

*Alimentary tract and pancreas*

## Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine

I BJARNASON, P WILLIAMS, P SMETHURST, T J PETERS, AND A J LEVI

*From the Departments of Clinical Sciences and Clinical Cell Biology, MRC Clinical Research Centre, Harrow, Middlesex*

**SUMMARY** Intestinal permeability was estimated in healthy subjects after ingestion of aspirin (1.2+1.2 g), ibuprofen (400+400 mg) and indomethacin (75+50 mg) at midnight and an hour before starting a <sup>51</sup>chromium labelled ethylenediaminetetraacetate absorption test. Intestinal permeability increased significantly from control levels following each drug and the effect was related to drug potency to inhibit cyclooxygenase. Intestinal permeability increased to a similar extent after oral and rectal administration of indomethacin showing that the effect is systemically mediated. Prostaglandin E<sub>2</sub> decreased intestinal permeability significantly but failed to prevent the indomethacin induced increased intestinal permeability. These studies show that non-steroidal anti-inflammatory drugs disrupt the intestinal barrier function in man and suggest that the morphological correlates of the damage may reside at the level of the intercellular junctions.

Several non-steroidal anti-inflammatory drugs (NSAIDs) induced characteristic intestinal damage in various animal species.<sup>1</sup> This is particularly severe in the rat where subcutaneous indomethacin leads to small bowel inflammation with ulceration, perforation, and ultimately death within 72 hours.<sup>2-5</sup> The precise mechanism underlying this sequence of events is unknown but there is substantial data to implicate both reduced synthesis of mucosal prostaglandins and the presence of intestinal bacteria in the pathogenesis of the lesions.<sup>6,7</sup> Thus the macroscopic damage is preceded by a period of profound inhibition of mucosal cyclooxygenase activity<sup>8</sup> and damage can be prevented by the simultaneous administration of a variety of prostaglandins.<sup>5,9,10</sup> The role of intestinal bacteria is suggested by findings that intestinal ulceration after NSAIDs is rarely seen in germ free animals and the damage is greatly reduced after the coadministration of various antibiotics by a mechanism which appears to differ from their 'cytoprotective' properties.<sup>11,12</sup>

Until recently the human small intestine was thought to be relatively unaffected by NSAIDs.

During studies into the importance of altered intestinal permeability in the pathogenesis of rheumatoid arthritis it was shown that NSAID treatment was associated with increased intestinal permeability to <sup>51</sup>Chromium labelled ethylenediaminetetraacetate (<sup>51</sup>CrEDTA).<sup>13</sup> Further studies showed that long term NSAID treatment leads to distinct migratory abnormalities of <sup>111</sup>indium labelled leucocytes to the ileum indicating small bowel inflammation.<sup>13</sup> Together with evidence of increased faecal <sup>111</sup>indium excretion, which is a specific and objective index of intestinal inflammation,<sup>14</sup> it is now clear that NSAIDs cause small bowel inflammation in a substantial number of patients receiving these drugs.<sup>15</sup> With reference to the animal model it seems possible that the increased absorption of <sup>51</sup>CrEDTA, which precedes the scan abnormality, reflects loss of intestinal integrity because of decreased prostaglandin production and the inflammation itself reflects a response to a bacterial invasion. Our purpose was thus to assess whether NSAID induced increased intestinal permeability in man relates to drug potency to inhibit cyclooxygenase, whether the permeability change is due to a direct irritant or a systemically mediated effect of the drugs. In addition the effect of indomethacin on the glomerular filtration rate was investigated as pre-

Address for correspondence: Ingvar Bjarnason, MD, Section of Gastroenterology, Division of Clinical Sciences, MRC Clinical Research Centre, Watford Road, Harrow, Middlesex, HA1 3UJ.

Received for publication 21 February 1986.

vious studies on this phenomenon were controversial,<sup>16-20</sup> and alterations in glomerular filtration rate might be expected to affect the urinary excretion of <sup>51</sup>CrEDTA. Finally we studied whether the increased intestinal permeability could be prevented by exogenous administration of prostaglandin since, if successful, it could have direct therapeutic implications for the prevention of intestinal inflammation.

