

# Cigarette smoking and rate of gastric emptying: effect on alcohol absorption

Richard D Johnson, Michael Horowitz, Anne F Maddox, Judith M Wishart, David J C Shearman

## Abstract

**Objective**—To examine the effects of cigarette smoking on alcohol absorption and gastric emptying.

**Design**—Randomised crossover study.

**Setting**—Research project in departments of medicine and nuclear medicine.

**Subjects**—Eight healthy volunteers aged 19-43 who regularly smoked 20-35 cigarettes a day and drank small amounts of alcohol on social occasions.

**Interventions**—Subjects drank 400 ml of a radio-labelled nutrient test meal containing alcohol (0.5 g/kg), then had their rates of gastric emptying measured. Test were carried out (a) with the subjects smoking four cigarettes an hour and (b) with the subjects not smoking, having abstained for seven days or more. The order of the tests was randomised and the tests were conducted two weeks apart.

**Main outcome measures**—Peak blood alcohol concentrations, absorption of alcohol at 30 minutes, amount of test meal emptied from the stomach at 30 minutes, and times taken for 50% of the meal to leave the proximal stomach and total stomach.

**Results**—Smoking was associated with reductions in (a) peak blood alcohol concentrations (median values in non-smoking versus smoking periods 13.5 (range 8.7-22.6) mmol/l v 11.1 (4.3-13.5) mmol/l), (b) area under the blood alcohol concentration-time curve at 30 minutes ( $264 \times 10^3$  (0.509  $\times 10^3$ ) mmol/l/min v  $140 \times 10^3$  (0.217  $\times 10^3$ ) mmol/l/min), and (c) amount of test meal emptied from the stomach at 30 minutes (39% (5-86%) v 23% (0-35%)). In addition, smoking slowed both the 50% gastric emptying time (37 (9-83) minutes v 56 (40-280) minutes) and the intragastric distribution of the meal. There was a close correlation between the amount of test meal emptied from the stomach at 30 minutes and the area under the blood alcohol concentration-time curve at 30 minutes ( $r=0.91$ ;  $p<0.0001$ ).

**Conclusion**—Cigarette smoking slows gastric emptying and as a consequence delays alcohol absorption.

## Introduction

Although alcohol and tobacco are among the most widely used drugs in the world and are often used together, little is known of their pharmacokinetic interactions. Like most other drugs, alcohol is absorbed predominantly from the small intestine by virtue of its enormous surface area as compared with the stomach. Because the rate of alcohol absorption is dependent on gastric emptying<sup>1,2</sup> factors which modify gastric emptying will also modulate the rate of alcohol absorption.<sup>2,4</sup> For example, the rate of alcohol absorption is slower when a beverage containing alcohol is consumed with or after a meal rather than on an empty stomach,<sup>2</sup> faster after administration of metoclopramide and various forms of gastric surgery, and slower after administration of propantheline.<sup>4,5</sup> The effect of tobacco smoking and nicotine on gastric emptying is controversial, studies finding increased,<sup>6</sup> decreased,<sup>7-10</sup> or unchanged<sup>6,11,12</sup> rates of gastric emptying. To our knowledge the effect of tobacco smoking on alcohol

absorption has not been studied. This study examines the effects of cigarette smoking on alcohol absorption and gastric emptying.

## Subjects and methods

The studies were performed in eight normal volunteers (seven men, one woman) aged 19-43 years (median 25) who smoked cigarettes regularly (20-35 a day). The subjects' body weights ranged from 65 to 98 kg (median 85 kg). None was receiving any medicines and none had evidence of gastrointestinal disease. All drank small quantities of alcohol on social occasions, but alcohol was avoided for 48 hours before each measurement of gastric emptying. Written, informed consent was obtained in all cases and the study was approved by the human ethics committee of the Royal Adelaide Hospital.

