Bezold-Jarisch reflex⁶ and help to explain the findings of this paper.

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Sulphinpyrazone in acute myocardial infarction

SIR,—The administration of sulphinpyrazone early after myocardial infarction was recently shown by Dr R G Wilcox and others (23 August, p 531) to be accompanied by a significant elevation of serum creatinine and urea. Moreover some of us had reported on four cases of acute renal failure within the first days after starting sulphinpyrazone therapy in patients with a recent myocardial infarction.¹

The mechanism of this renal functional deterioration has to be clarified. Little evidence supports the hypotheses of intratubular urate precipitation or of an immunologically induced interstitial nephritis. We propose that sulphinpyrazone impairs renal function by inhibiting synthesis of prostaglandins in the kidney, as it does in platelets.²

To test this hypothesis, we compared the effect of sulphinpyrazone and of indomethacin—a well-known inhibitor of prostaglandin synthesis—on the urinary excretions of prostaglandins E₂ (PGE₂) and F_{2α} (PGF_{2α}), which reflect the renal synthesis of PGE₂ and PGF_{2α}.³ Four healthy male volunteers with normal dietary salt intake collected their 24-hour urine during 10 consecutive days. Four doses of sulphinpyrazone 200 mg were taken on days 3 and 4 and three doses of indomethacin 50 mg on days 9 and 10; other days served as controls. Other medications, smoking, and sexual activity were withheld. Urinary PGE₂ and PGF_{2α} were measured by radioimmunoassay, as previously described.⁵ When compared with the mean of the values obtained during the two days preceding the drug therapies, the mean urinary PGE₂ concentration significantly decreased on the two days of sulphinpyrazone as well as of indomethacin therapy (see accompanying table). Both drugs produced a comparable effect on the urinary PGE₂. On the other hand, the mean urinary PGF_{2α} did not change under sulphinpyrazone therapy, but it was significantly reduced under indomethacin treatment. Neither drug produced a significant change in creatinine clearance; while sulphinpyrazone produced, as expected, an increase in the urate clearance.

The different handling of renal PGF_{2α} by the two drugs is not yet well understood. However, a drug such as sulphinpyrazone that reduces the formation of the vasodilating PGE₂ in the kidney and does not modify the formation of the vasoconstrictive PGF_{2α} could in certain clinical situations impair renal haemodynamics and even lead to acute renal failure. In the volunteers studied neither drug produced a consistent change in creatinine clearance. This contrasts with the decrease in renal function when sulphinpyrazone was prescribed soon after infarction reported by Dr Wilcox and his colleagues and by Boelaert *et al.*¹ It is possible, however, that sympathoadrenal activation and other vasoconstrictive stimuli characteristic of the post-infarction period lead to renal prostaglandin activation, withdrawal of which could result in decrease in renal blood flow and glomerular filtration. This is now under investigation.

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Salt and blood pressure in Scotland

SIR,—We read with interest the article by Dr D G Beevers and his colleagues concerning salt and blood pressure in Scotland (6 September, p 641). In the light of our results from a recent study of dietary salt intake and urinary sodium excretion in Swedish women with high and low blood pressure levels¹ we would like to comment on the results.

In our study 24-hour urine specimens were collected at five different occasions during a three-year period, and in connection with the last three collections food sampling was carried out by applying the duplicate portion technique.² Dietary sodium and potassium were highly correlated ($p < 0.001$) with the corresponding urinary excretion values in the two groups, indicating that the urinary excretion of sodium and potassium very well reflected the dietary intake of these substances. The reproducibility of the five different 24-hour

urinary collections was examined by analyses of variance for sodium and potassium excretion. These analyses did not show any significant differences between the five separate measurements of the 24-hour urinary excretion either for sodium or for potassium, despite the rather long period of time between the sampling occasions.

Thus it seems that urinary excretions of salt are highly reproducible and therefore that there is probably no need to "correct" for creatinine excretions. Like the data published by Dr Beevers and his colleagues, our data on salt intake do not support restriction of salt intake as a means of decreasing blood pressure in the population.

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Prevention or cure for stress-induced gastrointestinal bleeding?

SIR,—A recent leading article (6 September, p 631) has suggested that impaired coagulation may compound local lesions in cases of stress-induced gastrointestinal haemorrhage. It follows therefore that impaired platelet function may also be disadvantageous.

In order to establish whether cimetidine treatment could influence platelet function we studied its effect on platelet aggregation *in vitro*. Platelet-rich plasma was prepared from seven healthy volunteers and 400 μ l incubated for 10 minutes with 50 μ l of various dilutions of cimetidine in physiological saline (see table). 50 μ l of ADP or adrenaline

Mean percentage fall in optical density at various concentrations of cimetidine

	Final concentration cimetidine (μ mol/l)					
	0	160	240	320	400	480
ADP	76	72	67	53	50	32
Adrenaline	74	70	64	52	48	23
p*		NS	NS	0.05	0.01	0.01

NS = non-significant.
*Paired Wilcoxon's test.

