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Historical Development of Intestinal Antisepsis

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The study of intestinal antisepsis has been the concern of the author for the past 40 years. Pioneer studies of sulfanilamide, sulfanilylguanidine, succinylsulfanilamide, succinylsulfathiazole, and phthalylsulfathiazole in dogs are reported, and subsequent clinical trials are detailed. By 1948, intestinal antisepsis had become an established procedure to complement adequate mechanical cleansing. Careful attention to meticulous, gentle handling of tissues, preservation of maximum blood supply, and strict aseptic technique should be continued; intestinal antisepsis is not a substitute for surgical principles. A combination of neomycin-phthalylsulfathiazole, together with the above-named practices, has resulted in an abdominal wall wound infection rate below 3%, with no intra-abdominal complications due to postoperative infection.

In 1940, I embarked upon the study of intestinal antisepsis which has continued for the past 40 years. The consistent thread throughout has been to protect the patient's well-being. Clinical applications of antimicrobial therapy in intestinal antisepsis should take notice of the well-being of the host-patient as well as changes in the bacteriologic flora of the host's gut. In many respects, the colon of humans possesses characteristics which are truly remarkable for the proliferation of a relatively limited spectrum of strict and facultative anaerobic bacteria in a unique environment. The facultative anaerobes rapidly consume molecular oxygen in the lumen of the colon to establish an anaerobic steady state environment favoring anaerobic proliferation and unsuitable for strict aerobic growth. Although strict anaerobic microorganisms are resistant to certain antimicrobial agents in an anaerobic environment when tested in vitro, they need not be resistant in an aerobic environment in vivo, as in the colon after elimination of facultative anaerobes during intestinal antisepsis. Thus, a combination such as neomycin and phthalylsulfathiazole destroys the facultative anaerobes to lower the rate of molecular oxygen consumption permitting an increase in the pO_2 of the lumen contents from 5 up to 60 mm Hg; under such conditions, strict anaerobic microorganisms can no longer survive, even though they may not themselves be sensitive to the antimicrobial agents being used.

A mechanically cleansed, empty bowel must precede specific attempts to alter the bacterial flora of the human gut with antimicrobial agents. The procedure of whole-gut irrigation, advocated by Crapp [1], may clean the colon but is not recommended. Similarly, mineral oil should not be used in line with my 1942 observation that mineral oil coating of bowel mucous membranes, small particles of feces, and mucus reduces contact of water-soluble antibacterial agents with particulate matter and inhibits antibacterial activity.

Until recently, it was considered essential that antimicrobial agents be dyes that stained bacteria. A beautiful example surrounds the discovery of sulfanilamide, the prototype of the sulfonamides, and the beginning of the saga of specific antibacterial therapy. The drama of the birth of the sulfon-

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amides must be recalled. In 1936, I introduced Prontosil® (prior to its availability in the United States) for the treatment of streptococcus infections in the Bahrain Islands in the Persian Gulf when I was medical director for BAPCO of the Standard Oil Company of California. Not until a later date was it demonstrated that sulfanilamide is the active constituent and becomes activated when Prontosil® chemically decomposes in the body to yield sulfanilamide as one of the degradation products. This recognition of sulfanilamide as a specific antibacterial agent disproved the concept that a substance must be a dye in order to possess antibacterial properties and opened the "chemical floodgates" that resulted in the synthesis of some 1,200 sulfonamides by 1940.

Garlock and Seley [2] began the study of sulfanilamide as an aid to colon surgery in 1938. According to Dr. Seley (personal communication): "In January, 1938, I started the bacteriological studies of the surgical specimens as a preliminary step in an attempt to formulate a method of reducing the mortality and morbidity from the suppurative complications which at that time were almost prohibitive in gastroenteric surgery, especially involving the colon and rectum. When the cultures revealed *Streptococcus hemolyticus* in addition to *Escherichia coli, Clostridium welchii, Enterococcus* and others, it was decided to use oral sulfanilamide as a preoperative oral prophylactic measure. When the first series had been so prepared and operated upon, cultures were again taken of the specimens and the incidence of *Strep. hemolyticus* and *Cl. welchii* were both markedly reduced but more important the suppurative complications were far less frequent than prior to the use of preoperative oral sulfanilamide. In 1943, I reported the results of 123 colon and rectal cases using sulfanilamide preoperatively, the mortality rate from peritonitis was 4 per cent against 10 per cent then reported in the literature." This report reflects the results of the initial use of a sulfonamide. Unfortunately, sulfanilamide did not possess the properties and potency required to compete with the acetylated sulfonamides that replaced it.