**Protocol**—Each volunteer had measurements of gastric emptying performed in a crossover study (a) while smoking four cigarettes an hour, beginning 15 minutes before the study, and (b) while not smoking, having abstained from cigarettes for at least seven days. The order of the tests was randomised and they were conducted two weeks apart. Each study began at roughly 1600, the subject having fasted since eating a standardised breakfast between 0700 and 0800.<sup>13</sup> All the cigarettes were filtered, and their median nicotine and tar yields were 0.9 (range 0.6-1.1) mg and 10 (6-12) mg per cigarette respectively. The liquid test meal (400 ml) consisted of orange juice diluted in water, 0.5 g absolute alcohol per kg body weight, and 28-37 MBq indium-113m labelled diethylenetriaminepenta-acetic acid.<sup>2</sup> The energy content of the orange juice (total carbohydrate 21.2 g, sugar 16.4 g, protein 1.6 g, fat 0.2 g) was 402 kJ, and for a 70 kg subject an additional 1026 kJ was contained in the alcohol. The energy content for the meal for a 70 kg subject was therefore approximately 3.55 kJ/ml. The temperature of the meal ranged from 19° to 21°C and its pH ranged from 3.9 to 4.0.

**Measurement of gastric emptying**—Details of the isotope test have been reported.<sup>13</sup> Each study was performed with the subject seated in front of a scintillation camera. The test meal was consumed within two minutes and the point of completion of the meal taken as time zero. Data were corrected for movement of the subject, radionuclide decay, and  $\gamma$  ray (tissue) attenuation.<sup>13</sup> From the curves of gastric emptying (expressed as a percentage of the total meal remaining within the stomach over time) we derived (a) the duration of the lag phase before any of the meal emptied into the stomach, (b) the amount of the meal that had emptied from the stomach at 10, 30, and 60 minutes, and (c) the time to 50% emptying of the total stomach. The total stomach was divided into proximal and distal regions of interest by using a line drawn half way along and at 90 degrees to the long axis. The time taken for 50% of the meal to leave the proximal gastric region was measured.

**Measurement of blood alcohol concentrations**—In each study blood samples for measurement of alcohol concentrations were taken from a catheter situated in

Department of Medicine,  
Royal Adelaide Hospital,  
North Terrace, Adelaide,  
South Australia

Richard D Johnson, FRACP,  
senior visiting specialist  
Michael Horowitz, FRACP,  
associate professor of medicine  
Judith M Wishart, BSc,  
research assistant  
David J C Shearman, FRACP,  
professor of medicine

Department of Nuclear  
Medicine, Royal Adelaide  
Hospital, North Terrace,  
Adelaide, South Australia  
Anne F Maddox, MIR,  
research assistant

Correspondence and  
requests for reprints to:  
Dr Johnson.

BMJ 1991;302:20-3

a forearm vein five minutes before and five, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, and 210 minutes after the test meal had been taken. To avoid possible contamination the skin was previously cleaned with a non-alcoholic antibacterial solution. Samples of blood were stored at 4°C and assayed for alcohol within 72 hours by gas-liquid chromatography.<sup>14</sup> The areas under the venous blood alcohol concentration-time curves between zero and 30 minutes, zero and 60 minutes, and zero and 210 minutes were calculated.<sup>1</sup>

**Statistical analysis**—Data were analysed with the Wilcoxon matched pairs signed ranks test and Pearson's product moment correlation. 95% Confidence intervals were calculated and p values <0.05 taken as significant in all analyses.

## Results

**Blood alcohol concentrations**—The areas under the venous blood alcohol concentration-time curves between zero and 30 minutes and zero and 60 minutes and the peak blood alcohol concentrations were significantly less during the smoking period compared with values during the non-smoking period (fig 1, table I). Most of the subjects had detectable but low blood alcohol concentrations at 210 minutes, and there was a non-significant reduction in the area under the blood alcohol concentration-time curve between zero and 210 minutes in the smoking period compared with the non-smoking period (p=0.062).

**Gastric emptying**—Gastric emptying was significantly slower during the smoking period than when not smoking (table II, fig 2). In all subjects the emptying curve was non-linear, and in the non-smoking periods it usually approximated a monoexponential pattern. In all studies performed during smoking there was a lag phase (minimum duration four minutes) before any of the meal emptied from the stomach (table II). The 50% emptying time from the proximal gastric region was significantly greater during smoking (fig 2). There were significant correlations between the 50% emptying times from the proximal stomach and total stomach

