therapy and regular prophylactic disodium cromoglycate fail to control the asthma, then steroid therapy in one form or another should be considered. Later you state that systemic steroids should be confined to the rare patient whose asthma is not controlled with steroid inhalers or the small child who cannot use them.

No mention is made of other forms of management. The role of the house-dust mite has received considerable attention¹⁻³ and valuable results for measures to counteract the mite have recently been claimed by Sarsfield *et al.*⁴ The value of desensitization procedures remains a subject for debate but should not be overlooked.

There is an appreciable quantity of evidence demonstrating that removal of the child from the frequently stressful home environment has a beneficial effect on its asthma,^{5,6} and even removal of the parents, leaving the child at home, can lead to a remission of asthma in children in whom stress factors are important.^{7,8} Undercurrents of tension exist in any family. Pinkerton⁹ states that resolving these undercurrents could represent a first step in successfully reversing an otherwise progressive and cumulative sequence of aetiology. Liebman *et al.*¹⁰ describe the successful treatment of seven children with severe intractable asthma using family therapy techniques. Many other authors¹¹⁻¹⁴ have reported on the value of psychological methods of treatment for asthmatic children.

Asthma can be a severely handicapping and potentially fatal disease. As such we cannot afford to overlook treatments other than with drugs. I wish to suggest that in the refractory case or when the child fails to respond to conventional therapy other than steroids a full psychological assessment be made and treatment instituted where appropriate. As Pinkerton has stated, "family tensions operate in the most unsuspected cases and are not always easy to identify." The role of psychological intervention should never be discounted, however unlikely the superficial indications.—I am, etc.,

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"Impossible" Serum Gentamicin Levels

SIR,—A 33-year-old man with staphylococcal endocarditis who received cloxacillin and gentamicin by slow intermittent intravenous infusion for 10 days was found to have a

serum gentamicin level of 15 mg/l 11 hours after a dose of 80 mg. The level fell to 2 mg/l at 24 hours. The dose was reduced to 40 mg every 12 hours and 11 hours after the third dose the serum gentamicin level was 10 mg/l. Gentamicin was discontinued. His body weight was 78 kg and his blood urea varied between 9.9-13.2 mmol/l (60-80 mg/100 ml).

Four days later 80 mg of gentamicin was administered intravenously over 50 minutes. Five minutes after the injection was completed the blood level was 0.7 mg/l, but samples taken 1½, 3½, 6½, and 24 hours later apparently contained 16, 32.8, 15.25, and 2.6 mg/l respectively. Assays had been done by the agar-cup method with a *Klebsiella*. They were repeated with β -lactamase added to the serum. Professor J. Landon and Dr. Elizabeth Shaw are developing a radio-immune assay and kindly assayed these specimens. They have found that their results normally show only about half the gentamicin level expected and their results with our sera were approximately half those obtained by our diffusion method.

No explanation has been found for the high concentrations of gentamicin in this patient's serum. A level of 10 mg/l 11 hours after a dose of 40 mg seemed highly improbable: a level of 32.8 mg/l after a single dose of 80 mg is mathematically impossible. Similarly a peak blood level should occur immediately after an intravenous dose and not rise steadily after it has been completed.

Three explanations were considered. Firstly, that the activity of the gentamicin was being enhanced by some other drug the patient was receiving. No evidence was found to support this and the treatment given was common to all similar patients. No evidence was found of self-medication by the patient, and indeed it is difficult to see what else could be inhibiting the resistant *Klebsiella*. Lastly, Dr. J. W. Lightbown suggested that the rising levels might be due to the production of a metabolite with greater antibacterial activity than gentamicin itself.

We should be interested to hear of any other observations of this kind and in any further suggestions for an explanation.—We are, etc.,

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Hypotensive Treatment for Acute Myocardial Infarction

SIR,—Your leading article (15 February, p. 353) on recent observations relating to myocardial salvage by lowering the blood pressure following coronary occlusion will undoubtedly stimulate much interest in Britain. As early as 1970 it was suggested, on the basis of the low mortality among patients with myocardial infarction seen and treated early by the mobile coronary care unit operating from this hospital, that the haemodynamic state might influence the final quantity of tissue necrosis.¹

Though the apparent benefit from lowering the arterial pressure was demonstrated in patients who were hypertensive, it is suggested that the treatment may also be of

value in normotensive patients. Your article correctly emphasizes the dependence of coronary blood flow on the arterial pressure. I consider that this form of therapy should not be entitled "hypotensive treatment." This title is misleading and may induce those who have little understanding of the mechanisms involved to produce hypotension when it is likely to be harmful and to leave hypotension untreated when its correction is required. The benefits of reduction in left ventricular diastolic pressure in the experimental situation have been shown to be enhanced if the actual hypotensive effect of the therapy is prevented.²

The term "diastolic unloading of the left ventricle" would project more accurately the rationale of therapy and I suggest that this title should be adopted before hypotension gains a double-edged foothold in the management of our patients.—I am, etc.,

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- 1 Pantridge, J. F., *Quarterly Journal of Medicine*, 1970, 39, 621.
- 2 Epstein, S. E., *et al.*, *Annals of Internal Medicine*, 1973, 78, 918.

