AUTHOR'S REPLY,—Both the study that is commented on[1] and the update of the Steno studies 1 and 2[2] suggest that in normotensive patients with microalbuminuria those with the highest baseline urinary albumin excretion (100-300 mg/24 h) benefit most from the treatment. In addition, the spontaneous progression of urinary albumin excretion in patients with initial values between 30 and 100 mg/24 h was slow, at only 3% a year. The progression of microalbuminuria is also determined by the level of metabolic control and arterial blood pressure. Therefore, the arterial blood pressure, haemoglobin A_{1c} concentration, and urinary albumin excretion must be taken into account when the possible treatment for an individual patient with persistent microalbuminuria is evaluated.

We are still, however, unable to discriminate exactly between patients with persistent microalbuminuria who have a high as against a low risk of progression to nephropathy. Before this can be done longitudinal studies of the spontaneous course of the renal disease in insulin dependent diabetic patients with persistent microalbuminuria are needed, analysing the relative importance for progression to nephropathy of metabolic control, systemic blood pressure, baseline urinary albumin excretion, glomerular hyperfiltration, protein intake, serum lipid concentrations, etc.

In reply to Neil A Solomon, we have shown previously shown that a short term reduction in systemic blood pressure of 15 mm Hg leads to a significant reduction in urinary albumin excretion in normotensive patients with microalbuminuria.[3] The goal of the present study[1] was to prevent the expected rise in arterial blood pressure and, if possible, to reduce the diastolic blood pressure by 5 mm Hg in the treatment group. The mean diastolic blood pressure in the two groups was evaluated at six, 12, and 24 months. If the desired effect was not achieved the dose of captopril was subsequently doubled for every patient in the treatment group. At a given time all treated patients received the same dose of captopril and during the last 18 months also bendrofluazide. The change in the blood pressure and urinary albumin excretion in relation to the dose of captopril can be evaluated from figure 1. Neither at the start of the treatment nor when the dose was increased could any significant acute change in systemic blood pressure and urinary albumin excretion be detected.

In the control group the increase in urinary albumin excretion was not dependent on the baseline systemic blood pressure. When all values measured during the four year observation period were included in the calculations, however, a significant correlation between the changes in systemic blood pressure and in urinary albumin excretion was seen in the control group. No such correlation between the changes in systemic blood pressure and in urinary albumin excretion could be shown in the captopril group. The increase in systemic blood pressure may be secondary to the increase in urinary albumin excretion in patients with microalbuminuria, as previously suggested.[4] In seven of the 23 control patients and in 10 of the 21 treated patients a fall in diastolic blood pressure of at least 5 mm Hg was seen (not significant). Consequently, I do not find it reasonable to divide the patients into those who did and those who did not respond to treatment based on the blood pressure response as suggested.

Klavs Würgler Hansen has focused on the individual systemic blood pressure measured at baseline and at four year follow up (table II).[1] Unfortunately, he has missed table II, where we gave the annual change in blood pressure in the two groups. The precision of the figures was improved by including in the calculations all values measured during the four year observation period. The mean (95% confidence interval) change in blood pressure was −0·4 (−1 to 1)/−1 (−1 to 0) mm Hg a year in the captopril treated group and −0·3 (−1 to 1)/−0·7 (−2 to 0) mm Hg a year in the control group. These figures clearly showed that there was no significant difference in the annual change in blood pressure between the two groups.

In the present study it seems reasonable to conclude that the effect of captopril on the progression of the renal disease seemed to be independent of changes in systemic blood pressure. The gradual improvement in the urinary albumin excretion rate during treatment with captopril leads to the suggestion that a gradual improved selectivity of the glomerular barrier was the most important pathophysiological factor. I suggest that the effective dose of captopril is in the range 50-100 mg/24 h.

ELISABETH R MATHIESEN
Steno Memorial and Hvidøre Hospital,
2820 Gentofte,
Denmark

1 Mathiesen ER, Hommel E, Giese J, Parving H-H. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 1991;**303**:81-7. (13 July.)
2 Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. *Lancet* 1986;ii: 1300-4.
3 Hommel E, Mathiesen ER, Edsberg B, Bahnsen M, Parving H-H. Acute reduction of arterial blood pressure reduces urinary albumin excretion in type 1 (insulin-dependent) diabetic patients with incipient nephropathy. *Diabetologia* 1986;**29**:211-5.
4 Mathiesen ER, Oxenboll B, Johansen K, Svendsen PA, Deckert T. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1984;**26**:406-10.

