Gut intramucosal pH and intraluminal Po2 in a porcine model of peritonitis or haemorrhage

J B Antonsson, U H Haglund

Abstract

The tonometric method of detecting decreased gut intramucosal pH (pHi) is based on the fact that carbon dioxide can diffuse through the wall of the silastic balloon of the tonometer. By using deoxified saline and measuring Po2 as well as PcO2 this study aimed to follow changes in mucosal Po2 and relate them to changes in pH, in peritonitis versus haemorrhage. Twenty five pigs were used. Five were controls, in 10 peritonitis was induced by the instillation of faeces in the abdominal cavity, and 10 were bled, half of them stepwise during three hours, and half of them rapidly down to a mean (SEM) arterial pressure of 30 (10) mm Hg. The drop in pHi correlated well with decreasing intraluminal Po2 (r=0.63 (0.13)) in haemorrhage. In peritonitis this drop occurred within a very limited change in intraluminal Po2 (r=0.06 (0.17)). Thus oxygen seemed to be present in the mucosa at the same time as there were signs of anaerobic metabolism as evidenced by a low intramucosal pH. Impaired oxygen extraction or utilisation, or both, is proposed as an explanation to this seemingly paradoxical situation.

(Gut 1995; 37: 791–797)

Keywords: oxygen consumption, oxygen delivery, sepsis, small bowel, tonometry.

As the gut is an organ that suffers from early ischaemia during shock and as the ischaemic gut can act as a 'motor of shock' and thus aggravate the shock state, it has been shown to be of benefit to monitor gut ischaemia in experimental animals and patients in shock.1 2 This can be accomplished by the use of a tonometer, with which intramucosal pH (pHi) can be calculated. Low pHi is a sign of ischaemia, as anaerobic metabolism results in an accumulation of acid metabolites with increasing tissue acidity as a consequence. Ischaemia is mainly considered to be caused by an inadequate oxygen delivery to the gut, but earlier experiments show that in septic states other factors play an important part.3 Rasmussen and Haglund have shown that in the early stages of septic shock there is a drop in pHi when oxygen delivery is still unaffected or even increased.4 It might seem more obvious to monitor gastrointestinal tissue oxygen tension directly, but technical difficulties have limited the use of methods for direct measurements in clinical practice.5 6 In 1964 Bergofsky could estimate PCO2 and Po2 in urinary and gall bladders by measuring PCO2 and Po2 in saline that had been instilled in them. He could, by this method detect differences in Po2 caused by different concentrations of O2 in air inhaled.7 Dawson et al later used this technique in a loop of the small bowel.8 By measuring Po2 intraluminally in a hollow viscus they could thus detect changes in tissue oxygen tensions. Using a gas permeable silastic tube inserted subcutaneously and flushing it slowly with anoxic saline to determine Po2 of the perfusate Niinikoski and Hunt could estimate subcutaneous tissue Po2.9 The tonometric method of determining gut intramucosal pH is a combination of these techniques. Here CO2 of gut mucosa and lumen diffuses through the wall of a permeable balloon to its content of saline.10

The aim of this study was to monitor intramucosal pH in experimental animals (pigs) during peritonitis or haemorrhage. By using deoxified saline in the tonometer and measuring Po2 of the fluid as well, intraluminal Po2 could also be monitored. This will allow the relation between pH and intraluminal Po2 to be studied and to find out if the relations differ in peritonitis versus haemorrhage.

Methods

Medication and instrumentation

After 12 hours of starvation but with full access to water, 25 Landrace pigs of both sexes with a mean weight of 19·1 kg (range 15–22), were premedicated with ketamine (Ketalar, Parke-Davis, NJ), 7 mg/kg. They were then anaesthetised with an intravenous injection of pentobarbital, 20 mg/kg. The animals were intubated through a tracheostomy and connected to a respirator (Servo Ventilator System, Siemens-Elema, Sweden) and ventilated with a mixture of oxygen and room air to give an O2 concentration of 40% in air inhaled. Respiration was adjusted to give an arterial PCO2 of 40 (5) mm Hg. Anaesthesia was maintained with a continuous infusion of pentobarbital, 18 mg/h; this drug was given in 2·5% glucose (Rehydrox, Pharmacia, Uppsala, Sweden) at a rate of 15 ml/kg/h. Furthermore, an infusion of Ringer's acetate, 30 ml/kg/h, was given from the induction of anaesthesia. Thus, the total amount of fluid infusion was 45 ml/kg/h.

