Exercise and general practice

SIR,—Perhaps like many other organisers of courses predominantly for general practitioners I am bemused by what is recognised by regional advisers in general practice for the general practice postgraduate training allowance.

The British Association of Sport and Medicine organises weekend modular courses in various branches of sports medicine aiming at training general practitioners and other doctors who wish to take the examinations for the Society of Apothecaries or the Scottish Colleges Diploma in Sports Medicine. Most of our students are general practitioners with an interest in sports medicine, often with attachments to sports clubs or sports injury clinics of various types, to which they give their professional services. Most of the clinical modules are recognised without too much of a problem, but we are repeatedly finding that exercise physiology, a knowledge of which is sadly lacking in most doctors in Britain, is not considered part of a general practitioner's training even if they decide to spend much of their working time dealing with athletes and other people who take a lot of exercise. To quote one of the regional advisers in general practice, "The (appeal) committee agreed that the accreditation of your course should not be supported since its content was not directly related to the everyday work of the general practitioner."

This is a sad reflection on general practice if true. Do the physiology of locomotion, muscle fatigue, the effect of training, muscle strengthening, the physiology of adaptation to heat, acclimatisation, measurement of exercise capacity, anaerobic threshold, and body composition have no direct relation to the everyday work of the general practitioner? Is general practice limited to bed bound patients who never move? Are general practitioners never involved in the rehabilitation of a patient?

As a cardiologist I find a knowledge of exercise physiology invaluable in assessing cardiac patients, and I just cannot believe that general practitioners would not find it equally useful even simply to understand what happens to a leg that has been put in plaster for a few weeks and then taken out again.

The present system is arbitrary and encourages national course organisers, such as ourselves, to arrange courses only in specific regions of the country where they know the regional assessors are sympathetic to their topics. Is this really in the best interests of general practice?

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Drug Points

Effect of scheduling of buprenorphine (Temgesic) on drug abuse patterns in Glasgow

Dr M J STEWART (Institute of Biochemistry, Royal Infirmary, Glasgow G4 0SF) writes: In 1987 we were alerted to the abuse of buprenorphine (Temgesic) by addicts in the catchment area of this laboratory, which covers mainly the north and east sectors of the city. On introducing a screening service in March 1988 we found that 30% of drug abusers, many of whom were pregnant women attending a special antenatal clinic, were using buprenorphine, and this figure averaged out at about 45% over the months between March 1988 and September 1989. We were analysing about 200 specimens a month.

After restrictions on prescribing were introduced in September 1989 we expected a rapid fall in

Usage of buprenorphine among drug abusers attending clinics in east end of Glasgow

usage, but as can be seen from the figure it took three months for supplies to be consumed, after which there was a drop in incidence to about 20% in April 1990. This low figure was not maintained in the eight succeeding months. It would seem therefore, that the legal restrictions on prescriptions have had less effect than would have been hoped for, and the source of current supplies is unknown.

Of greater concern, however, is the concurrent effect on use of opiates. The average percentage of urine specimens that were positive on testing for opiates over the 18 months before restriction of buprenorphine was 7.5%, but from January 1990 the incidence has risen sharply to a mean of 17% with a peak in one month of 30%. The effect of the scheduling of buprenorphine has therefore resulted in only a temporary drop in the ability of users to obtain this drug, and it seems to have contributed to a doubling of the number of abusers who now use opiates, with the concomitant dangers associated with poor quality control of supplies.

Abuse of buprenorphine (Temgesic) by snorting

Dr JOHN STRANG (Drug Dependence Clinical Research and Treatment Unit, Bethlem Royal Hospital, Beckenham, Kent BR3 3BX) writes: The World Health Organisation has recently elected to impose only psychotropic controls on buprenorphine—as opposed to the narcotic controls more usually applied to an opioid analgesic.¹ In similar vein, the United Nations Committee on Narcotic Drugs concluded that "the degree of seriousness of the public health and social problems associated with abuse of this drug to date were found to be not great in terms of the numbers of individuals involved and the impact of the abuse on their well being."² Statements from the manufacturers continue to give reassurance that buprenorphine is an effective and useful analgesic³ despite evidence over many years of the intravenous abuse of the sublingual tablets.^{4,6}

