Effect of prostacyclin (PGI₂) on water and solute transport in the human jejunum

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SUMMARY Prostacyclin is an arachidonic acid metabolite, synthesised throughout the gastrointestinal tract, which has different effects on water and electrolyte transport across a variety of mammalian gastrointestinal epithelia. Using a perfusion technique in the human jejunum of 11 healthy subjects *in vivo*, the effect of intravenous prostacyclin, 4 ng/kg/min, on jejunal water and solute transport from a glucose electrolyte solution was investigated. In the prostacyclin group (n=5), prostacyclin was infused intravenously from 70-150 minutes, and buffer administered iv from 0-70 and 150-210 minutes. In the buffer group (n=6), iv buffer was administered from 0-210 minutes. In the prostacyclin group, net jejunal absorption of water was inhibited from 90-120 min (p<0.05), 150-180 min (p<0.01) and 180-210 min (p<0.01), of sodium was inhibited from 90-120 min (p<0.05), 120-150 min (p<0.05), 150-180 min (p<0.01) and 180-210 min (p<0.01), and of chloride was inhibited from 90-120 min (p<0.05), 120-150 min (p<0.005), 150-180 min (p<0.01) and 180-210 min (p<0.01). Prostacyclin had no effect on net movement of glucose, potassium or bicarbonate. These results are consistent with a role for prostacyclin in the endogenous humoral regulation of water and electrolyte transport in the human jejunum.

Prostacyclin (PGI₂), in common with other prostaglandins, is an arachidonic acid metabolite, which is synthesised throughout the gastrointestinal tract.¹ In tissues, arachidonic acid is released from membrane-bound phospholipids in response to a variety of physical and neurohumoral stimuli² and is then oxidised by the enzyme cyclooxygenase to PGI₂, PGE₂, PGF_{2α} and other metabolites.

Recent evidence has suggested that prostaglandins act as endogenous regulators of intestinal water and electrolyte transport.^{3,4} The role of PGI₂ in this respect is unclear, because previous reports of its effect on water and ion transport across mammalian gastrointestinal epithelia have varied depending on the species studied and the experimental techniques used. In one study in the rat small intestine, PGI₂ reduced luminal fluid accumulation ('enteropooling') and also inhibited enteropooling caused by cholera toxin and 16,16-dimethyl PGE₂.⁵ Prostacyclin decreased short circuit current across human jejunal mucosa *in vitro*,⁶ which suggested that it might also

possess antisecretory properties in man. PGI₂ elicits a secretagogue response, however, both in the rat jejunum and colon⁷ and in the guinea pig gall bladder.⁸

In view of these findings, the present study was done to investigate the effect of PGI₂ on water and solute transport in the human jejunum *in vivo*.

Methods

SUBJECTS

Eleven healthy subjects (five men, six women), aged 20-40 years, gave written informed consent for the study, which was approved by the ethical committee of St Bartholomew's Hospital, London.

INTESTINAL PERFUSION

After an eight hour fast, each subject swallowed a double lumen intestinal perfusion tube, incorporating a proximal occluding balloon, infusion and collection orifices placed 30 cm apart and a mercury bag.⁹ The tube was positioned fluoroscopically so that the balloon was situated at the ligament of Treitz with the infusion orifice located in the first 5 cm of jejunum. Using a peristaltic pump, a glucose

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electrolyte solution at 37°C was perfused through the infusion orifice at a rate of 15 ml/min. The solution contained (mmol/l): Na, 149; Cl, 124; HCO₃, 25; glucose, 10; polyethylene glycol (PEG 4000), 2.5 g/l and 1 µCi/l of [¹⁴C]PEG as a non-absorbable marker. The osmolality was 290 mosmol/kg. The solution was continuously gassed throughout each experiment with 95% O₂–5% CO₂. After a 30 minute equilibration period, serial 10 minute aspirates were collected by siphonage. Aliquots were taken for immediate bicarbonate estimation and samples for determination of other solute concentrations were stored at –20°C before analysis.

