Effect of Preoperative Neomycin-Erythromycin Intestinal Preparation on the Incidence of Infectious Complications Following Colon Surgery

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THE USE OF antimicrobial agents in routine elective colon resection remains a highly controversial issue. Areas of debate include whether they should be used; which of them should be used; and how, when, and for what length of time they should be administered.[4,13,14,25,26,29,32] Many regimens for preoperative colon preparation have failed to suppress the anaerobic microflora of the colon.[20,21] Since anaerobes are the most prevalent members of the intestinal microflora, failure to control them may help explain the high incidence of wound infections (10–20%) following elective colon resection, even where oral antibiotics are used.[9,10,14,16]

We previously studied preoperative preparation in patients who had no intestinal pathology and were undergoing laparotomy for cholecystitis. Following a brief, low-dose combination of neomycin and erythromycin base, these patients showed suppression of both colonic aerobes and anaerobes.[22] Our present study of patients with intestinal pathology who were undergoing elective colon resection was designed to determine whether preoperative preparation with neomycin-erythromycin base results in a uniform suppression of the colonic microflora, and whether this regimen of antibiotics can affect the incidence of postoperative wound complications.

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Methods—Part I

Selection and Preparation of Patients

The study group consisted of 20 patients who were consecutively admitted to the University of Illinois Hospital for elective colon resection, none of whom showed clinical evidence of large bowel obstruction to a degree that would interdict preoperative preparation. Each patient was randomly assigned to one of two treatment groups. One group was given both mechanical and antibiotic preoperative preparation (Table 1). The other group was prepared in an identical fashion, except that antibiotics were omitted.

No patient received additional antibiotics either parenterally or locally during the preoperative or intraoperative period. The operation was performed in each case by residents and was supervised by attending surgeons. The abdominal wound was closed primarily in all cases. Postoperative parenteral antibiotics were administered to three patients who had received preoperative mechanical preparation alone only after clinical evidence of sepsis appeared and specimens had been sent for culture and sensitivity studies. An impartial observer who had no knowledge of which preoperative preparation was used determined the occurrence of postoperative wound infections.

TABLE 1. *Neomycin-Erythromycin Base Colon Preparation*

Day 1:	Low residue diet
	Bisacodyl, 1 capsule orally at 6 p.m.
Day 2:	Continue low residue diet
	Magnesium sulfate, 30 ml. 50% solution (15 Gm.) orally at 10:00 a.m., 2:00 p.m. and 6:00 p.m.
	Saline enemas in evening until return clear
Day 3:	Clear liquid diet; supplemental IV fluids as needed.
	Magnesium sulfate, in dose above, at 10:00 a.m. and 2:00 p,m.
	No enemas
	Neomycin 1 Gm. } p.o. at 1:00 p.m.,
	Erythromycin base 1 Gm. } 2:00 p.m. and 11:00 p.m.
Day 4:	Operation scheduled at 8:00 a.m.

Sample Collection

During laparotomy a sample of colonic content was removed from each resected specimen using a syringe. The specimens were transferred to aerobic and anaerobic transport tubes by a physician trained in this technic and processed in the research microbiologic laboratory within 30 minutes of collection. Following operation, cultures were obtained from infected sites using similar technics, taking care to collect samples from the deepest area of the wound.

Microbiologic Technics

Colonic aspirates were studied both quantitatively and qualitatively. One ml. of each sample was thoroughly mixed in 9 ml. of Tryptic Soy Broth (Difco) and serially diluted tenfold. An aliquot of 0.1 ml. of each dilution was then spread over the surface of the following plates: blood-brain heart infusion agar (aerobic and anaerobic); blood-brain heart infusion agar with 25 μg/ml. neomycin (aerobic and anaerobic); BC agar (Schaedler), (aerobic and anaerobic); MacConkey agar; Staph 110 agar; Mitis-Salivarius agar; Sabouraud-dextrose agar; and Nagler-neomycin agar (anaerobic). The anaerobic plates were incubated for 72 hours in a vented jar, evacuated and filled with oxygen-free CO_2 (10%) and hydrogen (90%) in the presence of an active catalyst. Following operation, swabs from the infected sites were streaked onto pre-reduced blood-brain heart infusion agar with and without neomycin for aerobic and anaerobic incubation. Vitamin K and menadione were added to these media. Infected material was also streaked onto Nagler-neomycin agar and MacConkey agar. A swab was also inoculated under oxygen-free conditions into pre-reduced chopped meat-glucose broth. The broth was subcultured on pre-reduced blood plates at 48 hours and again after 3 weeks.