Bilateral neck cutdowns were performed: a polyethylene catheter was positioned through the carotid artery in the thoracic aorta and connected to a pressure transducer (PDCA 75, Druck Ltd, Groby, Leicestershire, UK) for recording of arterial pressure. One cephalic
vein was used for infusion and the other cannulated for injection of saline for determination of cardiac output; the thermodilution method was used and the results are the calculated means from three consecutive measurements (OximetrIX 3 computer, Abbott Laboratories, North Chicago, IL). A Swan-Ganz catheter was positioned in the pulmonary artery through a jugular vein and connected to the pressure transducer, its position being secured by the typical pressure pattern.

Through a skin incision the left femoral artery was cannulated for blood sampling and bleeding.

A midline laparotomy was performed. The superior mesenteric artery was identified close to its origin from the aorta and was cleaned from the surrounding tissue. An ultrasonic flow probe (Transsonic Systems, Ithaca, NY) was placed around the vessel and connected to a blood flow meter (T 201, Transsonic Systems, Ithaca, NY). A vein in the mesentery of jejunum was cannulated and a catheter was positioned with its tip in the superior mesenteric vein. A small anti-mesenteric incision was made in the mid-ileum and a tonometer (Tonomitor, Tonometrics Inc, Bethesda, MD) was placed in the lumen of the gut and secured with a purse string suture. In 10 animals autologous faeces were secured from a colostomy, which thereafter was closed with a purse string suture. The laparotomy was then closed, and the animals were allowed to rest for a period of one hour.

Experimental design

The animals were allocated into five groups (n=5 in all groups). One group served as controls (group C). In 10 animals the laparotomy was reopened after the resting period and peritonitis was induced by the instillation of autologous faeces immersed in 50 ml of saline into the abdominal cavity, whereafter the laparotomy wound was closed. In five of these 1 g×kg bw of faeces was used; in five 2 g×kg bodyweight. All these animals were infused with 45 ml/kg/h of fluid, as described above, from the start of anaesthesia till the end of the experiment. In group B I blood was withdrawn: 25% of the estimated blood volume at time=0, 15% at t=1 hour, 5% at t=2 hours, and 5% at t=3 hours. Blood volume was calculated on body weight. From t=0 these animals were given only 15 ml/kg/h of 2.5% glucose with pentobarbital, no Ringer’s acetate was given. Group B II was bled over a period of half an hour down to an arterial pressure of 30 mm Hg. If needed, additional bleedings were performed to keep the arterial pressure at 30±10 mm Hg. The same fluid regimen as in group B I was used. These two different models of haemorrhage were chosen to ensure one group with milder response (B I) and one with severe response (B II) within a limited time scope.

All animals were followed up for five hours with hourly haemodynamic measurements and sampling from arterial, central mixed venous, and mesenteric venous blood. The samples were analysed for blood gases (ABL 300,
Intramucosal pH and intraluminal Po2

Radiometer, Copenhagen, Denmark) and oxygen saturation and haemoglobin (OSM 3 Hemoximeter TM, Radiometer, Copenhagen, Denmark).

Gut intramucosal pH (pH) and gut intraluminal Po2

The tonometric method for calculation of gut intramucosal pH (pH) has been described before. The balloon of the tonometer placed in the mid-ileum was filled with 2.5 ml of saline. After one hour of equilibration through the wall of the balloon the saline was aspirated and PCO2 and Po2 of the sample determined in the blood gas machine. PCO2 from the tonometer and simultaneously obtained arterial [HCO3-] were used in the Henderson-Hasselbalch equation for calculation of pH.

The saline was flushed with nitrogen for at least one hour before the start of the experiment. PO2 of the saline was tested on four separate occasions during these procedures with three samples at each time: mean (SEM) PO2 was 173.9 (7.4) mm Hg before, and 23.4 (1.6) mm Hg after one hour of nitrogen flushing.

Calculation of oxygen delivery (DO2) and consumption (VO2)

Oxygen content (CO2) was determined according to the equation: CO2 = (PO2 × 0.003) + (Hgb × So2 × 1.36), where Hgb is haemoglobin and So2 is oxygen saturation. DO2 = Cardiac index × C02, where C02 is oxygen content of arterial blood.

