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Role of intestinal microflora in colonic pseudo-obstruction complicating jejunoileal bypass

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SUMMARY A double-blind crossover study using placebo and antibiotics effective against either aerobic or anaerobic organisms has been performed to elucidate the role of intestinal microflora in the pathogenesis of colonic pseudo-obstruction, which is now established as an important complication of jejunoileal bypass. Using strict Virginia Polytechnic Institute (VPI) technique, quantitative bacterial studies of the intestinal flora in the region of bypassed bowel have been correlated with symptoms of abdominal pain and distension. It has been shown that antibiotics effective against obligate anaerobes rapidly relieve the symptoms of pseudo-obstruction and this coincides with the disappearance of these organisms from this region of bowel. Symptoms rapidly recur when anaerobic organisms repopulate the bowel. It is concluded that obligate anaerobes may play a role in the pathogenesis of this complication.

Jejunoileal bypass has been used as a treatment for morbid obesity since early in the 1950s. Although this operation produces a substantial weight loss it is subject to the development of several serious complications. Recently, a syndrome of pseudo-obstruction of the colon has been recognised (Fikri and Cassella, 1974; Barry *et al.*, 1975a, b). This syndrome occurs as a late complication of jejunoileal bypass and of the 13 cases in our own experience no case showed any radiological evidence of organic obstruction to the lumen of the bowel. The serum electrolytes were normal in all cases and intrinsic nervous plexuses were normal in two cases which we have examined.

In those cases with an end-to-side bypass (Fig. 1), the dilatation affected the whole length of the colon, whereas in those patients with an end-to-end bypass the dilatation was localised to that part of the colon which was distal to the site of anastomosis with the defunctioned small bowel (Fig. 2). Resection of the affected colon in one case resulted in a recurrence of the pseudo-obstruction distal to the new site of drainage of the bypassed small bowel (Barry *et al.*, 1975a). These findings suggest that the contents of the bypassed small bowel draining into the colon may be a factor in the pathogenesis of this syndrome. A course of intravenous antibiotic in one case and an oral course in a second case resulted in a dramatic improvement in symptoms (Barry *et al.*, 1975a). For these reasons we have studied the bacterial flora in the region of the defunctioned bowel to assess their role in the pathogenesis of this complication.

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Methods

Five patients were studied. Three had had an end-to-side jejunoileal bypass performed and two an end-to-end jejunoileal bypass performed 1½ to three years previously. At the time of admission to the study, all had continuous symptoms of severe colicky abdominal pain, abdominal distension, and obstipation with nausea and occasional vomiting.

Antibiotics were administered in courses of five to seven days in a random sequence, double-blind, crossover study. After a five day pretreatment study period, each patient received either metronidazole (500 mg, six hourly by mouth) or kanamycin (500 mg, six hourly by mouth) for five to seven days, these two antibiotics then being crossed over for a further five to seven day treatment period. During a third five to seven day treatment period the patients received either an inert placebo or a combination of metronidazole plus kanamycin in the same doses as above which were then crossed

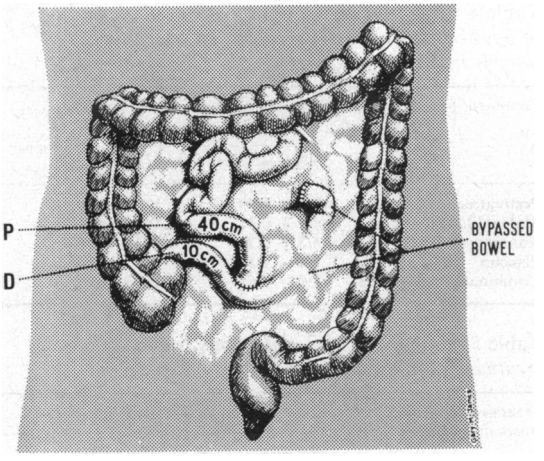

Fig. 1 *End-to-side jejunoileal bypass. Fluid for quantitative bacteriology obtained from functional bowel proximal (P) and distal (D) to the jejunoileal anastomosis where the bypassed small bowel drains.*

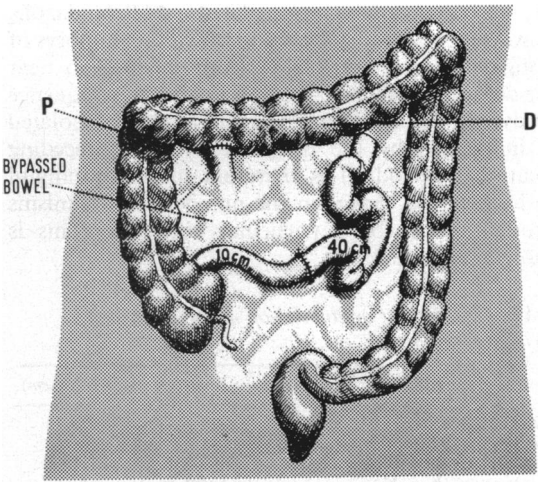

Fig. 2 *End-to-end jejunoileal bypass. Fluid for quantitative bacteriology obtained from functioning bowel proximal (P) and distal (D) to site of drainage of bypassed small bowel.*

over for the fourth and last five to seven day treatment period.