EXPERIMENTAL DESIGN

The glucose electrolyte solution was continuously perfused intrajejunally from 0 to 210 minutes in all 11 subjects. In five of these subjects, PGI₂ in buffer (0.5 ml/min) was infused *via* an indwelling cannula into an antecubital vein at a rate of 4 ng/kg/min from 70 to 150 minutes. The PGI₂ infusion was preceded and followed by intravenous administration of buffer alone at the same rate. In the other six subjects, intravenous buffer was infused at the same rate throughout the study period. Pulse and blood pressure were recorded at 15 minute intervals throughout each experiment.

CHEMICALS

Prostacyclin was reconstituted from a freeze dried preparation of the sodium salt with glycine buffer (pH 10.5) immediately before use. Prostacyclin was synthesised by Upjohn, Kalamazoo, Michigan, USA, and formulated by the Wellcome Foundation Ltd, Beckenham, Kent, UK. Glycine buffer was provided by the Wellcome Foundation Ltd.

ANALYSIS OF SAMPLES AND CALCULATIONS

The concentrations of glucose, sodium, potassium, chloride, bicarbonate and [¹⁴C]PEG were determined in each aspirate. [¹⁴C]PEG was measured in an LKB 1210 Ultrabeta liquid scintillation counter.¹⁰ Glucose was estimated by the glucose oxidase method.¹¹ Sodium and potassium concentrations were measured using an EEL 227 flame photometer (Evans Electroselenium Ltd, Halstead, Essex, UK) and chloride by an EEL chloridometer. Bicarbonate concentrations were measured as total CO₂ using an automated Corning 965 CO₂ analyser (Corning Ltd, Halstead, Essex, UK). Absorption rates of water and solutes from the test segment were calculated using standard formulae.¹² Net absorption (+) indicates a net transfer of water or solute from the lumen; net secretion (–) indicates net transfer of water or solute into the lumen.

STATISTICAL METHODS

The statistical significance of differences in intestinal transport rates between the group who received PGI₂ and those subjects in whom buffer was infused throughout was assessed using the non-parametric Mann-Whitney U test.¹³ The paired Student's *t* test was used to determine the level of significance of the systemic effects of PGI₂.¹³

Results

EFFECT OF PROSTACYCLIN ON WATER AND SOLUTE TRANSPORT

The effect of PGI₂ on net jejunal water and solute transport is shown in Table. Prostacyclin caused an inhibition of net absorption of water, sodium and chloride, but had no significant effect on the net transport of potassium, bicarbonate, or glucose. This inhibition of salt and water absorption by PGI₂ persisted between 150 and 210 minutes after the discontinuation of PGI₂ and showed no evidence of reversal, even in a single study which was continued to 300 minutes.

In order to confirm that these changes in water and ion transport were due to PGI₂ and not to the buffer nor to a decrease in the absorptive capacity of the jejunum with time, a group of subjects, in whom buffer alone was infused intravenously from 0–210 minutes was also studied. In this group, net jejunal absorption of water, sodium and chloride also tended to decrease with time, although these differences did not achieve statistical significance (Table). Statistical analysis was therefore carried out by comparing the change in net absorption of water, sodium and chloride with time for the PGI₂ and buffer groups (Figure). In the PGI₂ group, there was a statistically significant (*p* < 0.05) reduction in net jejunal absorption of water over the periods 90–120 and 150–210 minutes, and of sodium and chloride from 90–210 minutes.

SYSTEMIC EFFECTS OF PROSTACYCLIN

In all five subjects, PGI₂ caused facial flushing, which appeared within five minutes of starting PGI₂ infusion and resolved equally rapidly after its discontinuation. Mean pulse rate increased from 71 ± 5 beats/min in the pre-PGI₂ period to 91 ± 4 beats/min during PGI₂ infusion (*p* < 0.02). The tachycardia persisted (86 ± 4 beats/min) during the postinfusion period. There was no significant difference between the mean systemic blood pressure during the pre-PGI₂ (110/75 mmHg), PGI₂ (114/74 mmHg) and post-PGI₂ (114/79 mmHg) periods.

