:** 1481–86.
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SIR,—Dr Rothwell and colleagues state that "relative" adrenocortical insufficiency may be observed often in patients with septic shock. However, in our opinion, their data do not support this conclusion.

The response of cortisol to corticotropin is known to be dependent on baseline cortisol concentrations. In patients with high basal concentrations, an attenuated response would be expected. 6 of the 13 reported patients with adrenocortical impairment had strikingly increased baseline cortisol concentrations up to above 1500 nmol/l, which reflected the severity of the underlying disorder. Lack of a cortisol response to corticotropin may be because the pituitary-adrenal axis is already maximally stimulated in these patients.

Rothwell et al do not comment on plasma ACTH concentrations in their patients. Adrenocortical impairment of whatever origin in a complex setting such as septic shock cannot be established without complete biochemical investigation of the pituitary-adrenal axis. Did patients with a poor response to corticotropin have higher ACTH concentrations than patients with a "normal" response? Since cortisol is bound to steroid binding globulin, did Rothwell et al exclude the possibility that low total serum concentrations of

cortisol in their patients were merely due to protein (steroid binding globulin) loss in the interstitial space as is common in septic shock? If protein loss were an important factor, free cortisol concentrations could have been normal.

Rothwell et al also suggest a relation between a low cortisol response to corticotropin and mortality. Was the poor cortisol response reproducible? Was corticotropin given in the same way in all patients (via a peripheral vein or a central line)? How was mortality defined? Furthermore, histopathological data on the adrenal cortex are not given. Did patients have adrenalitis, adrenal haemorrhage, adrenal necrosis, or normal adrenal histology? We believe that further data are required before a final conclusion can be drawn. We remain unconvinced that adrenocortical impairment is a major difficulty in patients with septic shock.

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SIR,—Absolute adrenal insufficiency in overwhelming infection is rare. The notion of absolute adrenal insufficiency as a cause of refractory shock is gradually being replaced by the idea of relative adrenal insufficiency.[1] Dr Rothwell and colleagues noted a clear stratification of stimulated cortisol release between survivors and non-survivors, although basal cortisol concentrations were similar.

We have studied the interaction between the hypothalamic-adrenal axis and phospholipase A2 in septic shock. Circulating phospholipase A2 (PLA2) has been implicated in the pathogenesis of cardiopulmonary changes in septic shock, and serum concentrations of PLA2 correlate with outcome.[2] Two glucocorticoid-suppressible cytokines, tumour necrosis factor and interleukin-1, are signals for PLA2 synthesis and extracellular release.[3] We measured ACTH, cortisol, and PLA2 concentrations in a prospective study of ten episodes of septic shock.[4] Serum cortisol concentrations in individual patients varied up to four-fold, although peak values were similar in survivors (mean [SD] 1397 [314] nmol/l, range 662–2480) and non-survivors (1232 [328] nmol/l, range 450–2320). There was a complete discordance between serum cortisol and ACTH concentrations in all patients, irrespective of outcome. However, serum cortisol and PLA2 values were concordant in all survivors ($r^2 > 0{\cdot}69$, $p < 0{\cdot}0001$), but were discordant in non-survivors ($r^2 = 0{\cdot}26$). These data, together with those of Rothwell et al, suggest that adrenocortical responsiveness, whether assessed by ACTH challenge or by concordance with serum PLA2, is an important prognostic determinant of septic shock.

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SIR,—Our experience is similar to that of Rothwell et al. However, their report does not mention whether glucocorticoid replacement was given to patients who were "adrenocortically deficient"; if so, were any improvements seen, and did those patients still have a poor final outcome? We found that replacement was associated with both haemodynamic and clinical improvement.[1] Other workers have reported similar findings to ours.[2,3]

We have also shown that a blunted adrenocortical response to corticotropin may take place in critically ill patients who do not have established sepsis, and that treatment with steroids is associated with an improved haemodynamic and clinical state.[4] Our findings suggest that adrenocortical deficiency is not specific to septicaemia but may also occur in critically ill patients with other disorders (Rothwell et al include one patient in their series with acute pancreatitis who may have been in this category). The cause of this effect is uncertain, but several inflammatory mediators such as tumour necrosis factor are implicated, although these cytokines are released in critically ill patients who are not septic.[5] Adrenal failure may be an under-recognised component of multiorgan failure in patients who are critically ill, and should be sought actively.

Rothwell et al noted that all patients who failed to increase their cortisol by at least 250 nmol/l died. This group includes cases with a wide range of basal cortisol concentrations. Although it is possible that those with high baseline cortisol concentrations are "relatively adrenocortically deficient", the more likely explanation is synthetic hyperactivity. Such a response probably does not merit adjunctive steroid therapy.

What does an impaired response to corticotropin mean? Is it a marker of poor outlook, or does it imply that adrenal synthetic function is impaired to a point where adverse effects result? Little information is available on adrenal activity in critically ill patients. Endogenous ACTH activity, delivery of ACTH to the adrenal cortex, synthetic function in the gland, hormone release and plasma binding, and cortisol breakdown are all factors that need to be accounted for before concluding that a blunted response to exogenous corticotropin implies adrenal exhaustion.

We agree that evidence exists to suggest that some crtitically ill patients may merit adjunctive corticosteroid therapy as assessed by the short 'Synacthen' test, but such benefits may have been obscured in large clinical trials in which high doses of steroid have been given irrespective of endogenous adrenal function.

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Painful clitoral tumescence during bromocriptine therapy

SIR,—Bromocriptine, a dopaminergic agonist, is used to suppress lactation and prolactin secretion. We report a woman who had clitoral tumescence during bromocriptine therapy.

A healthy woman, aged 28, was delivered of a normal male child after an uneventful pregnancy. She was given paracetamol (500 mg thrice daily on the day of delivery). Because she chose not to breast-feed, she was given bromocriptine (2·5 mg twice daily starting one day after delivery). Three days after treatment was begun she had painful episodes of clitoral tumescence, lasting a few minutes and arising about ten times a day when she was upright. These episodes were not related to sexual arousal but an overall increased libido was noticed. The patient temporarily discontinued bromocriptine and had no futher episodes. However, she was again given the drug for breast congestion and the episodes reappeared 1–2 h after dosing. Bromocriptine treatment was discontinued 19 days after delivery. The side-effects disappeared in the next few days. The patient denied previous similar episodes. No other side-effects were noted.

In an assessment by French workers of unexpected or toxic drug reactions, the role of bromocriptine was regarded as convincing.[1] We are not aware of other reports of clitoral tumescence as a side-effect of this drug. As seen in our patient, increased libido can be induced by levodopa[2] and dopaminergic agonists,[3] but not by single-dose treatment.[4] Dopaminergic agents induce erection, a central nervous system effect mediated by dopamine, oxytocin, and adrenocorticotropin hormone in animals and man.[4-6]