Aprotinin and cardiac surgery

SIR,—We thank D W Bethune[1] and Lindsay C H John and colleagues[2] for their comments on our editorial on aprotinin and cardiac surgery.[3] Dr Bethune[1] suggested that there was evidence from Wang *et al*[4] that the prolongation of the activated clotting time seen when aprotinin is used during cardiopulmonary bypass surgery was an artefact caused by an interaction between the celite activator, heparin and aprotinin. We have performed similar experiments studying the effects of aprotinin on the activated partial thromboplastin time and the activated clotting time.[5] Aprotinin produced a dose dependent prolongation of both times with and without heparin; this occurred whether the activator was kaolin, celite, or micronised silica. Prolongation of clotting times which measure intrinsic pathway activation such as the activated partial thromboplastin time and the activated clotting time are to be expected with aprotinin, for as aprotinin inhibits kallikrein, an amplifier of intrinsic pathway activation, intrinsic coagulation activation will be limited and so prolong clotting times.

The comment from Dr John *et al*[2] that aprotinin may reverse an in vitro platelet inhibition related to heparin is an interesting hypothesis, and we look forward to seeing the original data. This does not, however, explain the efficacy of aprotinin in reducing perioperative bleeding in liver transplantation and vascular surgery when cardiopulmonary bypass and systemic heparinisation are not used and thus platelet damage is not induced. This led us to suggest that aprotinin's major mode of action is through its potent antifibrinolytic action rather than any major effect on platelets. The comments elicited by our editorial highlight the need for more research into the mechanisms of action of aprotinin.

BEVERLEY J HUNT
MAGDI YACOUB

Harefield Hospital,
Harefield,
Middlesex UB9 6JH

1 Bethune DW. Aprotinin and cardiac surgery. *BMJ* 1991;**303**:991. (19 October.)
2 John LCH, Rees GM, Kovac IB. Aprotinin and cardiac surgery. *BMJ* 1991;**303**:991-2.
3 Hunt BJ, Yacoub M. Aprotinin and cardiac surgery. *BMJ* 1991;**303**:660-1. (21 September.)
4 Wang J-S, Hung W-T, Karp R, Lun C-Y. Increase in ACT of heparinised blood in patients on aprotinin is caused by the celite activator. In: *Abstracts presented at the 13th annual meeting of the Society of Cardiovascular Anaesthesiologists, San Antonio, Texas 5-8 May 1991*. Richmond, Virginia: Society of Cardiovascular Anaesthesiologists, 1991.
5 Hunt BJ, Segal H, Yacoub M. Monitoring heparin by the activated clotting time when aprotinin is used during cardiopulmonary bypass. *Thromb Haemost* 1991;**65**:1025.

Glasgow coma scale and gag reflex

SIR,—C Moulton and colleagues have shown that the gag reflex may be impaired in apparently conscious patients requiring neurological observation in an accident and emergency department.[1] They recommend that the gag reflex should be assessed independently of the conscious level and used as an indicator of an "at risk" airway. Horner *et al*, however, showed in a series of 47 patients with stroke that the presence or absence of the gag reflex did not independently predict aspiration.[2]

The authors also mention that other reflexes are protective of the airway. It seems that the cough and swallow reflexes, though difficult to quantify, are more important in protecting the airway. In a series of 53 patients with closed head trauma a delayed or absent swallowing reflex, as shown by videofluoroscopy, was the most common cause of aspiration.[3] Another study of people with aspiration pneumonia showed an association with an impaired cough reflex.[4]

I therefore warn against relying unduly on a normal gag reflex indicating a safe airway. If there is doubt about whether patients are at risk of aspiration, ensuring that they receive "nil by mouth" until they improve or seeking a speech therapy assessment and then performing videofluoroscopy would be the safest course of action.