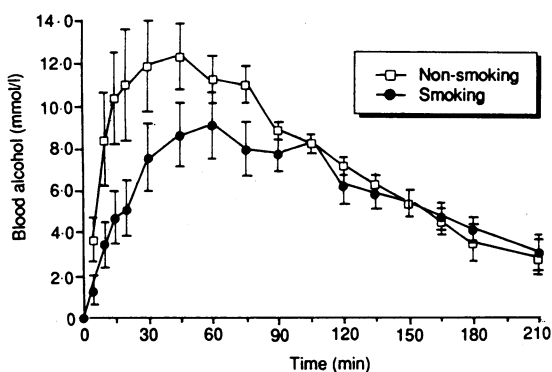


FIG 1—Mean blood alcohol concentrations after consumption of test meal during smoking and non-smoking periods. Bars are SEM

TABLE I—Median blood alcohol concentrations (ranges) during smoking and non-smoking periods

Variable	Non-smoking	Smoking	p Value
Peak blood alcohol (mmol/l)	13.5 (8.7-22.6)	11.1 (4.3-13.5)	0.008
Area under curve at 30 minutes (mmol/l/min) ( $\times 10^3$ )	264 (0-509)	140 (0-217)	0.014
Area under curve at 60 minutes (mmol/l/min) ( $\times 10^3$ )	647 (80-909)	469 (62-562)	0.013
Area under curve at 210 minutes (mmol/l/min) ( $\times 10^3$ )	1609 (913-2132)	1429 (498-1827)	0.062

TABLE II—Median gastric emptying values (ranges) during smoking and non-smoking periods

Variable	Non-smoking	Smoking	p Value
Lag (min)	2 (1-23)	13 (4-86)	0.010
Amount emptied at 10 minutes (%)	11 (0-52)	0 (0-8)	0.010
Amount emptied at 30 minutes (%)	39 (5-86)	23 (0-35)	0.014
Amount emptied at 60 minutes (%)	72 (28-95)	56 (0-83)	0.013
50% Emptying time from total stomach (min)	37 (9-83)	56 (40-280)	0.012
50% Emptying time from proximal stomach (min)	14 (4-45)	24 (8-130)	0.014

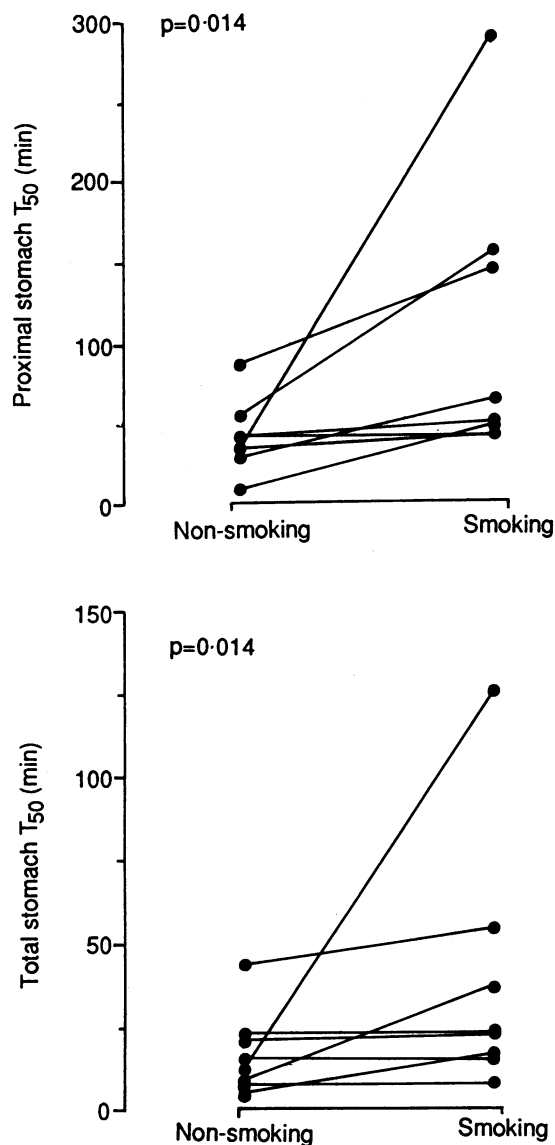


FIG 2—Individual 50% emptying times ( $T_{50}$ ) from total stomach and proximal stomach during smoking and non-smoking periods