VO2 = Cardiac index × (C02 - Cmvo2), where Cmvo2 is oxygen content of blood from the superior mesenteric vein.

Statistical methods

Data were analysed using a two way (group and time) analysis of variance (ANOVA) for repeated measures with Dunkan’s new multiple range test. Differences with respect to baseline within a group were analysed by using a one way ANOVA with Dunkan’s new multiple range test. Differences with respect to controls at matched time points were assessed by Mann-Whitney U test. p Values <0.05 were considered significant. All results are given as mean (SEM).

Figure 2: Mean (SEM) values of gut oxygen delivery (gut DO2 - open squares and full line) and gut oxygen consumption (gut VO2 - filled squares and broken line). For description of groups, see text. *Values significantly (p<0.05) different from baseline; †significant (p<0.05) difference from controls.
TABLE I Changes in mean (SEM) packed cell volume (% at baseline, three hours, and end point

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three hours</th>
<th>Five hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>28.0 (1.4)</td>
<td>28.4 (1.2)</td>
<td>29.0 (1.1)</td>
</tr>
<tr>
<td>P I</td>
<td>29.0 (0.5)</td>
<td>38.3 (2.2)++</td>
<td>38.0 (2.5)++</td>
</tr>
<tr>
<td>P II</td>
<td>38.8 (1.3)</td>
<td>36.5 (2.5)*+</td>
<td>37.2 (2.2)*+</td>
</tr>
<tr>
<td>B I</td>
<td>29.6 (1.0)</td>
<td>27.9 (1.6)</td>
<td>22.8 (2.0)*+</td>
</tr>
<tr>
<td>B II</td>
<td>28.4 (0.7)</td>
<td>21.2 (2.0)*+</td>
<td>20.3 (2.8)*+</td>
</tr>
</tbody>
</table>

*Values significantly (p<0.05) different from baseline; †values significantly (p<0.05) different from controls.

In establishing the relation between pH I and intraluminal PO2 in peritonitis and haemorrhage correlation coefficients were calculated for each animal separately, based on all six measure points in every animal. The slopes presented in Fig 5 are the means of the correlation coefficients for animals with peritonitis and haemorrhage, respectively.13

Ethics

This study was approved by the Institutional Review Board for the Care of Animal Subjects, and the care and handling of the animals was in accord with National Institutes of Health guidelines for the use of experimental animals.

Results

The response to the introduction of faeces into the abdominal cavity differed considerably from animal to animal and was not correlated to the amount used. Our aim was to have one group with mild and one with a more severe peritonitis, and this was not accomplished by increasing the amount of faeces. This can be caused by individual differences in the response to faecal challenge and by differences in the amount of bacteria in each faecal sample. Therefore, the results from the animals with peritonitis are presented in two groups independently of the amount of faeces used. Those with the five lowest pH I – values at end point form a group with more ‘severe’ peritonitis (P I) whereas those remaining five with higher pH I at end point constitute the group with ‘mild’ peritonitis (P II).

The packed cell volume remained unchanged in the control group, whereas a haemocentration was noted in the septic groups (P I and P II), and a haemodilution in the haemorrhagic groups (B I and B II) (Table I).

Mean arterial pressure remained stable in controls after an initial rise, probably because of the large amount of fluids given; in the experimental groups there was a continuous decrease in mean arterial pressure (mean arterial pressure in group B II of course had a rapid drop as an arterial pressure of 30 (10) mm Hg was a guideline for the amount of blood to be shed) (Fig 1). A progressive decrease in cardiac index was noted in group C, probably as a result of the cardiodepressing effects of anaesthesia. The decrease in CI was, however, more profound in all experimental groups (Fig 1).

Figure 2 shows the changes in gut oxygen delivery (gut DO2) and consumption (gut VO2). Peritonitis as well as haemorrhage resulted in a significant drop in gut DO2, whereas no changes in gut VO2 were noted.