The patient's response to each course of treatment was assessed by recording each day the presence or absence of abdominal pain and by measuring the abdominal girth at the level of the umbilicus at 8 a.m. before eating.

Before and at the end of each treatment period quantitative bacterial cultures were obtained in four of the five from two sites. The first site was immediately proximal to the anastomosis with the defunctioned bowel (indicated by P in Figs. 1 and 2). These specimens were obtained through a peroral tube positioned under radiological control. The second site was immediately distal to the anastomosis with the defunctioned bowel (indicated by D in Figs. 1 and 2) using a peroral tube under radiological control for the end-to-side bypass and a sealed tube through a colonoscope for the end-to-end bypass. One patient withdrew consent for further bacteriological studies after the pretreatment period so that complete bacteriological data is available on only four of the five patients in the study.

All bacteriological samples were transported in gassed vials to preclude aeration and processed immediately according to strict Virginia Polytechnic Institute (VPI) technique (Holdeman and Moore, 1972). Quantitation was determined in roll tubes for anaerobes and by quantitative loop for aerobes. Identification of anaerobes was according to Holdeman and Moore (1972), aerobes according to standard procedure. Antimicrobial sensitivity of anaerobes was performed by an agar-dilution technique (Chow *et al.*, 1975), aerobes by the Kirby-Bauer disc-diffusion method (Bauer *et al.*, 1966).

Results

The mean abdominal girth for each treatment period was calculated and the change from the mean in the previous treatment period of the random sequence is shown in Table 1. A plus (+) denotes an increase in mean girth and a minus (−) denotes a decrease. Metronidazole produced a decrease in mean girth in all five patients. The inert placebo resulted in an increase in mean girth over that of the previous treatment period in all five patients. As can be seen from Table 1, kanamycin produced a more modest decrease in girth and the combination treatment (metronidazole plus kanamycin) was only as effective as metronidazole alone. The effect of antibiotics on abdominal pain is shown in Table 2.

The numbers and type of bacterial flora isolated were very similar in all patients irrespective of the type of bypass performed or even the site from which the sample was taken. Thus the small bowel in the region of the bypassed loop harboured a flora very similar to that found in the colon. The numbers and types of organisms isolated from all patients before treatment are summarised in Table 3.

As the quantitative bacterial counts obtained immediately proximal to the bypassed bowel were virtually identical with those obtained distal to the bypassed bowel, a single figure, which is the mean of these two estimations is presented here (Table 4).

From Table 4 it can be seen that no treatment period produced a significant change in the numbers

of aerobic organisms isolated. Metronidazole, however, produced a dramatic fall in the numbers of obligate anaerobes isolated from this region near the defunctioned bowel. As this is a random sequence study, the absolute numbers or organisms isolated is influenced by the drug used in the preceding treatment period. It is therefore more meaningful to look at the *change* in the numbers of organisms brought about by a particular antibiotic. This is shown in Table 5.

Table 1 *Effect of antibiotics on mean abdominal girth in five patients*

Treatment period (random sequence)	*Mean change in girth (cm)*
Metronidazole	−2·9
Kanamycin	−1·2
Placebo	+3·0
Combination (K + M)	−1·5

Table 2 *Effect of antibiotics on presence or absence of abdominal pain in five patients*

Treatment period (random sequence)	*Pain-free days/total patient-days on treatment*
Pretreatment	0/33
Metronidazole	31/33
Kanamycin	14/33
Placebo	9/34
Combination (K + M)	29/34

Table 3 *Quantitative pretreatment intestinal microflora adjacent to site of anastomosis in five patients*

Organisms	*Number of patients from whom isolated*	*Mean bacterial counts ± SD Logs*
1 Aerobic organisms isolated		
Eschericia coli	5	7·6 ± 0·9
Streptococcus faecalis	4	6·6 ± 1·02
*Lactobacillus sp.**	3	9·4 ± 0·32
Klebsiella pneumoniae	2	7·1 ± 0·14
Enterobacter agglomerans	1	6·1
Proteus mirabilis	1	5·0
Pseudomonas aeruginosa	1	4·6
2. Anaerobic organisms isolated		
Veillonellaceae: *Veillonella sp.** *Acidaminococcus sp.** *Megasphera sp.**	5	8·9 ± 1·27
Anaerobic gram-positive non-sporing rods: *Bifidobacterium sp.** *Lactobacillus sp.**	4	7·5 ± 1·51
Clostridium sp.†	4	7·5 ± 1·04
Bacteriodes fragilis	4	8·8 ± 0·46
Bacteroides melaninogenicus	1	5·0
Bacteroides ruminicola	1	6·0
Bacteroides oralis	1	8·8
Fusobacterium necrogenes	1	8·6