We have recently encountered a new form of abuse of buprenorphine (Temgesic) tablets—by crushing the sublingual tablets and then snorting them like snuff. The tablets are crushed into a fine powder and then snorted in the same manner as black market amphetamines, cocaine, and (more rarely) heroin. This reputedly results in a more rapid psychoactive effect than the sublingual route and seems to be associated with strong hedonic tone: indeed, our two patients reported that their drug and route of preference was Temgesic by snorting, for which they would occasionally substitute black market heroin by snorting when Temgesic was not available. We understand that snorting of buprenorphine is now moderately well established as a pattern of abuse in parts of London and with contact groups in Glasgow. The sublingual tablets are sold on the black market for £2.50 each and represent a pharmaceutical grey market, being diversions of prescribed supplies.

It is interesting to consider whether HIV can be transmitted by this form of abuse. At first glance it seems to represent no direct risk, in stark contrast to the previously reported intravenous abuse of this drug.^{4,6} Nevertheless, more careful con-

sideration shows that risks are present because of the intermediate step of dependence: as the drug taker becomes dependent there is an associated increased likelihood of atypical drug taking or sexual behaviour, with a resulting increase in risk of HIV transmission (such as use of injectable drugs in the absence of the preferred drug or involvement in prostitution or sex for drugs transactions) as has occurred with both of our two patients.

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- 2 United Nations. *Thirty third session of the Commission of Narcotic Drugs: implementation and development of international instruments on the control of narcotic drugs and psychotropic substances*. Vienna: UN, 1989.
- 3 Varey NC. The safety of buprenorphine (Temgesic). *NZ Med J* 1990;103:882.
- 4 Strang J. Abuse of buprenorphine. *Lancet* 1985;ii:725.
- 5 Chowdhury AN, Chowdhury S. Buprenorphine abuse: report from India. *Br J Addict* 1990;85:1349-50.
- 6 O'Connor JJ, Moloney E, Travers R, Campbell A. Buprenorphine abuse among opiate addicts. *Br J Addict* 1988;83:1085-7.

Azapropazone and warfarin

Drs NAY WIN and D C MITCHELL (Derbyshire Royal Infirmary, Derby DE1 2QY), P A E JONES (City Hospital, Nottingham NG5 1PB), and E A FRENCH (University Hospital, Nottingham NG7 2UH) write: Although the interaction between azapropazone and warfarin is well documented,^{1,3} it is clearly not well known by prescribers. Recently we have seen four serious overdoses of warfarin due to concurrent administration of azapropazone.

A 67 year old man was stable taking warfarin after aortic valve replacement and coronary artery bypass surgery when azapropazone was prescribed for arthritic pain. One week later he developed nose bleeds and melaena and was admitted to hospital with a haemoglobin concentration of 42 g/l, prothrombin time 578 seconds (international normalised ratio (INR) >7 by 300 seconds). Blood and blood products could not be given for religious reasons and, although he was given vitamin K, he died within 24 hours of admission.

A 38 year old man was admitted with haematuria and renal colic. He had a history of paroxysmal atrial fibrillation and had been taking warfarin for three years. A week before admission he was given azapropazone for pain in the right hip. On admission his prothrombin time was 318 seconds and haemoglobin concentration was 138 g/l. Intravenous vitamin K 2.5 mg was given and the INR fell to 2.3. Warfarin was resumed seven days after admission.

An 81 year old man was taking warfarin for atrial fibrillation and aortic stenosis. He developed arthritis in the right hand and was started on azapropazone. Two days later he had a haematemesis. His prothrombin time was 378 seconds (INR >7 by 200 seconds) with a haemoglobin concentration of 52 g/l. He was resuscitated with fresh frozen plasma, blood, and vitamin K and made a good recovery.

