The observed sex difference suggests the importance of a complex sociocultural variable in the optimum selection of female athletic and sporting talent. It appears that other countries are failing to exploit the sporting potentialities of their women in the way that East Germany has done.

T KHOSLA

Department of Medical Statistics,
Welsh National School of Medicine,
Cardiff

Anti-inflammatory drugs for rheumatoid arthritis

SIR,—Clinical judgment should be based on fact rather than fantasy. This thought is provoked by the paper by Dr E C Huskisson and others (1 May, p 1048) but more particularly by the recent advert for Naprosyn which appeared as a pull-out supplement in your Journal (3 July). We would dispute the opening premise of this article, namely, that aspirin is no longer treatment of choice in rheumatoid arthritis. Out of the three references for this statement two were by Huskisson himself.

However, our major objections to this paper are not based on a matter of opinion but the following facts: (1) The tablets used were not matched, naproxen being different from the other three. (2) There are no baseline data and, moreover, no placebo group, which is so important in a short-term study. (3) There is the introduction of a new toxicity index which is neither defined nor evaluated. (4) The conclusions drawn do not appear to be justified from the data presented—namely, fenpropfen reduced morning stiffness and joint size better than the other agents, suggesting that fenpropfen was more anti-inflammatory in this study.

We believe that in this paper there are too few facts for too many conclusions and that great care should be taken in its interpretation.

A K CLARKE
E B D HAMILTON
C J GOODWILL
HEDLEY BERRY
LUKE FERNANDES

King's College Hospital,
London SE5

* * * We sent a copy of the above letter to Dr Huskisson and his colleagues, whose reply is printed below.—ED, *BMJ*.

SIR,—It was not our intention to present evidence that aspirin is no longer the first line of treatment for rheumatoid arthritis. Our introduction merely intended to say that if this were true it would be nice to know which of the propionic acid derivatives might have taken its place. We support the desire for fact in preference to fantasy. The facts put forward in our paper were that two of the drugs tested were more effective than the other two and that two more produced side effects. These facts were supported by statistical significance levels which are unusually high because of the large number of patients treated.

We are not impressed by the specific objections: (1) None of the tablets were matched but all were unrecognisable. We know of no evidence that colour affects the performance

of active analgesics, and for placebo, yellow is the worst colour.¹ Problems of bioavailability prevented us from using identical formulation. (2) Baseline data were collected and are available. However, the principle of a crossover trial is that a patient's state at the end of one treatment period is compared with his state at the end of another, and we cannot see the value of baseline data. Patients in trials always improve, and one could not use this improvement as evidence that the new treatment was better than the old. We did not set out to show that propionic acid derivatives were effective, which has been done, and didn't therefore need placebo. We set out only to compare the drugs. (3) Dr H Berry may remember the study of which he was a co-author,² in which side-effect scores were first used as a measure of toxicity. (4) The differences between fenpropfen and naproxen in morning stiffness and joint size were not statistically significant and there was no justification for the claim that its anti-inflammatory potency was greater.

We have examined the advertisement for Naprosyn and find the facts in it to be accurate. We regret only the omission of what for us was the most important conclusion of the study. Our trial showed for the first time that there is one particular drug which is right for one particular patient, and Dr Clarke and his colleagues may be interested to hear that for this reason some of our patients still take . . . aspirin.

E C HUSKISSON
D L WOOLF
H W BALME
JANE SCOTT
SUE FRANKLYN

St Bartholomew's Hospital,
London EC1

Wanstead Hospital,
London E11

¹ Huskisson, E C, *British Medical Journal*, 1974, 4, 196.
² Huskisson, E C, et al, *British Medical Journal*, 1974, 1, 176.