As a further check on the recovery of anaerobes, a gram-stained slide of the initial specimen was examined to reveal the minimum number of morphotypes to be recovered from the culture. Anaerobes were identified on the basis of morphology, fermentation and biochemical reactions, and analysis of acid end-products by gas liquid chromatography.[17] Subcultures and transfers of the anaerobes were performed under oxygen-free conditions.

The concentration of microorganisms is expressed as the logarithm to the base ten of the colony count per ml. of bowel content (*e.g.*, 6.0 = 10^6 = 1,000,000). The lower limit of recovering microorganisms is 2 logs or 100 organisms per ml. of intestinal content.

Results—Part I

The ten patients who received only vigorous mechanical preoperative preparation had a grossly clean colon at the time of operation. Cultures of colon aspirate in these patients produced luxuriant growth of both aerobes and anaerobes (Figs. 1 and 2). The mean concentrations of aerobes and obligate anaerobes were similar to those normally found in stool (Table 2).

The patients prepared preoperatively with oral neomycin and erythromycin base in addition to mechanical cleansing showed suppression of aerobes and anaerobes in each case (Figs. 1 and 2). The mean value of each microbial species enumerated was less than 2 logs, the lower limit at which our methods detect growth (Table 2). When these values are compared to those of the non-antibiotic prepared patients, the difference in total anaerobes, total aerobes, coliforms, streptococci, bacteroides, and peptostreptococci was highly significant ($p < 0.001$). There was no evidence of overgrowth of staphylococci or fungi in either group.

Clinical and bacteriologic monitoring after operation revealed that three of ten patients who received the mechanical preparation alone developed wound sepsis;

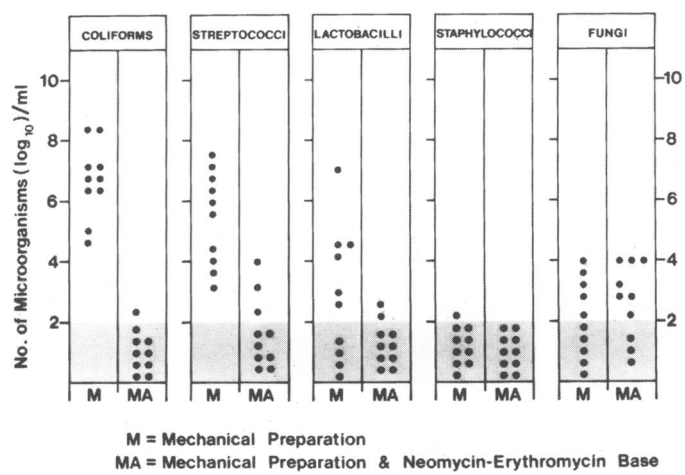

FIG. 1. Effect of neomycin-erythromycin on the aerobic colonic microflora. Cultures showing no growth are below the limit of sensitivity of our bacteriologic methods and are indicated in the shaded area (< 2 logs).

Escherichia coli was isolated in two of the cases and *Bacteroides fragilis* in the third. There were no wound complications in the patients who received the combination of neomycin-erythromycin base.

Methods—Part II

Selection and Preparation of Patients

Part II is a retrospective review of 98 colon resections, which were performed at the University of Illinois Hospital and the West Side Veterans Administration Hospital from July 1, 1970 to December 1, 1972 after completion of the Part I study. In every case the operation was performed by a resident and supervised by an attending surgeon. The colon pathology was carcinoma in 70% of the patients, and diverticulitis, ulcerative colitis, granulomatous colitis, multiple polyps, or recurrent sigmoid volvulus in the others. None of the cases were emergent; each was prepared for several days before the operation. None of these patients showed clinical evidence of obstruction. The patients' ages ranged from 20 to 92 years, with a mean of 58; males outnumbered females by a ratio of 3:1.

No attempt was made to randomize or control the choice of preoperative colon preparation. Every patient received mechanical cleansing, and the decision to use preoperative antibiotics was delegated to the chief resident. Sixty-nine patients also received neomycin-erythromycin base, according to the regimen in Table 1. The remaining 29 patients were prepared in other ways (Table 3).

Types of colonic resection were similarly distributed between the group that received neomycin-erythromycin and the group that received other preparations (Table 4). All colon anastomoses were performed using open technic. A wound infection was considered to be present if the wound spontaneously discharged purulent material, or if when opened on clinical grounds it contained purulent material. Any discharge from the wound during the postoperative period was collected and cultured using the technics described in Part I, thus assuring isolation of both aerobic and obligately anaerobic microorganisms. No cultures of the colonic content were taken at the operation, as was done in Part I.

