membranes varied in the same subject during the evolution of the disease, the enzyme defect being most pronounced when the skin lesions were severe. The small number of patients with arthritis (5) in this study meant we could not relate specific expression of that form of disease to the ability to bind cAMP. We have lately studied 3 patients with pustulous psoriasis and they had no defect in binding of cAMP analogue to red cell membranes. We believe that this finding is due to pustulous psoriasis being a different form of the disease.

The finding that retinoid treatment in 4 patients increased the binding of the cAMP analogue to the RI subunit of PKA confirmed our previous results in cultured psoriatic fibroblasts.[6] These results suggest that the biochemical defect of the cAMP-dependent protein kinase is not only expressed at the skin level, but is also a general defect affecting red blood cells and perhaps other cell types. Because it is easy to obtain erythrocytes from patients, this biochemical defect may be useful in establishing the presence of psoriasis and in following its evolution. The in-vivo retinoid effect on the cAMP-dependent protein kinases suggests that this enzyme may be a useful marker in pharmacological studies.

It is interesting that family members of psoriasis patients had significantly lower than normal binding of cAMP to PKA. 3 subjects (mother of propositus in family 2, aged 34; father of propositus of family 3, aged 46; brother of propositus of family 5, aged 6) had especially low levels of cAMP binding. It is possible that these subjects, who are young, will express the disease soon after the study or that they could have other signs of psoriasis not detected by a simple clinical examination. These results also support the hypothesis that the reduced ability of cAMP to bind to the RI regulatory subunit is related to a genetic defect.

This study shows for the first time in psoriasis a biochemical feature which correlates with the severity of the disease as well as its clinical evolution. These results will be helpful in clinical management of psoriatic disease for the choice of retinoid therapy and its follow up.

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BACTERIOTHERAPY FOR CHRONIC RELAPSING CLOSTRIDIUM DIFFICILE DIARRHOEA IN SIX PATIENTS

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Summary Six patients with chronic relapsing diarrhoea caused by *Clostridium difficile* were treated with rectal instillation of homologous faeces (one patient) or a mixture of ten different facultatively aerobic and anaerobic bacteria diluted in sterile saline (five patients). The mixture led to a prompt loss of *Cl difficile* and its toxin from the stools and to bowel colonisation by *Bacteroides* sp, which had not been present in pre-treatment stool samples. Strains of *Escherichia coli*, *Cl bifermentans*, and *Peptostreptococcus productus* in the mixture inhibited the in-vitro growth of *Cl difficile*, which in turn inhibited the growth of *Bacteroides ovatus*, *Bacteroides vulgatus*, and *Bacteroides thetaiotaomicron*. The finding that *Bacteroides* sp had been absent during the patients' illness but was present after recovery suggests that the absence of *Bacteroides* sp may result in chronic relapsing *Cl difficile* diarrhoea, and that its presence may prevent colonisation by *Cl difficile*.

Introduction

TOXIGENIC *Clostridium difficile* is the most important cause of antibiotic-associated diarrhoea and pseudomembranous colitis.[1–3] These disorders are usually precipitated by antibiotic therapy, but the interactions, if any, between host responses and environmental agents are poorly understood. In most cases discontinuation of the causative antibiotic restores normal colonic microflora and bowel function. Oral vancomycin is considered the treatment of choice for severe infection but recurrences occur in approximately one-third of cases.[4] However, a second course of vancomycin, or long-term treatment with gradual tapering of the dose, sometimes combined with cholestyramine, has cured most patients.[5,6] In rare instances in which *Cl difficile* could not be eradicated with antibiotics colectomy has been done to control *Cl difficile* infection.[7,8] Other approaches to treatment of recurrent diarrhoea due to *Cl difficile* include treatment with drugs other than vancomycin,[9] oral administration of a non-toxigenic avirulent strain of *Cl difficile*,[10] and replacement of normal colonic microflora by rectal infusion of homologous faeces.[11,12] Here we describe bacteriotherapy in six patients with chronic relapsing diarrhoea associated with toxigenic *Cl difficile* infection. One patient was treated with an enema of fresh faeces from a healthy relative and the other five patients received a rectal infusion of a mixture of colonic bacteria in saline.

Patients and Methods

Patients

The clinical details are given in table I.