(final concentration 2-5 μ mol/l) was added to initiate aggregation. Details of methods have been previously described.¹

Other workers² have shown that the average peak blood levels of cimetidine are 2.8 μ mol/l after a 200 mg oral dose and approximately 30 μ mol/l after a 100 mg intravenous bolus injection. On the basis of these data our

Urinary prostaglandin E₂ and F_{2α} excretion, serum uric acid and creatinine excretion, and creatinine and uric acid clearance before and during sulphinpyrazone or indomethacin (values are means $\pm$ standard errors of means)

	Time (days)	PGE ₂ (nmol/24 h)	PGF _{2α} (nmol/24 h)	Serum urate (mmol/l)	Serum creatinine (μ mol/l)	Creatinine clearance (ml/min)	Uric acid clearance (ml/min)
Control 1	Average of 2 days	0.66 $\pm$ 0.05	3.05 $\pm$ 0.50	0.37 $\pm$ 0.01	91.0 $\pm$ 7.1	109.8 $\pm$ 3.8	9.01 $\pm$ 1.14
During sulphinpyrazone	Day 1	0.35 $\pm$ 0.07†	3.75 $\pm$ 0.82				
	Day 2	0.26 $\pm$ 0.05†	2.64 $\pm$ 0.66	0.10 $\pm$ 0.01*	86.6 $\pm$ 4.4	122.8 $\pm$ 10.4	42.17 $\pm$ 1.30*
Control 2	Average of 2 days	0.76 $\pm$ 0.14	2.82 $\pm$ 0.27	0.34 $\pm$ 0.02	88.4 $\pm$ 5.3	113.6 $\pm$ 9.8	9.11 $\pm$ 1.74
During indomethacin	Day 1	0.26 $\pm$ 0.04†	1.68 $\pm$ 0.18†				
	Day 2	0.30 $\pm$ 0.07†	1.55 $\pm$ 0.23†	0.35 $\pm$ 0.02	91.0 $\pm$ 2.6	106.6 $\pm$ 8.0	9.02 $\pm$ 0.77

Conversion: SI to traditional units—Urate: 1 mmol = 16.8 mg; creatinine: 1 μ mol/l = 11.3 μ g/100 ml.

* $p < 0.001$
† $p < 0.02$
‡ $p < 0.05$ } compared with the average of the values obtained during the two days preceding sulphinpyrazone or indomethacin.

results (table) suggest that only very high concentrations of cimetidine inhibit platelet aggregation. However, nasogastric fluid concentrations of cimetidine after an oral dose can be several thousand times higher than concomitant blood levels.³ Might not these high concentrations influence local haemostasis? Another report⁴ concluded that in the prophylactic treatment of patients at risk of gastrointestinal haemorrhage antacids offered better protection than cimetidine. Up to 400 mg cimetidine was administered intravenously every four hours, probably repeatedly achieving considerably high peak levels. The possibility that cimetidine may have impaired platelet function and increased haemorrhagic tendency was not considered.

Several cases of thrombocytopenia occurring during cimetidine therapy have been discussed (14 June, p 1453). However, there appears to be only one study⁵ which investigated the possible effect of cimetidine on platelet aggregation. Administration of cimetidine to healthy volunteers and haemophilic patients had no effect on platelet aggregation but only the short-term effects of treatment were assessed and it is not clear to us whether the controls were tested after oral or intravenous administration of cimetidine.

We believe that further investigations are indicated, particularly to assess long-term treatment with cimetidine and the drug's effect on patients with impaired platelet function. Perhaps future studies, similar to those recently published (12 July, p 95; 16 August, p 473), evaluating various H₂-receptor antagonists should include an assessment of the effect on haemostatic mechanism.

We thank Smith Kline and French for supplying additive-free cimetidine.

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Postoperative deep-vein thrombosis: identifying high-risk patients

SIR,—I read Mr J D Hamer's letter (13 September, p 745) on this subject. We are not strangers. Therefore I hope I may remind him, and through him Mr A J Crandon and others (2 August, p 345), that low-dose heparin is not the sole and unchallenged method of preventing deep-vein thrombosis. Deep-vein thrombosis starts during the operation owing to the combined effects of tissue damage and venous stasis. Venous stasis can be prevented by electrical stimulation or passive compression of the calf muscles in the theatre. Both methods are efficient, very practical, and above all cheap, except for patients with a malignant lesion.

