both, is still lacking, there is enough evidence to require further investigation of the subject.

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⁴ Sohar, E, *et al*, *Israel Journal of Medical Science*, 1976, **12**, 1275.

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Syndrome of inappropriate antidiuretic hormone secretion

SIR,—I was interested to read the case report by Drs C Haslett and N J Douglas (23-30 December, p 1753). Despite its title of "Inappropriate antidiuretic hormone secretion associated with neurohypophyseal choristoma," the information with which we are provided is insufficient for diagnosis of the syndrome of inappropriate ADH secretion.

The most important omission is a description of the patient's fluid balance—a consideration which must be central to any discussion of the cause of hyponatraemia. It is also important to know about the urinary osmolality and electrolytes before water deprivation. The initially low plasma osmolality is entirely predictable from the figures we are given for plasma electrolytes (given the absence of circulating "hidden osmoles") and is of little use taken on its own.

Assuming that the patient's fluid balance was compatible with the syndrome of inappropriate ADH secretion, then the biochemical data with which we are provided merely indicates an inability to excrete a water load. This kind of defect can also be found in hypopituitarism and hypothyroidism. One wonders whether the alternative explanations way had been excluded.

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*.*We sent a copy of this letter to the authors, whose reply is printed below.—ED, *BMJ*.

SIR,—We agree with most of the points made by Dr Jenkins, but in our original case report it was necessary to omit some details in the interest of brevity (600 word limit on *BMJ* short case reports). It was not possible to discuss each of the many criteria^{1,2} necessary for the diagnosis of the syndrome of inappropriate ADH secretion or to exclude individually the numerous causes of the syndrome.³

As regards the patient's fluid balance, there was no clinical evidence of salt and water depletion or overload and no evidence of underperfusion. The patient was not on any diuretic agent which might have interfered with free water formation. We did not measure urine osmolality on the night of admission. This was done the next morning after a period of therapeutic fluid deprivation as we felt that her state of altered consciousness was at least in part related to the low plasma sodium.

However, we are aware that prolonged fluid deprivation might cause volume-mediated ADH release with concentrated urine and hypotonic plasma; but there was no evidence of volume depletion on admission and the effect of a few hours of fluid restriction would be negligible.

We cannot exclude abnormality of pituitary, thyroid, or adrenal function on biochemical evidence because the patient's condition suddenly deteriorated 18 hours after admission while she was still being investigated; and when she subsequently returned to our unit for terminal care it was felt that she should not be further investigated but allowed to die in dignity. However, it seems extremely unlikely that hypoadrenalism was a factor as the patient had a normal blood pressure, both lying and sitting; the plasma potassium concentration was low; and the pituitary and adrenals were normal at necropsy. Similarly, hypothyroidism seems unlikely as she was not clinically hypothyroid and, indeed, had a pulse rate of 120 per minute on admission.

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Bleeding massive gastric ulcer on diflunisal (Dolobid)

SIR,—I was interested to read Dr B B Scott's letter (17 February, p 489), in which he described the case of a patient suffering from a massive bleeding gastric ulcer while on diflunisal (Dolobid). The following report is of a similar experience with a patient taking diflunisal.

This patient was a 79-year-old widow who suffered from longstanding back pain due to severe osteoarthritis of her lumbar spine. In 1968 she had been admitted to hospital having vomited about half a litre of fresh blood. There was no previous history of indigestion, but at the time she was taking aspirin, phenacetin, and codeine tablets for her backache. A barium meal showed a small sliding hiatus hernia with reflux, but no evidence of ulceration. She was given two units of blood and made an uneventful recovery, with no subsequent indigestion.