Stool Cultures

At each follow-up point stool samples from three consecutive bowel movements were cultured to ensure that the findings were

representative of the colonic microflora at that specific time. After bacteriotherapy stool samples were examined weekly for 2 months and then every fortnight for 4 months. Patient 2, who did not respond to faecal instillation but did to a mixture of bacteria, was followed-up for 12 months.

Culture of Cl difficile.—*Cl difficile* was cultured on the selective cefoxitin cycloserine fructose agar (CCFA).[13] Approximately 1 g of faeces was thoroughly mixed with 1 ml of 56% v/v ethanol in a whirlmixer and then incubated for 1 h at room temperature. A sample of the mixture was subsequently inoculated into a semifluid thioglycolate medium and anaerobically incubated in a 'Forma' scientific glovebox chamber (system model 1024; Marietta, Ohio, USA) for 5 days in an atmosphere of 80% N_2, 10% H_2, and 10% CO_2 for detection of spore-producing bacteria. Visible growth was subcultured anaerobically on brain-heart infusion agar media for 2 days before identification of bacteria.

Quantification of bacteria.—Fresh faeces, diluted stepwise in saline to a concentration of 10^{-9} bacteria/ml, were used for the qualitative/quantitative stool cultures after anaerobic incubation in the glovebox chamber. Each dilution was cultured on the selective and enriched media discribed below to ensure the correct number of bacteria. The following media were used: salt agar (7% NaCl) for *Staphylococcus* sp; brain-heart infusion agar (BHIA) for anaerobes; McConkey agar for facultative gram-negative rods; and 10% horse-blood agar and BHIA agar with kanamycin in a concentration of 75 μg base/ml agar for *Bacteroides* sp. Colonies were counted after 48 h of aerobic or anaerobic incubation at 37°C. The facultative aerobic bacteria were identified by their O_2 requirement, colony morphology, and fermentation of sugars. The anaerobic bacteria were identified by their production of volatile fatty acids in peptone yeast extract medium by gas-liquid chromatography and by their fermentation of sugars in peptone yeast extract, with decrease in pH being used as endpoint.[14]

Toxin Assay

McCoy cells were used for assay of *Cl difficile* toxin; the test was judged positive if the actinomorphic changes observed were inactivated by *Cl difficile* antitoxin. 1 g faeces was thoroughly mixed with saline in a whirlmixer. After centrifugation at 12 000 rpm for 10 min the supernatant was filtered through a 25 μm 'Swinnex' micropore filter (Millipore Co, Bedford, Massachusetts, USA) and 0·2 ml was incubated with a monolayer of McCoy cells at 37°C for 48 h. If there was actinomorphic change a neutralisation assay with *Cl sordellii* antitoxin (standardisation department, Statens Seruminstitut) was done. 0·2 ml *Cl sordellii* antitoxin was added to 0·2 ml of the cytotoxic supernatant and left for 15 min before incubation with a monolayer of McCoy cells at 37°C for another 48 h. If there was no cytotoxic activity the sample was judged to be positive for *Cl difficile* toxin.

In-vitro Inhibition of Cl difficile

To examine the effects of *Cl difficile* and enteric strains on each other, *Cl difficile* strains were streaked upon BHIA agar and the strains instilled rectally (test strains) were then streaked from the left to the right, perpendicular to the *Cl difficile* streak (fig 1).

28 different strains of colonic bacteria from stools of healthy volunteers without signs or symptoms of gastrointestinal disease were tested as described above. To find out whether bacterial products might inactivate *Cl difficile* bacteriocins were looked for in