In 1940, Dr. Warfield M. Firor was using sulfanilylguanidine to sterilize the enteric tract [3]. I was studying the role of bacteria in intestinal obstruction and immediately began administering this compound to dogs, hoping to sterilize the enteric tract. Unfortunately, this drug failed to fulfill expectations. Dr. Firor requested that I study the bacteriologic response in patients to whom sulfanilylguanidine was being administered by mouth preoperatively, especially since a significant percentage of the patients were developing severe sensitivity reactions. These studies demonstrated that some 65% of the ingested drug was excreted essentially unchanged in urine, causing crystalluria. The drug had almost no antibacterial activity in the enteric tract of humans in the presence of an ulcerating malignancy. Mineral oil inhibited antibacterial activity also. Drug intolerance was much higher than originally thought, approximately 25%. Consequently, the use of this drug as an ancillary antibacterial agent in the preparation of the colon was discontinued even though no replacement was available. I was not then aware of the preliminary report published by Garlock and Seley in 1939 on the preoperative oral administration of sulfanilamide.

The failure of sulfanilylguanidine led to a search for an antimicrobial agent specifically for intestinal antisepsis, and having the following characteristics: (a) low toxicity for the host; (b) broad antimicrobial spectrum; (c) chemical stability in presence of digestive ferments and bacterial enzymes; (d) capacity to prevent outgrowth or development of resistant bacterial variants; (e) rapidity of action; (f) activity in presence of nutrients and essential metabolites permitting adequate food intake by the host; (g) low absorption from enteric tract; (h) aid to mechanical cleansing of bowel without causing dehydration; (i) nonirritant of enteric mucosa; (j) noninhibitor of healing; (k) low bactericidal dosage; (l) water soluble; (m) palatable; (n) antifungal activity; and (o) use restricted primarily to intestinal antisepsis.

The magnitude of such an undertaking and the probability of failure were realized, but the "stakes were high." At that time the mortality of surgery was 10–12% and suppurating wound infections occurred in 80–90% of the survivors in the best of reported series. Staged operations were frequent and colon anastomoses were usually of the "closed" type with proximal colostomies.

By the time it was demonstrated that sulfanilylguanidine was not an acceptable intestinal antiseptic, a simple and flexible mechanical device [4] had been designed and constructed to deliver test drugs contained in meatballs to individual dogs on a predetermined schedule. These meatballs constituted the animal's total food and could be regulated so that the animal devoured it immediately on delivery. If the animal refused the drugged meat after having accepted it initially, the compound under investigation was considered toxic and was not studied further. Simultaneously, stool specimens, obtained rectally, were streaked onto deoxycholate and eosin-methylene blue plates to determine *Escherichia coli*. If a significant lowering of this flora did not occur during 7 days of satisfactory medication, the drug was considered ineffective and was eliminated from the study.

These criteria eliminated the initial 60 compounds investigated, including the 10 sulfonamides then

being used therapeutically. Our interest extended to the sulfonamides that had been synthesized, tested for antibacterial activity, and discarded because they were inactive. It was hoped the lack of demonstrated activity was due to nonabsorption from the enteric tract. The then accepted method of testing for activity consisted of injecting mice intraperitoneally with a lethal strain of streptococcus and/or pneumococcus, administering the test agent by gavage, and assessing mortality. If the mice were not protected, death might have been due to nonabsorption of the drug.

Dr. William A. Feirer, then medical director of Sharp and Dohme, was supplying any substance I requested. One day Dr. M.L. Moore, an organic chemist at Sharp and Dohme, told me they had made succinylsulfanilamide (which was protected by a British patent) and that the sodium salt of succinylsulfanilamide possessed no bacteriostatic activity. (It is not absorbed from the enteric tract of mice). The sulfonamide is chemically modified by acetylation of the primary amino group with succinic acid. The acetylated compound was not absorbed from the enteric tract and served as a vehicle to deliver the substance to the colon where it would be deacetylated to regenerate the original sulfonamide which also was not absorbed from the colon. The stage was now set for the development of the sulfonamide era of intestinal antisepsis dominated, for all practical purposes, by succinylsulfathiazole and phthalylsulfathiazole.