## Methods

### SUBJECTS

Fourteen healthy white volunteers, age range 26-39 years, took part in these studies. On separate occasions intestinal permeability was estimated by the <sup>51</sup>CrEDTA absorption test in 10 subjects: (A) baseline, (B) after aspirin (1.2+1.2 g), (C) after ibuprofen (400+400 mg), (D) after indomethacin (75+50 mg).

These NSAIDs, listed in order of increasing potency to inhibit cyclooxygenase,<sup>21 22</sup> were administered at midnight and an hour before study in the quantities indicated.

Six of these subjects on a different occasion received rectally an indomethacin (100 mg) suppository an hour before study.

Glomerular filtration rate was measured in four subjects as baseline and after 75 mg indomethacin at midnight and 50 mg an hour before study.

Seven subjects carried out the <sup>51</sup>CrEDTA absorption test: (i) Baseline, (ii) After indomethacin (75 mg+50 mg at -8 and -1 h), (iii) After prostaglandin E<sub>2</sub> (Prostin E<sub>2</sub>; Upjohn), (1 mg at -14, -8, -1, +5, +11 h), (iv) After both (ii) and (iii), (v) After ranitidine (150 mg at -24, -12, -1, +12 h) and (iv).

The permeability estimations were done at least six days apart and in no particular order. Preliminary studies had shown that the effect of the drugs when given in these doses was not evident 48 hours after administration. Each subject abstained from alcohol for at least a week before study.<sup>23</sup>

### PERMEABILITY MEASUREMENTS

The test solution consisted of 100 µCi (3.7 MBq) of <sup>51</sup>CrEDTA (Amersham International, Amersham, Buckinghamshire, Code J13P) in 10 ml distilled water.<sup>23</sup> At 8 am, after an overnight fast, subjects drank the test solution followed by approximately 300 ml water and were allowed normal food and fluid intake two hours later. Urine was collected for 24 hours after ingestion of the test solution, made up to 2 litres in polyethylene bottles and counted for 100 seconds in a bulk sample counter along with appropriate standards.<sup>24</sup> The minimal detectable

activity of <sup>51</sup>CrEDTA is less than 0.001% of the orally administered dose. The precision of the urine counting (coefficient of variation) is less than 1%.

**GLOMERULAR FILTRATION RATE MEASUREMENTS**  
Subjects received 5 ml (70 µCi) of <sup>51</sup>CrEDTA intravenously at 9 am after an overnight fast. Blood samples were taken at five and 15 min and thereafter hourly for seven hours. Four millilitres serum was counted in a Wallac 1280 gamma counter along with 4 ml 1/500 dilution of the original. The coefficient of variation for this counting procedure is less than 1%. Glomerular filtration rate and the extracellular (<sup>51</sup>CrEDTA distribution) volume were calculated using a computer program based on the principles outlined by Veall and Gibbs<sup>25</sup> and subsequently validated by Watts *et al.*<sup>26 27</sup>

The paired Student's *t* test was used for statistical analysis.

These studies were approved by the Harrow Health Authority Ethical Committee.

## Results

For the control test A (n:10) the mean (±SD) 24 hour urine excretion of <sup>51</sup>CrEDTA was 1.9±0.5% (range 1.0-2.6%). There was a significant and stepwise increase in excretion values after ingestion of the NSAIDs in accordance with their potency to inhibit cyclooxygenase (Test B, C, D). Thus the urine excretion of <sup>51</sup>CrEDTA increased after aspirin (n:6) to 2.3±0.3% (range 1.3-3.4%, p<0.05), ibuprofen (n:10) 2.9±1.2% (range 1.6-5.6%, p<0.001) and indomethacin (n:10) to 4.7±1.3% (range 2.9-7.2%, p<0.001).

The urine excretion of <sup>51</sup>CrEDTA after rectal administration of indomethacin, 4.5±0.9% (range 3.3-5.8%), differed significantly (p<0.001) from that of control levels but not from that obtained when indomethacin was ingested.

Indomethacin decreased glomerular filtration rate significantly (p<0.01) from baseline values of 137, 140, 105, 118 ml/min to 127, 130, 93 and 104 ml/min which is a reduction of 8, 7, 11 and 12% respectively. There was no significant change in the distribution space of <sup>51</sup>CrEDTA (extracellular volume) before and after indomethacin (18.9±3.3 and 18.5±2.9 l respectively).