TABLE 2. *Effect of Preoperative Preparation on the Colonic Microflora in the Resected Segment (Log$_{10}$ mean ± S.E. organisms/ml.)*

	Group 1	Group 2
	Mechanical preparation	Mechanical preparation and antibiotics
Aerobes		
Coliforms	6.7 ± 0.4	1.2 ± 0.2†
Streptococci	5.5 ± 0.5	1.7 ± 0.4†
Lactobacilli	3.0 ± 0.7	1.3 ± 0.2
Staphylococci	1.1 ± 1.1	1.0 ± 0.0*
Fungi	2.1 ± 0.4	2.7 ± 0.4
Anaerobes		
Bacteroides	8.7 ± 0.2	1.2 ± 0.2†
Peptostreptococci	5.8 ± 0.9	1.0 ± 0.0†
Bifidobacteria	3.6 ± 1.1	1.0 ± 0.0
Fusobacteria	3.6 ± 1.1	1.3 ± 0.2
Clostridia	2.4 ± 0.4	1.9 ± 0.4

* 1.0 ± 0.0 is the value assigned for statistical calculations when no growth is detected.
† $p < 0.001$

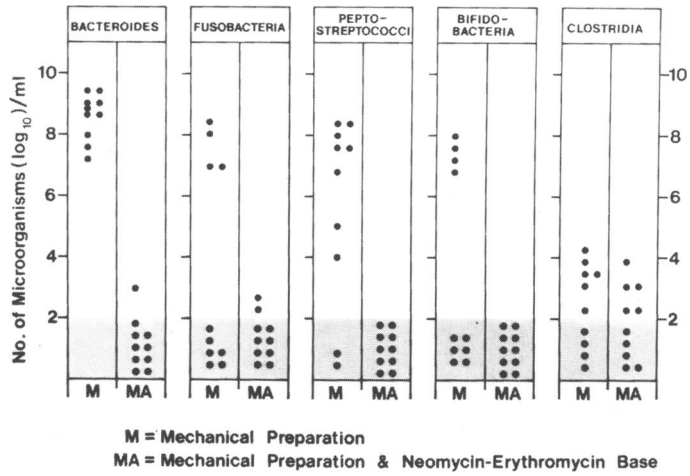

FIG. 2. Effect of neomycin-erythromycin on the anaerobic colonic microflora. Cultures showing no growth are below the limit of sensitivity of our bacteriologic methods and are indicated in the shaded area (< 2 logs).

Results—Part II

Table 3 records the various types of preoperative colon preparations and the occurrence of postoperative infectious wound complications with each type. In the group that received neomycin-erythromycin base, no wound sepsis was observed in 69 patients. Five infections developed in the other 29 patients, a rate (17%) comparable to that usually reported in elective colonic surgery. No surgeon had more than one wound infection, and no type of resection seemed more likely to result in infectious complications in this relatively small series.

Obligate anaerobes were cultured from the infected wounds in four of the five septic patients. Bacteroides

TABLE 3. *Types of Preoperative Bowel Preparations and Related Infections*

Preoperative Preparation	Number of Cases	No. of Wound Infections
Neomycin-Erythromycin base	69	0
Mechanical preparation only	16	3
Neomycin	8	1
Neomycin-Sulfathalidine	2	1
Kanamycin	2	0
Kanamycin-Sulfathalidine	1	0
	98	5

TABLE 4. *Types of Colonic Resections and Preoperative Preparation (98 cases)*

Type of Resection	Neomycin-Erythromycin Preparation No.	%	All other Preoperative Preparations No.	%
Anterior Resection	17	25%	8	28%
Right hemicolectomy	18	26%	11	38%
Left hemicolectomy	10	14%	5	17%
Subtotal colectomy	5	7%	2	7%
Abdominal-peritoneal resection	7	10%	1	3%
Total colectomy-ileostomy	4	6%	2	7%
Total colectomy-ileoproctostomy	4	6%	0	0%
Colotomy	4	6%	0	0%
Totals	69	100%	29	100%

was isolated in three patients, and peptostreptococci and clostridia were each isolated in one. Coliforms were also present in four of these patients (Table 5). There was no wound sepsis due to *Staphylococcus aureus:* this organism accounted for approximately 2% of all postoperative wound infections in our two hospitals during the period of this study.

