LETTERS TO THE EDITOR

● The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.

● All letters must be typed with double spacing and signed by all authors.

● No letter should be more than 600 words.

● In general, no letter should contain more than six references (also typed with double spacing).

International Primary Pulmonary Hypertension Study

SIR,—In December 1993 (*British Heart Journal* 1993;70:537-41) Brenot and colleagues reported 15 new cases of primary pulmonary hypertension (PPH) with a history of exposure to appetite suppressants.¹ The series brought this problem to the attention of the scientific and medical community. Brenot *et al* concluded that the results of a European case-control study are awaited.

We wish to comment briefly on this European study. Indeed, as Brenot *et al* state, the reported case series "provides no definitive answers about a cause and effect relation". This cautious conclusion arises out of the many difficulties associated with interpreting such case reports. For instance, appetite suppressants are most often used by those who are also at higher risk of PPH, that is young women. They are also more likely to have been exposed to other alleged risk factors for PPH such as pregnancy or the use of oral contraceptives or both. Exposure to one appetite suppressant is very rarely unique: thyroid compounds, amphetamine-like drugs, other drugs, and special diets are often also "tried" by those who want to lose weight. Appetite suppressants are sometimes prescribed to reduce obesity in patients presenting with dyspnoea, a prodromic sign of PPH. All these factors and other sources of bias mean that it is difficult to assess independently of other factors the exact contribution of one factor to the development of the disease, especially in a retrospective case series. This was why an epidemiological study was organised. Epidemiological data on primary pulmonary hypertension are almost non-existent.

The International Primary Pulmonary Hypertension Study (IPPHS) is recruiting incident cases of PPH in five countries: France (including Dr Brenot's and Dr Simonneau's centre), the United Kingdom, Belgium, The Netherlands, and Switzerland. The study is examining all the alleged risk factors for PPH, not only fenfluramine derivatives. More than 150 centres are participating in the study with the objective of recruiting 100 validated cases and 400 properly matched controls. Cases reported to the IPPHS are screened by local specialists and reviewed by an international

panel. The selection of controls is physician-based. This is carefully done to obtain a valid basis to compare the exposure in a control population, a key issue when the exposure to alleged risk factors in the general population is widespread but unevenly distributed. Interviewers are blind to the hypotheses under study. Our aim was to complete the study within two years from 1 September 1992. It is very likely that this goal will be reached because two thirds of the required validated cases in all the participating countries have been recruited to date. In France, where the case series reported by Brenot *et al* originates, we have been able to identify only 46 incident cases of PPH over a 13 month period. To achieve this level of recruitment we contacted more than 80 centres every three months. The expected number of incident cases of PPH in a country such as France was a priori thought to be around 100 per year.

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1 Brenot F, Herve P, Petitpretz P, Parent F, Duroux P, Simonneau G. Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993;70:537-41.

Are streptokinase antibodies clinically important?

SIR,—A recent editorial and paper examined the clinical significance of streptokinase (SK) antibodies.^{1,2} There are two problems associated with the presence of specific SK antibody. Firstly, there is the possibility of impairing the thrombolytic action of SK and secondly there is the increased likelihood of allergic reactions. Higher titres potentially increase these problems in patients treated with SK in the previous two and a half years.^{2,3} The present dose of SK used for the first time is as efficacious as the other thrombolytic agents but its efficacy in patients receiving a second dose for re-infarction has not been evaluated. Significant inhibition of SK activity by specific antibody has been shown *in vitro*.⁴ However, one cannot extrapolate directly from the laboratory bench to the intracoronary thrombus. Though SK binds to plasminogen on an equimolar basis, the plasminogen-SK complex is a far more potent activator of plasminogen than SK alone and generates plasmin in a cascade fashion. Thus it is possible that even if the number of molecules of the SK-plasminogen complex formed were reduced, enough may be present to activate all circulating plasminogen and plasminogen bound to plasmin to generate a thrombolytic state. In the Third International Study of Infarct Survival (ISIS-3) SK was readministered to a large subgroup of patients (21.7% had previous myocardial infarction) and the overall results did not suggest reduced efficacy of SK (or anistreplase) compared with alteplase. A study by White *et al*⁵ had too few patients for any conclusions to be drawn. The potential problem of impaired

efficacy of SK readministration needs to be evaluated *in vivo*.

