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, sulfanilyguanidine, 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 \( \text{pO}_2 \) 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 sulfonilamide, the prototype of the sulfonamides, and the beginning of the saga of specific antibacterial therapy. The drama of the birth of the sulfon-
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 sulfanilamides 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 antisepic, 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