Although Wessler demotes venous stasis to a role subordinate to a mystical state of general hypercoagulability,¹ clinical experience since 1964 has established that in most patients with a benign lesion preventing venous stasis is all

that is required to avoid deep-vein thrombosis. If the condition is malignant heparin should be used.

Out of 51 022 gynaecological admissions in the West Midlands, there were 1578 (3.09%) malignant conditions. Mr Crandon and Mr Peel have a simple answer to their problem of the high-risk patient. They need give heparin only to those with a malignant lesion—that is, to very few. Mr Hamer could save a lot of money in general surgery because out of 113 425 admissions there were only 11 592 (10.1%) malignant conditions; the other 101 833 patients, having benign lesions, did not need heparin.

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¹ Wessler F. In: Kakkar VV, Jouhar AJ, eds. *Thromboembolism: diagnosis and treatment*. Edinburgh: Churchill Livingstone, 1972:13-23.

Factor VIII supply and demand

SIR,—I should like to comment on the published dialogue between Dr A Aronstam (21 June, p 1532 and 20 September, p 810), and Dr J Cash (23 August p 656).

I have had some time to reflect why the National Health Service cannot provide more than a fraction of factor VIII concentrate required for the adequate treatment for haemophilia A. As early as 1957,¹ when the preparation and use of human factor VIII concentrate was described, and again in 1963,² when modifications for regional production of factor VIII concentrate were published, I was personally made aware of the very severe financial restrictions that the Health Service imposed on the production of and research into blood products. In part, these restrictions were responsible for the closure of the Lister Institute of Preventive Medicine, where much of the original work on the preparation of blood products for this country was carried out by Drs R A Keckwick and M E Mackay. The basic problem as I see it is as follows. The DHSS stipulates that since human blood is given as a voluntary donation its products cannot be financially exploited. The result of this dictum is that over the years "free" human blood products in this country have been in very short supply, so that for research and treatment human blood products have to be purchased from Sweden, the USA, or France.

If the rather rigid attitude of the DHSS were modified and blood products derived from free blood donations could be sold both here and abroad—the revenue being earmarked for expansion of production and research on human blood constituents—the escalating shortfalls of factor VIII and other blood constituents would probably disappear. Such a change of policy appears to me quite ethical and I have the impression that most blood donors would support such a policy of self-help by the Health Service.

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SIR,—We write to comment on the letters of Drs A Aronstam (20 September, p 810) and J D Cash (23 August, p 565).

When supplies of fresh frozen plasma exceed the capacity of the fractionation centres the extra plasma can be diverted to the preparation of dried cryoprecipitate, a product now available in Australia¹ and most of the EEC countries, including the Irish Republic,² which lacks fractionation facilities. We have been producing dried cryoprecipitate over the last year by a simple technique in which the cryoprecipitates from five donations of plasma are pooled and freeze dried with no appreciable loss of factor VIIIc in the drying process. The excellent yield of factor VIII obtained with conventional cryoprecipitate made by the rapid 4°C thaw method is maintained in this dried product. Our product provides 400 IU (range 300-700 IU) per litre of plasma used. It is rapidly reconstituted in 50 or 100 ml of distilled water, the specific activity is 0.19 IU/mg of protein, the fibrinogen accounts for 15% of the total protein present, and factor VIIIc:fibrinogen ratio is 1.26 IU/mg. The material has so far been given only to a small number of patients but it has been found efficacious and no side effects have been reported. A fuller description of the methods and clinical efficacy of the product will be offered for publication later.

The projected factor VIII requirement for the UK population is 1.8 IU per head of population per annum (1800 per 1000). When donor plasma supplies are limited to 8 litres/10³ per year or less it is not possible to meet the requirements without using a certain amount of conventional cryoprecipitate, which Hassig and Lundsgaard Hansen³ issue as a freeze-dried small pool product.

These two letters and the letter by Dr P Jones (21 June, p 1531) on factor VIII supply and demand underline a major unresolved problem. Perhaps the time has come to reassess our methods and to accept, as many other countries have done, the fact that there is room for both high-technology (low-recovery) and low-technology (high-recovery) products in the management of haemophilia.

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Percutaneous central venous cannulation

SIR,—May we describe a further refinement to the technique of ultrasound identification of the subclavian vein reported by Mr J L Peters and others (30 August, p 618)?

In the co-operative conscious adult a sharp expiration against a closed glottis produces immediate cessation of flow in the subclavian vein. The venous hum heard with an ultrasound probe stops completely, thus confirming that one has located the vein and is not listening to extraneous noise. In an anaesthetised subject raising the intrathoracic pressure for a few seconds by squeezing the reservoir bag produces the same Valsalva effect, again