Figure 3: Mean (SEM) values of gut intramucosal pH (pH I – open triangles and full line) and changes in intraluminal PO2 (filled triangles and broken line). For description of groups, see text. *Values significantly (p<0.05) different from baseline; †Values significantly (p<0.05) different from controls.
Both these parameters were unaffected in controls.

\[ \text{pH}_2 \] did not change during the experiment in controls. In peritonitis there was a significant drop in both groups: from 7.35 to 7.08 in P I and from 7.31 to 7.18 in P II. It should, however, be noted that \[ \text{pH}_2 \] at end point was used to group these animals. There was a drop from 7.32 to 7.02 in B I and from 7.32 to 7.09 in B II (Fig 3). A drop in \[ \text{pH}_2 \] can result from either increased gut lumen \[ \text{Pco}_2 \], or decreased [\[ \text{HCO}_3^- \]], or both. Table II shows [\[ \text{HCO}_3^- \]] at baseline, three hours, and at end point. From this it can be seen that [\[ \text{HCO}_3^- \]] showed a significant decrease from baseline only in group B II.

Intraluminal \[ \text{P}_{O_2} \] did not change in controls and peritonitis (C, P I, and P II). A progressive drop was seen in B I. The rapid bleeding in B II resulted in a rapid drop of intraluminal \[ \text{P}_{O_2} \] at \( t = \) one hour, followed by a plateau and then by a slight decrease (Fig 3).

Figure 4 illustrates the correlation between \[ \text{pH} \], and intraluminal \[ \text{P}_{O_2} \] in controls, haemorrhage, and peritonitis, respectively. Each line represents an individual animal. Based on calculations using each measure point in every animal a good correlation was noted in haemorrhage (\( r = 0.63 (0.13) \)) whereas there was no correlation at all in peritonitis (\( r = 0.06 (0.17) \)). The difference between them was significant (\( p < 0.002 \)) (Fig 5).

### Discussion

From a theoretical point of view some objections can be raised against the tonometric method of measuring intraluminal \[ \text{P}_{O_2} \]. Firstly, when using the tonometric method subcutaneously, the silastic tube is in full contact with the surrounding tissue, but the tonometer in the small bowel may not necessarily be in full contact with the mucosa, parts of it may be in free lumen. Secondly, \[ \text{CO}_2 \] diffuses easily through tissue planes and it has been shown that intramucosal \[ \text{Pco}_2 \] is in equilibrium with that of the lumen. Whether this is also the case with oxygen, has not been investigated. Thirdly, the time to reach an equilibrium between the gut lumen and the contents of the tonometer balloon is not known and no correlation factor has been established. Finally, the implication of the counter-current exchange and its impacts on the diffusion of oxygen in the mucosal villi has to be studied. It could be argued that the method in itself needs more investigation and validation and we therefore present our data as per cent of baseline, as we are confident that changes in intraluminal \[ \text{P}_{O_2} \] reflect changes in mucosal \[ \text{P}_{O_2} \]. Probably it is not necessary to detoxify the saline in the tonometer as the oxygen most probably will equilibrate irrespective of direction of flow. It should also be emphasised that this method is very sensitive to errors caused by negligent handling. Even a small amount of air, accidentally sucked into the syringe, may give falsely high values.

**Table II** Changes in mean arterial bicarbonate concentration (mmol/l) at baseline, three hours, and end point.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Three hours</th>
<th>Five hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>26.8</td>
<td>28.9*</td>
<td>29.2*</td>
</tr>
<tr>
<td>P I</td>
<td>25.4</td>
<td>24.2†</td>
<td>24.0†</td>
</tr>
<tr>
<td>P II</td>
<td>25.9</td>
<td>24.5†</td>
<td>24.0†</td>
</tr>
<tr>
<td>B I</td>
<td>25.0</td>
<td>23.8†</td>
<td>23.7†</td>
</tr>
<tr>
<td>B II</td>
<td>25.6</td>
<td>19.0*†</td>
<td>22.5*†</td>
</tr>
</tbody>
</table>