TABLE I—CLINICAL DETAILS

—	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex age (yr)	F/60	M/59	F/69	F/83	F/81	F/72
Clinical symptoms at diagnosis						
Weight loss (kg)	4	4	3	0	2	0
GI symptoms (months)	6	2	12	<1	<1	<1
Vomiting	+	−	−	+	−	−
Abdominal pain	+	+	+	+	+	+
Watery/bloody diarrhoea	+/+	+/+	+/+	+/+	+/−	+/−
No of stools per day (range)	6–10	6–8	8–12	5–8	2–8	4–8
Marker of inflammation						
Serum-orosomucoid (μmol/l) (normal:11–30)	66	20	ND	ND	45	ND
Marker of leakage						
Serum-albumin (μmol/l) (normal 550–760)	320	600	ND	450	318	374
Inflammation at colonoscopy						
Rectum	−	+	−	+	+	ND
Sigmoid/descending colon	+	+	−	−	−	ND
Inflammation on histology	+	+	ND	+	+	ND
Previous antibiotic treatment	?	Penicillin	Sulphamethizole	Ampicillin, Tobramycin, Metronidazole	Pivampicillin	Pivampicillin
Indication for antibiotics	−	Sinusitis	Urinary tract infection	Septicaemia	Pneumonia	Bronchitis
No of relapses	2	4	2	2	2	2
Cl difficile *in stools at relapse*						
Culture (toxin) positive	14/14 (14/14)	21/21 (21/21)	6/6 (6/6)	8/8 (8/8)	4/4 (2/2)	6/6 (3/3)
Days before relapse (range)	14–45	5–24	18–20	5–10	5–21	10–20
Antibiotics for intercurrent infections	−	−	−	Ampicillin, Mecillinam	Penicillin G Erythromycin	Erythromycin
Treatment of diarrhoea before isolation of Cl difficile	'Lomotil' opioids'	Sulphasalazine Prednisolone	'Lomotil'	'Lomotil' opioids'	Opioids	'Lomotil'
Previous treatment for Cl difficile	Vancomycin × 2 Cholestyramine*	Metronidazole* Vancomycin × 3 Fusidic acid*	Vancomycin × 2 Metronidazole*	Vancomycin × 2 Metronidazole*	Vancomycin × 2 Metronidazole*	Vancomycin × 2 Metronidazole*
Proven Cl difficile *diarrhoea before bacteriotherapy (months)*	15	18	6	7	5	4
Bacteriotherapy						
Faecal enema	+	+	−	−	−	−
Bacterial enema†	−	+	+	+	+	+

*Continuous growth of *Cl difficile* during treatment; M/F = male or female; ND = not done.
†Given thrice at 2 day intervals, after a 5-day course of vancomycin.

(1) sonicated bacteria, (2) culture supernatants, which were added to the plates and to newly streaked cultures of *Cl difficile* on BHIA agar plates, and (3) test strains grown on BHIA overnight. After removal of the test strain *Cl difficile* was cultured on the same agar plate for another 24 h and examined for differences in growth.

Preparation of Bacteria or Faeces for Infusion

Each of the ten strains of bacteria selected for bacteriotherapy grew in a fluid medium for 48 h until a concentration of approximately 10^9 bacteria/ml was reached. 2 ml of each medium, containing one of the ten strains selected were mixed with 180 ml saline pretreated in the anaerobic glovebox chamber for 24 h. Immediately before rectal instillation in patients the bacteria were quantified. All ten strains were viable and were present in concentrations of 10^8–10^9 bacteria/ml.

The faecal enema given to patients 1 and 2 consisted of 50 g freshly passed stool from the patient's husband and daughter, respectively, thoroughly mixed in 500 ml saline.

Results

During recurrences stool samples from the six patients with chronic relapsing *Cl difficile* diarrhoea were positive for *Cl difficile* and its toxin (table I). In all patients cytotoxin assays were always negative after start of vancomycin treatment, but the organism was isolated and the toxin demonstrated in five of the patients while they were on metronidazole.

Rectal instillation of the bacterial mixture or of homologous faeces was followed promptly by a loss of *Cl difficile* and its toxin (fig 2) from the stools, restoration of normal bowel function within 24 hours, and disappearance of abdominal symptoms. All patients gained weight and serum albumin and serum orosomucoid concentrations returned to normal. Stool cultures and toxin assays for *Cl difficile* remained negative during the year's follow-up (fig 2).

Stools from all six patients did not contain *Bacteroides* sp before bacteriotherapy and during vancomycin therapy, when patients still had symptoms. By contrast, *Bacteroides* sp were regularly cultured during the follow-up period, in concentrations of 10^5–10^8 bacteria/ml.