The Figure shows the results after ingestion of prostaglandin E<sub>2</sub> and indomethacin. Baseline 24 hour urine excretion of <sup>51</sup>CrEDTA (n:7) was 2.2±0.6%. Prostaglandin administration (n:7) decreased the 24 hour excretion modestly but significantly to 1.5±0.7% (p<0.01), while indomethacin (n:7) increased the excretion to 4.6±1.5% (p<0.001). The administration of prostaglandin E<sub>2</sub> before, with

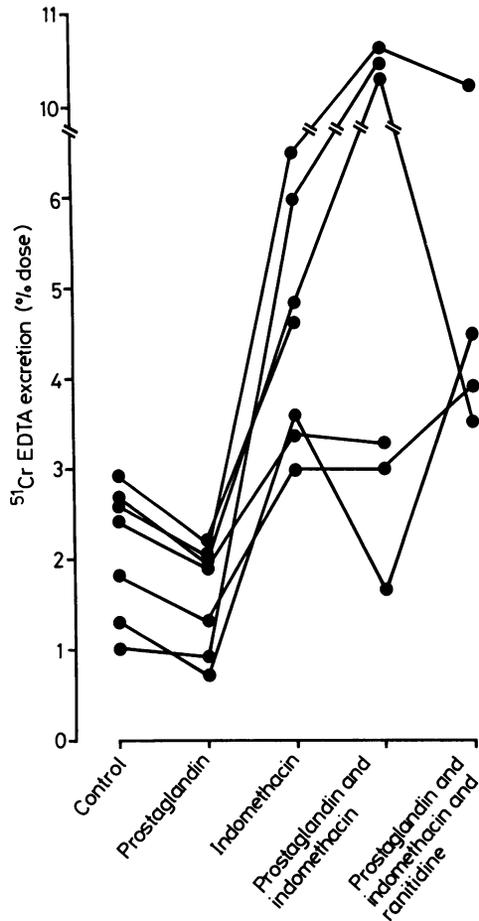


Figure The 24 hour urine excretion of <sup>51</sup>Cr-ethylenediaminetetraacetate after prostaglandin E<sub>2</sub> and indomethacin ingestion.

and after indomethacin (n:6) did not prevent the indomethacin induced increased intestinal permeability; urine excretion  $6.6 \pm 4.4\%$ , nor was there a significant change when gastric acid secretion was decreased with ranitidine in the four subjects studied, urine excretion  $5.6 \pm 3.2\%$ .

### Discussion

The beneficial effects of NSAIDs in the treatment of rheumatic and related arthropathies is coupled with the inescapable risk that they frequently cause untoward effects. The most common side effects relate to the gastrointestinal tract in the form of abdominal pain, nausea, heart burn and dyspepsia.<sup>28</sup> The cause for these symptoms is often unknown

Bjarnason, Williams, Smethurst, Peters, and Levi

although in a proportion of patients these are attributed to gastritis or aggravation of peptic ulcer disease. There is now growing evidence that NSAID ingestion may also adversely affect small and large bowel integrity and function in man. Langman *et al* have thus shown that a significant number of patients with small bowel and colonic perforations and/or haemorrhage requiring hospitalisation are receiving NSAIDs,<sup>29</sup> and Rampton *et al* have shown that an excessive number of patients with ulcerative colitis in relapse have received analgesics in the preceding weeks.<sup>30</sup> A few doses of indomethacin (0.2–0.3 mg/kg) produced small bowel perforations in four out of 44 neonates and preterm infants requiring the drug for closure of a patent *ductus arteriosus* confirming the original observation of Nagaraj *et al*.<sup>31, 32</sup> Additionally it appears that NSAIDs can cause small bowel strictures and it is clear that in one of the earliest descriptions of potassium induced small bowel ulceration and strictureing, many patients were also receiving NSAIDs.<sup>33–36</sup> More recent studies with <sup>111</sup>indium leukocytes suggest that up to 70% of long term NSAID users have evidence of small bowel inflammation which may underly the aforementioned complications.<sup>15</sup>

