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Effects of prostaglandin E_2 on disease activity, gastric secretion and intestinal permeability, and morphology in patients with rheumatoid arthritis

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SUMMARY The effects of oral natural prostaglandin E_2 (PGE_2) on symptoms, disease activity, and gastrointestinal functions in rheumatoid arthritis (RA) were studied in an open pilot trial. Twelve patients, six taking and six not taking non-steroidal anti-inflammatory drugs (NSAIDs), received 1 mg natural PGE_2 three times a day for six weeks. The treatment was tolerated well and the only side effect noted was slightly looser stools in three patients. Half of the patients reported subjective improvement and none had aggravation of symptoms. The Ritchie articular index and several biochemical inflammation markers decreased and were significantly reduced at the end of the treatment period. The thickness of the small intestinal mucosa increased during the PGE_2 treatment. The intestinal permeability pattern, measured by urinary excretion of polyethylene glycols (PEG 400), differed between the patients taking and not taking NSAIDs. The initially high urinary PEG 400 excretion values in the patients taking NSAIDs decreased and the initially low excretion values in patients not taking NSAIDs increased during the PGE_2 treatment. The jejunal contents became sterile in 5/6 patients not taking NSAIDs and remained sterile in 1/6 patients taking NSAIDs at the end of the treatment. The treatment period was associated with a reduction of lactobacilli in patients not treated with NSAIDs. Thus the treatment appeared to decrease disease activity and to improve small intestinal functions in patients with RA, findings that need confirmation in a controlled trial.

Key words: non-steroidal anti-inflammatory drugs, microflora, gastrin.

Rheumatoid arthritis (RA) is associated with altered gastric and intestinal functions, and microbial flora.[1–4] Such changes may facilitate the absorption of antigens or other biologically active substances and be of significance in the pathogenesis of RA.[5–7]

Patients with RA, even those without any overt Sjögren's syndrome, display significantly reduced secretions of saliva[8] and gastric juice,[1] combined with hypergastrinaemia.[7 9 10] Reduced secretory capacity is often associated with a microbial overgrowth of the small intestine,[11 12] and the finding of faecal *Clostridium perfringens* type A in most patients with RA[1] may suggest a pathological small intestinal microflora in these patients.

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Prostaglandins help protect the gastroduodenal mucosa[13 14] and have trophic effects on gastrointestinal mucosa in the rat.[15] Prostaglandin of the E series has been found to prevent adjuvant arthritis in mice, to improve established arthritis,[16] and to affect other autoimmune phenomena in mice.[17]

The aim of this open pilot study in patients with RA was to examine the effects of PGE_2, administered orally over a six week period, on gastric secretion, intestinal permeability and morphology, gastrointestinal microflora, and the disease activity.

Patients and methods

PATIENTS

Twelve patients (four men and eight women) with an average age of 50 years (range 21–66) partici-

pated in the investigation. All patients had classical or definite RA according to the criteria of the American Rheumatism Association,[18] and all had symmetrical, peripheral, and erosive arthritis. Ten were seropositive for the rheumatoid factor, and one had subcutaneous nodules. The mean duration of the disease was three years (range six months to eight years) as evaluated from the onset of symptoms. The physical disability of the patients was evaluated as functional capacity and graded I to IV.[19] Seven patients were rated grade II and five grade III. At the time of the study three patients were without medication, three were occasionally receiving analgesics, paracetamol or paracetamol/dextropropoxyphene, and the remaining six were continuously taking non-steroidal anti-inflammatory drugs (NSAIDs). There was no difference in age, duration of disease, disease activity, or functional capacity between the groups taking and not taking NSAIDs. Over three months before the study three patients had been treated with chloroquine and one of the three had also been treated with gold. All patients displayed a normal renal function.

PROTOCOL

All patients received 1 mg PGE_2 orally three times a day for six weeks, and investigations were carried out before, during, and at the close of treatment, before the first daily dose (Fig. 1).

Clinical assessment included determination of the Ritchie articular index[20] and duration of morning stiffness; measurement of pain relief by the visual analogue scale[21]; and an assessment by the patient of global response (three grades—worsening, unchanged, or improved). Each patient was always examined by the same doctor and at the same time of day.