Confidence limits

SIR,—In his article "Statistics at Square One, XI—The *t* tests" Dr T D V Swinscow (31 July, p 291) falls into a trap which many of us are at pains to warn our students about. After finding the 95% confidence limits for a population mean to be 120.97 and 109.03 he writes, "We therefore conclude that the chance of the population mean lying below 109.03 or above 120.97 is only 5% or less." The "or less" is, on any interpretation, redundant and misleading, but the major point is that the standard theory of confidence limits does not allow this conclusion. The correct interpretation is that if the unknown population mean were to lie below 109.03 or above 120.97 then, on his data, an event with a chance of only 5% must have happened: either the mean lies between those limits, or something rather improbable has happened, and we usually prefer to assume the former.

In fact there is a very ingenious argument, known as the fiducial argument, advanced by Sir Ronald Fisher from 1930 onwards, which purports to justify statements of the kind made by Dr Swinscow. But it is not generally accepted by statisticians, least of all those who advocate confidence limits. Oddly enough its origins can be traced back to the very paper by "Student" that Dr Swinscow quotes, but

in general it is prudent to avoid making any statement about the probability of the population mean lying in an interval and to warn students away from it. There is deep water all round.

A W F EDWARDS

University Department of Community Medicine,
Cambridge

* * * Dr Swinscow writes: "Dr Edwards is correct in his interpretation. The lapse is theoretical rather than practical in its implications but will be repaired when the article is revised for publication in book form later this year. I am grateful for the correction—italics and all."—ED, *BMJ*.

Accidental injection of Immobilon

SIR,—A few weeks ago the product licence for Immobilon—a potent veterinary neuroleptanalgesic combination of the opiate etorphine hydrochloride and a phenothiazine, acepromazine or methotrimeprazine—was suspended on the advice of the Veterinary Products Committee following the death, due to accidental self-injection of Immobilon, of a member of the veterinary profession.¹ In this case the recommended accident procedure, which involves the injection of a narcotic antagonist, was not followed. In other cases when accidental injection has been promptly treated by injection of a suitable antagonist recovery has been uneventful.²⁻⁵

After consideration of the circumstances of this accident and the evidence on the use of Immobilon during the past six years the Veterinary Products Committee has now recommended the reinstatement of the product licence and the recommendations for the treatment of accidental injection have been revised. The product is now again available.

It is possible that doctors may be called to treat cases of accidental administration of Immobilon and it is therefore essential that all doctors are aware of the correct treatment and have the appropriate antagonist to hand. The revised procedure recommends the use of naloxone but allows for the emergency use of nalorphine and Revivon (diprenorphine hydrochloride), the veterinary antagonist which always accompanies Immobilon. The following accident procedure appears on the reverse of the pack and also in the product literature.

ACCIDENT PROCEDURE—IMMOBILON

Immobilon is a very potent neuroleptanalgesic with a high toxicity in man. In the event of accidental administration to man, or if there is a possibility that absorption may have occurred, the procedure given below should be adopted. Symptoms caused by Immobilon are dizziness, nausea, and pin-point pupils, followed by respiratory depression, fall in blood pressure, and cyanosis. In extreme cases loss of consciousness and cardiac arrest occur.

SUMMON MEDICAL HELP IMMEDIATELY

If there is any danger that absorption of Immobilon may have occurred INJECT A REVERSING AGENT IMMEDIATELY.

(1) *Spillage on skin or splashing of eyes.* Wash immediately with copious quantities of water.

(2) *Accidental injection.* Inject one of the following reversing agents: (i) 1 ml Narcan (0.4 mg naloxone) intravenously or intramuscularly. Repeat at 2–3-min intervals if symptoms are not reversed. (ii) If Narcan is not available inject 1 ml Lethidrone (10 mg nalorphine) intravenously or intramuscularly. Repeat at 5-min intervals if necessary up to a total of 4 ml. There are Lethidrone formulations

for veterinary and human use. Use human Lethidrone (veterinary Lethidrone contains 20 mg nalorphine/ml). (iii) If neither Narcan nor Lethidrone is available inject 0.1 ml of the appropriate veterinary antagonist (small/large animal Revivon) intramuscularly, or if the actual dose of Immobilon is known a similar volume of Revivon should be given; repeat the dose if respiratory depression is not reversed.