A J STANNERS
Department of Medicine for the Elderly,
St James's University Hospital,
Leeds LS9 7TF

1 Moulton C, Pennycock A, Makover R. Relation between Glasgow coma scale and the gag reflex. *BMJ* 1991;**303**:1240-1. (16 November.)
2 Horner J, Massey EW, Riski JE, Lathrop DL, Chase KN. Aspiration following stroke: clinical correlates and outcome. *Neurology* 1988;**38**:1359-62.
3 Lazarus C, Logemann JA. Swallowing disorders in closed head trauma patients. *Arch Phys Med Rehabil* 1987;**68**:79-84.
4 Sekizawa K, Ujiie Y, Itabashi S, Sasaki H, Takishima T. Lack of cough reflex in aspiration pneumonia. *Lancet* 1990;**335**:1228-9.

Rugby injuries

SIR,—Having some experience of rugby injuries, I entirely agree with W M Garroway and colleagues that problems exist "with both the numerator and the denominator"[1] as the total number of rugby players in the United Kingdom is not known, only the number of clubs; similarly, the number of games in which each player takes part each week is not known. This problem with the numerator and the denominator makes injury rates a matter of speculation.

When I looked at catastrophic injuries to 67 rugby players in 1984[2] and a further 19 players in 1988[3] it took a great deal of time to obtain accurate information about how they had been sustained. I wrote:

It is salutary to realise that, although it is such a catastrophic injury for which compensation would be payable (all members of affiliated clubs have to be covered by insurance), neither the Welsh Rugby Union nor the Rugby Football Union had information on 2 such injuries from their insurance company, or information on a further 7 which were on record. This situation was due to clubs and schools failing to inform their respective national unions, which makes any calculation based on the official figures available to the

Rugby Unions of less value in establishing the outcome of any changes in policy.[1]

I support the need for a register of injuries, but such a study has to be prospective and a standard form has to be produced. Someone in each club, whether it be a doctor, team captain, or physiotherapist, will have to take responsibility for filling up these forms, checking them, noting time off work and how the injuries were sustained, etc, and seeing that they are centrally registered. It is no good leaving it to the players to fill in forms as self notification is notoriously inaccurate, and, particularly with minor injuries, players may well not report to their general practitioners.

J R SILVER

Stoke Mandeville Hospital,
Aylesbury,
Buckinghamshire HP21 8AL

1 Garraway WM, Macleod DAD, Sharp JCM. Rugby injuries: *BMJ* 1991;**303**:1082-3. (2 November.)
2 Silver JR. Injuries of the spine sustained in rugby. *BMJ* 1984;**288**:37-43.
3 Silver JR, Gill S. Injuries of the spine sustained during rugby. *Sports Med* 1988;5:328-34.

SIR,—In their editorial W M Garraway and colleagues highlight the problem of injury in rugby football and suggest the need for formal audit.[1] In fact, a study is currently under way.

Since 1985 the English Rugby Football Union has conducted a survey of injuries, involving all affiliated clubs and schools. At the beginning of each season copies of a detailed form relating to the nature and circumstances of injury are circulated and a request made for an officer from each organisation to be responsible for their completion and return. The data form the basis of an annual report that is available free from the English Rugby Union. This endeavour encompasses the aims outlined in the editorial and is likely to produce useful information.

FERGAL MONSELL

Southport Rugby Union Football Club,
Southport,
Merseyside

1 Garraway WM, Macleod DAD, Sharp JCM. Rugby injuries. *BMJ* 1991;**303**:1082-3. (2 November.)

SIR,—I endorse the suggestions in W M Garraway *et al*'s editorial on rugby injuries that the rugby football unions establish a case register of injuries[1] but suggest that such a register be extended to cover minirugby. Minirugby (6-13 years) was set up to encourage the game in light of the demise of school rugby. It has been an overwhelming success.

The rules of minirugby are in a constant flux mainly because of the need to mitigate injury in such young players. The register could settle once and for all the most appropriate age to introduce the tackle and the hand off, and whether age or body weight should be the determining criterion when selecting a team. Although age is generally a good marker in younger boys, during the pubescent year quite remarkable weight and height differences can lead to unbalanced teams and consequent injuries. Further, those clubs that practise at the limits of the rules would be identified formally (we all know them). Paradoxically, this might allow some reasonable relaxation of rules designed to curb such clubs but often to the detriment of the natural rhythm of the game.