However, she continued to suffer from backache, for which various analgesics were prescribed over the years. These included paracetamol, phenylbutazone, ibuprofen, ketoprofen, and pentazocine, none of which caused symptoms of gastric irritation. In April 1978, with a worsening of her back pain, she was started on diflunisal 250 mg twice daily with food. After five weeks at this level, and with no symptoms related to her gastrointestinal tract, the dosage was increased to 500 mg twice daily. She was also taking Navidrex K (cyclopenthiiazide and potassium chloride), one tablet each morning, for hypostatic oedema of her legs; but she had received this preparation over the previous four years without any problems. Two weeks after starting the higher dose of diflunisal, she vomited over three-quarters of a litre of fresh blood and was admitted to hospital. She then admitted that she had started to suffer from epigastric pain, nausea, and anorexia almost immediately after the dose of diflunisal had been increased, but continued with the drug.

On admission to hospital she was pale but not shocked, and her haemoglobin concentration was 7.9 g/dl. The diflunisal was stopped, and she was given three units of blood. Over the course of the next 10 days her haemoglobin rose to 11.4 g/dl, her faecal occult blood tests became negative, and her indigestion disappeared. A barium meal showed thickened gastric rugae on the greater curve of the stomach, but no actual ulceration was seen. Her subsequent progress has been uneventful, although her backache persists.

As with the case described by Dr Scott, all the indications here are that the diflunisal was the cause of her haematemesis. The makers of Dolobid recommend caution when this product is prescribed for patients with a previous history of gastrointestinal haemorrhage, and this case should serve to underline this point.

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Assessment of renal concentrating ability

SIR,—We were interested to read the paper by Dr J R Curtis and B A Donovan (3 February, p 304) on the assessment of renal concentrating ability and would like to make the following comments.

The assessment of concentrating ability in the ambulant patient by the measurement of osmolality on aliquots of all urine specimens passed in a normal 24-hour period is an attractive possibility but is time consuming by comparison with the shorter intranasal desmopressin tests previously described¹⁻³ and is, as the authors state, not certain of success. In addition, we were surprised at the dosage of 4 µg desmopressin in the intramuscular test since we have previously demonstrated achievement of maximum osmolality with half this dosage intramuscularly in a shorter overnight test.²

We feel that the short intranasal desmopressin test provides the most convenient method of assessing renal concentrating ability. When investigating polyuria it must obviously be preceded by some form of water deprivation test. In this context control observations of urine osmolality throughout 24 hours may be unhelpful if excessive water drinking forms part of the differential diagnosis.

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¹ Aronson, A S, and Svenningsen, N W, *Archives of Disease in Childhood*, 1974, **49**, 654.

² Monson, J P, and Richards, P, *British Medical Journal*, 1978, **1**, 24.

³ Delin, K, Aurell, M, and Ewald, J, *British Medical Journal*, 1978, **1**, 757.

SIR,—We have reported on the use of the deamino-D-arginine vasopressin (desmopressin) test (25 March 1978, p 757). The intranasal desmopressin test appeared to be as good as the pitressin test for measurement of the maximal urinary concentration. We would like to add a few comments.

We suspected that technical problems might arise with the intranasal administration of the drug. The correct administration is, of course, a very crucial point in the procedure. We have therefore tested intravenous administration of an equivalent dose—that is 4 µg, as it is held that 10% of the 40 µg given intranasally is

reabsorbed. It soon became clear, however, that intravenous administration of the drug did not induce a maximal urinary concentration. We therefore proceeded to try 4 µg given as an intramuscular injection. This gives satisfactory results when compared with the intranasal desmopressin test. The mean difference between the two tests performed on 24 patients is 4 ± 20 (SEM) mmol(mOsm)/kg, the results ranging from 500 to 1100 mmol/kg (regression line: $y = 0.86x + 90$, where y = concentration at intramuscular test and x = concentration at intranasal test; $r = 0.80$). We have adopted the procedure of using intranasal administration routinely, but if technical difficulties arise we check the test with an intramuscular administration.