IT IS VITAL THAT ADEQUATE RESPIRATION AND HEART BEAT BE MAINTAINED UNTIL MEDICAL HELP ARRIVES. IF NECESSARY APPLY ARTIFICIAL RESPIRATION AND EXTERNAL HEART MASSAGE.

GLYN N VOLANS

Poisons Unit,
Guy's Hospital,
London SE14

B A WHITTLE

Reckitt and Colman,
Pharmaceutical Division,
Hull

¹ Ministry of Agriculture, Fisheries and Food, *Veterinary Record*, 1976, **98**, 514.

² Firm, S, *Lancet*, 1973, **2**, 95.

³ Firm, S, *Lancet*, 1974, **1**, 577.

⁴ Vaudrey, J C, *Veterinary Record*, 1974, **94**, 52.

⁵ Unpublished reports to Reckitt and Colman Pharmaceuticals.

added to the routine tests of the clinical microbiology laboratory, especially where an electron microscope is not readily available.

B D SCHOUB
A S GREEFF
G LECATSAS

Department of Microbiology and
Microbial Genetics Unit of the MRC,
University of Pretoria,

W PROZESKY

National Institute of Virology,
Sandringham,

I T HAY
J G PRINSLOO

Department of Paediatrics,
Kalafong Hospital,
Pretoria,
South Africa

¹ Schoub, B D, *et al*, *Lancet*, 1975, **1**, 1093.

² Schoub, B D, *et al*, *South African Medical Journal*, 1976, **50**, 1124.

³ Spence, L, *et al*, *Lancet*, 1975, **2**, 322.

⁴ Middleton, P J, *et al*, *Journal of Clinical Pathology*, 1976, **29**, 191.

Dosage of neomycin sulphate

SIR,—With reference to the letter from Mr M G Thuse and Mr D P Morgan (31 July, p 303) neomycin sulphate tablets contain 350 000 units of neomycin activity, but they are actually marketed as tablets of neomycin sulphate 500 mg and hence it seems convenient for users to have the dose expressed in weight rather than potency units. The dose given in the *British Pharmaceutical Codex* is that recommended by its actions and uses subcommittee and appears to be in accordance with established usage. The dose recommended by the British Pharmacopoeia Commission is somewhat higher, but no doubt both authorities will be reviewing these doses in the light of the discrepancy to which attention has been drawn.

G R BROWN

Secretary,

Codex Revision Committee

Pharmaceutical Society of Great Britain,
London WC1

Raised alpha-fetoprotein levels and congenital defect

SIR,—The observation (3 July, p 22) of a raised amniotic alpha-fetoprotein (α -FP) level in association with a minor congenital defect, postanal dimple, is disquieting. To date a raised amniotic α -FP level has indicated in the fetus either an open neural tube defect¹ or other major congenital abnormalities, namely, oesophageal atresia,² congenital nephrosis,³ Turner's syndrome,⁴ and omphalo-coele.⁵ Although the explanation for the raised amniotic fluid α -FP is not apparent, it is unlikely to be related to the postanal dimple.

We have monitored four pregnancies with normal amniotic α -FP levels which resulted in infants with postanal pits or sinuses (table). We would agree that so far as possible additional investigations should be used to confirm the abnormality in the fetus before the pregnancy is terminated.

NORMAN C NEVIN

Department of Medical Genetics,
Queen's University of Belfast

W THOMPSON

Department of Midwifery and
Gynaecology,
Queen's University of Belfast

GERALDINE ROBERTS

Biochemistry Laboratory,
Royal Victoria Hospital, Belfast

¹ Brock, D J H, and Scrimgeour, J B, *Lancet*, 1972, **2**, 1252.

² Seppälä, M, *Obstetrics and Gynecology*, 1973, **42**, 613.

³ De Bruijn, H W A, and Huisjes, H J, *Lancet*, 1975, **1**, 525.

⁴ Seller, M J, *et al*, *British Medical Journal*, 1974, **2**, 524.

⁵ Nevin, N C, and Armstrong, M J, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1975, **82**, 826.