Increasing the dose of SK was proposed as a possible solution to higher antibody titres. However, in the presence of high titres of circulating antibody this would, probably, increase even further the risk of immune reactions. Whereas the commonly encountered mild reactions to SK are not necessarily related to the antibody titre,⁶ serious immune reactions—for example, serum sickness—are. Increasing the concentration of administered antigen would result in the formation of more immune complex and its deposition in various organs. Early studies evaluating the therapeutic dose of SK found much increased incidence of allergic reactions in patients receiving prolonged SK infusions, a situation that resembles a repeat bolus dose (both methods of administrations cause high circulating concentrations of specific antibody). Allergic reactions were mild (hypotension, fevers, and prolonged pyrexia) or severe (serum sickness). Recently, there has been interest in the transient proteinuria associated with SK treatment in some patients with acute myocardial infarction, which may prove to be related to immune complex deposition in the glomeruli. If it is, an increased dose may worsen the proteinuria.

The editorial and paper^{1,2} mentioned the need for a bedside test to measure specific antibody concentration. Skin testing may prove to be a predictor of circulating antibodies, however, so far too few patients have been studied.^{7,8} A bedside test that is inexpensive and rapid would be helpful for the readministration of SK.

Clearly the efficacy of repeat administration of SK needs to be evaluated by a study of coronary artery patency. We need to evaluate the present dose of SK in patients presenting at least two and a half years after their initial infarct. Until the immune problems associated with SK have been investigated, increasing the dose should probably not be regarded as an option. In the meantime, when patients re-presented with a further infarction between three days and two and a half years of their SK-treated infarction administration of a thrombolytic agent other than SK or anistreplase should be considered.

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- 1 Buchalter M. Are streptokinase antibodies clinically important? *Br Heart J* 1993;70:101-2.
- 2 Patel S, Jalihal S, Dutka DP, Morris GK. Streptokinase neutralisation titres up to 866 days after intravenous streptokinase for acute myocardial infarction. *Br Heart J* 1993;70:119-21.
- 3 Lynch M, Littler WA, Pentecost BL, Stockley RA. The immunoglobulin response to intravenous streptokinase in acute myocardial infarction. *Br Heart J* 1991;66:139-42.
- 4 Jalihal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990;335:184-5.
- 5 White HD, Cross DB, Williams BF, Norris NM. Safety and efficacy of repeat thrombolytic treatment after acute myocardial infarction. *Br Heart J* 1990;64:177-81.
- 6 Lynch M, Littler WA, Pentecost BL, Stockley RA. Why do patients develop reactions to streptokinase? *Clin Exp Immunol* 1993;94:279-85.

- 7 McGrath KG, Zeffren B, Alexander J, Kaplan K, Patterson R. Allergic reactions to streptokinase consistent with anaphylactic or antigen-antibody complex-mediated damage. *J Allergy Clin Immunol* 1984;73:453-7.
- 8 Lynch M. The immunology of streptokinase. University College Galway, National University of Ireland, 1992;5:79-114. MD thesis.

BRITISH CARDIAC SOCIETY NEWSLETTER

The Government's announcement on the Calman proposals is disappointing: it does not set targets for an expansion of consultant numbers or identify extra funding. The possible expansion of staff grade appointments and a relaxation in the control of senior house officer posts may lead to greater staffing at lower grades because the specialist training grades have shorter training periods. However, there will be less time available for service work and an increase in protected training time. Standards of care of patients and of research and development will be maintained and enhanced only by a vigorous and sustained expansion of consultant staffing. The British Cardiac Society will continue to exert pressure centrally but it is of the utmost importance that all cardiologists and cardiac surgeons support these developments in their own units. Any proposal that leaves units with inadequate consultant staffing for patient care, training, and research and development must be resisted.

The BCS Council will be keeping developments under review on a national basis and is keen to help colleagues if any difficulties develop locally. Please write to the President about any concerns you have.

The British Pacing and Electrophysiology Group

Anthony Nathan writes: "The British Pacing and Electrophysiology Group (BPEG) is delighted to continue its participation at the British Cardiac Society Annual General Meeting and this year will hold a symposium on "How to Treat Difficult Ventricular Arrhythmias", with the aim of enlightening the audience on how to handle different forms of ventricular tachycardia. All are welcome to attend."