The intestinal barrier function is fully developed early in neonatal life and it has been suggested that its disruption plays an important part in the aetiology of various gastrointestinal disease.<sup>37, 38</sup> The intestinal barrier to passive diffusion is thought to be the first cell layer along with the intercellular junctions between adjacent enterocytes.<sup>39</sup> The <sup>51</sup>CrEDTA absorption test specifically tests the integrity of these junctions.<sup>40, 41</sup> This study shows that NSAIDs increase intestinal permeability to <sup>51</sup>CrEDTA rapidly and the effect appears to be reversible in normal subjects because many normal baseline permeability estimations were done after the studies with NSAIDs. The precise site of increase absorption of <sup>51</sup>CrEDTA, and in particular the contribution of the gastric mucosa is however uncertain because NSAIDs frequently cause gastric damage. Two lines of evidence would, however, suggest that the stomach is not contributing significantly to the overall absorption of <sup>51</sup>CrEDTA. First, in a previous study in rheumatoid patients on NSAIDs it was clear that increased excretion of <sup>51</sup>CrEDTA applied to both the 0–6 and the 6–24 hour urine collection, after oral administration.<sup>13</sup> Second, this study shows that the NSAID effect on increasing intestinal permeability differs markedly from their potency to cause gastric damage. Thus, aspirin which is most frequently implicated in gastric mucosal damage only increased intestinal permeability slightly while indomethacin, which

appears to cause less damage, has a more marked effect on permeability.<sup>28</sup> The effect is systemically mediated and the increased permeability is proportional and related to drug potency to inhibit cyclooxygenase. Quantitatively the increased permeability after indomethacin is similar to that seen in patients with active Crohn's disease<sup>42</sup> and in untreated patients with coeliac disease<sup>43</sup> where freeze fracture studies show structural abnormalities and widening of intercellular junctions.<sup>44</sup> It is of particular relevance that NSAID induced increased intestinal permeability cannot be explained by a change in the permselectivity of the tight junctions.<sup>39</sup> Thus at a neutral pH a proportion of the <sup>51</sup>CrEDTA is ionised and bears a single negative charge.<sup>45</sup> This, in effect, facilitates its absorption under normal circumstances as there is an electrostatic gradient across the paracellular shunt pathway, the lumen being negatively charged in relation to the serosa.<sup>46</sup> NSAIDs decrease the charge across the mucosa, as assessed by measurement of potential differences,<sup>47</sup> and this should in effect, other factors being unchanged, decrease the absorption of <sup>51</sup>CrEDTA. The morphological correlate of NSAID induced barrier disruption is therefore likely to reside at the level of the intercellular junction as previously suggested using other techniques.<sup>47</sup> The increased urine excretion of <sup>51</sup>CrEDTA after oral administration of indomethacin is not caused by increased glomerular filtration rate as some have suggested.<sup>48 49</sup> On the contrary, our data shows that indomethacin reduced glomerular filtration rate by about 10% in normal subjects. This is in accordance with other studies where less sensitive techniques were used to assess glomerular filtration rate.<sup>17 18 50</sup> Theoretically it would seem clear that a two-fold increase in glomerular filtration rate would only fractionally increase recoveries of <sup>51</sup>CrEDTA in 24 hour urines<sup>51</sup> and as the renal handling of <sup>51</sup>CrEDTA is similar to urea it can be estimated that glomerular filtration rate needs to be reduced to less than 30 ml/min before the 24 hour urine recoveries of <sup>51</sup>CrEDTA would be appreciably affected.

Increased intestinal permeability due to NSAIDs precedes evidence of inflammation by some months if not by a year or two. This differs from that seen in the experimental animal where there is a latent period of 24 hours after NSAIDs, characterised by greatly reduced cyclooxygenase activities and this in turn is followed by macroscopic evidence of inflammation which probably represents a bacterial infection.<sup>8</sup> The NSAID doses used therapeutically in man and in the present study are, however, many times smaller than used in animals and are likely to achieve the same levels of cyclooxygenase inhibition. Whether reduced mucosal prostaglandin pro-

duction, the concomitant metabolic diversion of arachidonic acid through the lipooxygenase pathway or even an imbalance between the products of the two pathways is responsible for the observed increased intestinal permeability is unknown. The precise mechanism(s) by which such changes cause damage to the intercellular junction is speculative and could be due to a number of factors such as reduced blood flow, mast cell degranulation, lysosomal release, etc.<sup>22 47</sup> The NSAID induced damage to the intercellular junctions is, however, unlikely to be the only factor contributing to weakened mucosal resistance to microbial invasion because small intestinal inflammation is not seen in chronic alcoholics who also have increased intestinal permeability and quantitatively to a similar extent as seen following NSAIDs.<sup>23</sup>