Discussion

Prostacyclin inhibited net jejunal absorption of

Table Effect of prostacyclin on jejunal water and solute transport

Time (mins)	H ₂ O		Na		Cl		K		HCO ₃		Glucose	
	Buffer	PGI ₂	Buffer	PGI ₂	Buffer	PGI ₂	Buffer	PGI ₂	Buffer	PGI ₂	Buffer	PGI ₂
30-70	179 (189, 116-224)	207 (212, 166-240)	28.6 (31, 19-35)	32.8 (33, 26-39)	17.4 (18, 10-23)	19.7 (18, 17-24)	-1.47 (-1.52, -1.19/-1.75)	-1.42 (-1.45, -1.24/-1.54)	10.5 (10.1, 8.4-14)	12.5 (12.9, 7.9-15.9)	8.49 (8.55, 8.11-8.64)	8.55 (8.62, 8.30-8.78)
90-120	167 (156, 109-263)	138 (117, 84-207)	26.8 (26, 18-41)	21.6 (18, 14-31)	15.4 (15, 9-26)	10.5 (8, 5-18)	-1.54 (-1.55, -1.21/-1.78)	-1.51 (-1.55, -1.19/-1.69)	—	—	8.51 (8.54, 8.19-8.69)	8.29 (8.49, 7.29-8.62)
120-150	155 (159, 109-203)	139 (173, 74-186)	24.8 (26, 17-31)	21.7 (27, 12-29)	14.4 (14, 8-21)	9.7 (11, 5-14)	-1.54 (-1.49, -1.30/-1.94)	-1.49 (-1.52, -1.26/-1.82)	10.0 (9.5, 7.5-13.5)	12.0 (12.4, 7.1-18.1)	8.63 (8.74, 8.19-8.83)	8.30 (8.50, 7.54-8.76)
150-180	142 (137, 115-177)	90 (89, 46-137)	22.4 (24, 18-26)	14.5 (15, 7-21)	12.2 (11, 8-18)	5.7 (6, 4-8)	-1.57 (-1.71, -1.10/-1.90)	-1.61 (-1.57, -1.43/-1.88)	—	—	8.60 (8.61, 8.30-8.85)	8.55 (8.60, 8.11-8.87)
180-210	148 (172, 93-186)	95 (87, 71-135)	23.2 (25, 15-31)	15.1 (15, 11-20)	13.4 (15, 7-19)	6.4 (8, 2-9)	-1.52 (-1.65, -1.13/-1.87)	-1.57 (-1.53, -1.25/-1.99)	10.1 (10.1, 7.2-13.8)	10.7 (11.6, 5.1-14.3)	8.63 (8.61, 8.36-8.96)	8.56 (8.71, 8.02-8.80)

Net water absorption is represented in ml/30 cm/h and net solute absorption in mmol/30 cm/h. Minus (—) values indicate net secretion. In the buffer group (n=6), iv buffer was administered throughout. In the PGI₂ group (n=5), PGI₂ was infused iv from 70-150 minutes, and buffer administered iv from 0-70 and 150-210 minutes. The results for each time period are the mean of successive 10-minute jejunal aspirates collected during that period. The values in brackets are the median and range of the data for each period. The equilibration periods were from 0-30 and 70-90 minutes.

Figure Change (Δ) in net jejunal water and solute absorption with time. Δ net water absorption is expressed in ml/30 cm/h and Δ net solute absorption in mmol/30 cm/h. The pooled results of three successive 10 minute jejunal aspirates from 90–210 minutes are represented in the histograms, which show the Δ between the mean of the pooled aspirates collected over that period and the mean of the control aspirates (30–70 min). Minus sign (–) = decreased absorption. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, where p values refer to the level of significance of the differences between the PGI₂ and buffer groups.

water, sodium and chloride from the glucose electrolyte solution, whilst net transport of potassium, bicarbonate and glucose was unchanged. This inhibition of salt and water absorption persisted after discontinuation of PGI₂.

The findings of the present study are very similar to those observed in the guinea pig gall bladder. In this model, both PGI₂ and its metabolite, 6,15-diketo-PGF_{1 α} , produced a dose dependent inhibition of fluid absorption and, at high concentrations, stimulated secretion. 6-keto-PGF_{1 α} , another degradation product of PGI₂, showed a similar, albeit less potent, effect.⁸ This inhibition of fluid absorption in guinea pig gall bladder still persists five hours after exposure to a single dose of PGI₂ (Wood JR, personal communication). Because PGI₂ has a half-life in blood of only two to three minutes,¹⁴ its longer acting metabolites, 6-keto-PGF_{1 α} and 6,15-diketo-PGF_{1 α} , may cause the prolonged inhibition of salt and water absorption in the human jejunum.

