(which is usually in the right iliac fossa).

The point is not entirely academic or historical in its importance but has a truly practical application even today. The authority of your editorials is such that young surgeons and others reading your statement of "Murphy's triad" may be persuaded that the diagnosis of acute appendicitis can never be established or accepted when the patient has a normal temperature. They will then refrain from operating when operation without delay may indeed be very necessary.—I am, etc.,

ROBERT S. LAWSON

Melbourne, Australia

1 Murphy, J. B., *American Journal of the Medical Sciences*, 1904, **128**, 187.

Isoprenaline plus Phenylephrine in Chronic Obstructive Lung Disease

SIR,—Dr. L. H. Harris's results (5 December, p. 579) add considerably to the evidence already favouring the use of combined isoprenaline-phenylephrine preparations in relieving chronic obstructive lung disease.[1 2] In contrast, the inhalation of isoprenaline alone causes a number of unwanted cardiovascular effects. Besides the risk of hypoxaemia patients may experience ventricular irritability, and eventually arrhythmia. The "sudden and unexpected" deaths in asthma have been attributed to one or more of these cardiovascular effects.[3 4]

I have carried out a double-blind study on ten normal human subjects, using four aerosol preparations; isoprenaline, phenylephrine, the two together (Medihaler-Duo), and an inert placebo. Blood pressure and heart rate were measured before and after the four treatments. The mean results are given in the Table.

Phenylephrine administered simultaneously with isoprenaline appreciably reduces the effect on blood pressure and heart rate of isoprenaline alone. These results are compatible with those of Unger *et al.* obtained in a study on asthmatics.[1] As far as the present results can be extrapolated to the diseased state, the use of an alpha-receptor stimulant appears to reduce the unwanted and potentially dangerous effects of isoprenaline inhalation.

NEVILLE A. MARSH

Department of Physiology,
Queen Elizabeth College,
London W.8

1 Unger, D. L., Temple, D. E., and Unger, L., *Journal of Allergy*, 1968, **41**, 285.
2 Cohen, B. M., *Journal of the American Geriatrics Society*, 1968, **16**, 786.
3 Chapman, T. T., and Hughes, D. T., *British Medical Journal*, 1967, **2**, 639.
4 Speizer, F. E., Doll, R., and Heaf, P., *British Medical Journal*, 1968, **1**, 335.

Tumours of the Bladder

SIR,—The article by Mr. J. Cosbie Ross on management of bladder carcinoma (12 December, p. 661) is an object lesson in how to handle a difficult subject. His criticism of partial cystectomy is timely, and those of us who have had to deal with abdominal wall implants can support his contention that recovery from this is virtually unknown.

It is refreshing that a surgeon of Mr. Ross's stature should pay due tribute to the success of megavoltage therapy in infiltrating tumours of the bladder. Many surgeons will undoubtedly be surprised to learn that post megavoltage cystectomy, although technically difficult, is the most favourable cystectomy from the survival aspect. Surgeons are sometimes disheartened by initial technical failure, but with experience success is the rule. An excellent case can be made out for the referral of post megavoltage recurrences to a specialized unit, and in the Liverpool region this appears to be occurring.

Late complications following megavoltage therapy, such as intractable bleeding and contracted bladder, are becoming less common since the antibacterial agent noxytiolin became part of the planned management.[1] On the first three days of treatment this agent is instilled into the bladder and left in the viscus for at least one hour. Noxytiolin is also useful in inducing haemostatis when bleeding occurs as a late complication of megavoltage therapy. In tumours recurrent after radiotherapy I would not advise thiotepa, in view of the considerable risk of massive mucosal necrosis with secondary infection and intractable pain.—I am, etc.,

M. J. GARRETT

Liverpool Regional Radiotherapy Centre,
Clatterbridge Hospital West,
Wirral, Ches

1 Garrett, M. J., *British Journal of Clinical Practice*, 1969, **23**, 407.

Trachoma in Britain

SIR,—Over seven years ago you published a letter of mine (25 May, 1963, p. 1412) which suggested there might be a risk of trachoma appearing in this country through the medium of immigration. I suggested that this contagious eye disease should be notifiable. You were good enough following a confirmatory letter (22 June 1963, p. 1673) by Mr. Lionel M. Green, ophthalmologist to one of the large dock hospitals in the East End of London, to print an editorial in which you quoted the opinion of the World Health Organization on this matter (22 June 1963, p. 1626). The latter suggested that immigrants, if trachoma was still in the state of evolution (that is, usually in a young man or middle-aged person) should be given effective treatment. This is impossible, of course, without notification, as I suggested. You also pointed out that it would be difficult to assess whether trachoma constitutes an appreciable risk to public health unless the disease was made notifiable.

I am unaware of any action having been taken by either Government in this matter. My own assessment was that during the next five years there might be a few cases cropping up among children or adults. and that in the next five years small endemic sources might occur despite the high level of hygiene in the greater part of this island. In the light of the recent discovery of the presence of this disease in an active form reported in the newspapers as affecting thirteen British members of the staff at a 5-star, golfing hotel, may I be allowed to ask the Department of Health "what happens now?"—I am, etc.,

F. C. RODGER

Princess Margaret Hospital,
Swindon, Wilts.