Naturally occurring prostaglandin E<sub>2</sub> have been shown to be cytoprotective for aspirin and indomethacin induced gastric erosions in man and the coadministration of prostaglandin E<sub>2</sub> and NSAIDs has been advocated in the hope of preventing the stomach side effects.<sup>52-4</sup> In view of the prevalence of small bowel inflammation caused by NSAIDs and the possible role of decreased mucosal prostaglandin levels in increasing intestinal permeability it was of particular interest to study whether coadministration of prostaglandin E<sub>2</sub> with indomethacin would be effective since if successful, this might offer a way of preventing the subsequent development of inflammation. While prostaglandin E<sub>2</sub> decreased the basal absorption of <sup>51</sup>CrEDTA modestly it did not prevent the indomethacin induced increased intestinal permeability. Prostaglandin E<sub>2</sub> is rather unstable in acid which could have accounted for the lack of effect. The administration of ranitidine did not, however, further reduce the absorption of <sup>51</sup>CrEDTA. This lack of effect does not exclude the possibility that NSAIDs increase intestinal permeability through their inhibitory action on cyclooxygenase as the dose of prostaglandin E<sub>2</sub> was low which may have resulted in inadequate levels in the more distal parts of the intestine. Larger doses that afford substantial protection in the stomach are, however, associated with nausea and diarrhoea. The recently developed potent and stable prostaglandin analogues with less gastrointestinal side effects may be more suitable for the prevention of NSAID induced increased intestinal permeability.<sup>55</sup>

The authors are grateful to Dr Norman Veall and the staff of the Radioisotopes Division for their help with the supply and measurements of the <sup>51</sup>CrEDTA.