It is my experience, as an attending medical officer, that the number of injuries increases exponentially during competition matches. Intraclub matches rarely give rise to injury and I cannot recall an injury of note during training sessions. Interclub matches, however, always give rise to some injuries. I feel this is in part due to the often vociferous support from parents on the touchline, driving their boys to take unnecessary risks. The proposal in the editorial is overdue and would lead to a fall in the number of minirugby injuries which, although not great, must always be of concern.

J HUBERT LACEY

St George's Hospital and Medical School,
London SW17 0RE

1 Garraway WM, Macleod DAD, Sharp JCM. Rugby injuries. *BMJ* 1991;**303**:1082-3. (2 November.)

Chorionic villus sampling

SIR,—We find it remarkable that, at a time when the initial confusion over the safety and accuracy of chorionic villus sampling is being clarified by centres with large accumulated experience, Richard J Lilford suggests that the procedure should become history.[1] Provided that chorionic villus sampling is performed after 10 weeks in centres with experience, there is no increased risk of disturbance to embryogenesis and the rate of fetal loss is comparable with that associated with amniocentesis in the second trimester.[2-4]

Inaccuracy is almost entirely due to confined placental mosaicism,[5] which occurs in approximately 1% of cases (provided cytogenetic analysis is performed with both the direct preparation and culture).[6] (Mosaicism occurs with amniocentesis and can be of a similar order of magnitude.[7]) In more than four fifths of this 1% of cases[5] the fetus does not seem to be clinically affected as the effect of mosaicism depends on the chromosomes involved and the proportion of cells in the individual tissues.[8] Therefore it is possible for mosaicism to be diagnosed by chorionic villus sampling but not confirmed by amniocentesis or fetal blood sampling,[9] although this is believed to be rare. The implications for management are that termination should never be performed for mosaicism without further investigation and expert interpretation.

In conclusion, we consider that in centres with experience chorionic villus sampling has "risen" and should not be aborted.

J S SMOLENIEC
D K JAMES

Bristol Maternity Hospital,
Bristol BS2 8EG

P A SMITH

Southmead Hospital,
Bristol

1 Lilford RJ. The rise and fall of chorionic villus sampling. *BMJ* 1991;**303**:936-7. (19 October.)
2 Smidt-Jensen S, Philip J. Comparison of transabdominal and transcervical CVS and amniocentesis: sampling success and risk. *Prenat Diagn* 1991;**11**:530-7.
3 Young SR, Shipley CF, Wade RV, Edwards JG, Waters MB, Cantu ML, *et al*. Single center comparison of results of 1000 prenatal diagnoses with CVS and 1000 diagnoses with amniocentesis. *Am J Obstet Gynecol* 1991;**165**:255-63.
4 Smoleniec JS, James DK. Evaluation of chorionic villus sampling. *Lancet* 1991;**338**:449.
5 Miny P, Hammer P, Gerlach B, Tercanli S, Horst J, Holzgreve W, *et al*. Mosaicism and accuracy of prenatal cytogenetic diagnoses after chorionic villus sampling and placental biopsies. *Prenat Diagn* 1991;**11**:581-9.
6 Ledbetter D. Cytogenetic results of chorionic villus sampling: high success rates and diagnostic accuracy in the USA collaborative study. *Am J Obstet Gynecol* 1990;**162**:495-501.
7 Medical Research Council Working Party on the Evaluation of Chorionic Villus Sampling. Medical Research Council European trial of chorionic villus sampling. *Lancet* 1991;**337**:1491-9.
8 Hoehn H, Rodriquez ML, Norwood TH, Maxwell CI. Mosaicism in amniotic fluid cell cultures: classification and significance. *Am J Med Genet* 1978;**2**:253-66.
9 Hammer P, Holzgreve W, Karabacak Z, Horst J, Miny P. "False-negative" and "false-positive" prenatal cytogenetic results due to "true" mosaicism. *Prenat Diagn* 1991;**11**:133-6.

