other action of beta-blocking drugs in the lung. There is recent evidence to suggest that this may be the case.[4] The practical implication of this is that the allegedly greater safety of cardioselective beta-blockers in asthma may be based on a false premise. Hence, while I agree that on present evidence selective drugs are preferable to unselective ones, I do feel that great caution is required.

A possible alternative to a cardioselective beta-blocker in the treatment of hypertension in asthma is labetalol, an unselective beta-blocker with additional alpha-blocking properties. In a placebo-controlled comparison with propranolol this drug was shown to have no adverse bronchial effect in asthmatics.[5] Whether this makes it safer in clinical practice than pure beta-blockers is not clear—perhaps its apparent safety lies in the fact that it is rarely used in asthmatics.

Dr Raine and her colleagues describe near-fatal bronchoconstriction and refer to another near-fatal case. Fatal cases have in fact been reported.[6]

Finally, the acute effects we have so far been considering may not be the greatest danger to asthmatics with beta-blocking drugs. Previously mild asthma may become much worse and remain so long after the beta-blocker is stopped.[7]

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SIR,—The recent report by Dr June M Raine and others (14 February, p 548) of severe bronchospasm occurring in a known asthmatic with hypertension when treated with nadolol is a useful and timely reminder of the potential hazard of giving a beta-blocker to a patient with a previous history of obstructive airways disease—especially, as in this case, where hospitalisation has been necessary. Before prescribing any member of this extremely useful group of drugs the doctor should inquire carefully into any previous history of wheeze from any cause.

I am, however, somewhat perturbed by the inference that a so-called cardioselective agent may be considered "safe" in such patients, in case unwary doctors are given a false sense of security regarding cardioselectivity in relation to bronchospasm. There is considerable evidence that cardioselectivity among beta-receptor antagonists is not absolute but relative[1] and is dose dependent, selectivity being lost at plasma concentrations attained in some subjects with accepted therapeutic doses, particularly the high doses sometimes needed in patients with hypertension. A study reported by Formgren[2] comparing practolol and metoprolol (both selective) found that the forced expiratory volume in one second (FEV_1) was reduced by both drugs at the higher dose level (practolol 400 mg daily, metoprolol 200 mg daily), a third of the patients experiencing exacerbation of their asthma despite administration of a beta-agonist bronchodilator throughout the study.

The small degree of FEV_1 reduction with atenolol referred to in the paper and reported by Benson[3] was the FEV_1 assessed at rest. This is a somewhat unnatural state in view of the known variability of asthma, in which FEV_1 in a well-stabilised patient can suddenly dip under the stimulus of exercise or allergen insult. A better-designed study reported by Ruffin[4] assessed cardioselectivity using inhaled histamine bronchial provocation in asthmatics treated with propranolol, metoprolol, and timolol in equivalent doses and concluded that "there is no evidence to suggest that anyone of them is more cardioselective than the others," all producing reduction in FEV_1.

Despite the reported comparative safety of atenolol in airways obstruction, it must be borne in mind that a paper on the nature and incidence of unwanted effects with this drug[5] recorded the incidence of frequent bronchospasm as 5% and sporadic bronchospasm as 10% among 2600 patients, which should be compared with the incidence of 2% reported among 10 000 patients with the non-selective agent nadolol.[6]

The above references and others[7 8] emphasise, to my mind, that when an antihypertensive or antianginal agent is being chosen for patients with a history of airways obstruction, however mild, all beta-blocking agents should be avoided.

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Effect of antiepileptic drugs on the hypothalamic-pituitary axis

SIR,—We read with interest the article on pituitary responsiveness to gonadotrophin releasing and thyrotrophin-releasing hormones in children receiving phenobarbitone by Dr Antonio Masala and others (1 November, p 1175).