Succinylsulfanilamide became the first compound in our series that promptly and significantly reduced both the strict and facultative anaerobic flora of the canine enteric tract and was subjected to rigid toxicologic, bacteriologic, and physiologic testing before human administration. Eighty compounds were synthesized for investigation. This resulted in the discovery of several substances that possessed antibacterial properties, were poorly absorbed from the gastrointestinal tract, and were nontoxic in therapeutic doses. The two most promising were succinylsulfathiazole (Sulfasuxidine®) and phthalylsulfathiazole (Sulfathalidine®). The bacteriostatic activity and toxicity of these two compounds were studied exhaustively in dogs. Sulfathalidine® was found to be 2 to 4 times as effective as Sulfasuxidine® in reducing coliform organisms in the gut. Approximately 5% of the ingested dose of either drug was excreted in the urine. The toxicity of the two was equivalent.

Clinical Application

Succinylsulfanilamide was the first administered to humans, followed closely by succinylsulfathiazole which immediately was recognized as being superior [5, 6]. Consequently, further clinical administration of succinylsulfanilamide was discontinued, and succinylsulfathiazole was evaluated by 1941 [7]. Numerous studies with these compounds used for intestinal antisepsis were published subsequently, including two major reviews [8, 9]. Questions arose such as: (a) was there a need for preoperative antibacterial preparation in colon surgery, other than mechanical preparation; (b) would an imbalance of the usual gut flora result in an overgrowth of pathogens, precipitating some catastrophic complication like pseudomembranous enterocolitis; (c) would these agents, by altering the synthesis of vitamin K, precipitate a deficiency and increase postoperative bleeding; (d) could additional time and cost to affect bacteriologic preparation be justified; (e) would these new complementary safeguards undermine established surgical asepsis; and (f) other fantasies of the imagination.

Many studies have tried to answer these questions. At the Johns Hopkins Hospitals, a standard routine was employed. In the absence of obstruction, patients were placed on forced clear liquids and low-residue or residue-free diets, and purged with castor oil. The dosage schedule of Sulfasuxidine® was 3 grams, 6 times daily for 7 days. The feces became fluid, small in volume, odorless, and clear, and contained between 50 and 100 grams of Sulfasuxidine® per liter. An enema of 5% sodium Sulfasuxidine® was administered to demonstrate that the bowel was empty. In the presence of partial obstruction, the preoperative preparation was modified to ensure maximum mechanical preparation. Sulfathalidine® was not recommended as an intestinal antiseptic alone even though it was more potent antimicrobially than Sulfasuxidine®, because it caused fecal material to become more solid, tenacious, and difficult to evacuate. Since Sulfasuxidine® is sparingly absorbed (between 3 and 5%), it was maintained in situ during the postoperative paralytic period in essentially full concentration; in fact, solid drug was usually present in the rectum. I have not encountered a single instance of pseudomembranous enterocolitis in conjunction with intestinal antisepsis in the 40 years I have used and supervised these procedures. The influence of intestinal antisepsis in the presence of ischemia of the bowel is pronounced and represents an excellent experimental method for evaluation of different antibacterial agents. The distal ileum, 30 cm proximal to the ileocecal valve, because of its easily controlled, finite vascularity, makes an excellent "test object." I have utilized a number of experimental demonstrations to show the protection rendered ischemic large and small bowel with results exceeding one's possible hopes [7], even to the

point of dividing transversely one-third across a Sulfasuxidine®-prepared descending colon of the dog, and dropping the open colon into the peritoneal cavity with an 80% survival [10].

Waksman and Lechevalier described neomycin in 1949. Its great potentiality was immediately evident upon being subjected to the established investigative regimen. A preliminary report [11] covering the initial 50 patients suggested the possibility that neomycin was a rapidly acting and complete antibiotic for intestinal antisepsis. However, when *Enterobacter aerogenes* began to be found in stool cultures, Sulfathalidine® was administered in addition at that time to suppress this species. Sulfathalidine® was chosen rather than Sulfasuxidine® because it is 2 to 4 times more potent and because it aids evacuation. The combination of neomycin and Sulfathalidine® proved the most effective combination encountered. Neomycin rapidly replaced streptomycin and had no real competitor for several years until kanamycin was introduced by Cohn in 1958 [12]. Only a few of the known aminoglycosides have been studied as possible intestinal antiseptics. Streptomycin (1944), the first of these compounds investigated, resulted in rapid development of resistance [13]. Neomycin (1950) seldom resulted in resistance, but cross-resistance developed when organisms became resistant to kanamycin. Some strains of *Enterobacter aerogenes* are not sensitive to neomycin. Kanamycin is more effective. The importance of the combination of neomycin and erythromycin requires attention. Erythromycin base is absorbable from the gastroenteric tract where it is also vulnerable to destruction. Erythromycin is not a desirable choice because of its tendency to cause nausea and vomiting.

