Hormones, elderly testes, and carcinoma of the prostate

SIR,—There is growing evidence that male hormone action at the target site is not initiated by the circulating androgens but by products of the reductive and oxidative metabolism of these steroids in the responsive tissue. Recent work carried out in our laboratory on the estimation of the endogenous levels of testosterone, dihydrotestosterone, and androstenedione in the plasma and prostatic tissue of patients with benign prostatic hypertrophy and carcinoma of the prostate suggests that the pathological changes within the prostate gland may be the outcome of a number of biochemical factors manifested exclusively at the target organ level.

Although our studies did not reveal any significant differences in the plasma hormone levels of patients with either type of prostatic disease when compared with normal subjects of comparable age it was evident from the preliminary results (see table below) that the concentrations of testosterone and androstenedone were significantly greater in the malignant tissue than in the hypertrophied glands while those for dihydrotestosterone were considerably lower.

While the mechanism responsible for the pathological changes in the prostate gland remains unexplained, there is evidence that the progress of carcinoma of the prostate in some patients is hormone-dependent. However, in contrast to your leading article (5 July, p 2) and the subsequent letter from Mr F J Bramble and Dr H S Jacobs (2 August, p 307), our data suggest that tumours in the prostate gland are not associated with changes in levels of steroids in the peripheral pool but are associated with a decrease in the 5α-reductase activity in the prostate. This is evidenced by the low levels of dihydrotestosterone and the accumulation of testosterone demonstrated in the malignant tissues. Measurement of the various androgens in the plasma pool would appear unlikely to be of value either in the diagnosis of carcinoma of the prostate or in predicting the response to subsequent orchidectomy or hormonal therapy.

F K HABIB
S R STITCH

Division of Steroid Endocrinology,
University Department of Chemical Pathology,
Leeds

Ischaemic necrosis of lesser curve of stomach

SIR,—I have followed with interest the various recent reports of ischaemic necrosis of the lesser curve of the stomach after vagotomy. One accepts that the lesser curve has a relatively poorer blood supply than other parts of the stomach and that vagotomy reduces gastric mucosal blood flow (Dr J F Halvorsen and others, 14 June, p 590), but there may be additional factors; otherwise this complication might be expected to occur more frequently.

It is possible that the arteriae comites of the gastric branches of the vagus nerve may make a significant contribution to the blood supply of the lesser curve. In a personal study[1] of the blood supply of the intra-abdominal portion of the vagus nerve I was impressed by the size of the vasa nervorum, which, in stillborn infants at least, gave small twigs to the stomach's surface. These vessels were derived from the ascending oesophageal branches of the left gastric artery and turned downwards to accompany the vagus nerve back on to the stomach and therefore would be cut at vagotomy. Further, the coeliac artery and its branches are subject to variation and if the left gastric artery is small the ascending oesophageal branches are usually derived from the left phrenic artery.[2] Variations of this type would increase the risk of potential ischaemia and it would be interesting to know if any anomalies of the coeliac artery were present in the fatal cases reported.

PETER MOHR

Manchester Royal Infirmary,
Manchester

1 Mohr, P D, BSc Thesis, Manchester, 1967.
2 Michels, N A, *Blood Supply and Anatomy of the Upper Abdominal Organs*. London, Pitman, 1955.

Deaths in asthma

SIR,—In their letter on this subject (8 November, p 345) Dr W N Dodds and his colleagues stated that β_2-selective bronchodilators may have been used in greater quantities than isoprenaline in recent years, the inference being that the mortality figures favour salbutamol. While it is true that the prescription of salbutamol inhalers over the past five years has exceeded that of isoprenaline inhalers by some 25%, in terms of doses isoprenaline usage has appreciably surpassed that of salbutamol (most isoprenaline inhalers contain twice as many doses). There has thus been less use of salbutamol by inhalation over a period when the number of reported deaths associated with both agents has been equal.

This finding must throw considerable doubt on the hypothesis that cardiac stimulation from excessive doses of bronchodilator drugs has been the cause of increased mortality in asthma. I cannot accept the statement that all deaths reported to the Committee on Safety of Medicines were due to "cardiorespiratory failure with underlying ventricular arrhythmias." Since most deaths were probably unexpected it is unlikely that cardiac function was being monitored at the time. Furthermore, in hypoxic dogs both isoprenaline and salbutamol caused death in similar doses without evidence of arrhythmia; cardiac standstill was preceded by progressive bradycardia.[1] In the severely hypoxic asthmatic patient the pharmacological effect of these drugs on the heart is probably quite different from normal.

The fact that any correlation between deaths and usage of bronchodilator aerosols seems now to be independent of the drug administered supports the view that drug toxicity has not been the cause of death in most cases. It substantiates the statement by Inman[2] that we may be dealing with a paradoxical situation brought about by a highly effective rather than an intrinsically dangerous form of self-treatment. When a bronchodilator inhaler becomes ineffective airway obstruction is no longer due to reversible bronchospasm but to more sinister pathological changes. Almost all the necropsies reported by Speizer *et al*[3] revealed extensive mucus plugging of the airways. This is a potentially fatal condition which takes time to develop; it is delay in its recognition which leads to tragedy.

I would re-emphasise the advice given by all manufacturers of bronchodilator inhalers. It is imperative that patients be firmly warned to report immediately if their usual dose fails to give relief. This is one of the most valuable signs that there is deterioration requiring urgent intervention.

H E LEWIS
Medical Director,
Riker Laboratories
Loughborough, Leics

1 Shanks, R G, and Swanton, J G, *Proceedings of the European Society for Drug Toxicity*, 1971, 12, 147.
2 Inman, W H W, in *Proceedings of an Asthma Research Council Symposium, October 1973*, p 191. Trust for Education and Research in Therapeutics, 1974.
3 Speizer, F E, *et al*, *British Medical Journal*, 1968, 1, 339.

Lung cancer and chronic bronchitis

SIR,—Drs M Caplin and Freda Festenstein (8 November, p 348) let the cat out of the bag—and a cat that should not have been there in the first place. I was indeed under a misapprehension (11 October, p 100). I never imagined that in a study of the development of lung cancer in patients with chronic bronchitis (20 September, p 687) they would include patients who already had cancer at entry. If these are excluded, as they should be, the deaths from lung cancer in those with severe airways obstruction remains at none out of 76, and in those without it becomes six out of 152. (I assume that all five with cancer died.)

Mean hormonal concentrations (± standard error of mean) in plasma and prostatic tissue of patients with benign prostatic hypertrophy (BPH) and carcinoma of the prostate (CA) compared with normal subjects (10 in each group)

Group	Plasma			Tissue		
	Testosterone (nmol/l)	Dihydrotestosterone (nmol/l)	Androstenedione (nmol/l)	Testosterone (ng/g dry weight)	Dihydrotestosterone (ng/g dry weight)	Androstenedione (ng/g dry weight)
BPH	19·7±2·6	2·6±0·9	5·5±1·7	4·1±0·7	13·2±1·7	8·7±2·2
CA	16·9±2·8	2·4±0·5	4·4±1·1	11·5±1·8	6·8±0·7	12·2±2·3
N	17·2±2·9	2·4±0·6	—	4·6±1·1	4·8±0·9	—

Conversion: SI to traditional units—testosterone, dihydrotestosterone, and androstenedione: 1 nmol/l ≈ 0·29 ng/ml.