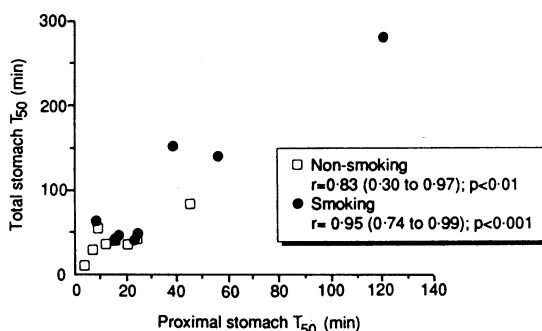


FIG 3—Relations between 50% emptying times ( $T_{50}$ ) from proximal stomach and total stomach during smoking and non-smoking periods. (r Values expressed with 95% confidence intervals in parentheses)

(fig 3) in both the non-smoking ( $r=0.83$  (95% confidence interval 0.30 to 0.97);  $p<0.01$ ) and smoking ( $r=0.95$  (0.74 to 0.99);  $p<0.001$ ) periods.

**Relation between alcohol absorption and gastric emptying**—The areas under the venous blood alcohol concentration-time curve between zero and 30 minutes and zero and 60 minutes correlated significantly with the amount of the meal emptied from the stomach at 30 minutes and 60 minutes respectively (fig 4). In the non-smoking periods the correlations were  $r=0.95$  (95% confidence interval 0.74 to 0.99;  $p<0.001$ ) and  $r=0.90$  (0.53 to 0.98;  $p<0.001$ ) respectively, whereas in the smoking periods the correlations were  $r=0.78$  (0.17 to

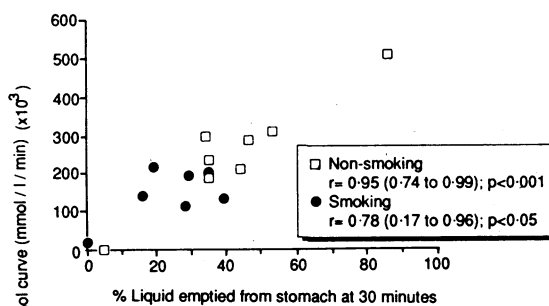


FIG 4—Areas under venous blood alcohol concentration-time curve plotted against percentage of liquid meal emptied from stomach at 30 minutes and 60 minutes during smoking and non-smoking periods. (r Values expressed with 95% confidence intervals in parentheses)

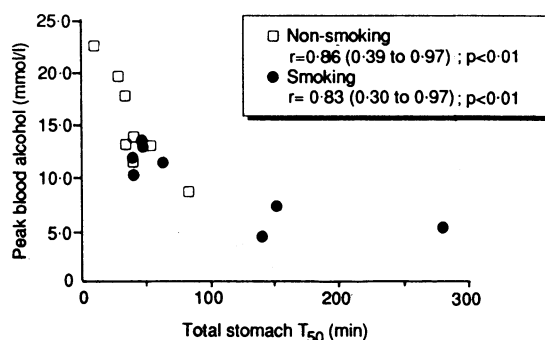
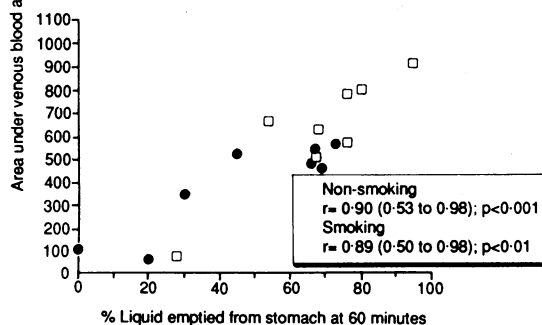


FIG 5—Relations between peak blood alcohol concentrations and 50% total gastric emptying time during smoking and non-smoking periods. (r Values expressed with 95% confidence interval in parentheses)

0.96;  $p < 0.05$ ) and  $r = 0.89$  (0.50 to 0.98;  $p < 0.01$ ). In both the non-smoking and smoking periods there was a significant inverse relation between the peak blood alcohol concentrations and the 50% gastric emptying time (non-smoking period:  $r = 0.86$  (95% confidence interval 0.39 to 0.97),  $p < 0.01$ ; smoking period:  $r = 0.83$  (0.30 to 0.97),  $p < 0.01$ ) (fig 5).

### Discussion

After ingestion of an equivalent, weight adjusted dose of alcohol there is considerable interindividual and intraindividual variation in the rate of absorption and peak blood alcohol concentrations.<sup>1</sup> Our findings confirm that these differences are largely attributable to variations in the rate of gastric emptying.<sup>12</sup> We studied only eight subjects. Nevertheless, a crossover design was used, which in seven of the eight subjects showed that the rate of total gastric emptying was slower during smoking. In the remaining subject the rate was unchanged (fig 2). Thus in this series cigarette smoking significantly reduced peak blood alcohol concentrations and delayed alcohol absorption, presumably by slowing gastric emptying.