SIR,—I was interested in your leading article (15 February, p. 353) on the use of hypotensive treatment with trimetaphan for acute myocardial infarction, particularly as I am one of many anaesthetists who have discarded this agent and changed to sodium nitroprusside for hypotensive anaesthesia.

Sodium nitroprusside acts by directly inhibiting vascular smooth muscle but has no effect on myocardial contractility. It was recently used for 30 hours to improve cardiac output after mitral valve replacement¹ and I have used it for 16 hours on a vasodilator in the management of a case of septic shock. As it has the advantage over ganglion-blocking agents of acting directly on vascular smooth muscle it therefore overcomes the effects of circulating catecholamines or any other substance which may increase vascular tone by direct action. Its short duration of action contrasts with the prolonged effect of phenoxybenzamine and permits a high degree of control of peripheral vascular resistance. Hydroxocobalamin was given to my patient to prevent acidosis due to accumulation of derivatives of nitroprusside. The dose range used (60-90 mg/h) was such that this might have been an unnecessary precaution.

I hope that the clinicians using vasodilators for acute circulatory problems will review the evaluation of agents used by anaesthetists for induced hypotension.—I am, etc.,

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- 1 Brown, D. R., and Starek, P., *Anaesthesiology*, 1974, 41, 521.

Seasonal Variations in Urinary Excretion of Calcium

SIR,—By studying 410 healthy individuals and 385 renal stone formers on a free diet Dr. W. G. Robertson and his colleagues (23 November, p. 436) were able to demonstrate noticeable seasonal variations in the daily

urinary excretion of calcium even when differences in glomerular filtration rates were disregarded. As possible explanations for their observation of maximum excretion during the period May-September, with a zenith in July or August, they mentioned changes in dietary calcium intake and the seasonal variations which the serum level of 25-hydroxycholecalciferol (25-OHCC) is known to undergo, or possibly a combination of both, since the zenith of serum 25-OHCC occurs later than that of the urinary calcium excretion.

We have studied the same problem by performing simultaneous determinations of the 24-hour urinary calcium excretion and the 24-hour clearance of creatinine in 26 healthy volunteers taking a standard diet. The estimated contents of this diet were 800 mg of calcium, 900-1100 mg of phosphorus, and 60-140 mmol (mEq) of sodium per day and 1 g of protein per kg body weight per day. There were 17 male subjects aged 21-29 (average 24) years and nine females aged 20-54 (average 34) years. Twelve, including five females, were studied from May to September inclusive and 14 (four females) from October to April inclusive. Assessment was undertaken as well of the 24-hour urinary calcium excretion, both uncorrected (UCaV (mg/24 h)), and corrected for variations in the clearance of creatinine (Ccr (ml/min)) according to the formula $(UCaV \times 100)/Ccr$. The importance of relating UCaV to Ccr in one way or another has been stressed repeatedly.¹⁻⁴ As evaluated by Student's *t* test the clearance-corrected excretion was found to be significantly higher during summer, the mean ($\pm$ S.D.) being 225 ± 61 mg/24 h as against 165 ± 37 mg/24 h during the winter ($t = 3.115$, $P < 0.01$). The figures for uncorrected excretion were 230 ± 66 mg/24 h and 199 ± 47 mg/24 h respectively ($t = 1.404$, $P > 0.10$). Despite the small number of observations the monthly averages displayed a pattern (see fig.) very similar to that so nicely presented by Dr. Robertson and his colleagues.

This pattern was recognizable even when males and females were considered separately.

Our observations indicate that seasonal variations in the daily urinary excretion of

calcium may take place independently of dietary changes.—We are, etc.,

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- 1 Nordin, B. E. C., Hodgkinson, A., and Peacock, M., *Clinical Orthopedics*, 1967, 52, 293.
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Liver Flukes: a Warning

SIR,—I would like to correct a point in Dr. A. T. Hunt's letter (1 March, p. 510) dealing with liver flukes. The Tidenham epidemic¹ in fact occurred in the winter of 1968-9 and not in June 1972 as he states.—I am, etc.,

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- 1 Hardman, E. W., Jones, R. L. H. and Davies, A. H., *British Medical Journal*, 1970, 3, 502.