By 1948, "intestinal antisepsis" had become an established procedure to complement adequate mechanical evacuation of the enteric system. Meticulous, gentle handling of tissues, preservation of maximum blood supply, and strict practice of asepsis should be continued since intestinal antisepsis is not a substitute for surgical principles.

"Mechanical" preparation of the colon prior to operation is of such great importance that it should be standardized. Liquid petrolatum, an inert hydrocarbon, was observed in 1941 to suppress the antibacterial activity of sulfanilylguanidine and other sulfonamides, and should not be administered during mechanical evacuation of fecal material in conjunction with intestinal antisepsis. Purgation and enemata increase secretion of mucus by the bowel and the particles of mucus are likewise impregnated and coated with mineral oil, thereby preventing contact with the water-soluble antibacterials and thus preventing antimicrobial activity. Castor oil, a triglyceride, does not have these properties of mineral oil.

Nichols, Condon, Gorbach, and Nyhus [14] based a study on groups of 6 patients (Fig. 1 A–E) and drew certain statistical conclusions with which the author would differ. Specimens were collected in bedpans and might well have been contaminated. Three specimens taken aseptically at operation were from a rather restricted portion of the bowel, that is, from distal ileum to mid-transverse colon. A specimen might have been taken from the distal sigmoid transabdominally or by proctoscope per anum from the upper rectum. All patients received identical mechanical preparation including magnesium sulfate. Magnesium sulfate is antagonistic to aminoglycosides, and the bivalent magnesium ion might well be a factor in the poor antimicrobial activity demonstrated for kanamycin in Fig. 1-B, and for neomycin in Fig. 1-C.

I do not find support for the concluding statement: "Neomycin alone or in combination with phthalylsulfathiazole reduced aerobic and facultative bacteria but allowed persistence of anaerobes in approximately one-half of the subjects. Neomycin and erythromycin base administered in low doses during the 19 hours prior to operation resulted in reduction of aerobes and facultative organisms in all subjects. Aerobes were completely suppressed in 5 of 6 patients and were present only in low numbers in the cecum and feces in the 6th patient." Consider Fig. 1-D where anaerobes were not eliminated from 2 patients nor were facultative streptococci in 2 patients. The difference between Figs. 1-C and 1-D are quite striking, but I see essentially no significant difference between Figs. 1-D and 1-E.

Attention is called to the following statement by Condon [15]: "When [neomycin-phthalylsulfathiazole] was studied prospectively, it was found not to be effective. Rosenberg and colleagues found no significant difference between neomycin-phthalylsulfathiazole combination therapy as compared either with oral sulfonamide alone or with patients receiving only mechanical bowel cleansing but no antimicrobials." The patients studied by Rosenberg et al. [16] did not receive adequate preparation. They received 4–5 days of preoperative mineral oil, which effectively prevents contact between feces, muscus, mucosa, bacteria, and the therapeutic agents, and thereby inhibits antimicrobial activity. The article chosen to demonstrate the poor quality of the neomycin-phthalylsulfathiazole combination did not follow appropriate techniques for mechanical preparation or for the drug dosage schedule, therefore, the poor results observed cannot be compared with similar studies carried out under proper conditions.

Comparison of neomycin-erythromycin and neomycin-phthalylsulfathiazole does not show a superi-