Case	Obstetric history	Amniocentesis			Outcome of pregnancy
		Indication	Gestation	Amniotic α -FP (μ g/ml)	
1	Para 4	Previous anencephaly	17	18.4 (16.02; 30.38)	Female with postanal pit
2	Para 2	Rhesus isoimmunisation	17	11.0 (16.02; 30.38)	Female with neurodermal sinus lower lumbar area; x-ray no abnormality of spine; oval soft tissue shadow posterior to L4
3	Para 2 + 1	Previous infant with spina bifida	15	15.0 (18.46; 32.8)	Male with hairy area lower spine with a postanal sinus; x-ray normal
4	Para 2 + 1	Previous spina bifida infant	16	19.2 (17.08; 32.20)	Male with small postanal pilonidal sinus

Figures in brackets: mean and 95th percentile for amniotic fluid α -FP for this gestation.

Enterotoxinogenic bacteria in Africa

SIR,—We read with interest the letter from Dr T Wadström and others (5 June, p 1401) on enterotoxinogenic bacteria in Ethiopian children. This is, however, not the first report on enterotoxin-producing bacteria in an African community. In April 1975 we reported the isolation of three stable toxin (ST)-producing *Escherichia coli* strains from 101 Black infants with acute gastroenteritis in Baragwanath Hospital, South Africa.¹

We have since completed a microbiological investigation of acute sporadic summer gastroenteritis in 36 Black infants under two years of age admitted to Kalafong Hospital near Pretoria. Enterotoxin production was assessed by the Chinese hamster ovary and the suckling mouse techniques for labile (LT) and stable (ST) toxins respectively.

A total of 16 enterotoxinogenic bacteria were found in 15 out of 36 patients (42%), comprising *E coli* 9 (56%), klebsiella 4 (25%), enterobacter 2 (12%), and proteus 1 (6%). In one of the patients two different enterotoxinogenic species, an *E coli* and a klebsiella, were isolated. No invasive strains of *E coli* were found with the Serény guinea-pig keratoconjunctivitis test. By means of negative staining electron microscopy rotaviruses were detected in only 2 (5%) patients. We feel, however, that this figure is unusually low since most patients are admitted to hospital at a relatively late stage in their illness when the excretion of rotavirus particles is too low for detection by electron microscopy.²

We fully endorse the view of Dr Wadström and his colleagues that testing for enterotoxin should be performed before the isolated strains are speciated, as enterotoxinogenicity is clearly not confined to *E coli*. Indeed, in future diagnostic laboratories may well dispense with the species determination of isolated bacteria in cases of sporadic gastroenteritis and merely report on whether enterotoxinogenic or invasive bacteria were isolated. In addition, recently described simpler techniques for the diagnosis of rotavirus infections, such as reverse complement fixation³ and counter-immunoelectro-osmophoresis,⁴ should be

Early gastric cancer

SIR,—Your leading article (24 July, p 198) implies that it is highly desirable to make a diagnosis of "early" gastric cancer in a greater number of cases, as at that stage of the disease there is a greatly improved prognosis (95% 5-year survival). With that implication we wholeheartedly concur, but feel that there is not sufficient clarity on exactly how this is to be achieved.

Cancer of the stomach (as cancer of many other internal organs) gives specific symptoms only late in its life cycle, and the first point needing emphasis is that earlier diagnosis in significant numbers will be achieved only by testing individuals in an "asymptomatic" phase. The Japanese have been able to produce their large series of "early" gastric cancer by screening an asymptomatic population by means of the double contrast barium meal technique, the gastric camera, and endoscopy, combined with greater use of wash and brush cytology and microbiopsy histology.¹

We in this country have a low incidence of cancer of the stomach compared with the Japanese or some Central European and Scandinavian countries, but the high risk groups of chronic atrophic gastritis, gastric ulcer, polyps, pernicious anaemia, and some familial conditions have been recognised for many years.² It is also becoming apparent that cytological examination of all patients attending a gastroenterological clinic (with or without gastroscopy) will produce a number of latent cancers, as was found in the Massachusetts General Hospital, where early cancer (undiscovered by other diagnostic tests) was