Gut, 1967, **8**, 530

Population control in the small bowel

Microbial populations in the human intestine form complex relationships between themselves and their environment. The study of this interaction is known as microbial ecology. Applying the lessons derived from other ecological settings, *e.g.*, soil and water, two principles have special relevance to the human microflora: (1) the numbers and types of microorganisms in such a system are regulated by specific control mechanisms, and (2) the presence of certain microorganisms may produce biochemical and physiological alterations in the environment, in this instance, the human host.[1-3] An understanding of these principles may shed light on the clinical conditions which are characterized by disturbances in the microbial equilibrium of the intestine.

In man, the small and large bowel appear to possess distinct microbial populations. The small intestine normally contains low numbers (10^1-10^3/g.) of Gram-positive organisms such as streptococci, aerobic lactobacilli, and fungi. Utilizing capsules or long tubes, these microorganisms can be demonstrated at all levels from the stomach to the ileum.[4,5] The oral cavity is probably the origin of these microbial forms. Despite the vagaries of oral intake and gastric acidity, segmental sampling in individual subjects has demonstrated a fairly uniform pattern of microbial growth throughout the small bowel. These same Gram-positive forms may also be seen microscopically in the mucous layer of jejunal biopsy specimens from normal subjects, demonstrating the 'indigenous' nature of this microflora.[6]

The normal distal ileum contains a variable microflora. Some individuals maintain low microbial counts in this region as in the duodenum and jejunum. Others have a substantial increase in the numbers of microorganisms representing an apparent reflux of colonic bacteria. In these individuals the distal ileum becomes a transitional zone between the scanty Gram-positive forms of the upper bowel and the abundant mixed flora of the colon.

The true contrast between small and large bowel microecologies can best be demonstrated by siting a double-lumen tube with orifices proximal and distal to the ileocaecal valve. Simultaneous sampling reveals a marked increase in the numbers of bacteria across the ileocaecal valve.[5] The caecal flora, closely resembling the faecal flora, contains coliforms and large numbers of obligate anaerobes, *i.e.*, bacteroides and anaerobic lactobacilli (Bifidobacteria). These anaerobes are very rare in the small bowel, but in the colon they comprise 99% of the cultivatable flora.[1,7,8]

The colonic flora in man is distinct from the small bowel flora and characteristically includes coliforms and obligate anaerobes. Man is probably unique in this respect since all other animals have the same types of microorganisms resident in the small and large intestine.[9] This is due to a combination of coprophagy, compartmentalized stomachs, and perhaps physiological differences in the small bowel mucosa of such animals.

The ecological differences between man and other animals make it difficult to transpose information from laboratory models to the human situation. This is especially true for the rat which recycles 35-50% of its faecal output by coprophagy.[10] This animal is widely used for studies of small bowel function, stagnant loop, B_{12} absorption, etc.; since its small bowel is constantly dealing with faecal microorganisms and their metabolic products, there may be important physiological differences in this organ between the rat and man.

There are a variety of clinical situations in which the small bowel becomes contaminated, either permanently or temporarily, by colonic microorganisms.[11] The permanent disorders may result from specific anatomical defects, such as gastrectomy, achlorhydria, duodenal and jejunal diverticula, strictures, fistulae, and resections.[12-15] Generalized conditions of the small bowel can lead to a similar disruption of the microbial populations as in scleroderma, radiation enteritis, diabetic autonomic neuropathy, and administration of ganglionic blockers.[16-18] Transient small bowel contamination may be seen in diarrhoeal disorders and has been reported in association with enteropathogenic

strains of *E. coli* and non-specific diarrhoea of the tropics.[19,20] Temporary colonization by colonic bacteria may also follow saline perfusion of small bowel in normal volunteers.[21]

Although a variety of diseases may alter the bacteriology of the small intestine by introducing a colonic flora, the mere presence of these microorganisms does not necessarily have invidious significance. Patients with achlorhydria or gastric resection can harbour large numbers of colonic bacteria in the upper small bowel and remain entirely asymptomatic. The host apparently lives in complete harmony with these commensals, and in this situation, the microorganisms are merely dining at the same table. In some circumstances, however, these bacteria do not remain harmless commensals. Certain nefarious metabolic activities of bacteria may cause grievous harm to the host, in particular by interfering with the absorption of fat and vitamin B_{12} (stagnant loop syndrome[22,23]). Although bacteria are associated with these disorders, a question remains why some patients with small bowel contamination develop malabsorption while others remain unscathed.