## References

- 1 Whittle BJR, Salmon JA. Biosynthesis of prostacyclin and prostaglandin E<sub>2</sub> in gastro-intestinal tissue. In: Turnburg LA, ed. 2: *Intestinal secretion*. Oxford: Oxpriint, 1983: 69–73.
- 2 Kent TH, Cardelli RM, Stamler FW. Small intestinal ulcers and intestinal flora in rats given indomethacin. *Am J Pathol* 1969; **54**: 237–45.
- 3 Brodie DA, Cook PG, Bauer BJ *et al*. Indomethacin-induced intestinal lesions in the rat. *Toxicol Appl Pharm* 1970; **17**: 615–24.
- 4 Wax J, Clinger WA, Vamer P *et al*. Relationship of the enterohepatic cycle to ulcerogenesis in the rat small bowel with flufenamic acid. *Gastroenterology* 1970; **58**: 772–80.
- 5 Fang WF, Broughton A, Jacobson ED. Indomethacin-induced intestinal inflammation. *Dig Dis* 1977; **22**: 749–60.
- 6 Miller TA, Jacobson ED. Gastrointestinal cyto protection by prostaglandins. *Gut* 1979; **20**: 75–87.
- 7 Robert A. Cytoprotection by prostaglandins. *Gastroenterology* 1975; **77**: 761–7.
- 8 Whittle BJR. Temporal relationship between cyclooxygenase inhibition, as measured by prostacyclin biosynthesis, and the gastrointestinal damage induced by indomethacin in the rat. *Gastroenterology* 1981; **80**: 94–8.
- 9 Robert A. Effects of prostaglandins on the stomach and the intestine. *Prostaglandins* 1974; **6**: 523–32.
- 10 Robert A. An intestinal disease produced experimentally by a prostaglandin deficiency. *Gastroenterology* 1975; **69**: 1045–7.
- 11 Robert A, Asano T. Resistance of germ free rats to indomethacin-induced intestinal lesions. *Prostaglandins* 1977; **14**: 331–41.
- 12 Satoh H, Guth PH, Grossman MI. Role of bacteria in gastric ulceration produced by indomethacin in the rat: cytoprotective action of antibiotics. *Gastroenterology* 1983; **84**: 483–9.
- 13 Bjarnason I, Williams P, So A *et al*. Intestinal permeability and inflammation in rheumatoid arthritis: effects of non-steroidal anti-inflammatory drugs. *Lancet* 1984; **ii**: 1171–4.
- 14 Saverymattu SH, Peters AM, Lavender JP *et al*. Quantitative fecal Indium-III labelled leucocyte excretion in the assessment of disease in Crohn's disease. *Gastroenterology* 1983; **85**: 1333–9.
- 15 Bjarnason I, Williams P, Zanelli G *et al*. Non-steroidal anti-inflammatory drug (NSAID) induced intestinal inflammation in man. *Gastroenterology* 1985; **88**: 1327.
- 16 Beeley L, Kendall MJ. Effect of aspirin on renal clearance of <sup>125</sup>I-diatrizolate. *Br Med J* 1971; **1**: 707–8.
- 17 Robert M, Fillastre JP, Berger H, Malandain H. Effect of intravenous infusion of acetylsalicylic acid on renal function. *Br Med J* 1972; **2**: 466–7.
- 18 Berg KJ. Acute effects of acetylsalicylic acid on renal function in normal man. *Eur J Clin Pharmacol* 1977; **11**: 117–23.
- 19 Donker AJM, Arisz L, Brentjens JRH, Van der Helm GK, Hollemans HJG. The effect of indomethacin on kidney function and plasma renin activity in man. *Nephron* 1976; **17**: 288–96.
- 20 Muther RS, Bennett WM. Effects of aspirin on glomerular filtration rate in normal humans. *Ann Intern Med* 1980; **92**: 386–7.
- 21 Wardle EN. Anti-inflammatory drugs: In: Wardle EN, ed. *Cell surface science in medicine and pathology*. Lancaster: MTP Press Ltd, 1985: 440–9.
- 22 Metz SA. Anti-inflammatory agents as inhibitors of prostaglandin synthesis in man. *Med Clin North Am* 1981; **65**: 713–57.
- 23 Bjarnason I, Ward K, Peters TJ. The leaky gut of alcoholism; possible route of entry for toxic compounds. *Lancet* 1984; **ii**: 179–82.
- 24 Cronquist AG, Mackenzie J, Smith T. A high resolution bulk sample counter with variable geometry. *Int J Appl Radiat Isotopes* 1975; **26**: 89–91.
- 25 Veall N, Gibbs GP. The accurate determination of tracer clearance rates and equilibrium distribution volumes from single injection plasma measurements using numerical analysis. In: Joeke AM, Constable AR, Brown NJG, Tauxe WN, eds. *Radionuclides in nephrology*. London and New York: Academic Press, 1982: 125–30.
- 26 Watts RWE, Veall N, Purkiss P. Sequential studies of oxalate dynamics in primary hyperoxaluria. *Clin Sci* 1983; **65**: 627–33.
- 27 Watts RWE, Veall N, Purkiss P. Oxalate dynamics and removal rates during haemodialysis and peritoneal dialysis in patients with primary hyperoxaluria and severe renal failure. *Clin Sci* 1984; **66**: 591–7.
- 28 Rainsford KD. An analysis of the gastro-intestinal side-effects of non-steroidal anti-inflammatory drugs, with particular reference to comparative studies in man and laboratory species. *Rheumatol Int* 1982; **2**: 1–10.
- 29 Langman MJS, Morgan L, Worrall A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. *Br Med J* 1985; **290**: 347–9.
- 30 Rampton DS, McNeil NI, Sarnier M. Analgesic ingestion and other factors preceding relapse in ulcerative colitis. *Gut* 1973; **24**: 187–9.
- 31 Alpan G, Eyal F, Vinograd I *et al*. Localised intestinal perforations after enteral administration of indomethacin in premature infants. *J Pediatr* 1985; **106**: 277–81.
- 32 Nagaraj HS, Sandhu AS, Cook LN, Buchino JJ, Groff DB. Gastrointestinal perforation following indomethacin therapy in very low birth weight infants. *J Pediatr Surg* 1981; **16**: 1003–7.
- 33 Sturges HF, Krone CL. Ulceration and stricture of the jejunum in a patient on long term indomethacin. *Am J Gastroenterol* 1973; **59**: 162–9.
- 34 Neoptolemos JP, Locke TJ. Recurrent small bowel obstruction associated with phenylbutazone. *Br J Surg* 1983; **70**: 244–5.
- 35 Lang J, Bjarnason I, Levi AJ, Price AB. Pathology of iatrogenic ileal strictures due to NSAIDs. [Abstract]. *Gut* 1985; **26**: A542.
- 36 Davies DR, Brightmore T. Idiopathic and drug-induced ulceration of the small intestine. *Br J Surg* 1970; **57**: 134–9.
- 37 Udall JN, Pang K, Fritze L, Kleinman R, Walker WA. Development of gastrointestinal mucosal barrier. I.