These observations have considerable social and medicolegal relevance. It is legally permissible to back calculate to the time of a motor vehicle accident the blood alcohol concentration in motorists suspected of drink-driving offences. The variability in peak blood alcohol concentrations in this study points to the limitations of back calculation of blood alcohol concentrations.<sup>15</sup> Moreover, smoking and nicotine intake should be controlled for in studies of alcohol absorption, unlike in previous studies.<sup>16-19</sup>

The effect of smoking and nicotine on gastric

emptying has been the subject of several studies.<sup>6-12</sup> In all but one study<sup>6</sup> smoking was found to delay gastric emptying of a digestible solid meal.<sup>7-10</sup> Miller *et al* and Petring *et al* found that smoking did not affect the rate of emptying of a liquid meal.<sup>10,11</sup> Petring *et al* used the rate of paracetamol absorption as an indirect measure of liquid gastric emptying, and this technique is known to be fairly insensitive.<sup>20</sup> Miller *et al* studied gastric emptying of water, and their observations may be accounted for by the absence of nutrients in the liquid meal. We have shown that smoking significantly slows gastric emptying of a liquid meal containing nutrients and that this delay reflects, at least in part, slowing of the intragastric distribution of the meal.

The contribution of nicotine to the delay in gastric emptying produced by cigarette smoking remains controversial. Gritz *et al* found that gastric emptying of a solid meal was slightly but significantly delayed after smoking high versus low nicotine cigarettes.<sup>9</sup> They did not, however, include a "non-smoking" test. In other studies ingestion of nicotine gum had no effect on gastric emptying.<sup>10,12</sup>

There is little information about the motor mechanisms by which cigarette smoking slows gastric emptying. McDonnell and Owyang have recently shown that smoking inhibits antral contractions,<sup>21</sup> which may account for slowed gastric emptying of digestible solid meals. Nicotine reportedly inhibits antral contractions in dogs.<sup>22</sup> Valenzuela *et al* reported that smoking decreased basal pyloric pressure,<sup>23</sup> but in the light of current knowledge<sup>24</sup> the methodology used in their study must be considered to be technically inadequate and the results viewed with scepticism. The slowing of the intragastric distribution suggests that cigarette smoking decreases proximal gastric tone, which may account for the slowed emptying of a nutrient liquid meal.<sup>25</sup> In view of the probable crucial role of the pylorus in the regulation of nutrient liquid emptying, however,<sup>26,27</sup> the effect of smoking on pyloric motility warrants further study with improved methodology. Muller-Lissner reported that duodeno-gastric reflux is increased by smoking.<sup>8</sup> The retardation of gastric motility produced by smoking may be important in the pathogenesis of gastroesophageal reflux<sup>28</sup> and the reported effects of cigarette smoking on satiety.<sup>29</sup>

The area under the blood alcohol concentration-time curve at 30 minutes was taken as the index of the rate of alcohol absorption in this and other studies<sup>1,2</sup> on the basis that the rate of absorption at 30 minutes was much greater than the rate of hepatic metabolism. We now know, however, that the stomach metabolises alcohol by virtue of the presence of alcohol dehydrogenase in gastric mucosa,<sup>6-19</sup> and at low doses of alcohol (0.15 g/kg) consumed in the fed state this "first pass" effect is significant. The magnitude of this effect is likely to be greater if there is more prolonged contact of alcohol with the gastric mucosa because of slowed gastric emptying. Therefore, although much higher doses of alcohol (0.5 g/kg) were used in our study and the subjects were fasting, possibly gastric metabolism of alcohol contributed to the significant reduction in the area under the blood alcohol concentration-time curve at 30 and 60 minutes and the trend for a significant reduction at 210 minutes in the smoking period as well as slower gastric emptying. We could not assess total alcohol absorption because the blood alcohol concentrations did not reach zero in all subjects.

The computer program used to divide the stomach into proximal and distal regions was developed by Mr P Collins. The study was funded by the Australian Associated Brewers.