Neither antibiotic solutions for local intraoperative peritoneal instillation nor wound irrigation was used in the 98 patients in this series. A variety of parenteral antibiotics was prescribed in the early postoperative period in 33 of the 98 patients (Table 6). Of the five patients who developed postoperative infection, three had received parenteral antibiotics in addition to preoperative mechanical bowel cleansing. The agents that were used are listed in Table 7. It was impossible in this study to estimate the influence of postoperative parenteral antibiotics on the incidence of wound infections. Nevertheless, it should be stressed that among the 46 patients (66%) who received oral preoperative neomycin-erythromycin base no other antibiotics were prescribed and no wound complications were noted.

Discussion

Postoperative sepsis following elective colon operations usually is due to endogenous microorganisms escaping from the bowel to contaminate adjacent tissues during the operation. Although the degree of contamination is minimized by strict adherence to principles of good surgical technic, microbial seeding may be unavoidable. Complete sterilization of colonic content is probably impossible; however, transient reduction of endogenous bacteria is possible and probably advantageous.[22] Suppression of the luxuriant colonic flora must be maximal at the time of operation, but it should be of brief duration thereafter in order to prevent overgrowth of resistant organisms.

Antimicrobial agents should be selected as oral antiseptics only if they meet the requirements first proposed by Poth[28] and later modified by Cohn.[8] Essentially, they must be poorly absorbed from the gastrointestinal tract and have low local and systemic toxicity. We would also emphasize that the drugs chosen should be active against all elements of the colonic microflora, including aerobic and anaerobic microorganisms.[20] We have studied the effects of many intestinal antiseptics on the colonic microflora.[22] Many commonly utilized antimicrobial agents either singly or in combinations were unable to predictably suppress the anaerobic flora of the colon. Other investigators have confirmed this observation.[26] The use of ineffective antibiotics for preoperative colon preparation may account for the high rate of postoperative infections observed following elective colonic surgery.

Obligately anaerobic bacteria, including bacteroides, peptostreptococci, bifidobacteria, and fusobacteria, rarely were reported as the cause of major surgical infections in the past. Recent work has shown that these organisms have very fastidious growth requirements, and this fact undoubtedly accounts for their absence from wound exudate studies in which only conventional bacterilogic technics were employed. With modern anaerobic technics for both specimen collection and cultur-

TABLE 5. *Infections Following Colon Resection*

Patient	Operation	Types of Preoperative Preparation	Infectious Complication	Organisms Isolated
1	Right hemicolectomy	Mechanical	Pelvic abscess	*E. coli*, Bacteroides, Clostridia
2	Left hemicolectomy	Mechanical	Wound abscess	*E. coli*, Peptostreptococci
3	Subtotal colectomy	Neomycin	Wound abscess	Bacteroides
4	Abdominal peritoneal resection	Mechanical	Wound abscess	*E. coli*
5	Subtotal colectomy	Neomycin-Sulfathalidine	Wound abscess	*E. coli*, Bacteroides
*6	Anterior resection	Mechanical	Anastomatic leak	Bacteroides
*7	Left hemicolectomy	Mechanical	Wound abscess	*E. coli*
*8	Right hemicolectomy	Mechanical	Wound abscess	*E. coli*

* Patients from Part I of Study

ing, increasingly frequent reports have implicated obligate anaerobes as an important cause of surgical sepsis.[1,6,30,36] Indeed, Herter[15] has recently isolated bacteroides in over 50% of wound infections that developed following colon operations. Schumer and colleagues[31] isolated *Bacteroides fragilis* in 25% of patients with intraabdominal abscesses and in over 40% of patients with postoperative septicemia. Gorbach and associates[12] have recovered strict anaerobes from 40 of 43 intraabdominal infections.

In the present study, the effect of preoperative mechanical cleansing alone has been compared to mechanical cleansing together with preoperative administration of neomycin and erythromycin base. These antibiotics were chosen because of previous studies which demonstrated that neomycin was effective in suppressing aerobes, and that the combination of neomycin and erythromycin inhibited growth of colonic anaerobes more effectively than did any of the more commonly used intestinal antimicrobials.[22] In our previous study, the antibiotics were administered in low doses, a total of 3 Gm. of each drug being given over the 19 hours immediately before operation. The purpose of this schedule was threefold: 1) to deliver antimicrobials to the lower ileum and colon prior to and during operation; 2) to minimize the emergence of resistant microorganisms due to prolonged drug exposure; and 3) to reduce the expense and inconvenience to the patient.