*Values significantly \( p < 0.05 \) different from baseline; †values significantly \( p < 0.05 \) different from controls.
The mean (SEM) value for all tonometric measurements of P0₂ at baseline (n=25) was 71.9 (1.83) mm Hg. Bergofsky found a P0₂ of 48 mm Hg in saline instilled in the urinary bladder after three hours of equilibration; this value increased after the breathing of pure oxygen. Dawson et al estimated mucosal P0₂ in the small bowel of dogs to range between 35 and 45 mm Hg. In one normal volunteer it was found to be 45 mm Hg. Hamilton et al found a wide range of P0₂ values in dogs using a tonometric method with fluids instilled in loops of the bowel. Their maximum value was 57 mm Hg. Korsbäck measured P0₂ in deoxygenated saline slowly flushed through a gas permeable catheter implanted subserosally in the jejunum of pigs and found a mean at baseline of 35 mm Hg. In Korsbäck’s experiment the O₂ of the tissue equilibrated over the wall of the implanted tube to saline flushed through the tube, whereas, in our experiment, intraluminal O₂ could equilibrate with saline that was kept in the balloon of the tonometer for a full hour. Bohlen, using oxygen micro-electrodes in the mucosa of rats, found a P0₂ of only 14.8 mm Hg at the villus apex. The tissue P0₂ is, however, known to increase towards the base of the villus, and it can be assumed that intraluminal P0₂ is influenced by that of the crypts, or, more specifically, by P0₂ in the fluid of the crypts.

In all of the above experiments, as well as in experiments by Sheridan et al on rats and on humans using a Clark oxygen electrode on the serosal surface of the bowel, changes in gut tissue oxygen tension occurred simultaneously with changes in arterial P0₂. The animals in the present series had 40% oxygen in their breathing air and consequently a high arterial P0₂, 183 (4.9) mm Hg (n=25) at baseline. This, together with our long equilibration time (one hour), might explain our seemingly high P0₂ values.

When comparing the mean values for changes in intraluminal P0₂ in the separate groups no statistical differences were found in controls and peritonitis. In haemorrhage values were different from baseline from t=4 hours in B I and from t=2 hours in B II; a difference from controls was noted only at end point in B II. This can be explained by a considerable overlap because of the individual differences in the response to the challenge of intraperitoneal faeces or haemorrhage. It might be assumed that, if an individual animal in, for example, haemorrhage only developed a minor change in pHi, it would also show only a minor change in intraluminal P0₂ as well as in other variables. More profound changes in pHi would, on the other hand, be accompanied by more profound changes in intraluminal P0₂. To test this and to establish the relation between mucosal ischaemia (that is, a fall in pHi) and intraluminal P0₂ each individual measurement of P0₂ was plotted against the measurement of pHi at the same time point. The slope was then calculated for the animals with peritonitis (groups P I and P II) and for those with haemorrhage (groups B I and B II) (Fig 5).

From this graph, where the correlation between pHi and intraluminal P0₂ in haemorrhage was 0.63 (0.13), it can be seen that a drop in pHi from 7.42 to 6.46 was concomitant with a change in P0₂ from 100 at baseline down to 59%, or vice versa. If it is accepted that intraluminal P0₂ mirrors the P0₂ of the gut mucosa, it follows that a drop in mucosal P0₂ is accompanied by a drop in pHi, indicating increasing anaerobic metabolism. This becomes even more clear if we look at the decreasing DO₂ in these two haemorrhagic groups. The chain of events in haemorrhage thus seems to be as follows: DO₂ dropped because of a decreased mesenteric blood flow and decreased oxygen carrying capacity, as a result of a fall in the packed cell volume. The result of this was a drop in tissue oxygen tension to the extent that aerobic metabolism could not be maintained and was therefore replaced by anaerobic processes. As a consequence tissue acidity increased, which here was shown by a fall in pHi.

The pattern for the septic animals was different, however, and less straightforward. The drop in pHi preceded that in gut DO₂— that is, at a time point where no statistically significant decrease in pHi was accompanied in DO₂. pHi had decreased significantly. It can therefore not be assumed that low DO₂ was the sole, or even the most important, cause for gut mucosal acidity. This is in accordance with the findings by Fink et al. When pHi dropped from 7.42 to 7.06 only a minor, insignificant, change in pHi was noted, from 100 to 96.1 (the haemorrhagic animals had a lower pHi at end point but at a pHi of 7.06 in this group the corresponding P0₂ was 84.1). Although a significant drop in DO₂ takes place in both groups with peritonitis only minor changes are detected in intraluminal P0₂. Furthermore, these minor changes are accompanied by a significant drop in pHi. Thus we have a seemingly paradoxical situation where decreased DO₂ only results in minor, or even no, changes in intraluminal P0₂ but still there is a drop in pHi implying anaerobic metabolism. As the animals with peritonitis did not have as low pHi at end point as those with haemorrhage, we cannot determine the relation between pHi and intraluminal P0₂ at pHi below 7.06, which was our lowest calculated pHi value in this series of peritonitis. The possibility cannot be excluded that, with pHi values in a lower range, the correlation curve would reach a deflection point where a further drop in pHi would be accompanied by a steeper drop in P0₂. Furthermore, the difference between peritonitis and haemorrhage might be questioned as the range was wider in haemorrhage, with pHi values below 7.0 whereas the single lowest value in peritonitis was 7.06. We, therefore, recalculated the correlation between pHi and changes in P0₂ in haemorrhage excluding those three animals that had a pHi value at any timepoint below 7.0. We still found a correlation (r=0.55 (0.17)).