Blood samples were analysed before and every second week during the treatment for erythrocyte sedimentation rate, C reactive protein, orosomucoid, haptoglobin, complement, routine haematological variables, and routine liver and kidney tests. Rheumatoid factor, antinuclear antibodies, gastrin, zinc, folic acid, and iron were measured before and at the end of the treatment period.

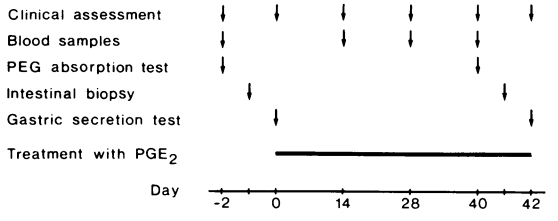

Fig. 1 *Design of the study.*

POLYETHYLENE GLYCOL (PEG) ABSORPTION TEST

After an overnight fast the patients were given 10 g PEG 400 in 500 ml water by mouth and an additional 250 ml water during the subsequent two hours. Urine was collected for six hours in polyethylene plastic containers and frozen at −70°C for subsequent analysis for different sized polyethylene glycols.[22]

BIOPSY SPECIMENS

Intestinal biopsy specimens were taken from 10 cm distal to the ligament of Treitz, oriented on Micropore filters (Millipore Corp, Bedford, Mass), and embedded in plastic. Sections (2 μm thick) were cut at least 10 μm apart from each other, and stained with periodic acid-Schiff reagent-haematoxylin. The sections were coded and examined blind by light microscopy (×20). The villous height and the depth of the jejunal crypts were measured in 10 well oriented crypt-villous columns with an ocular micrometer.

GASTRIC SECRETION TEST

Saliva samples were collected for microbial cultivations. Before swallowing a tube for the gastric secretion test patients rinsed their mouths with an antiseptic solution of ascorbic acid, sodium bicarbonate, and copper sulphate. Patients lay on their left side, with the tube (Fg 14, Portex, England) located in the stomach, to ensure optimal recovery. The saliva was collected by a suction device. After three 15 minute collections of the basal gastric secretion pentagastrin 6 μg/kg was given as a subcutaneous injection.

Collections of gastric secretions were continued for four 15 minute periods after stimulation, Samples (2–4 ml) of the gastric contents were aspirated with a sterile syringe 15 minutes before and 45 minutes after the pentagastrin injection for aerobic and anaerobic microbial cultivations. The volume and pH of the gastric recoveries were determined. The acidity of the samples was determined by titration with 0·1 M NaOH at pH 7 (Radiometer, Copenhagen, Denmark). The basal gastric acid secretion was expressed as the acid output during 30 minutes before stimulation, and the peak acid output as the sum of the two highest consecutive periods after pentagastrin.

RADIOIMMUNOLOGICAL DETERMINATIONS

Gastrin concentrations were determined according to the method described by Nilsson[23] using antiserum 2604, which recognises both gastrin 17 and 34, and unsulphated and sulphated forms of gastrin, with the same sensitivity. Fasted plasma levels <50 pmol/l are considered normal.

MICROBIOLOGICAL INVESTIGATION

Samples of saliva and of basal and stimulated gastric secretion were prepared for aerobic and anaerobic microbial cultivation within two hours. Homogenised parts of the jejunal biopsy specimens and concomitantly aspirated jejunal contents were also examined. Samples were suspended in prereduced peptone-yeast extract medium,[24] diluted, inoculated on media, and processed as described by Heimdahl and Nord.[25] The aerobic agar plates were incubated for 24 hours at 38°C and the anaerobic plates for 48 hours at 37°C in anaerobic jars (Gas Pak, BBL, Cockeysville, Maryland, USA). The micro-organisms isolated were then identified as described elsewhere.[25]

STATISTICAL METHODS

Values are given as medians or means and range. The Wilcoxon matched pairs signed ranks test, the randomisation test for matched pairs, and the

Table 1 *Results of clinical assessment in 12 patients with RA before and during six weeks' treatment with prostaglandin E_2*

	Week			
	0	*2*	*4*	*6*
Ritchie articular index	11 (1–28)	5** (1–11)	8 (0–15)	8* (0–21)
Morning stiffness (min)	90 (10–160)	98 (10–160)	91 (10–160)	60 (10–160)
Visual analogue pain score	45 (6–70)	40 (7–70)	43 (5–76)	37 (12–90)

Values are median (range).
Compared with values at week 0: *p<0·05; **p<0·01 (Wilcoxon matched pairs signed ranks test—two tailed).

