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Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Letters should not exceed 400 words and should be typed double spaced and signed by all authors, who should include their main degree.

Wasting blood

SIR,—May we suggest that recent reports of transmission of the acquired immune deficiency syndrome virus by blood transfusion should cause a reappraisal of transfusion practice in the United Kingdom. The transfusion of a single unit of blood can rarely if ever be justified and closer attention needs to be paid to the balance of risks and benefits.

In a study which we undertook of the transfusion practice of UK anaesthetists it was apparent that 10 g/dl of haemoglobin was regarded by most anaesthetists as the level below which preoperative measures to raise the haemoglobin level were indicated. We believe that by adopting 8 g/dl as a lower acceptable level for patients undergoing major surgery we could reduce the requirements for blood transfusion considerably, thus minimising the associated risks to patients.¹ For patients undergoing short operative procedures with little risk of haemorrhage even lower haemoglobin levels could be accepted provided the patient was otherwise fit.²

Several papers have recently shown that for most operations blood loss can be reasonably predicted, and the modern anaesthetist should be able to plan intraoperative transfusion regimens which protect the patient from

the dangers of haemorrhage and also avoid unnecessary transfusion.³

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- 1 Pineda AA, Braica GM, Taswell HF. Haemolytic transfusion reaction, recent experience in a large blood bank. *Mayo Clin Proc* 1978;**53**:378.
- 2 Graves CL, Allan RM. Anaesthesia in the presence of severe anaemia. *Rocky Mountain Medical Journal* 1970;**67**:35.
- 3 Stehling LC. Guidelines for ordering blood for elective surgery. *Int Anesthesiol Clin* 1982;**21**:45.

Noradrenaline: a circulating inhibitor of sodium transport

SIR,—Mr A Riozzi and coworkers (20 October, p 1025) describe a noradrenaline mediated, dose dependent reduction of leucocyte sodium efflux rate constant which was due to decrease in ouabain sensitive sodium pump activity. They also report that this effect was blocked by propranolol, suggesting that it was mediated by β adrenoceptors. Furthermore, they suggest a possible circulating inhibitory role for catecholamines on sodium transport.

Using mixed human leucocytes we showed a stimulatory effect of adrenaline (9 nmol/l) on both rubidium (equivalent to potassium) influx and sodium efflux and that this was mediated by β_2 adrenoceptors. We were unable to show any such effects using fresh noradrenaline (10-300 nmol/l).² Our findings are compatible with the known effects of adrenaline infusion, which causes hypokalaemia in vivo, without increased urinary potassium loss, presumably by moving potassium into cells^{3,4}; noradrenaline infusion does not affect plasma potassium concentration.⁵

Leucocytes are thought to possess β_2 adrenoceptors but not β_1 adrenoceptors,⁶ and noradrenaline is also known to act principally on α_1 , α_2 , and β_1 adrenoceptors.⁷ Consequently, it would be surprising to observe any mediated effects of noradrenaline on human leucocytes. Studies using adrenergic challenge in man have supported the contention that the relation between the sodium pump—that is, Na^+ , K^+ -ATPase—and catecholamines is mediated through β_2 adrenoceptors.⁸

The discrepancies between our results and those of Mr Riozzi and others are likely to be caused by differences in the experimental models. They exposed leucocytes, in serum, to noradrenaline for 10 minutes during loading

of cells with ^{22}Na , washed them, and after resuspending the cells in serum measured sodium efflux rate constants while noradrenaline was no longer present. In contrast, we used Ringer-phosphate-bicarbonate-buffer (pH 7.6), not serum, and adrenaline or noradrenaline was present while the flux rates were measured. Possibly the serum preparations became more alkaline during the experiment (no evidence was presented), since on standing serum becomes considerably more alkaline within 30 minutes, even at 25°C . We have shown that pH significantly affects Na^{+} , K^{+} -ATPase activity,⁹ and it is therefore important that flux rates are measured at constant pH in all experiments. Moreover, Na^{+} , K^{+} -ATPase activity is affected by changing the concentration of sodium, potassium, and magnesium, and it would be more difficult to ensure the same concentration of all these substances in all experiments if serum (and not buffer) is used. Serum also contains many substances that may affect leucocyte ion flux, alone or in synergism with catecholamines, such as triiodothyronine (Khan and Baron, in preparation).