Clonidine in Treatment of Hypertension

SIR,—The paper by Dr. A. Amery, and others (14 November, p. 392) on the treatment of hypertension with clonidine raises several pertinent questions as to its use in hypotensive therapy.

They have compared a centrally acting inhibitor of sympathetic activity, clonidine,[1] with a peripheral adrenergic-blocking drug, methyldopa, and achieved good results with both, although patients taking clonidine developed a greater incidence of undesirable side effects. The efficacy of methyldopa and a diuretic in the treatment of hypertension seems to be well established, and it is unlikely to be superseded by a drug having a greater incidence of side effects. Therefore the value of clinical trials would seem to be to evaluate whether a third drug, like clonidine, provides an additional advantage when used together with methyldopa and a diuretic.

We have treated 108 hypertensive patients with clonidine, in various combinations, over a period of two years. Thirty-five patients were treated with clonidine alone, 52 patients were treated with clonidine and a diuretic, and 54 patients were treated with clonidine, methyldopa,

	Placebo			Phenylephrine (240 µg)			Isoprenaline (160 µg)			Isoprenaline, 160 µg and Phenylephrine 240 µg		
	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change
Heart rate Beats/min. ..	79·7	76·0	−3·7	78·6	78·2	−0·4	77·3	94·9	+17·6	78·1	81·5	+3·4
Blood Pressure mm/Hg ..	105·3/67·3	101·9/66·4	−3·4/−0·9	102·2/67·2	103·9/68·0	+1·7/+0·8	103·2/68·1	112·6/55·5	+9·4/−12·6	104·4/68·5	108·4/61·1	+4·0/−7·4
Pulse Pressure mm/Hg ..	38·0	35·5	−2·5	35·0	35·9	+0·9	35·1	57·1	+22·0	35·9	47·3	+11·4

Results from ten subjects. Mean values before drug administration, taken from four steady state readings; mean values after drug, taken from the greatest change recorded.

and a diuretic. Some of these results have already been reported.[2] In the group taking clonidine and a diuretic, our results are in substantial agreement with those of Dr. Amery and colleagues, the major side effects being dryness of mouth and drowsiness. However in patients taking clonidine, methyldopa, and a diuretic, we achieved good control (standing systolic $\leqslant$ 150 mm Hg) in 44 out of 54 patients, while the incidence of side effects was reduced because lower doses were necessary when compared to the group taking clonidine with a diuretic.

These results indicate that the triple drug regimen allows good control of blood pressure with a minimum of side effects and its use would appear to be of some benefit especially in the irritable, nervous, hypertensive patient requiring some sedation.—We are, etc.,

A. EBRINGER
A. E. DOYLE
J. K. DAWBORN
C. I. JOHNSTON
M. L. MASHFORD

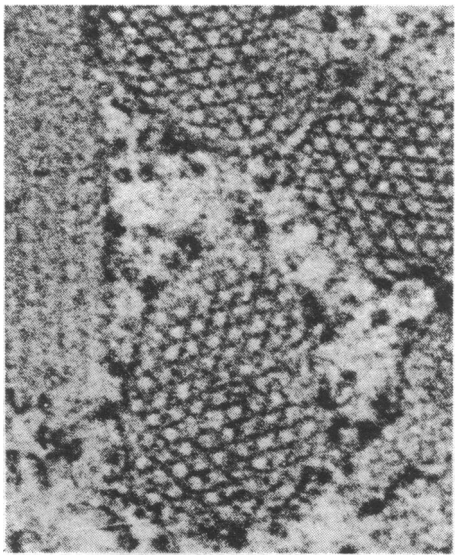
University of Melbourne Department of Medicine, Austin Hospital, Victoria, Australia

1 Rand, M. J., and Wilson, J., *European Journal of Pharmacology*, 1968, 3, 27.
2 Ebringer, A., Doyle, A. E., Dawborn, J. K., Johnston, C. I., and Mashford, M. L., *Medical Journal of Australia*, 1970, 1, 524.

Ulcer-related Antigens?

SIR,—Your leading article on the immunoglobulins (21 November, p. 445) and the paper by Dr. D. B. Kaufman and others (p. 463) deal with the particular situation of IgA produced in the salivary glands, bronchi, and intestine; the last is the more thoroughly investigated organ in this respect. We know that each square millimetre of intestinal mucosa contains 352,000 plasma cells making IgA; 51,000 cells that make IgM; 15,000 that make IgG; and 3,000 that make IgD.[1]

Studying with the electron microscope some histological preparations of duodenal ulcers taken at operation, I saw in addition to short, misshapen, and rarefied villi indicative of coeliac disease, plasma cells with the endoplasmic reticulum transformed into vesicles filled with proteinic matter with a periodical structure of about 200 A (Fig).[2]



Details of plasma cell in the duodenal mucosa of a patient with duodenal ulcer: vesicles of endoplasmic reticulum filled with proteinic matter with a periodical structure of about 200 A (× 107,215).