*These groups were not further identified.
†Consisting of *Clostridium perfringens, tertium, sphenoides, glycolycum,* and *ramosum.*

Table 4 *Effect of antibiotics on bacterial population of bowel at site of drainage of defunctioned bowel (means from four patients)*

Treatment period	*Number of organisms $\log_{10}$ per ml (M ± SD)*	
	Aerobes	*Anaerobes*
Pretreatment	8·7 ± 0·39	9·1 ± 0·30
Metronidiazole	8·1 ± 0·17	0·9 ± 1·64
Kanamycin	8·2 ± 0·71	5·9 ± 2·91
Placebo	8·1 ± 0·89	4·7 ± 1·54
Combination (K + M)	8·0 ± 0·65	2·0 ± 1·99

Table 5 *Change in bacterial counts from previous treatment period (means from four patients)*

Treatment period (random sequence)	*Change in bacterial counts $\log_{10}$ per ml*	
	Aerobes	*Anaerobes*
Metronidazole	−0·2 ± 0·67	−8·1 ± 1·37
Kanamycin	−0·1 ± 1·4	+1·5 ± 2·02
Placebo	0 ± 0·90	+3·1 ± 2·8
Combination (K + M)	−0·1 ± 1·21	−2·7 ± 1·36

It can be seen that the mean number of obligate anaerobes decreased dramatically when metronidazole was administered. Also, the numbers of obligate anaerobes increased markedly during treatment with the inert placebo. Kanamycin, although not influencing the number of aerobes, did bring about a modest increase in the numbers of anaerobes isolated.

In summary, the disappearance of abdominal pain and the decrease in abdominal girth are associated with a dramatic decrease in the numbers of obligate anaerobes in the region of the bypassed small bowel. When there is a return of obligate anaerobes to this area there is also a rapid return of the symptoms of pseudo-obstruction.

Discussion

Metronidazole and kanamycin were selected because of the narrow specificity of their spectrum of action. Metronidazole is effective specifically against anaerobes and has no known action on aerobes. Conversely, kanamycin is effective only against aerobes and has no significant effect against anaerobes. Thus the effect of these two drugs on the clinical symptoms of pseudo-obstruction may be expected to delineate the relative roles of aerobes and anaerobes in the pathogenesis of this complication.

It has been postulated on the basis of the preliminary observations outlined previously that bacteria proliferating in the defunctioned small bowel and draining into the colon may be responsible in part for this syndrome of colonic ileus. Since it was not technically possible to obtain bacteriological

samples directly from the loop of defunctioned bowel itself, the study was designed to obtain the bacterial flora proximal and distal to the site of drainage of this loop. Thus any change in the numbers and types or organisms distally compared with the proximal samples might be expected to indicate the nature of the effluent from the defunctional bowel. However, there was no significant difference between these two sites. Changes caused by the antibiotic treatment occurred simultaneously at both sites.

Metronidazole always produced a dramatic relief of symptoms (Tables 1 and 2) and this was associated with the disappearance of obligate anaerobes from the region of the bypassed small bowel. During treatment with placebo, the rapid return of symptoms coincided with the return of obligate anaerobes to this region of the bowel. This would suggest that obligate anaerobes play a role in the development of symptoms of pseudo-obstruction. A similar pseudo-obstruction, but affecting the small intestine, is well recognised in other situations in which bacterial overgrowth may occur in the small intestine—for example, jejunal diverticulosis (Phillips, 1953).

The role, if any, of the aerobic population is difficult to assess from this study as kanamycin failed to produce a significant change in this group of organisms. Unlike metronidazole, kanamycin is not absorbed to any appreciable extent and thus cannot be expected to reach an effective concentration in the lumen of the bypassed small bowel which may be the site of proliferation of the flora. No quantitative change in aerobic flora was detectable in the lumen of the functional bowel near the anastomosis as a result of treatment with kanamycin. However, all aerobes isolated after a course of treatment with kanamycin were resistant to this drug, although they had been shown to be sensitive to it before the drug's use. There had therefore been a qualitative change in the aerobic flora though not a quantitative one. Also, kanamycin produced a modest increase in the anaerobic population (Table 5). This is presumably an opportunistic increase as a result of the effect of kanamycin on the aerobic population because the effect was independent of whether metronidazole had been used in the preceding treatment period. Kanamycin had a small effect on symptoms compared with the placebo, but the combination treatment (kanamycin plus metronidazole) was no more effective than metronidazole alone.

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