A 52 year old woman was stable taking warfarin after mitral valve replacement. INR >8 was recorded on 30 March and again on 16 October and no apparent causative factor could be ascertained. Fresh frozen plasma was given and warfarin resumed with an INR of 3.2. Three days later the INR was again >8 and on questioning the patient remembered having taken azapropazone one tablet (300 mg) daily for three days during the week before 16 October and also had taken one tablet shortly before 30 March. Fresh frozen plasma was given and warfarin resumed three days later.

There are well established problems with the use of non-steroidal anti-inflammatory drugs in patients taking warfarin. Azapropazone is more dangerous than other non-steroidal anti-inflammatory drugs (with the exception of phenylbutazone). It is structurally related to

phenylbutazone, and the mechanism of interaction with warfarin is also similar. Azapropazone displaces warfarin from protein binding sites and also alters the renal clearance of R and S isomers of warfarin.^{4,5} Other non-steroidal anti-inflammatory drugs are less hazardous because they do not interfere with renal clearance of isomers of warfarin.

Azapropazone is absolutely contraindicated in patients taking warfarin. This potentially hazardous interaction should be highlighted further in both the data sheet¹ and the *British National Formulary*.⁶

- 1 Association of the British Pharmaceutical Industry. *ABPI data sheet compendium 1990-1991*. London: Datapharm, 1991:1378-9.
- 2 Powell-Jackson PR. Interaction between azapropazone and warfarin. *BMJ* 1977;ii:1193.
- 3 Green AE, Hort JF, Korn HET, Leach H. Potentiation of warfarin by azapropazone. *BMJ* 1977;ii:1532.
- 4 Griffin JP, D'Arcy PF. *A manual of adverse drug interactions*. 3rd ed. Bristol: J Wright, 1984:120.
- 5 McElroy JC, D'Arcy PF. Interaction between azapropazone and warfarin. *BMJ* 1977;ii:773-4.
- 6 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British national formulary No 20*. London: BMA and Pharmaceutical Press, 1990:320-3.

Allergy to spiramycin during prophylactic treatment of fetal toxoplasmosis

Drs L S OSTLERE, J A A LANGTRY, and R C D STAUGHTON (Westminster Hospital, London SW1P 2AP) write: A 38 year old primigravida who was 29 weeks pregnant was admitted with a three week history of an erythematous pruritic rash. This had initially affected her hands and spread to her trunk and limbs. Eight weeks before she had been started on spiramycin 1.5 g twice daily for a positive maternal IgM titre indicating toxoplasma infection, which may have occurred up to one year before conception. Fetal blood sampling for toxoplasma antibody was negative and ultrasonography had shown no abnormality. She had a history of atopic eczema and was taking other drugs. On examination she had a widespread maculopapular rash sparing the umbilicus and forming erythematous plaques. There was no vesiculation or pustulation. The fundal height was consistent with 29 weeks' gestation. She was not feverish, and general examination was normal.

The white cell count was $11.7 \times 10^9/l$ (normal range 4-11) with eosinophils $2.8 \times 10^9/l$ (0-0.4 $\times 10^9/l$). She had a raised γ -glutamyltransferase concentration of 82 U/l (5-55) and the other liver enzymes were normal. A skin biopsy showed focal spongiosis and occasional parakeratosis. There was dermal oedema with a moderately severe perivascular infiltrate of chronic inflammatory cells, eosinophils, nuclear dust, and occasional extravasated red cells. Results of direct immunofluorescence of affected skin were negative.

She was initially treated with beclomethasone dipropionate 0.025% (Propaderm) ointment and emollient wet wraps to good effect but relapsed when the topical steroids were stopped. Because of the temporal relation to starting spiramycin treatment, eosinophilia, raised γ -glutamyltransferase concentration, and negative results of direct immunofluorescence, the rash was thought to have been caused by allergy to spiramycin. The risk of continuing spiramycin was considered greater than the possible benefits and the drug was stopped. Over the next two weeks the pruritus and rash resolved and remained clear. Her eosinophil count fell to $0.1 \times 10^9/l$ and γ -glutamyltransferase concentration settled within the normal range. She delivered a healthy girl at 37 weeks' gestation. Her skin remained clear and at 6 weeks her daughter had normal ophthalmological findings.