Absorptive and secretory processes in the enterocyte are regulated intracellularly by the cyclic nucleotides and calcium/calmodulin.¹⁵ An increase in the intracellular concentration of cyclic AMP and calcium both result in an inhibition of coupled sodium chloride absorption across the brush border membrane¹⁶ and a stimulation of active chloride secretion into the intestinal lumen.^{17, 18} Prostaglandin induced secretion has classically been thought to be mediated *via* activation of adenylate

cyclase/cyclic AMP.^{19, 20} This view has, however, been challenged by the finding that prostanoids may cause intestinal secretion at concentrations below those which normally affect cyclic AMP.⁶ It has therefore been suggested that prostanoids may also promote calcium entry across the serosal membrane into the enterocyte.²¹ Prostacyclin stimulates cyclic AMP production in human small intestinal mucosa, but only at unphysiologically high concentrations, being much less potent than PGE₂ in this respect.²² The inhibition of water, sodium and chloride absorption by PGI₂ in the present study is consistent with a cyclic AMP-mediated mechanism, although an effect on calcium/calmodulin might also be involved. A role for the latter mechanism is suggested by the recent demonstration that PGI₂ induces secretion in the rat colon and that this secretion was inhibited by the calcium channel blocker nifedipine and by the calmodulin inhibitor, trifluoperazine.²³ In the human jejunum, PGI₂ does not appear to be as potent a secretagogue as PGE₂,²⁴ which might reflect their relative effects on mucosal cyclic AMP production. Limitations in the dosage of PGI₂, however, which can comfortably be tolerated by man^{25, 26} and also its short half-life,¹⁴ prevent a full assessment of the magnitude of its effect on transmucosal epithelial fluid transport. The interpretation of the finding that PGI₂ inhibited jejunal salt and water absorption should be tempered by the fact that a single, possibly supra-

physiological, dose of PGI₂ was studied.

The dose of PGI₂ (4 ng/kg/min) administered in this study is of the order used therapeutically to prevent platelet aggregation in extracorporeal circulations.^{27,28} This dose was chosen as it may be calculated to result in local concentrations at the enterocyte in the order of magnitude of 10⁻⁸M, which is within the physiological range found in the intestine.⁶ Both the buffer and PGI₂ were infused *via* an indwelling cannula positioned in an antecubital vein, as this appears to reduce the frequency of local venous reactions, which may be because of the high pH of the buffer.²⁶ No such reaction was observed in the present study. Prostacyclin was administered intravenously to ensure that adequate concentrations of PGI₂ were achieved at the serosal border of the enterocyte, where prostanoids act to effect secretion. Moreover, the high pH of the buffer precluded intraluminal administration of PGI₂. Infusion of PGI₂ caused flushing and tachycardia as previously reported.²⁹ The persistent tachycardia after discontinuation of PGI₂ has not been reported in other studies.²⁹ These haemodynamic changes may have contributed to the prolonged inhibition of salt and water absorption observed following PGI₂ infusion. Prostacyclin increases intestinal blood flow in the dog,³⁰ and changes in the intestinal microcirculation may be important in the regulation of epithelial fluid transport.³¹ It is possible that the inhibition of salt and water absorption by PGI₂ is simply blood flow dependent and this may explain why the human jejunum responds differently *in vivo* than *in vitro*, where PGI₂ caused a 6–12% decrease in short circuit current, suggesting a stimulation of ion absorption.⁶ On the basis of these *in vitro* findings and also the anti-enteropooling effect of PGI₂ in the rat small intestine,⁵ it has been suggested that PGI₂ and PGE₂ have diametrically opposed effects on intestinal water and electrolyte transport.³² The present study, however, shows the PGI₂ has similar effects to PGE₂²⁴ in the human jejunum *in vivo*. This highlights the importance of confirming, *in vivo*, observations made *in vitro*, where haemodynamic effects, amongst others, are eliminated.