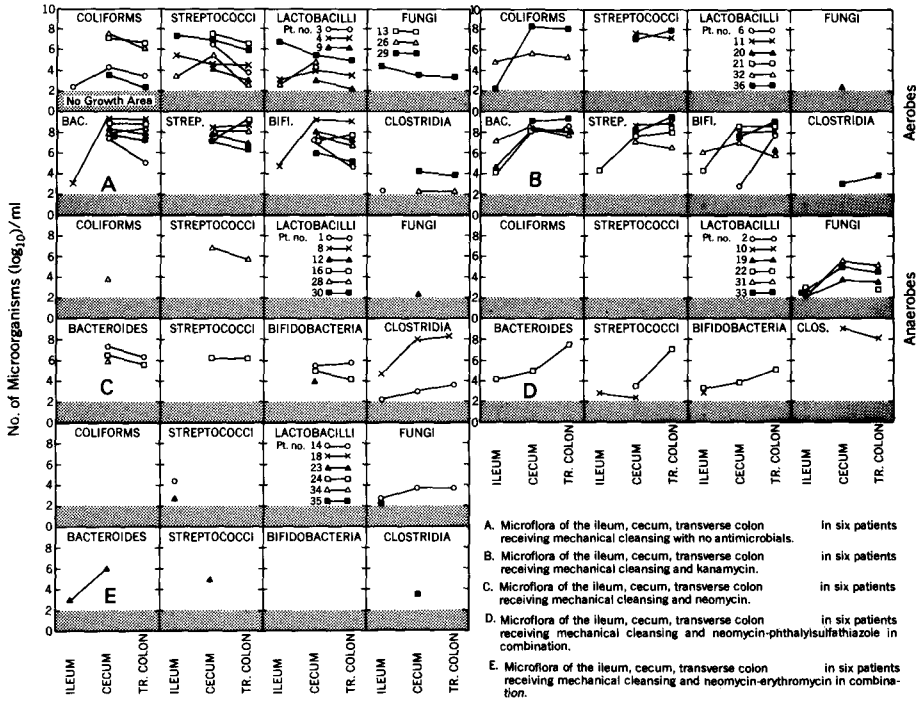

Fig. 1. Microflora of the ileum, cecum, and transverse colon in 5 groups of 6 patients receiving mechanical cleansing alone or in combination with antimicrobials. Modified and compiled from Nichols et al. [12].

ority for the neomycin-erythromycin combination. For example, data on 53 patients undergoing elective colon anastomoses and receiving neomycin-erythromycin show a postoperative infection rate of 9.4% [17], whereas data on 58 similar patients receiving neomycin-phthalylsulfathiazole show a postoperative infection rate of 3.4% [18].

In my experience with neomycin-phthalylsulfathiazole since 1950, there has not been a single death attributable to failure of intestinal antisepsis, and the abdominal wall wound infection rate is below 3%. Intra-abdominal complications due to postoperative infection have not occurred. The UC-18 phage-type staphylococcus, which now has largely disappeared in the United States, has not occurred in a single case that I have managed during 40 years of experience with intestinal antisepsis. I have seen only 2 cases of pseudomembranous enterocolitis. Both patients were small children with influenza-like respiratory infections, and both received a tetracycline derivative. Both died within a week's period. I am aware that in Cleveland and Cincinnati, enterotoxic staphylococcal infections were major problems for several years.

Complication rates must be looked at carefully. In one controlled clinical trial [9] of 53 patients undergoing elective colorectal operations, the complication rate was 67% with one preparation and 27% with another. The magnitude of the complications due to postoperative infection in both of these preparations is unacceptable. I would certainly not suggest that these data be used to eliminate any drug combination from being considered for intestinal antisepsis.

It is worthwhile to outline the management of a frequently recurring type of colon operation for malignancy (Fig. 2). The standard form of mechanical and antibiotic preparation should be initiated. The operation is illustrated schematically by Fig. 2-C. The entire bowel is empty and collapsed. The small bowel is enclosed in a nylon mesh retainer after the tumor is located. The sites of resection, *1* and *1*, are determined. Atraumatic proximal and distal closures of the colon, *2* and *2*, are accomplished without disturbing the vascular supply, followed by inserting and securing the two sampling tubes, *4* and *4*. Crushing clamps, *3* and *3*, are applied. No specimens are obtainable from the cross-hatched, isolated segments on aspiration via *4* and *4*. Therefore, 10 ml of oxygen-free normal saline solutions are instilled, mixed to yield approximately 10 ml of a finely flocculent, bile-stained aspirate for quantitative aerobic and anaerobic culturing, and immediate smears for Gram's stains and for determination of the oxygen-absorbing properties of the specimen. If the pO_2 does not vary, then few facultative organisms are present. If the Gram's stain shows no microorganisms, few bacteria are present. However, if there are numerous organisms visible on the Gram's stain and the pO_2 decreases rapidly, the bacteriologic studies will likely show the antimicrobial preparation to be unsatisfactory.