Three of the strains selected for bacteriotherapy (table II) inhibited the in-vitro growth of *Cl difficile*, whereas the six *Cl difficile* strains inhibited the in-vitro growth of all

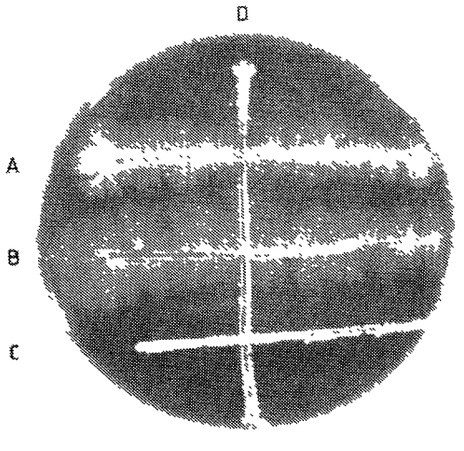

Fig 1—Interaction between *Cl difficile* and test organisms.

(A) Inhibition of *Cl difficile* by *Cl bifermentans*.
(B) No interaction between *Cl innocuum* and *Cl difficile*.
(C) No interaction between *E coli* 1109 and *Cl difficile*.
(D) Vertical streak of *Cl difficile*.

TABLE II—EFFECT OF BACTERIAL STRAINS USED FOR BACTERIOTHERAPY ON GROWTH OF CL DIFFICILE STRAINS ISOLATED FROM PATIENTS AND VICE VERSA

Bacterial strain (registration number)	Patient					
	1	2	3	4	5	6
S faecalis (1108-2)	0	0	0	0	0	0
Cl innocuum (A27-24)	0	0	0	0	0	0
Cl ramosum (A31-3)	0	0	0	0	0	0
Bact ovatus (A40-4)	×	×	×	×	×	×
Bact vulgatus (A33–14)	×	×	×	×	×	×
Bact thetaiotaomicron (A33-12)	×	×	×	×	×	×
E coli (1109)	0	0	0	0	0	0
E coli (1108-1)	+	+	+	+	+	+
Cl bifermentans (A27-6)	+	+	+	+	+	+
P productus (1108-2)	+	+	+	+	+	+

0 denotes "no inhibition"
× denotes "test strain inhibited by *Cl difficile*"
+ denotes "*Cl difficile* inhibited by test strain.

Bacteriodes sp. No growth inhibition by bacteriocins was observed by testing with any of the three methods described above.

Discussion

Diarrhoea associated with *Cl difficile* often recurs, even after treatment with vancomycin, when relapse rates vary from 12–40%.[1,2,10,12] When the chronic relapsing diarrhoea is due to toxins produced by *Cl difficile*, eradication of the microorganism by antibiotics may be impossible, which is why alternative approaches to treatment have been attempted. Colonisation with a non-cytopathogenic *Cl difficile* and adminsitration of faecal enemas prepared from relatives have been effective treatments for recurrent *Cl difficile* associated enterocolitis.[10,12] The recent discovery that *Bacteroides* sp protect against invasive *E coli*,[17] the observation that fatty acids from anaerobic bacteria re-establish colonic ecology,[15-17] and the therapeutic effect of *Bacteroides* sp in animals deliberately infected with *Salmonella* sp[18] suggest that *Bacteroides* sp may be important in maintaining normal bowel function and strengthening the resistance to gastrointestinal infections.

All our patients did not have *Bacteroides* sp in their gut before therapy, and all had complete clinical recovery after recolonisation of the gut with the organism. Rectal infusion of homologous faeces was successful in the first, but not in the second, patient in whom this procedure was attempted. In the first patient recolonisation occurred gradually during the follow-up period, with fifteen new species being introduced, although only two species of enteric bacteria other than *Cl difficile* were cultured before rectal instillation of the homologous faeces. *Bacteroides* sp were the major constituents of the new flora. In the other patient, the illness did not improve with two faecal enemas but did with administration of a mixture of cultured bacteria. The mixture of cultured bacteria also produced improvement in the four remaining patients. In the five patients who received the bacterial mixture, colonisation with *Bacteroides* sp was maintained, whereas *Cl bifermentans* and *Peptostreptococcus productus*, respectively, colonised only 1 patient each. Acquisition of anaerobic species other than those given therapeutically occurred after clinical remission and recolonisation with *Bacteroides* sp, which suggested that bacteria acquired from the environment were not responsible for clinical recovery.