Toxoplasmosis is a worldwide infection of humans and animals caused by the protozoan *Toxoplasma gondii*. During pregnancy toxoplasma may cause fetal infection, with potentially serious

effects.¹ Spiramycin, one of the group of macrolide antibiotics, is thought to reduce the risk of fetal toxoplasmosis by more than half in toxoplasma infection during pregnancy.² It has been in clinical use for 15 years with little serious associated toxicity.³ In the United Kingdom it is available only on a named patient basis and is used to treat toxoplasmosis and cryptosporidiosis. In other European countries it is used with similar indications to those for erythromycin. The incidence of drug rash is approximately 1% (J G Bainbridge, personal communication), the most common being a transient erythema, and one case of allergic vasculitis has been reported.⁴ Other side effects include gastrointestinal upset and increased activity of liver enzymes.

France has had a national prevention programme for congenital toxoplasmosis since 1976. It includes mandatory serological screening of all pregnant women with monthly follow up tests if results are negative and treatment with spiramycin when acute infection is diagnosed. In the United Kingdom the prevention of congenital toxoplasmosis has received considerable attention in the mass media and the requests for antenatal screening have increased.⁵ Spiramycin is now recommended as first line treatment in pregnancy when maternal toxoplasma infection is proved or strongly suspected.⁶ It is increasingly important to recognise the side effects of spiramycin.

- 1 Desmonts G, Couvreur J. Congenital toxoplasmosis: a prospective study of 378 pregnancies. *N Engl J Med* 1974;290:1110-6.
- 2 Daffos F, Forestier F, Capella-Pavlosky M, et al. Prenatal management of 746 pregnancies at risk of congenital toxoplasmosis. *N Engl J Med* 1988;318:271-5.
- 3 Descoters J, Vial T, Delattre D, Evreux JC. Spiramycin: safety in man. *J Antimicrob Chemother* 1988;suppl B:207-10.
- 4 Galland MC, Rodor F, Jougla J. Spiramycin allergic vasculitis: first report. *Therapie* 1987;42:227-9.
- 5 Anonymous. Antenatal screening for toxoplasmosis in the UK. *Lancet* 1990;336:346-8.
- 6 Hohlfield P, Daffos F, Thulliez P, et al. Fetal toxoplasmosis: outcome of pregnancy and infant follow-up after in utero treatment. *J Pediatr* 1989;115:765-9.

Lung and skin hypersensitivity to 5-aminosalicylic acid

Drs V LE GROS, H SAVEUSE, G LESUR (Hôpital Ambroise Paré, 92104 Boulogne Cedex, France) and N BRION (Centre Hospitalier de Versailles, 78157 Le Chesnay Cedex, France) write: 5-aminosalicylic acid (5-ASA) is a half active component of sulphasalazine and has been used alone in the treatment of ulcerative colitis.¹ Sulphapyridine, a half inactive component, is held responsible for most side effects of sulphasalazine, including sulphasalazine induced lung diseases.^{2,3} We report a case of lung and skin hypersensitivity to 5-ASA. Neither the French adverse effect drug system nor the drug company have received previous reports of this.

A 54 year old woman was admitted to hospital for fever and erythematous skin rash occurring five days after treatment with 5-ASA (mesalazine) was initiated for an acute episode of ulcerative colitis (250 mg oral doses three times a day). She had no history of intolerance to salicylates but 10 years previously had developed a skin rash after three weeks of treatment with sulphasalazine. A chest radiograph disclosed bilateral interstitial opacities. Lung function tests showed a carbon dioxide pulmonary diffusion capacity of 53% of the expected value. Bronchoalveolar lavage fluid contained 138×10^6 cells/ml with 63% macrophages, 1.5% eosinophils, 0.5% neutrophils, and 35% lymphocytes with a CD4/CD8 ratio of 0.95 (1.70 in blood). A blood test of basophil degranulation in presence of 5-ASA was positive at 60%. 5-ASA was given for 17 days. After drug withdrawal the fever abated within 24 hours, lung opacities disappeared within 10 days, and skin rash disappeared within three weeks. One month later, the lung diffusing capacity was at 86% of the expected value.