Table 2 *Laboratory findings in 12 patients with RA before and during six weeks' treatment with prostaglandin E_2*

	Normal range	*Week*			
		0	*2*	*4*	*6*
ESR (mm/h)	1–20	49 (17–95)	47 (15–93)	43 (13–91)	44 (15–90)
CRP (g/l)	≤10	19·3 (7–43)	19·7 (5–39)	18·1 (5–50)	15·8* (5–40)
Orosomucoid (g/l)	0·5–1·0	1·63 (1·1–2·8)	1·61 (0·8–2·20)	1·57 (0·7–2·5)	1·54 (0·7–2·55)
Haptoglobin (g/l)	0·4–2·5	3·43 (2·4–5·6)	3·20 (2·0–5·6)	3·12 (2·0–4·7)	2·93** (1·6–5·3)
Complement C3 (g/l)	0·4–1·0	0·85 (0·65–1·1)	0·77 (0·6–0·9)	0·74** (0·6–0·9)	0·73** (0·6–0·9)
Complement C4 (g/l)	0·1–0·5	0·31 (0·2–0·45)	0·30 (0·1–0·5)	0·28 (0·1–0·4)	0·27* (0·1–0·45)
Haemoglobin (g/l)	≥120	133 (108–164)	133 (107–159)	131 (105–162)	129 (103–149)
White cell count ($\times 10^9$/l)	4·0–9·0	9·1 (4·1–15·1)	7·9* (4·8–12·7)	7·8* (3·8–12·7)	7·7** (3·6–11·8)
Platelet count ($\times 10^9$/l)	150–400	288 (175–356)	287 (195–430)	295 (207–426)	277 (157–394)
Folic acid (nmol/l)	5–30	7·2 (4·2–9·1)	ND	ND	5·6* (3·0–8·5)
Zinc (μmol/l)	14–24	13·5 (11–17)	ND	ND	12·7 (10–18)
Iron (μmol/l)	11–32	12·2 (5–24)	ND	ND	10·3 (6–15)

Values are mean (range).
Compared with values at week 0: *p<0·05; **p<0·01 (Wilcoxon matched pairs signed ranks test—two tailed).
ESR=erythrocyte sedimentation rate; CRP=C reactive protein; ND=not determined.

randomisation test for two independent samples were used to test significance. A p value <0·05 was considered significant.

Results

CLINICAL ASSESSMENT

All the patients included completed the six week treatment study. Slightly looser stools were experienced by three patients, but no other side effects were noted.

The results of the clinical assessment showed a significant reduction of the Ritchie articular index (Table 1). The decreases in the visual analogue pain score and in morning stiffness were not significant. At the end of the study six patients reported overall improvement, while the remaining six experienced no change. Haptoglobin, C reactive protein, complement factors C3 and C4, white cell count, and serum concentrations of folic acid decreased significantly, while other laboratory parameters remained unchanged during the treatment period (Table 2). Patients receiving NSAIDs continuously did not seem to respond differently from those not receiving such treatment in respect of disease activity.

GASTROINTESTINAL FUNCTION

Gastric acid secretion

The average basal gastric acid secretion before the study (n=10) was 0·65 mmol/30 min (range 0–1·61) compared with 1·18 mmol/30 min (range 0–4·73) after the treatment period (n=9). The corresponding peak responses to pentagastrin were 7·57 mmol/30 min (range 0·46–12·41) and 8·81 mmol/30 min (range 0–16·16) respectively. Two patients receiving NSAIDs and one patient not undergoing such treatment had basal achlorhydria.