The critical factor in fat malabsorption appears to be the development of a specific microflora at the site of a stagnant segment of small bowel. Significant stasis allows inordinately large numbers of coliforms to proliferate and permits the growth of fastidious anaerobes such as bacteroides. Faecal strains of bacteroides are capable of deconjugating bile acids,[24] and if this biochemical reaction occurs in the upper small bowel, steatorrhoea may result.[25] Hence, patients with stagnant loops associated with gastrectomies or duodenal-jejunal diverticula often develop steatorrhoea. On the other hand, if the stagnant loop is confined to the ileum, as in Crohn's disease or tuberculous enteritis, the presenting symptom may be megaloblastic anaemia as a result of interference with B_{12} absorption. Steatorrhoea may be insignificant or absent in this situation.

The mechanisms which regulate microbial populations in the normal small bowel are grossly disturbed in cases when there is contamination by colonic microorganisms. In the normal individual, several controlling factors appear to be involved. Gastric acid is an important deterrent at the portal of entry since most bacteria cannot tolerate low *p*H conditions. The few microorganisms which manage to survive passage through the stomach—lactobacilli, streptococci, and fungi—are somewhat resistant to gastric acidity. Bile is also known to possess antimicrobial activity against many Gram-positive bacteria and the oral strains of bacteroides. Dack *et al.* and Dixon have further shown that peristalsis is an important bacterial clearing factor in animals,[26,27] although there are no studies to confirm this in humans; however, this mechanism may be of vital significance in intestinal stagnation or stricture.

Besides the acid-bile barrier and peristalsis, other factors, as yet undefined, are probably operative. Although colonic bacteria may be present as a backwash in the distal ileum of normal subjects, these microorganisms do not generally colonize the proximal segments of small bowel. The mechanism for eliminating these colonic bacteria is clearly selective, since in the same subject small numbers of Gram-positive microorganisms can be found at all levels. This phenomenon is also demonstrated in patients with an ileostomy. Abundant faecal microorganisms are present in ileostomy effluent, but the duodenum and upper jejunum may contain only small numbers of Gram-positive forms.[28] The upper small bowel has selectively disposed of the coliforms and bacteroides while allowing the streptococci, lactobacilli, and fungi to survive. Smith has recently described specific antimicrobial activity in gastric and small bowel mucosa of the rabbit,[29] and it is possible that a similar mechanism is present in man.

The distribution of Gram-negative bacteria in the diseased small bowel is not entirely arbitrary and there are apparently controlling factors which maintain a stable ecology.[25] A reproducible microflora at specific levels of the small bowel is found in patients with the stagnant loop syndrome when studied on different occasions. Furthermore, following radical disruption of the microbial populations by antibiotics, there is generally a return of the same microbial species in similar numbers after cessation of therapy. Gastric acid, when present in patients with ileal stagnant loops, may display antimicrobial activity. In these cases colonic contamination often spreads retrogradely to the upper jejunum, but the stomach and duodenum may remain free of bacteria.

Treatment of the stagnant loop syndrome attempts to re-establish artifically the ecology of the

small bowel by reducing the numbers of colonic bacteria. Specifically, this requires an antibiotic which is active against many strains of coliforms and bacteroides. Tetracycline is widely used for this purpose and usually results in prompt amelioration of symptoms. However, the basic pathology remains and in some instances the condition requires corrective surgery.

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