- The effect of age on intestinal permeability to macromolecules. *Pediatr Res* 1981; **15**: 241–4.
- 38 Walker WA, Isselbacher KJ. Uptake and transport of macromolecules by the intestine. Possible role in clinical disorders. *Gastroenterology* 1974; **67**: 531–50.
- 39 Powell DW. Barrier function of epithelia. *Am J Physiol* 1981; **241**: G275–88.
- 40 Bjarnason I, Peters TJ, Levi AJ. Intestinal permeability: clinical correlates. *Surv Dig Dis* 1986; **4**: 83–92.
- 41 Menzies IS. Transmucosal passage of inert molecules in health and disease. In: Skadhauge E, Heintze K, eds. *Intestinal absorption and secretion (Falk Symposium 36)* Lancaster: MTP Press, 1983: 527–43.
- 42 Bjarnason I, O'Morain C, Levi AJ, Peters TJ. Absorption of <sup>51</sup>Chromium-labelled ethylenediaminetetraacetate in inflammatory bowel disease. *Gastroenterology* 1983; **85**: 318–22.
- 43 Bjarnason I, Peters TJ, Veall N. A persistent defect of intestinal permeability in coeliac disease demonstrated by a <sup>51</sup>Cr-labelled EDTA absorption test. *Lancet* 1983; **1**: 323–5.
- 44 Madara JL, Trier JS. Structural abnormalities of jejunal epithelial membranes in coeliac sprue. *Lab Invest* 1980; **43**: 254–61.
- 45 Lokken P. Studies on <sup>51</sup>CrEDTA and its evaluation as a reference substance in gastrointestinal research. In: *Norwegian Monog Med Sci* Oslo: Universitetsforlaget, 1970.
- 46 Rask-Madden J. Absorptive function of the colon. In: Barbara L, Miglioli M, Phillips SF, eds. *New trends in pathophysiology and therapy of the large bowel*. Amsterdam: Elsevier Science Publications, 1983: 19–34.
- 47 Miller TA. Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. *Am J Physiol* 1983; **245**: G601–23.
- 48 Simpson LO. NSAID and the leaky gut. *Lancet* 1985; **i**: 218–9.
- 49 Struthers GR, Andrews DJ, Gilson RJC, Reynolds GA, Low-beer T. Intestinal permeability. *Lancet* 1985; **i**: 587–8.
- 50 Walshe JJ, Venlito RC. Acute oliguric renal failure induced by indomethacin: possible mechanism. *Ann Intern Med* 1979; **91**: 47–9.
- 51 Veall N. Intestinal permeability. *Lancet* 1985; **i**: 588.
- 52 Cohen MM, Cheung G, Lyster DM. Prevention of aspirin induced fecal blood loss in men with prostaglandin E<sub>2</sub>. *Gut* 1980; **21**: 602–6.
- 53 Konjurek SJ, Kwiecien N, Obtulowicz W *et al.* Comparison of prostaglandin E<sub>2</sub> and ranitidine in prevention of gastric bleeding by aspirin in man. *Gut* 1983; **24**: 89–93.
- 54 Cohen MM, Pollett JM. Prostaglandin E<sub>2</sub> prevents aspirin and indomethacin damage to human gastric mucosa. *Surg Forum* 1976; **27**: 400–1.
- 55 Cohen MM, McCready DR, Clark L, Sevelius H. Protection against aspirin-induced antral and duodenal damage with enprostitic. *Gastroenterology* 1983; **88**: 382–6.