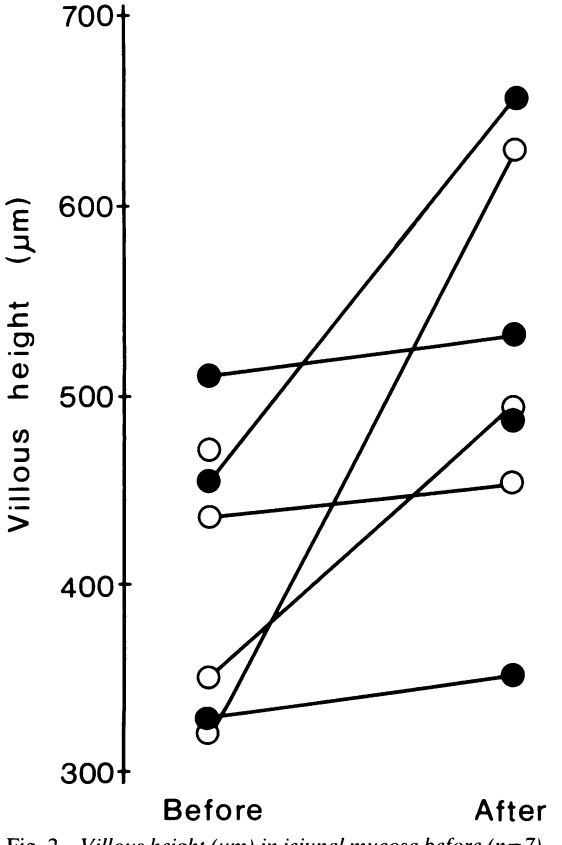

Fig. 2 *Villous height (μm) in jejunal mucosa before (n=7) and after (n=7) treatment with prostaglandin E_2 in patients with RA taking (●) and not taking (○) non-steroidal anti-inflammatory drugs. In six of the patients biopsy material was obtained both before and after the treatment.*

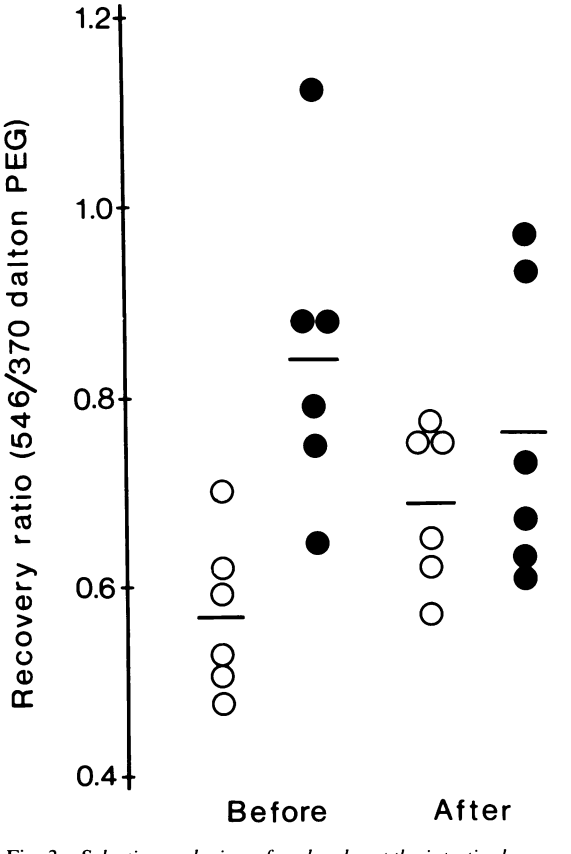

Fig. 3 *Selective exclusion of molecules at the intestinal wall, as described by the ratio between 546 and 370 dalton PEG in patients with RA taking (●) (n=6) and not taking (○) (n=6) non-steroidal anti-inflammatory drugs before and after treatment with prostaglandin E_2. The bars indicate mean values.*

The median fasting plasma gastrin concentration was 27 pmol/l (range 8–264) before and 25 pmol/l (range 8–196) after treatment (n=12).