Earlier experiments have shown that the drop in pHi seen in septic states, is not solely dependent upon decreased oxygen delivery.
Intramucosal pH and intraluminal PO₂

Rasmussen and Haglund recently found that, in the early stages of septic shock, pHᵢ was decreasing even when DO₂ was still normal or increased – that is, during the hyperdynamic phase of shock. Fink et al found that endotoxemia in pigs resulted in a decrease of gut DO₂ and of pHi. If, however, the blood flow in the superior mesenteric artery was mechanically decreased to the same values as in the septic animals no change in pHi was noted. Thus, it seems justified to conclude that low DO₂ alone cannot account for the gut intramucosal acidity seen in sepsis.

In our model of peritonitis, we thus have obtained evidence that normal concentrations of oxygen are present in the mucosa and yet there is anaerobic metabolism as evidenced by a drop in pHᵢ. An explanation of this seemingly paradoxical situation could be that the uptake of oxygen in the individual cell is blocked in sepsis, or that the utilisation of oxygen in the intracellular metabolism is somehow limited. The most probable function to be disturbed in sepsis seems to be the oxidative phosphorylation taking place in the mitochondria, as a lack of oxygen here leads to an anaerobic pathway with production of an excess of [H⁺] explaining the acidity detected in the mucosa as well as in other tissues in septic states.

Although Dawson et al assessed that mitochondrial function is enhanced by sepsis, there are abundant data supporting the idea that mitochondrial function is impaired in sepsis, either by bacterial endotoxins directly or, more probably, by toxic mediators released by them. Mela et al, in 1971, could show defects in liver mitochondrial energy linked functions in haemorrhagic and endotoxin shock. They proposed the destruction of mitochondrial membranes by lysosomal enzymes as an explanation. Astiz and coworkers, in an experiment using caecal ligation in rats, showed an impaired oxidative metabolism and energy production in muscle tissue, expressed as increased lactate/pyruvate ratio and decreased high energy phosphates. This was the case even if blood circulation was kept at control values by albumin infusion and tissue PO₂ was unchanged. Hotchkiss et al could not detect signs of cellular hypoxia in septic rats using [18F]fluoromisonidazole. Yet there was increased blood lactate concentrations in their experimental settings indicating anaerobic metabolism. However, the gut was not examined in their experiment. Schaefer and coworkers have recently shown that cellular oxidative phosphorylation in endotoxemic rats was impaired. In the brain they noted that these changes were correlated to the decreased blood flow induced by endotoxemia, but in the small bowel they found this defect to be disproportionately great and independent of maintenance of normal blood flow. In conclusion, we found a drop in mucosal pH to correlate well with a drop in gut intraluminal PO₂ in haemorrhage. In peritonitis, on the other hand, a significant drop in pHᵢ occurred within a very limited and insignificant change of intraluminal PO₂. This can be explained by a limited oxygen uptake in the individual cell, possibly resulting from an impairment of mitochondrial function, as has been seen in sepsis by earlier investigators.

This study was sponsored by grants from the Swedish Medical Research Council, project 4502, the Swedish Medical Society, and Trygg Hansa.

Gut intramucosal pH and intraluminal PO2 in a porcine model of peritonitis or haemorrhage.

J B Antonsson and U H Haglund

Gut 1995 37: 791-797
doi: 10.1136/gut.37.6.791

Updated information and services can be found at:
http://gut.bmj.com/content/37/6/791

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/