Looking into the data, it is also obvious that urine samples taken immediately before the desmopressin administration—that is, urine produced during the last hour of thirst before the test—often have attained maximal concentration. Urine produced after overnight thirst could therefore be used in a screening test. The use of the desmopressin test has also been reported by Monson and Richards¹ and by Curtis and Donovan.²

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¹ Monson, J P, and Richards, P, *British Medical Journal*, 1978, 1, 24.

² Curtis, J R, and Donovan, B A, *British Medical Journal*, 1979, 1, 304.

Klebsiella, spondylitis, and uveitis

SIR,—We were interested in the report by Dr Roland Ebringer and others (10 February, p 383). At a recent meeting of the Heberden Society we reported a prospective study of faecal *Klebsiella* carriage in 89 outpatients with ankylosing spondylitis (AS) and in 82 patients with rheumatoid arthritis (RA) attending the rheumatology department of Westminster Hospital. Using ampicillin peptone water and a carbenicillin inositol indicator agar, *Klebsiella* spp was isolated from 24 patients with AS (27%) and 26 with RA (32%). In a three-month period (early in 1978), we found no correlation between the activity of joint disease and *Klebsiella* carriage at initial assessment. This study is being reported in full.¹

Since 1976, we have studied the faecal flora of patients with acute anterior uveitis (AAU) diagnosed at Moorfields Hospital and referred to Westminster Hospital for rheumatological assessment. Fifty-two patients with AAU were seen within one month of the start of their attack of AAU (mean 15 days). Twenty-nine (18 men) had no rheumatic symptoms and no associated disorder; 19 (17 men) had the New York criteria for AS. The remaining four patients were excluded because they had Reiter's disease, RA, or spondylitis associated with ulcerative colitis or Crohn's disease. Two patients with no rheumatic disease and one with AS had second episodes of AAU in this period; the second episodes have been excluded from our results. Without using ampicillin peptone water enrichment for *Klebsiella*, we isolated *Klebsiella* or *Enterobacter aerogenes* from 7/29 (24%) of patients with AAU alone and 4/19 (21%) of those with both AAU and AS. *Klebsiella* carriage was no commoner in females. We cannot, therefore, support the

observation of Ebringer *et al* that *Klebsiella* was carried in the faeces of 13/17 (76%) of cases of AAU associated with AS. Although we have no matched unassociated patients examined over the same period, in our 1978 study we isolated *Klebsiella* using carbenicillin agar alone in 21/114 (19%) of AS patients and in 22/89 (24%) of RA patients. We have therefore found no difference in *Klebsiella* isolation rates from the faeces of individual patients with AS alone, AS and AAU, AAU alone, and RA.

We have also sought any organism which cross-reacts with *Salmonella*, *Shigella flexneri* or arthritogenic *Yersinia enterocolitica* strains, and which either appears in faeces or is detectable by seroconversion on paired sera in relation to attacks of AAU. Paired sera (taken one month apart) from 22 patients with AAU were examined for agglutinating antibodies to formalinised or boiled formalinised suspensions of 83 strains of aerobic Gram-negative rods isolated from initial faeces cultures of each individual. In 17 of these patients we have further examined the paired sera for antibodies against 74 coliform strains isolated from a second faecal sample obtained one month later. We have found no change in agglutinin titre against any of these Gram-negative rods, including strains of *Klebsiella* and *Enterobacter aerogenes*. We have, however, previously demonstrated that a wide variety of biotypes, serotypes, and bacteriophage types of *Klebsiella* are recovered from AS patients.¹ Thus we were unable to find evidence of serological changes in individual AAU patients representing reactions to their normal Gram-negative bacterial flora. By analogy with the HLA-B27-associated acute arthritis (after intestinal infection with *Salmonella*, *Campylobacter*, and *Yersinia enterocolitica*), such seroconversion might be expected if the normal Gram-negative bacterial flora were a provocative factor in acute anterior uveitis. We have also been unable to implicate—by serology or culture—arthritogenic *Yersinia enterocolitica* serotypes 3 or 9 in any of our patients with AAU.