Small intestinal biopsy specimens

Sufficient biopsy material was obtained in seven patients before or after PGE_2 treatment, or both. Pretreatment villous height was on average 412 μm (range 324–511) before the study and 514 μm (352–656) after its completion (Fig. 2). Well oriented sections both before and after were available in six patients, who all displayed increased villous height (Fig. 2). The corresponding figures for crypt depth were 152 μm (range 110–184) and 166 μm (range 121–212) respectively.

Absorption of PEGs

There was a distinct difference in PEG excretion between the patients undergoing continuous treatment with NSAIDs and those not receiving such treatment, and the results are presented separately (Table 3). Patients (n=6) not taking concomitant NSAIDs increased their six hours' urinary recovery of different sized PEGs ($p<0.05$), while a slight reduction was observed in patients (n=6) taking concomitant antiphlogistic drugs. Pretreatment values were lower in the patients not taking than in those taking NSAIDs, but this difference was not statistically significant. The recovery ratio between 546 and 370 dalton PEG (Fig. 3) increased significantly ($p<0.05$) in patients not taking NSAIDs and decreased in those taking NSAIDs. There was a significant difference ($p<0.05$) between the two groups before but not after the treatment with PGE_2.

Microflora

Intestinal juice for bacterial cultivations was sampled before and at the end of the PGE_2 treatment from 10 patients, four taking and six not taking NSAIDs. Intestinal biopsy specimens were concomitantly obtained from all these patients with lack of one specimen after PGE_2 in a patient not taking NSAIDs. Saliva and gastric juice were sampled from all the 10 patients with lack of gastric juice samples in one patient after PGE_2 treatment.

Positive bacterial cultivations of gastric juice were found only in patients with basal achlorhydria (n=3). The number of bacterial species increased during treatment with PGE_2 (Fig. 4). Only one patient displayed a negative pretreatment culture of the jejunal contents, but in the post-treatment period an additional five patients were free from bacterial contamination, all of them belonging to the patient group not taking NSAIDs. Of the corresponding biopsy specimens, two showed no growth either before or after treatment. The treatment period was associated with a reduction of lactobacilli in patients not treated with NSAIDs.

Table 3 *Effect of prostaglandin E_2 treatment on gastrointestinal permeability as described by six hours' urinary recovery of different sized polyethylene glycols in 12 patients with RA taking and not taking non-steroidal anti-inflammatory drugs (NSAIDs)*

Molecular size (daltons)	*Not taking NSAIDs (n=6)*			*Taking NSAIDs (n=6)*			*All patients*		
	Week 0	*Week 6*	*p**	*Week 0*	*Week 6*	*p**	*Week 0*	*Week 6*	*p**
282	9·4 (5·7–16·5)	11·9 (5·9–13·7)	NS	10·0 (3·9–21·1)	10·8 (4·3–13·4)	NS	9·4 (3·9–21·1)	11·4 (4·3–14·5)	NS
326	11·4 (6·5–23·0)	16·9 (6·4–26·1)	NS	15·1 (4·5–32·4)	14·4 (5·2–21·3)	NS	10·0 (4·5–32·4)	16·4 (5·2–26·1)	NS
370	13·2 (7·0–23·5)	20·7 (6·0–29·4)	<0·05	17·3 (4·6–33·6)	15·7 (5·7–25·5)	NS	13·2 (4·6–33·6)	19·7 (5·7–29·4)	NS
414	12·4 (5·4–20·2)	20·3 (4·4–27·7)	<0·05	16·8 (3·7–30·9)	15·3 (4·9–25·7)	NS	12·4 (3·8–30·9)	20·1 (4·4–27·7)	NS
458	9·9 (4·8–14·6)	15·9 (4·4–22·0)	<0·05	15·7 (3·9–29·5)	13·5 (5·3–21·5)	NS	10·5 (3·9–29·5)	15·9 (4·4–22·0)	NS
502	9·5 (4·2–13·1)	16·5 (3·9–20·8)	<0·05	16·3 (3·9–27·9)	13·0 (5·0–21·7)	NS	10·0 (3·9–27·9)	16·4 (3·9–21·7)	NS
546	8·6 (3·6–11·6)	15·5 (3·4–18·4)	<0·05	15·8 (3·6–28·0)	11·6 (4·3–21·4)	NS	8·8 (3·6–28·0)	15·1 (3·4–21·4)	NS
590	7·4 (3·0–9·5)	13·1 (2·3–16·5)	<0·05	14·0 (3·0–24·6)	9·6 (3·5–19·8)	NS	5·6 (3·0–24·6)	12·8 (2·3–19·8)	NS

Values are median (range). NS=not significant.
*The randomisation test for matched pairs—one tailed test.