One potential shortcoming in using this perfusion technique to examine the effect of PGI₂ on jejunal fluid transport is that the occluding balloon might influence local intestinal prostaglandin biosynthesis. Certainly, in the human ileum, fluid secretion occurs in response to an acute increase in intraluminal pressure,³³ and the finding that indomethacin inhibits fluid secretion occurring in response to distention in the rat intestine³⁴ suggests that the secretion is mediated by endogenous prostaglandins. While the experimental technique used in

the present study did not permit measurements of intestinal prostaglandin biosynthesis, the balloon was inflated to a constant volume throughout each period in order to minimise any variations in endogenous prostaglandin synthesis in the jejunum during the studies.

Recent evidence suggests that the cyclooxygenase metabolites of arachidonic acid, mainly PGE₂, mediate the fluid secretion in some diarrhoeal diseases.^{35,36} The findings of the present study suggest that PGI₂ may also contribute to the fluid secretion stimulated after arachidonic acid release in man. Further, in view of its localisation within the gastrointestinal tract,¹ PGI₂, as well as PGE₂, may participate in the endogenous regulation of water and electrolyte transport in the human jejunum.

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References

- 1 LeDuc LE, Needleman P. Regional localization of prostacyclin and thromboxane synthesis in dog stomach and intestinal tract. *J Pharmacol Exp Ther* 1979; **211**: 181–8.
- 2 Rask-Madsen J, Bukhave K. The role of prostaglandins in diarrhoea. *Clin Res Rev* 1981; **1**: suppl 1: 33–48.
- 3 Binder HJ. New modes for regulating intestinal ion transport. *Gastroenterology* 1980; **78**: 642–4.
- 4 Rask-Madsen J, Bukhave K. Inhibitors and gastrointestinal function. In: Ramwell PW, ed. *Prostaglandins and related lipids*. Vol. 1. *Prostaglandin synthetase inhibitors: new clinical applications*. New York: Liss, 1980: 375–96.
- 5 Robert A, Hancher AJ, Lancaster C, Nezamis JE. Prostacyclin inhibits enteropooling and diarrhea. In: Vane JR, Bergström S, eds. *Prostacyclin*. New York: Raven Press, 1979: 147–71.
- 6 Bukhave K, Rask-Madsen J. Saturation kinetics applied to *in vitro* effects of low prostaglandin E₂ and F_{2α} concentrations on ion transport across human jejunal mucosa. *Gastroenterology* 1980; **78**: 32–42.
- 7 Hardcastle J, Hardcastle PT, Redfern JS. The effect of prostacyclin on intestinal ion transport in the rat. *Life Sci* 1980; **26**: 123–31.
- 8 Ashbrooke AB, Wood JR. Inhibition of gall-bladder fluid absorption by prostacyclin. *J Physiol* 1981; **318**: 66.
- 9 Sladen GE, Dawson AM. Further studies on the perfusion method for measuring intestinal absorption