This finding suggests that the 200-A proteinic matter could be IgA, and I believe that these plasma cells might be the expression of a local autoimmune situation brought about by ulcer-related antigens. In other words, one might postulate a new type of autoimmunity, being eminently local and bound to local IgA produced by the plasma cells.—I am, etc.,

CARLO SIRTORI

Istituto Gaslini,
Genoa, Italy

1 Crabbé, P. A. and Heremans, J. F., *Intestinal Absorption and Malabsorption*, ed. D. H. Shmerling, H. Berger and A. X. Prader, p. 161, Basel, Karger, 1968.
2 Sirtori, C., *Gazzetta Sanitaria*, 1970, 41, 408.

Xanthinuria Discovered in Population Screening

SIR,—In a population health survey of Busselton, Western Australia,[1] a 54-year-old man was found to have a serum uric acid level of 0·3 mg/100 ml (by modified AutoAnalyzer N13b method). He is in good health and has no history of significant past illness or surgical operation. He has no siblings. His son aged 18 and daughter aged 16 had serum uric acid levels of 6·2 and 5·5 mg/100 ml respectively. There is no family history of renal stones.

Using the more specific method of Klinenberg *et al.*[2] the subject's plasma uric acid concentration subsequently was found to be 0·39 mg/100 ml and plasma xanthine plus hypoxanthine 0·31 mg/100 ml. Without dietary restriction his urine contained 80 mg uric acid and 482 mg xanthine plus hypoxanthine per 24 hour. He declined to submit himself to intestinal biopsy to provide tissue for xanthine oxidase assay, but we consider the chemical features establish this as a further case of xanthine oxidase deficiency to be added to the seven other well documented cases of this rare condition.—We are, etc.,

D. H. CURNOW
J. R. MASAREL
K. J. CULLEN
M. G. MCCALL

Busselton Population Studies Group,
University of Western Australia,
Perth, Western Australia

1 Curnow, D. H., Cullen, K. J., McCall, M. G., Stenhouse, N. S. and Welborn, T. A., *Australian Journal of Science*, 1969, 31, 281.
2 Klinenberg, J. R., Goldfinger, S., Bradley, K. H. and Seegmiller, J. E., *Clinical Chemistry*, 1967, 13, 834.

Renal Failure and Contrast Media

SIR,—We read with interest the article by Dr. J. McEvoy and others on renal failure after radiological contrast media (19 December, p. 717). We regret that the authors chose to speculate freely on the hazards of excretion urography from their experience of renal failure after renal arteriography and intravenous cholangiography. Such a practice has already accounted for much of the confusion regarding the dangers of excretion urography. It is quite unacceptable to compare selective angiography with excretion urography, the concentration of contrast medium delivered to the small renal vessels being totally different.

Despite the fact that none of their patients showed any adverse reaction to urography, the authors emphasized the potential danger of high-dose urography in patients with renal failure. Many workers including ourselves have experience of this valuable technique, and there are numerous reports showing no ill effects using modern contrast media provided dehydration is avoided.[1] A recent careful study of renal and hepatic function before and after high-dose urography in patients with impairment of renal and/or hepatic function from four centres in the United States revealed no evidence of nephrotoxicity or hepatic damage due to the contrast media.[2]

It is unfortunate also that no details were given of the doses of contrast media used for the renal arteriographic studies or of the clinical status of the patients during and following the investigation. Before ascribing nephrotoxicity to contrast media alternative causal factors must be excluded. Thus no comment was made on the possible importance of a surgical operation in the genesis of the renal failure in Case 2.

No contrast examination is, however, completely free of hazard, particularly in sick patients, and we would entirely support the authors' plea that "the possibility of adverse side effects in any diagnostic procedure must be weighed against the usefulness of the information it may provide."—We are, etc.,

I. KELSEY FRY
W. R. CATTELL

Department of Diagnostic Radiology,
St. Bartholomew's Hospital,
London E.C.1

1 Fry, I. K., and Cattell, W. R., *British Journal of Hospital Medicine*, 1970, 3, 67.
2 Davidson, A. J., Becker, J., Rothfield, N., Unger, G., and Ploch, D. R., *Radiology*, 1970, 97, 249.

Living it up with Concorde

SIR,—Dr. I. C. Perry (12 December, p. 685) suggests that a visit to any aviation medicine library would satisfy those correspondents, including myself, who query whether safety in the air could be compromised by disturbances in circadian rhythms of air crew.

May I respectfully dissent from this view. The investigations which I and my colleagues in Manchester have made, and the work of many other investigators which we have reviewed, indicates that marked disturbances in circadian rhythms, both physiological and psychological, occur after flights across a series of time zones.[1] I know of no evidence which would suggest that pilots are in some way exempt from these effects, or that crew rosters are at present so arranged as to completely exclude them.—I am, etc.,

RICHARD CONROY

Department of Physiology,
Royal College of Surgeons in Ireland,
Dublin 2

1 Conroy, R. T. W. L., and Mills, J. N., *Human Circadian Rhythms*, London, Churchill, 1970.