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- 1 Bradlaugh R, Riozzi A, Heagerty AM, Bing RF, Swales JD, Thurston H. Inhibition of sodium pump activity by physiological doses of noradrenaline in human leucocytes and rat aortae. *Clin Sci* 1984;67:41.
- 2 Baron DN, Green RJ, Khan FA. Adrenaline and ion flux in isolated human leucocytes. *Clin Sci* (in press).
- 3 Brown MJ, Brown DC, Murphy MB. Hypokalaemia from β_2 -receptor stimulation by circulating epinephrine. *N Engl J Med* 1983;309:1414-9.
- 4 Struthers AD, Reid JL, Whitesmith R, Rodger JC. Effect of intravenous adrenaline on electrocardiogram, blood pressure and serum potassium. *Br Heart J* 1983;49:90-3.
- 5 Ball SG, Berkin KE, Inglis GC. Hypokalaemia from β_2 -receptor stimulation by epinephrine. *N Engl J Med* 1984;310:1330.
- 6 Motulsky HJ, Insel PA. Adrenergic receptors in man. Direct identification, physiological regulation, and clinical alterations. *N Engl J Med* 1982;307:18-29.
- 7 Van Zwieten PA, Timmermans PBMWM. The sub-classification of α -adrenoceptors. *Research and Clinical Forums* 1983;5(2):27-34.
- 8 Smith SR, Kendall MJ. Metabolic responses to β_2 -agonists. *J R Coll Physicians Lond* 1984;18:190-4.
- 9 Baron DN, Khan FA. Optimal conditions for measurement of Na^{+} , K^{+} -ATPase of human leucocytes. *Clin Sci* (in press).

*Dr Riozzi and others reply below.—ED, BMJ.

SIR,—We would agree with Professor Baron and colleagues that the apparent discrepancy between the results of their experiments and ours is probably attributable to differences in experimental method. Like them, we cannot produce consistent effects with noradrenaline in the leucocyte using synthetic media. This is true of other cells. For example, exposure of erythrocytes to 8 nM noradrenaline in buffer revealed no effects (ouabain sensitive efflux rate constant 0.14 (0.03) v 0.14 (0.01)/h with noradrenaline). Repeating the experiments in plasma, however, gave similar findings to our report on leucocytes (ouabain sensitive efflux rate constant 0.2 (0.01) v 0.16 (0.02)/h with noradrenaline; $p < 0.05$). The results cannot be explained by pH changes occurring during the incubation period because control experiments were performed simultaneously, and the addition

of noradrenaline to plasma did not affect pH when compared with control without noradrenaline.

It would be surprising to explain our report by an effect of noradrenaline on β_2 adrenoceptors, in view of the much greater affinity of adrenaline for such receptors.¹ In our studies abolition of noradrenaline-induced inhibition of the sodium pump could be achieved only with a high concentration of propranolol. Nevertheless, catecholamines have been shown to depress the sodium pump in cardiac and aortic muscle,²⁻⁴ although the mechanism remains to be fully elucidated. These effects are clearly tissue specific, since, as Professor Baron and colleagues point out in other tissues, stimulation of Na^{+} , K^{+} -ATPase may occur. The fact remains that physiological concentrations of plasma catecholamines appear to influence profoundly leucocyte and erythrocyte sodium transport, two tissues widely studied in experiments on cation handling in hypertension. In view of these findings correct interpretation of such experiments will have to take into account the possible influence of catecholamines.

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- 1 Brown MJ, Brown DC, Murphy MB. Hypokalaemia from β_2 -receptor stimulation by circulating epinephrine. *N Engl J Med* 1983;309:1414-9.
- 2 Struthers AD, Davies DL, Harland D, Quigley C, Brown MJ. Adrenaline causes potassium influx in skeletal muscle but potassium efflux from cardiac muscle. *Clin Sci* 1984;67:75.
- 3 Bradlaugh R, Riozzi A, Heagerty AM, Bing RF, Swales JD, Thurston H. Inhibition of sodium pump activity by physiological doses of noradrenaline in human leucocytes and rat aortae. *Clin Sci* 1984;67:41.
- 4 Buckler KJ, Bhattacharya SS, Flear CTG. Actions of catecholamines and betablockers on Na^{+} pump activity in heart and skeletal muscle. *Clin Sci* 1982;63:381.