- in man: the effects of a proximal occlusive balloon and a mixing segment. *Gut* 1970; **11**: 947–54.
- 10 Wingate DL, Sanberg RJ, Phillips SF. A comparison of stable and ¹⁴C-labelled polyethylene glycol as volume indicators in the human jejunum. *Gut* 1972; **13**: 812–5.
 - 11 Lloyd JB, Whelan WJ. An improved method for enzymic determination of glucose in the presence of maltose. *Anal Biochem* 1969; **30**: 467–70.
 - 12 Sladen GE, Dawson AM. An evaluation of perfusion techniques in the study of water and electrolyte absorption in man: the problem of endogenous secretions. *Gut* 1968; **9**: 530–5.
 - 13 Snedecor GW, Cochran WG. *Statistical methods*. 7th ed. Ames, Iowa: Iowa State University Press, 1980.
 - 14 Dusting GJ, Moncada S, Vane JR. Disappearance of prostacyclin (PGI₂) in the circulation of the dog. *Br J Pharmacol* 1978; **62**: 414–5P.
 - 15 Field M. Regulation of small intestinal ion transport by cyclic nucleotides and calcium. In: Field M, Fordtran JS, Schultz SG, eds. *Secretory diarrhea*. Baltimore, Maryland: Am Phys Soc, Waverley Press, 1980: 21–30.
 - 16 Frizzell RA, Field M, Schultz SG. Sodium-coupled chloride transport by epithelial tissues. *Am J Physiol* 1979; **236** (Renal Fluid Electrolyte Physiol 5): F1–8.
 - 17 Field M. Ion transport in rabbit ileal mucosa. II. Effects of cyclic 3',5'-AMP. *Am J Physiol* 1971; **221**: 992–7.
 - 18 Davis GR, Santa Ana CA, Morawski S, Fordtran JS. Active chloride secretion in the normal human jejunum. *J Clin Invest* 1980; **66**: 1326–33.
 - 19 Kimberg DV, Field M, Johnson J, Henderson A, Gershon E. Stimulation of intestinal mucosal adenyl cyclase by cholera enterotoxin and prostaglandins. *J Clin Invest* 1971; **50**: 1218–30.
 - 20 Kimberg DV, Field M, Gershon E, Henderson A. Effects of prostaglandins and cholera enterotoxin on intestinal mucosal cyclic AMP accumulation. *J Clin Invest* 1974; **53**: 941–9.
 - 21 Rask-Madsen J, Bukhave K. Prostaglandins and intestinal secretion. In: Turnberg LA, ed. *Intestinal secretion*. Welwyn Garden City: Smith, Kline and French Laboratories Limited, 1983: 76–83.
 - 22 Simon B, Müller, P, Kather H, Kommerell B. Cyclic nucleotides and intestinal secretion. *Clin Res Rev* 1981; suppl 1: 49–61.
 - 23 Goerg KJ, Wanitschke R, Roth R. Prostacyclin, a specific colonic stimulator of active chloride secretion. *Gastroenterology* 1984; **86**: 1091.
 - 24 Mize BF, Wu WC, Whalen GE. The effect of prostaglandin E₂ (PGE₂) on net jejunal transport and mean transit time. *Gastroenterology* 1974; **66**: 747.
 - 25 Data JL, Molony BA, Meininger MM, Gorman RR. Intravenous infusion of prostacyclin sodium in man: clinical effects and influence on platelet adenosine diphosphate sensitivity and adenosine 3':5'-cyclic monophosphate levels. *Circulation* 1981; **64**: 4–12.
 - 26 Pickles H, O'Grady J. Side effects occurring during administration of epoprostenol (prostacyclin, PGI₂), in man. *Br J Clin Pharmacol* 1982; **14**: 177–85.
 - 27 Longmore DB, Bennett JG, Hoyle PM et al. Prostacyclin administration during cardiopulmonary bypass in man. *Lancet* 1981; **1**: 800–4.
 - 28 Gimson AE, Braude S, Mellon PJ, Canalese J, Williams R. Earlier charcoal haemoperfusion in fulminant hepatic failure. *Lancet* 1982; **2**: 681–3.
 - 29 Fitzgerald GA, Friedman LA, Miyamori I, O'Grady J, Lewis PJ. A double blind placebo controlled crossover study of prostacyclin in man. *Life Sci* 1979; **25**: 665–72.
 - 30 Fondacaro JD, Jacobson ED. The role of prostacyclin (PGI₂) in metabolic hyperemia. *Prostaglandins* 1981; **21**: suppl: 25–32.
 - 31 Granger ND. Intestinal microcirculation and trans-mucosal fluid transport. *Am J Physiol* 1981; **240** (Gastrointest Liver Physiol 3): G343–9.
 - 32 Whittle BJ, Salmon JA. Biosynthesis of prostacyclin and prostaglandin E₂ in gastrointestinal tissue. In: Turnberg LA, ed. *Intestinal secretion*. Welwyn Garden City: Smith, Kline and French Laboratories Limited, 1983: 69–73.
 - 33 Wright HK, O'Brien JJ, Tilson MD. Water absorption in experimental closed segment obstruction of the ileum in man. *Am J Surg* 1971; **121**: 96–9.
 - 34 MacGregor IL, Lavigne ME. Inhibition by indomethacin of intestinal distension induced secretion in the rat. *J Surg Res* 1979; **26**: 167–70.
 - 35 Manning DC, Snyder SH, Kachur JF, Miller RJ, Field M. Bradykinin receptor-mediated chloride secretion in intestinal function. *Nature* 1982; **299**: 256–9.
 - 36 Musch MW, Kachur JF, Miller RJ, Field M. Bradykinin-stimulated electrolyte secretion in rabbit and guinea pig intestine: involvement of arachidonic acid metabolites. *J Clin Invest* 1983; **71**: 1073–83.