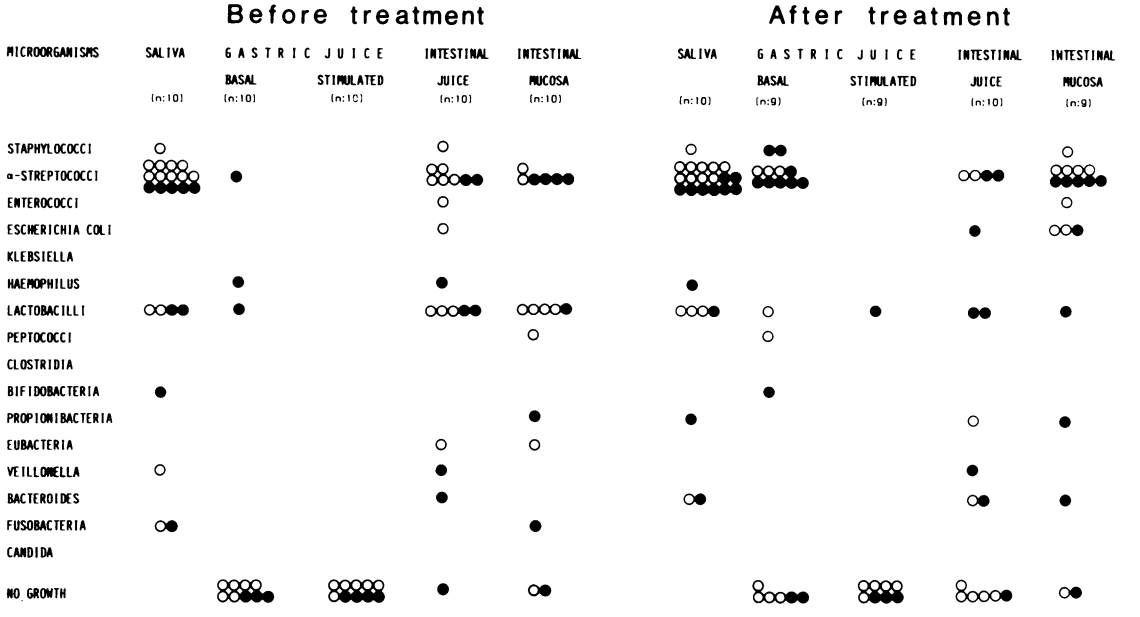

Fig. 4 *Different micro-organisms in saliva, gastric and intestinal juice, and in intestinal mucosa before and after treatment with prostaglandin E_2 in patients with RA taking (●) (n=4) and not taking (○) (n=6) non-steroidal anti-inflammatory drugs.*

Discussion

The present study shows that a six week long treatment period with PGE_2 1 mg three times a day was tolerated well by patients with RA. All patients completed the open pilot trial and, except for slightly looser stools in some patients, no side effects were noted.

The supplementation period was associated with a drop in the biochemical inflammation markers and a declining score on the joint index. As the study was open the doctor's bias and possible placebo effects or a spontaneous improvement in the disease activity have to be considered.

These findings have some support in studies on experimental animals. Prostaglandin E_2 was shown to prevent the onset of adjuvant arthritis in mice and to improve already established disease.[16] Furthermore, in NZB/NZW mice (a strain that spontaneously develops a systemic lupus erythematosus like syndrome) PGE_1 was found to delay death from lupus nephritis.[17] It is thus possible that orally administered PGE_2 is absorbed also in man and acts to reduce the disease activity in cases of rheumatoid arthritis. An ameliorating effect on RA may also, at least partly, be secondary to effects on gastrointestinal morphology and function.