SIR,—Dr A Riozzi and others reported that noradrenaline inhibits ouabain sensitive sodium efflux from normal leucocytes. As part of a systematic study of the action of various compounds on membrane ion transport we have also examined the effect of some adrenoceptor agonists and antagonists on erythrocyte and leucocyte sodium efflux. In these studies normal red cells were washed and loaded with ^{22}Na under physiological conditions as described elsewhere¹ and incubated in 0.005 M glycine-imidazole buffer containing 0.15 M saline and one of the following: isoprenaline (10 nmol/l), noradrenaline (10 and 25 nmol/l), phenylephrine (10 nmol/l), propranolol (1 $\mu\text{mol/l}$), and both noradrenaline (10 nmol/l) and propranolol. Sodium efflux was measured as the appearance of radioactivity in the supernatant fluid. First order efflux rate constants for sodium were 0.31/h for the control sample and 0.31, 0.30, 0.34, 0.32, 0.35, and 0.31/h for samples incubated with the above compounds, respectively. Thus no effect of α or β adrenoceptor agonists or blockers on erythrocyte sodium efflux was found.

A corresponding result was obtained in leucocytes prepared similarly to those of Dr Riozzi and his colleagues, though in this case

only the effect of noradrenaline (10 and 100 nmol/l) was studied. Efflux rate constants for the control and noradrenaline containing samples were less than those reported by Dr Riozzi and colleagues but again no effect of noradrenaline was observed. Values obtained were 0.86 (control), 0.85 (10 nmol/l noradrenaline), and 0.81/h (100 nmol/l noradrenaline). The small reduction noted at 100 nmol/l noradrenaline is unlikely to be of physiological significance. A sample containing ouabain (1 mmol/l) gave a value of 0.51/h.

The possibility raised by the authors that noradrenaline may interact differently with patients' cells and thereby produce or exaggerate abnormal sodium transport was studied in a patient with untreated essential hypertension (lying blood pressure 200/107 mm Hg) and one with borderline hypertension (147/87 mm Hg), also untreated. First order rate constants for red cell sodium efflux were 0.31 (control), 0.33 (noradrenaline 10 nmol/l) and 0.09 (ouabain 1 mmol/l)/h respectively in the first patient and 0.33, 0.34, and 0.09/h in the second.

Our conclusion from these studies, in contrast to that of Dr Riozzi and others, is that noradrenaline has no effect on erythrocyte or leucocyte sodium transport in either normal or hypertensive subjects.

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- 1 Millar JA, Bramley PM, Paulin JM, Simpson FO. Evidence against a circulating ouabain-like inhibitor as a cause of increased red cell sodium in essential hypertension. *Journal of Hypertension* (in press.)

Lymphocytes are rhythmic: is this important?

SIR,—Drs Martin S Knapp and Roy Pownall (17 November, p 1328) highlighted the possible implications of the diurnal variation in T cell subsets in normal subjects. We studied variation in T cell subsets over 12 months in 30 atopic subjects with hay fever.

Subjects were defined using OKT3, OKT4, and OKT8 monoclonal antibodies in July-August 1983, February-April 1984, and July-August 1984. All blood samples were taken between 0900 and 1200 and prepared the same day. Two hundred cells were counted under a microscope using phase contrast and ultraviolet light. The mean OKT4:OKT8 ratios were significantly higher in the summer months (see table) than our laboratory control of 1.41 (SD 0.35) ($p < 0.05$) and this was due to a significantly reduced OKT8 subset ($p < 0.01$). A reduction in the OKT4:OKT8 ratio was noted in the winter, due to a significant increase in the OKT8 subset ($p < 0.01$).

As far as we are aware seasonal variation in the OKT4:OKT8 ratio has not been described, and its mechanism is obscure. Fc-IgG surface receptors on T cells, expressing a suppressor population (T_γ

Seasonal variation in T cell subsets in hay fever sufferers. Results are mean percentages (SD) of total number of lymphocytes

	Summer '83	Winter '84	Summer '84
OKT3	62.2 (9.5)	65.7 (12.8)	61.2 (12.2)
OKT4	43.8 (9.2)	46 (9.8)	42.9 (7.8)
OKT8	24.7 (8.5)**	31.9 (11.8)	25.1 (7)**
OKT4:OKT8	1.94 (0.81)*	1.56 (0.64)	1.87 (0.67)*

* $p < 0.05$; ** $p < 0.01$. Significance values comparing values in summer '83 and '84 with those in winter '84.