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¹ Warren, R E, and Brewerton, D A, *Annals of the Rheumatic Diseases*, in press.

Male sexual dysfunction and cimetidine

SIR,—In a recent report (10 March, p 659) Dr N R Peden and others claim that a prima facie case has been made against cimetidine as a cause of male impotence. The experience of the following patient may partly redress the balance.

A 57-year-old man with a 20-year history of dyspepsia presented with a severe relapse of symptoms. Endoscopy confirmed the presence of a duodenal ulcer, and cimetidine was started in a dose of 1600 mg/day for six months. His ulcer symptoms disappeared within two weeks of starting treatment and endoscopy at three and six months confirmed ulcer healing. Four weeks after starting cimetidine he requested referral for vasectomy. Further inquiry established a sustained increase in libido accompanying the improvement in ulcer symptoms. This unexpected

bonus from his cimetidine treatment was confirmed by his wife.

Most of the reported adverse effects of cimetidine have been in the form of anecdotal reports, and the recent report from Dundee is no exception. These are to be expected after the introduction of any new drug¹ and occasionally may give a useful indication of serious toxicity. Nevertheless, undue importance should not be attached to poorly validated reports.

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¹ Laurence, D R, *Clinical Pharmacology*, p 411. Edinburgh, Churchill Livingstone, 1973.

Fats and atheroma

SIR,—Dr John Vane (17 February, p 484) emphasises views put forward many years ago^{1,2} concerning the putative importance of dietary essential fatty acids (EFAs) in the pathogenesis of ischaemic heart disease, and his letter stimulates me to speculate on the possible relevance of these ideas to the extraordinarily high mortality in Scotland. Sinclair¹ suggested that atherosclerosis might be due to a chronic deficiency of arachidonic acid when diets are high in saturated fat or unnatural fats and fairly low in EFAs. Are such diets encountered? he asked. We have some evidence that in Scotland they are:

(1) The linoleic acid (C18:2w6) content of plasma cholesterol esters, plasma triglycerides, and adipose tissue in 40-year-old healthy Edinburgh men is significantly lower than that of comparable 40-year-old healthy Stockholm men.³ (2) There is also a lower arachidonic acid (C20:4w6) content of adipose tissue in Edinburgh men. (3) The polyunsaturated:saturated ratio in adipose tissue of Edinburgh men was 0.30 compared with 0.44 in Stockholm men ($P < 0.001$). (4) The fatty acid content of a seven-day weighed dietary survey is still being analysed, but the correlation between dietary linoleic acid and adipose tissue linoleic acid in both cities is in the region of 0.8. (5) Adipose tissue fatty acid composition reflects long-standing dietary fatty acid consumption, because of a very slow turnover rate, and is not influenced by day-to-day or even week-to-week dietary changes. Thus the differences between the Edinburgh and Stockholm populations appear to establish a real difference in EFA consumption.

A significantly lower proportion of linoleic acid has previously been reported in the adipose tissue of two populations dying suddenly. It was 6% lower in Japanese dying in Tokyo than in Americans dying in Cleveland, and the latter showed a higher incidence of myocardial infarction or coronary occlusion as the cause of death.⁴

Most of the work suggesting a balance⁵ between prostacyclin and thromboxane A_2 in relation to platelet aggregation is based on the effects of the addition of precursors of prostaglandins, such as arachidonic acid. An interesting question is whether a longstanding deficiency of certain EFA precursors for prostacyclin, other prostaglandins, and thromboxanes might lead to a low-grade thrombotic tendency. Recent evidence indicates not only that arachidonic acid stimulates the formation of a prostacyclin-like material from human endothelial cells but also that it results in less inhibition of platelet aggregation in the presence of long-chain saturated fatty acids.⁶

The bearing of this on mortality from ischaemic heart disease in Scotland might be that there is a greater thrombotic element to its clinical presentation than in communities where the EFA precursors of prostaglandins are more "in balance" with the saturated fat composition of the diet. No excess in