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, Jaliha 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 Jaliha 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.