SIR,—Richard J Lilford has always advocated decision analysis and frequently expounds on the question of choice. His editorial is subtitled "midtrimester amniocentesis is usually preferable"[1] and the inference from this—that first trimester chorionic villus sampling is passé—contradicts the idea of appropriate risk management, something that most practising clinicians appreciate.

The higher rate of fetal loss with villus sampling before 28 weeks' gestation reported in the European trial[2] was not substantiated by the Canadian study.[3] Lilford conceded that operator experience and expertise counts. The European trial in which 17% of procedures were considered difficult and 31% required more than one attempt to obtain adequate diagnostic material cannot suggest villus sampling is more risky than amniocentesis. Villus sampling, however, should be done by experts.

World cohort and personal experience of over 1000 samplings suggest that the rate of fetal loss with villus sampling is within 1-2% of the rate with amniocentesis (1·6% in the European trial[2]). Who should choose the screening procedure? Many mothers would not consider midtrimester amniocentesis preferable when faced with the emotive and physical cost of a midtrimester abortion.[4,5]

Facial clefting defects are common abnormalities[6] and are often associated with limb defects[7] in many syndromes. These defects are evident by the third or fourth week and established by the sixth week of gestation. The question of risk framing is important as many women seeking prenatal diagnosis may not consider oromandibular or limb hypogenesis a threat when the calculated incidence is 0·3 per 1000.[1]

The ambiguous results for mosaic chromosomal abnormalities reported in the Canadian trial were not a major problem in the European trial or the United States multicentre study of over 6000 women.[1] Clearly there is also a learning curve for cytogenetists and experience counts.[7,8] With regard to amniocentesis before 12 weeks' gestation, apart from the safety question, where are the amniotic fluid cells from?

Chorionic villus sampling was developed to meet women's needs to avoid midtrimester diagnosis and late abortion. As a member of the working party for the European trial I am acutely aware that participants were still on the learning curve and results will differ if the trial is repeated. Lilford must remember trials are conducted to provide answers and figures—the ingredients for risk framing and decision analysis. The choice must remain with the consumer, who may not be impressed by risk below statistical detection.

D T Y LIU

City Hospital,
Nottingham NG5 1PB

1 Lilford RJ. The rise and fall of chorionic villus sampling. *BMJ* 1991;**303**:936-7. (19 October.)
2 MRC Working Party. Evaluation of chorionic villus sampling. *Lancet* 1991;**337**:1491-9.
3 Canadian Collaborative CVS-Amniocentesis Clinical Trial Group. Multicentre randomised clinical trial of chorionic villus sampling and amniocentesis. *Lancet* 1989;i:1-6.
4 McCormack MJ, Rylance ME, MacKenzie WE, Newton J. Patients attitudes following chorion villus sampling. *Prenatal Diagnosis* 1990;**10**:253-5.
5 Abramsky B, Lenore G, Rodeck CH. Women's choice for fetal chromosome analysis. *Prenatal Diagnosis* 1991;**11**:23-8.
6 Romero R, Pilu G, Jeanty P, Ghidini A, Hobbins JC. *Prenatal diagnosis of congenital abnormalities*. California: Appleton and Lange, 1988:101-5.
7 Romero R, Pilu G, Jeanty P, Ghidini A, Hobbins JC. *Prenatal diagnosis of congenital abnormalities*. California: Appleton and Lange, 1988:89-95.
8 Ledbetter DH, Martin AO, Verlinsky Y, Pergament E, Jackson L, Yang-Feng T, *et al*. Cytogenetic results of chorionic villus sampling. High success rate and diagnostic accuracy in the United States collaborative study. *Am J Obstet Gynecol* 1990;**162**:495-501.
9 Rooney DG. The interpretation of cytogenetic results. In: Liu DTY, ed. *A practical guide to chorion villus sampling*. Oxford: Oxford Medical Publications, 1991;62-72.

Oral and intravenous rehydration therapy

SIR,—Angela Mackenzie and Graeme Barnes compared oral and intravenous rehydration therapy in children and came to the surprising but comforting conclusion that "rehydration by mouth or nasogastric tube is a safe and effective treatment in moderately dehydrated children with gastro-