The diagnosis of hypersensitivity to 5-ASA was based on the absence of any other aetiology; a history of hypersensitivity to sulphasalazine; lymphocytosis and low CD4/CD8 ratio in bronchoalveolar lavage fluid; blood tests positive for basophil degranulation in the presence of 5-ASA; and rapid improvement after drug withdrawal. This case suggests that 5-ASA moiety of sulphasalazine may be the responsible agent in some cases of lung diseases induced by sulphasalazine.

- 1 Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989;298:82-6.
- 2 Jones GR, Malone DNS. Sulphasalazine-induced lung disease. *Thorax* 1972;27:713-7.
- 3 Thomas P, Seaton A, Edwards J. Respiratory disease due to sulphasalazine. *Clin Allergy* 1974;4:41-7.
- 4 Moseley RM, Barwick KW, Dobuler K, Deluca VA. Sulphasalazine-induced pulmonary disease. *Dig Dis Sci* 1985;30:901-4.

Catatonias in the allopurinol hypersensitivity syndrome

Drs C E COLLINS, D J B THOMAS, and J M GUMPEL (Mount Vernon Hospital, Northwood, Middlesex HA6 2RN) write: A 67 year old woman presented with a 24 hour history of vague affect, a widespread itchy maculopapular rash, and a temperature of 37.5°C. She was uncommunicative, staring into space; her elbows, hips, and knees were flexed and unyielding. Eight weeks previously she had suffered a "flare up" of her longstanding gout, which was being treated with indomethacin (Indocid R 75 mg thrice daily). At the time of admission her only medication was allopurinol 100 mg thrice daily, which she had started six weeks previously. Her urea concentration had been 12 mmol/l, serum urate concentration 609 mol/l, and haemoglobin concentration 104 g/l when she was first prescribed allopurinol.

The following investigations were abnormal after admission: erythrocyte sedimentation rate 133 mm in the first hour, urea concentration 29 mmol/l, creatinine concentration 391 mmol/l, haemoglobin concentration 96 g/l falling to 69 g/l three days later. There were atypical red cell antibodies with specificity for anti-D. Tests for smooth muscle antibodies, antinuclear factor, and double stranded DNA antibodies were negative. The patient was treated with intravenous hydrocortisone 200 mg six hourly for 48 hours, followed by oral prednisolone 40 mg daily for two weeks; the allopurinol was discontinued. The catatonias, rash, and temperature rapidly improved and the renal function returned to its previous level. The gouty arthritis was successfully treated with tiaprofenic acid, which is a uricosuric non-steroidal anti-inflammatory drug. The patient remained well without taking steroids.

The allopurinol hypersensitivity syndrome is a rare, life threatening complication that usually affects patients who are also being treated with diuretics, particularly patients with impaired renal function.^{1,2} Catatonias has not been described with this syndrome and its presence is difficult to explain. There was no previous psychiatric history in this patient, and allopurinol does not have any known neuroleptic activity.³ Whatever the aetiology of the catatonias in this patient, it seemed to be sensitive to steroids, improving within two hours and disappearing within 10 hours when intravenous hydrocortisone was given. Paradoxically, prednisolone was incriminated as a causative factor when catatonias developed in a patient with myeloma.⁴

- 1 Mills RM. Severe hypersensitivity reactions associated with allopurinol. *JAMA* 1971;216:799-802.
- 2 Young JL, Boswell RB, Nies AS. Severe allopurinol hypersensitivity. *Arch Intern Med* 1974;134:553-8.
- 3 Fricchione GL. Neuroleptic catatonias and its relation to psychogenic catatonias. *Biol Psychiatry* 1985;20:304-13.
- 4 Grigg JR. Prednisolone mood disorder with associated catatonias. *J Geniatr Psychiatry Neurol* 1989;2:41-4.