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(Accepted 18 September 1990)

## Relation between humoral responses to HIV gag and env proteins at seroconversion and clinical outcome of HIV infection

Rachanee Cheingsong-Popov, Christina Panagiotidi, Stella Bowcock, Anthony Aronstam, Jane Wadsworth, Jonathan Weber

### Abstract

**Objective**—To study the contribution of the humoral response to HIV-I at seroconversion to disease outcome after 84 months.

**Design**—A retrospective longitudinal study.

**Setting**—Two haemophilia centres in the United Kingdom.

**Patients**—88 Haemophiliac patients infected with HIV-I for whom sera were available from before seroconversion and in whom clinical follow up data were available.

**Results**—Kaplan-Meier survival analysis showed a significant difference between a high titre (>1600) p24 antibody response at seroconversion and prolonged time before the development of HIV related disease ( $p=0.0008$ ). In contrast, higher titres of antibody to gp120 at seroconversion (>25 600) correlated with more rapid clinical deterioration ( $p=0.025$ ).

**Conclusions**—The first humoral response to HIV proteins at seroconversion is associated with clinical outcome; patients with an initial low titre antibody response to the gagp24 protein have a significantly faster rate of progression to CDC stage IV disease. Patients with a high titre p24 antibody response progress to AIDS more slowly, and these data provide an explanation why p24 antigenaemia is not universally detected in patients with AIDS. It is unclear whether the association between a strong initial p24 antibody response and slower progression of HIV disease is causal and if so whether it is due to viral or host factors.

### Introduction

After infection with HIV-I there is a vigorous humoral response to structural and regulatory viral antigens.<sup>1-8</sup> Antibodies to the env gene products

gp160/gp120 and gp41 are produced early followed shortly by antibodies to the gag gene product p24.<sup>9-10</sup> By studying sequential serum samples from infected patients we and other investigators have found that there is an apparent lowering of titre of p24 (gag) antibodies in patients with more rapid progression to HIV related disease (AIDS related complex and AIDS)<sup>11-17</sup> whereas no such change is seen with gp41 (env) antibodies.

Subsequently, it has been repeatedly shown that 50-70% of patients with AIDS have detectable titres of serum p24 antigen whereas only rarely is p24 antigen detectable in asymptomatic patients<sup>18,21</sup>; detection of p24 antigen before symptomatic disease correlated significantly with prognosis over 27 months.<sup>19</sup> The loss of antibody precedes p24 antigenaemia by 12-18 months,<sup>22</sup> and this has been interpreted as being due to the formation of immune complexes of p24 antibodies with rising concentrations of p24 antigen.<sup>23,24</sup> We have recently shown, however, that undetectable titres of p24 antibodies in antigenaemic patients do not rise after the reduction of p24 antigen titre with zidovudine treatment<sup>25</sup>; this suggests that the mechanism for the decline in titre of p24 antibody is unlikely to be the simple formation of immune complexes. Cohort data have shown that over time increasing numbers of patients with preserved high titres of p24 antibody and without detectable titres of p24 antigen develop AIDS, and the association of loss of p24 antibodies with prognosis becomes less significant (unpublished data).<sup>25</sup> No explanation has yet been offered for these findings or for the failure to detect viral antigens in 30-50% of patients with AIDS, even when plasma viraemia can be readily detected.<sup>26,27</sup> As the presence of p24 antigen has been used as a surrogate marker of virus replication these data require elucidation.

We thus studied the role of the first humoral response to HIV gag, env proteins at seroconversion

Infectious Diseases Unit,  
Department of Medicine,  
Royal Postgraduate  
Medical School, London  
W12 0HS

Rachanee Cheingsong-  
Popov, PHD, senior research  
officer  
Christina Panagiotidi, MSC,  
technician  
Jonathan Weber, MRCP,  
senior lecturer

Department of  
Haematology, Royal  
Postgraduate Medical  
School, London W12 0HS  
Stella Bowcock, MRCP, senior  
registrar

Treloar Haemophilia  
Centre, Lord Mayor  
Treloar College,  
Hampshire  
Anthony Aronstam,  
FRCPATH, consultant  
haematologist

Academic Department of  
Public Health, St Mary's  
Hospital Medical School,  
London W2 1PG  
Jane Wadsworth, PHD, senior  
lecturer

Correspondence to:  
Dr J Weber,  
Jefferiss Wing, St Mary's  
Hospital Medical School,  
London W2 1NY.

BMJ 1991;302:23-6