"The Annual General Meeting of BPEG will take place on Friday 1 July, 1994, at the Royal College of Physicians, London, and will last all day. The scientific sessions will be chaired by Dr Janet McComb; and Professor Lukas Kapenberger of Lausanne will give the guest lecture on "Pacing in cardiomyopathy". A mini-symposium on the mechanisms and treatment of atrial fibrillation will follow and a review of the current

relevant studies on bradycardia and tachycardia will also be presented."

"Modernisation and revision of the pace-maker registry has continued and we hope that by the time this newsletter is published a new user interface will be available based upon *Microsoft Windows* rather than the previous text-based screens. The implantable cardioverter defibrillator registry has been running hand-in-hand with this and will become part of the European Registry of Implantable Defibrillators network. Hart-Line, a fax information service on arrhythmias, was launched in December and is proving popular. Any further information on this or any other topic can be obtained from the BPEG offices: tel 071 637 0016, fax 071 323 5867 (9 Fitzroy Square, London W1P 5AH)."

British Association for Cardiac Rehabilitation

Hugh Bethell writes: "The British Association for Cardiac Rehabilitation has now become a reality. The inaugural meeting was held in September 1992; a meeting to adopt the constitution in April 1993; and, following election of a committee, the first AGM was held in September 1993. The Association is multidisciplinary and members include cardiologists, physicians, general practitioners, nurses, physiotherapists, psychologists, dietitians, and exercise physiologists. The aims of the association are to provide a forum for all professionals concerned with the rehabilitation of cardiac patients, to promote the widespread provision of cardiac rehabilitation, and to encourage high standards of practice. There is a quarterly newsletter and an annual scientific and educational meeting is planned." The association would benefit greatly from the support of cardiologists and we hope that all those specialists interested in rehabilitation will join. There is a small annual membership fee (£25). For further details, membership forms and the constitution please write to BACR, c/o Action Heart, Wellesley House, 117 Wellington Road, Dudley, West Midlands DY1 1UB.

European Society of Cardiology

Phillip Poole-Wilson writes: "The Education and Training Programme at the European Heart House includes the following programme:

19-21
May	Evolution of myocardial viability: assessment of revascularisation after myocardial infarction
9-11
June	The syndrome of angina in normal coronary arteries: pathophysiology, diagnosis and treatment
22-24
September	Endocarditis: prophylaxis, diagnosis, and management
13-15
October	Management of patients with automatic defibrillators: indications, implantation, follow up

20-22
October	Management of myocardial infarction: early detection, pre-hospital management thrombolysis and other reperfusion therapy, and follow up
24-26
November	Integrated approach to interventional cardiology: indications for different devices and practical instruction for their use
9-11
December	Primary and secondary prevention of coronary artery disease: a message for the Christmas period.

The cost for attending these programmes ranges from Fr 3000 to Fr 4000 depending on hotel accommodation. The price includes the scientific programme, bus transport, hotel, meals, and coffee breaks. The price does not include travel. The meetings usually last three days. The programmes are of high quality and low cost. If you are interested please write to ECOR, Meeting Services, c/o Acte-Les Espaces Delta-BP 037, 80 Route des Lucioles, 06901 Sophia Antipolis, France."

Other news

It is sad to record the death of Dr J B Lowe who was a pioneer in invasive cardiology. A New Zealander, he trained in medicine in Edinburgh and in cardiology at the National Heart Hospital with the late Paul Wood. He was appointed cardiologist to Green Lane Hospital in Auckland in 1953 and together with Sir Brian Barratt-Boyes and the late Sir Douglas Robb he founded and developed cardiology at Green Lane to a pre-eminent position in Australasia. He will be remembered with great respect and affection by the generations of cardiologists whom he trained.

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NOTICES

The 1994 Annual Meeting of the **British Cardiac Society** will take place at the Riviera Centre, Torquay from 17 to 20 May.

The **Second International Symposium on Fibrinogen and Cardiovascular Disease** organised by the Royal College of Physicians will take place in Edinburgh on 1 and 2 November 1994. Further details are available from Royal College of Physicians Education, Audit and Research Department, 9 Queen Street, Edinburgh EH2 1JQ (tel: 031-225 7324, fax: 031-220 3939).