Our observation that *Cl difficile* inhibits the growth of *Bacteroides* sp, which account normally for more than 90%

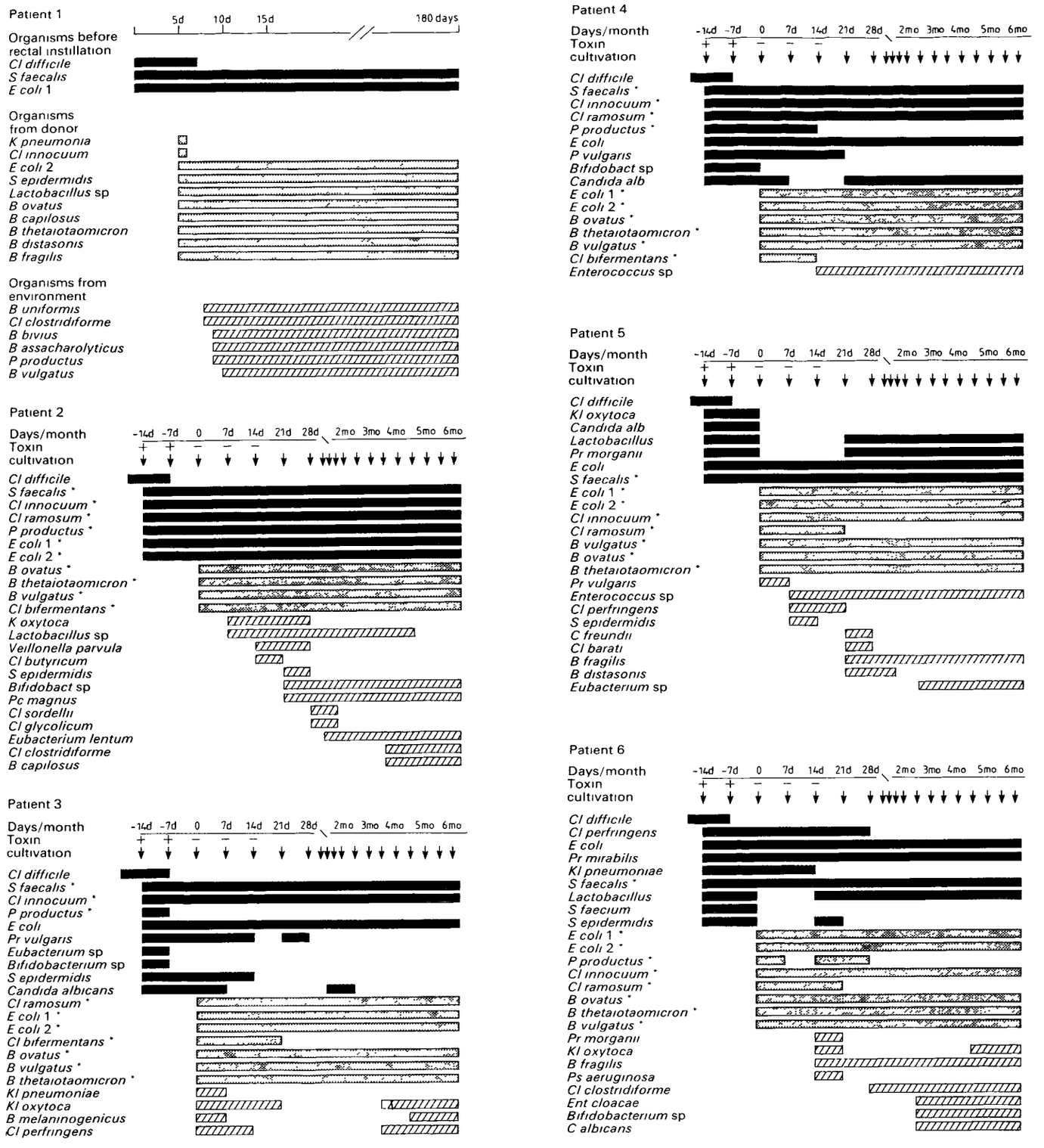

Fig 2—Bacterial findings after faecal enema (patient 1) or instillation of mixture of bacteria (patients 2–6).

