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. 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 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.

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 worldwide. Although interferon alpha is effective in about one-third of patients, 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 (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.

These data show that HBV-specific antisense oligodeoxynucleotides can block viral gene expression and replication. Inhibition of both human immunodeficiency virus infection and lymphoma growth 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 lypopolysaccharides that play an important part in endotoxin-mediated septic shock. It has been suggested that these cytokines stimulate the ACTH-cortisol axis. 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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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 adrenals, adrenal hemorrhage, adrenal necrosis, or normal adrenal histology? We believe that further data are required before a final conclusion can be drawn. We remain unconvincd that adrenocortical impairment is a major difficulty in patients with septic shock.

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 2 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 3 Two glucocorticoid-suppressible cytokines, tumour necrosis factor and interleukin-1, are signals for PLA2 synthesis and extracellular release.4 5 We have 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 (r²=0.69, p<0.0001), but were discordant in non-survivors (r²=0.26). 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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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 further episodes. However, she was again given the drug for breast congestion and the episodes reappeared 1-2 h after dosing. Bromocriptine was stopped after 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 levodopa2 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.5 6