We have measured serum levels of prolactin, gonadotrophins, testosterone, and sex-hormone binding globulin (SHBG) in 79 epileptic patients (47 women and 32 men, age range 16-40 years) and compared the results with those of a group of 32 sex- and age-matched volunteers. All female patients were studied at the follicular stage of the menstrual cycle, and none was on the oral contraceptive pill. Twenty of the female patients were on monotherapy (10 carbamazepine, two phenytoin, two sodium valproate, three primidone, and one phenobarbitone). Twenty-eight patients (14 women and 14 men) were on primidone or phenobarbitone in combination with one of the above mentioned drugs. The majority of the patients had partial seizures with secondary generalisation. However, none of the patients had experienced an attack within 12 hours of the test.

Four samples of blood were obtained from each patient over a period of 90 minutes through an indwelling butterfly needle by the technique described by Jeffcoate.[1] Hormones were measured by radioimmunoassay using the standard techniques in this laboratory. Despite higher sex-hormone-binding globulin levels in both male and female patients testosterone levels remained normal. Luteinising hormone levels were significantly elevated in female patients, and there was a trend to an elevation in our male patients. These findings have been reported in full elsewhere.[2] Levels of luteinising and follicle-stimulating hormones and sex-hormone-binding globulin were also elevated in patients who were receiving primidone or phenobarbitone (table).

Our observation in adult patients differs from that of Dr Masala and colleagues, who showed that baseline luteinising and follicle-stimulating hormone levels were low in children receiving phenobarbitone as prophylaxis in febrile convulsions. It is possible that this difference may be explained by the fact that their patients were prepubertal children while ours were mature adults. It is likely that free sex hormone concentration was low in our patients, accounting for the elevated luteinising hormone levels from activation of the feedback mechanism. However, it is possible that antiepileptic drugs may influence the hypothalamus or pituitary directly, and it would be of interest to determine the responsiveness of the axis to gonadotrophin-releasing hormones in this group of patients. We are currently carrying out these studies.

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Mean levels of luteinising hormone (LH), follicle-stimulating hormone (FSH), sex-hormone-binding globulin (SHBG), and testosterone in patients receiving either phenobarbitone or primidone in addition to other antiepileptic drugs

	LH (U/l)	FSH (U/l)	SHBG (nmol/l)	Testosterone (nmol/l)
Male patients, n = 32	7·75 ± 2·7 (NR = 2·4–9·7)	2·05 ± 2·6 (NR = 0·8–5·7)	46·25 ± 19·2 (NR = 17–55)	26·3 ± 3·8 (NR = 10·4–38·2)
Female patients, n = 47	23 ± 28·6 (NR = 2·5–14·1)	5·7 ± 8·9 (NR = 1·2–11·1)	116·5 ± 24·7 (NR = 55–105)	2·5 ± 1·2 (NR = 0·5–2·1)
Male volunteers, n = 14	5·6 ± 2·2	2·5 ± 1·3	22·5 ± 3·8	24·5 ± 2·6
Female volunteers, n = 18	5·1 ± 2·2	2·8 ± 1·3	51·4 ± 16·3	1·8 ± 0·6

NR = normal range.
Conversion: SI to conventional units—SHBG (measured as dihydrotestosterone)—1 nmol/l ≈ 29 ng/100 ml: testosterone—1 nmol/l ≈ 28·8 ng/100 ml.

Double pathology as a cause of occult gastrointestinal blood loss

SIR,—The report "Double pathology as a cause of occult gastrointestinal blood loss" by Dr J W Riley and others (21 February, p 626) prompts me to make the following observations.

Case 1—In early 1974 a 60-year-old obese woman was admitted with recurrent upper and mid-abdominal pain, suggestive of peptic ulcer, and anaemia (haemoglobin 8 g/dl). There was no history of haematemesis or melaena. At gastroscopy I found a prepyloric ulcer which I thought was responsible for both pain and anaemia. Meanwhile, "in error" the house physician forgot to cancel the barium enema, which showed some filling defects in the caecum and which because of the indifferent bowel preparation I thought was due to faeces. Nevertheless, after blood transfusion,