Several studies have found a high prevalence of mucosal lesions and peptic ulcers in patients with rheumatic diseases during treatment with antiphlogistic compounds.[26] By blocking the enzyme cyclooxygenase, NSAIDs prevent the formation of prostaglandins, of which PGE_2 is a major product in the gastrointestinal mucosa and a stimulator of several recognised mucosal defence factors. That the ulcerogenic effects are related to such cyclo-oxygenase blocking properties is supported by several studies, in which the mucosal lesions produced by the drugs could be prevented by oral supplementation with a small dose of PGE_2.[27 28]

Previous studies have demonstrated a high prevalence of atrophic changes in the gastric, jejunal, and colonic mucosa in patients with RA.[3 29] It has not been possible to determine whether such changes result from the rheumatic disease itself or from the treatment with NSAIDs, which are known to produce atrophic changes in the gastric and intestinal mucosa in the rat.[30] In the present study the patients showed no abnormal pretreatment height of jejunal villi in small intestinal biopsy specimens.[31] Interestingly, the villous height increased in the small number of patients from whom well oriented biopsy specimens were obtained both before and after the treatment period. The trophic actions of E

prostaglandins on gastrointestinal epithelia are well documented in the rat[15 30] as are the trophic actions on the gastric mucosa in man.[32]

All patients displayed changes in the excretory pattern of PEG molecules during the treatment period, but the divergent effects of PGE_2 in patients taking and not taking NSAIDs tended to obscure the group values. The lowest urinary recovery of PEG 400 was observed in the group of patients with RA not taking NSAIDs, with a statistically significant increase after PGE_2 treatment. On the other hand, patients with RA treated with NSAIDs showed higher PEG 400 pretreatment values and a decrease during PGE_2 treatment, though these differences were not statistically significant.

Impaired intestinal absorption of different sized PEG 400 molecules, as evidenced by reduced urinary recovery of the test molecules, has previously been reported in RA,[22 33] but an increased intestinal absorption of PEGs of larger molecular size has also been reported in patients with RA with a high disease activity.[33] In a previous study on fasting in patients with RA a decrease in disease activity was accompanied by a decrease in urinary recovery of PEG 400, but the influence of a concomitant postponement of NSAIDs was not evaluated.[34] Patients with RA seem to display initially a normal intestinal absorption of ^{51}Cr edetate but an increased absorption of this test substance after treatment with indomethacin, an increase that was not prohibited by pretreatment with PGE_2.[35] The influences of RA itself, of the disease activity, and of NSAIDs and PGE_2 administration on the intestinal absorption patterns of various test substances thus appear to be complex.

As previously reported by our group, achlorhydria appears at an earlier age in patients with RA.[7] In the present study the achlorhydric state was found to be associated with bacterial overgrowth not only in the stomach but also in the luminal contents and the mucosal tissue of the small intestine. In repeated investigations of gastrointestinal microflora after the treatment period half of the patients examined were free from bacterial contaminations of the jejunal content, as compared with one patient before the treatment. The finding of less lactobacilli in the intestinal contents and mucosa after treatment is of particular interest. It has recently been reported that adjuvant arthritis in the rat follows a more severe clinical course when induced in germ free rats concomitantly inoculated with Gram positive bacteria, e.g., lactobacilli, as compared with those inoculated with Gram negative bacteria.[36]

It is not known whether gastrointestinal disturbances are of primary importance in RA. Such disturbances may be a part of the disease, an effect of pharmacotherapy, or more or less parallel phenomena. Combined disturbances in intestinal permeability and microbial flora may increase the load of substances of possible pathogenic significance in RA.

It can be concluded that oral supplementation with PGE_2 not only prevents damaging effects on the gastric mucosa from concomitantly administered NSAIDs, as shown previously,[27] but may actually help to improve small intestinal functions in patients with RA. Also, a beneficial effect on disease activity cannot be excluded. The results of this study, if confirmed in a controlled trial, would suggest that prostaglandin of the E series may be useful through multiple effects in the treatment of patients with RA.

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