As soon as a specimen is aspirated, the isolated segment of colon is moderately distended with half-

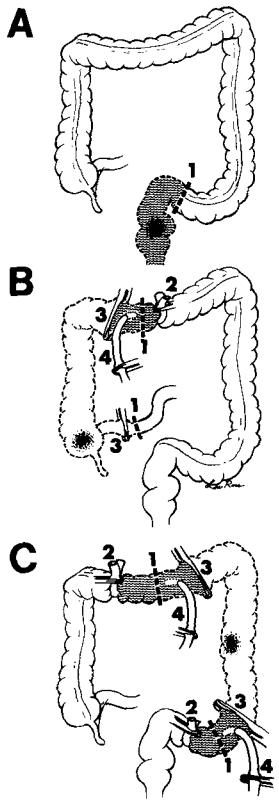

Fig. 2. A schematic representation of 3 operative procedures for carcinoma of the colon.

strength modified Dakin's solution, which destroys nearly all bacteria in seconds, and also dissolves mucus and destroys free-floating tissue cells on contact. It was shown to possess this lethal property in 1961 [19], when its clinical use for this purpose was introduced to prevent malignant implantation at the intestinal suture line. The recommended strength of Dakin's does not irritate the bowel mucosa or interfere with healing after 30 minutes' exposure. During this 30 minutes, the dissection is completed and the left colon resected between beveled intestinal clamps [20] after the operative field is isolated with lap pads soaked in 0.5% neomycin solution. The Dakin's solution in the isolated colon should be aspirated. The colon is anastomosed end-on using the "Cushing" suture technique [21], employing 3-0 braided nylon or equivalent, nonabsorbable suture material, and all knots are tied on the outside serosal surface. The operative site is irrigated with generous quantities of 1% neomycin, which is completely removed by suction. Muscle relaxants, especially succinylcholine, are proscribed during anesthesia. Respiratory inhibition has not been a problem. During closure of the abdominal incision, without drainage, it is irrigated with 0.5% neomycin solution.

Comments

How does it happen that anaerobes are destroyed by antimicrobial combinations which in vitro possess little antibacterial activity against these bacteria? Is there a role played by molecular oxygen in the colon? The lumen of the normal human colon characteristically has a pO_2 equal to or less than 5 mm Hg. This rises to approximately that of the pO_2 of the arterial capillary blood of the mucosa of the colon as the facultative organisms, which use molecular O_2 and establish the anaerobic environment in the colon, are destroyed by antimicrobials. This change from an anaerobic environment to an aerobic one may be sufficient to destroy anaerobes, such as *Bacteroides fragilis* subspecies *fragilis,* directly because they have a low oxygen tolerance, or greatly increase the susceptibility of the anaerobes to the antimicrobials. Bornside [22] demonstrated the toxicity of hyperbaric oxygen against bacteria in the colon of the rat, and the lower pO_2 in conventional rats as compared to germ-free animals, which might reflect the oxygen metabolism by the intestinal bacteria in the conventional animals.

An attempt to trace the historical aspects of intestinal antisepsis is rather frustrating. The subject is quite complex. One regimen is claimed superior to another without direct and precise clinical comparisons. Under the best of circumstances, the variables are myriad and largely unknown. The nearest approach is the so-called blind study planned to reduce the variables. I, personally, have resisted for nearly 40 years conducting a "blind study" between even the earliest intestinal antiseptic combinations with a placebo control because the hazard to human life had become too great.

I recommend that any new antimicrobial studied as an intestinal antiseptic be compared to a combination such as neomycin-phthalylsulfathiazole which has had a reliable record for 30 years. Preliminary observations indicate that parenteral antimicrobials such as Staphcillin® and/or cefoxitin, a broad-spectrum cephalosporin antibiotic, may well serve as complementary therapeutic agents to the nonabsorbable oral intestinal antiseptics, but not as substitutes for them especially in the presence of ischemia at the anastomotic suture line. Intestinal antisepsis must be closely supervised and basic studies will demand new regimens. The "stakes" are still high.

Résumé

Depuis 40 ans l'auteur s'est intéressé au problème de l'antisepsie intestinale. Après des études initiales consacrées à l'action de multiples agents médica-

menteux chez l'animal il les a employés chez l'homme, les différents essais étant exposés en détail. Dès 1948 la préparation intestinale par les agents antiseptiques est venue s'ajouter en tant que méthode complémentaire à l'évacuation du contenu intestinal. Pour importante que soit la préparation de l'intestin en particulier par les agents antiseptiques elle n'autorise aucune défaillance dans la technique opératoire qui doit être rigoureuse et impose la manipulation atraumatique de l'intestin, le respect méticuleux de la, vascularisation, l'emploi strict de techniques antiseptiques. L'observation de ces préceptes combinée à la préparation de l'intestin à l'aide de ménomycine et de phtalysulfathiazol a permis de réduire l'infection pariétale à un taux inférieur à 3 pour cent et l'infection intrapéritonéale à 0 pour cent.

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