** The mistake was ours, not Dr. Hunt's, and was inadvertently introduced in transferring a reference from the text to the foot of his letter. The relevant passage should have read: "In my description of the Tidenham epidemic, published in June 1972. . . ." We apologize for any misunderstanding that this may have caused.—ED., B.M.J.

Schistosome Antigen in Transplanted Kidney

SIR,—I was enlightened to read of the demonstration of circulating soluble antigens and antibody in schistosomiasis by Drs. M. A. Madwar and A. Voller (22 February, p. 435). I have recently treated a patient with a long history of schistosomiasis (*Schistosoma mansoni*), nephrotic syndrome, and ultimate renal failure. Renal biopsy and nephrectomy studies revealed the glomerular hallmarks of immune-complex nephropathy. The patient received a renal transplant and subsequently underwent antischistosome therapy with niridazole. He developed a transient "one-shot" immune complex nephritis. With the use of specific anti-schistosomal adult worm antiserum the antigen was revealed in the glomerular mesangium of the transplant biopsy. Thus that "prerequisite for immune-complex disease" has been found in the kidney. These studies will soon be reported in full elsewhere.—I am, etc.,

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Abuse of Fenfluramine

SIR,—Fenfluramine has been considered to be not a drug of abuse, because of initial unpleasant side effects.¹ Hawks² found no evidence of its abuse among addicts asso-

ciated with the addiction research unit. Götestam and Gunne³ showed that amphetamine-dependent subjects had no preference for fenfluramine against placebo. However, Levin⁴ described 60 drug-dependent young males who claimed to have used fenfluramine as a drug of abuse. Euphoria, derealization, and perceptual changes were reported effects. I wish to report a case of fenfluramine abuse.

The patient, a 28-year-old woman, was referred because she had been forging prescriptions for fenfluramine for the past six months. She had begun taking fenfluramine four years previously when her weight was about 170 lb (77 kg) and her height 5 ft 5 in (1.62 m). Initially she noticed nausea, vomiting, dizziness, and drowsiness on dosages of 80 mg a day. Weight loss was quite rapid, and for the past year she had remained at about 115 lb (52 kg). Her longest period of abstinence was six months. In the past seven months while taking on average 240 mg of fenfluramine daily she had noticed feelings of euphoria, excess energy, and little need for sleep. There was increased appetite and libido. There were no obsessional-compulsive symptoms. She found alcohol potentiated the effect of fenfluramine-induced euphoria. During this seven-month period she noticed increasing tolerance to the dosage. She had forged prescriptions on three or four occasions. She did not appear to have been abusing any other drug.

The patient's desire to lose weight was sufficient to overcome the initial unpleasant side effects. This pattern has been observed with more classical drugs of abuse—for example, morphine. There is little reference in the literature to the very obvious stimulant effect of fenfluramine found in this case.—I am, etc.,

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- 1 Oswald, I., et al., *British Medical Journal*, 1971, 3, 70.
- 2 Hawks, D. V., *British Medical Journal*, 1970, 1, 238.
- 3 Götestam, K. G., and Gunne, L. M., *British Journal of Addiction*, 1972, 67, 39.
- 4 Levin, A., *British Medical Journal*, 1973, 2, 49.

Serum Muramidase Activity in Untreated Cancer

SIR,—We read with interest the paper by Professor E. H. Cooper and others (14 September, p. 662) on raised serum muramidase levels in colorectal cancer. They consider that the raised muramidase activity results from stimulation of the reticuloendothelial system. It is accepted, however, that muramidase is mostly derived from disintegrating granulocytes and that serum muramidase levels are an index of granulocyte destruction.^{1,2} When granulocyte production equals destruction muramidase levels are also an index of granulocyte bone marrow production,¹ and they have been used for monitoring recovery of granulopoiesis in patients with neutropenia.^{2,4} The results, however, were unreliable in patients with fever and bacterial infection,² since in cases of bacterial infection serum muramidase levels are raised owing to increased destruction.^{2,5}

We measured by the turbidometric method of Litwack⁶ the serum muramidase levels in 120 patients with various untreated malignant tumours, including 20 cases of colorectal cancer, and compared them with the levels in 50 controls. All were within the normal range and there was no significant difference between the patients and the controls. This agrees with the findings of Jollès et al.⁷ Our patients with colorectal