Asterisks denote bacteria given therapeutically.
Solid bars = species present before bacteria therapy. Stippled bars = species given therapeutically. Hatched bars = new colonising species.
In patient 5, *Cl bifermentans* and *P productus* instilled but no growth obtained.
In patient 6, *Cl bifermentans* given but no growth obtained.
Downward arrows indicate time of stool examination.

of the colonic microflora, accords with previous findings. Thus our success with bacteriotherapy may be due in part to the initial eradication of *Cl difficile* by vancomycin. It should be noted that the patient in whom colonisation of *Bacteroides* sp was established with infusion of homologous faeces had not been pre-treated with vancomycin. Other donor and/or recipient factors may also have influenced response because rectal instillation of faeces containing a normal range of *Bacteroides* species in the second patient was unsuccessful, both before and after treatment with vancomycin. Nevertheless, the observation that, in this second patient, a mixture of cultured bacteria given rectally restored normal microflora and bowel function after colonisation by *Bacteroides* spp strongly suggests that these organisms are

essential in colonic resistance to reinfection or relapses with *Cl difficile*.

All patients in the present study had initially been treated with metronidazole without any success. The drug might be responsible for the eradication/limitation of normally occurring *Bacteroides* sp, which are extremely sensitive to this antibiotic. If so, vancomycin should be preferred to metronidazole for treatment of diarrhoea caused by *Cl difficile* to avoid suppression of *Bacteroides* sp.

Since all patients harboured both *Cl innocuum* and *P productus* during the period of chronic diarrhoea these microorganisms were unlikely to have been responsible for the recovery observed. Similarly, *E coli* 1108-1 and 1109 were isolated from patient 2 during the period of diarrhoea, so they too were unlikely to have been responsible for recovery. *P productus* did not establish itself in patient 4, and *Cl bifermentans* colonised only one patient. The reason for including the *E coli* and the gram-positive anaerobes in the mixture used for bacteriotherapy was their ability to inhibit the growth of any remaining endospores. The *Bacteroides* sp were included because they were completely absent during the diarrhoeal periods in all six patients, a most unusual finding since these organisms normally account for more than 90% of the total number of bacteria in faeces. Although we were unable to demonstrate any curative effect of *P productus*, which was present during the long chronic phase of diarrhoea, a beneficial synergistic effect of gram-positive bacteria cannot be excluded. We would tentatively conclude, therefore, that colonisation with *Bacteroides* sp provides a natural defence mechanism against intracolonic growth of *Cl difficile*.

Controlled clinical trials on the efficacy of bacteriotherapy are justified but not very likely to be done because few patients have multiple relapses of *Cl difficile* diarrhoea. Nevertheless, the prompt loss of *Cl difficile* and its toxin from the stools of all patients following bacteriotherapy suggests a therapeutic effect of the approach. This claim is substantiated by the observation that patients who relapse continue to excrete *Cl difficile* if vancomycin is not given. The administration of defined and identified microorganisms seems to be a major improvement over giving a suspension of faeces by enema and represents a therapeutic option that may be considered for use on a much wider basis.

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References continued at foot of next column

RANDOMISED, CONTROLLED TRIAL OF FAECAL OCCULT BLOOD SCREENING FOR COLORECTAL CANCER

Results for First 107 349 Subjects

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Summary To assess the effectiveness of screening by faecal occult blood tests, 107 349 people without symptoms of colorectal disease identified from general practitioner records have been randomly allocated to test and control groups. 53 464 test subjects were invited to carry out the screening test; 27 651 (53%) of the 52 258 who received the tests did so. Further investigation of the 618 (2·3%) with positive tests showed 63 cancers (52% stage A) and 367 adenomas (266 subjects). Rescreening of subjects with negative results every 2 years (9510 first rescreen, 3639 second) has shown a significant fall in the rate of positive results (1·7% of 7344; 0·3% of 2906). Cancers have also been diagnosed in 20 subjects presenting in the interval between a negative test and rescreening, and in 83 non-responders. The incidence of cancer in the control group (123 subjects; 10·6% stage A) was 0·72 per 1000 person-years. Cancers detected by screening were at a less advanced pathological stage, but it is too early to show any effect of screening on mortality from colorectal cancer.

Introduction

COLORECTAL cancer is the second commonest cause of death from malignant disease in England and Wales—more than 17 300 deaths in 1987.[1] Despite advances in the diagnosis and treatment of symptomatic colorectal cancer, there has been little reduction in mortality over the past

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