Mechanical cleansing removed gross stool in all patients and facilitated the surgical procedure. After only mechanical cleansing, however, the residual colonic content showed the same concentrations of both aerobic and anaerobic microorganisms as are normally found in stool.[23] Clinical infections following only mechanical preparation were caused by aerobic *E. coli* and by various anaerobes, especially bacteroides. With the use of neomycin-erythromycin base preparation, clinical sepsis was absent from both the prospective (Part I) and the retrospective (Part II) studies. Although other investigators have reported overgrowth of resistant bacteria and fungi following preoperative antibiotic preparation,[2,26] our results as well as those of Thieme and Fink[34] do not indicate overgrowth. This effect was probably due to the short duration of antibiotic preparation.

We did not investigate the efficacy of adding parenteral or local wound antibiotics to preoperative oral antisepsis. Reports in the surgical literature disagree regarding this point.[4,5,14,18,35] In a series of elaborate investigations, Burke showed that systemic antibiotics maximally suppressed infections only when administered before bacteria entered the tissues.[7] In animal experiments, he found that antibiotics given 3 hours after infection with *Staphylococcus aureus* had no effect on the primary site of sepsis. This has been confirmed clinically by Fullen, Hunt and Altemeier,[11] who noted a significantly decreased postoperative infection rate in patients with penetrating abdominal trauma if broad-spectrum parenteral antibiotics were begun prior to the operative incision.

TABLE 6. *Patients Receiving Parenteral Antibiotics in Addition to Preoperative Preparation*

Type of Preoperative Preparation	No. of Patients Prepared	Received Parenteral Antibiotics No.	%
Neomycin-Erythromycin base	69	23	33%
Mechanical	16	6	38%
Neomycin	8	3	38%
Neomycin-Sulfathalidine	2	1	50%
Kanamycin	2	0	0%
Kanamycin-Sulfathalidine	1	0	0%
Total	98	33	34%

Polk and Lopez-Mayor[27] in a well-planned, controlled study of the rate of infection following elective colorectal operations have reported a decrease from 30% to 7% with use of cephaloridine given intramuscularly on call to the operating room and repeated 5 and 12 hours after operation. Patients in this study received only mechanical preoperative cleansing of the intestine and no intraoperative antibiotic wound irrigation. Although cephaloridine usually fails to suppress anaerobes, no infection involving these organisms was reported in their study.

The choice of parenteral antimicrobials in penetrating abdominal trauma is also critical. In a double-blind study, Thadepalli *et al.*[33] recently showed that the use of clindamycin—an effective drug against anaerobes—results in a reduction of intraabdominal abscess formation and septicemia when compared to cephalothin—an agent with poor activity against anaerobes. It should be noted that these studies concerned traumatic intestinal perforation, a situation in which bowel preparations are not applicable.

On the basis of our current study and previous reports in the literature, elective colon resection should be approached with adequate preoperative mechanical and oral antibiotic preparation; the addition of routine systemic antibiotics appears to be an unwarranted and unrewarding measure.

TABLE 7. *Parenteral Antibiotics in Colon Resection*

Antibiotics Prescribed	No. of Patients
Cephalothin-Kanamycin	9
Ampicillin	8
Clindamycin-Kanamycin	8
Lincomycin-Kanamycin	6
Penicillin-Kanamycin	1
Penicillin-Streptomycin	1
Total	33

Antibiotic irrigation of the operative incision prior to closure has been reported frequently in the past few years.[3,19,24] In a study of patients with traumatic and spontaneous perforations of the gastrointestinal tract, Noon and colleagues[24] reported that antibiotic wound irrigation prior to and during peritoneal closure resulted in half the number of local wound infections as occurred after only saline irrigation. However, they found no difference between the rates of intraabdominal abscess formation in the two groups. Other studies of antibiotic wound irrigation in elective colon operations have reported similar results.[3,19] The judicious use of local wound irrigation with antibiotics that suppress both aerobic and anaerobic intestinal microflora appears to have a place in the treatment of emergent and elective intestinal problems.

Summary

Preoperative intestinal antibiotic preparation with neomycin and erythromycin base in addition to thorough mechanical colon cleansing was compared with mechanical cleansing alone in a prospective, randomized study of 20 patients. Vigorous mechanical cleansing removed gross feces but did not decrease the concentration of fecal microorganisms in the residual colonic content. Three of ten patients having only a mechanical preparation developed wound infections. The addition of neomycin and erythromycin base produced suppression of fecal bacteria. None of the ten patients receiving oral antibiotics developed a wound infection.

Subsequently, 98 consecutive patients who had elective colon operations are reviewed retrospectively in this report. Five of 29 patients (17%) who received a variety of ineffective preoperative colon preparations developed wound infections. None of the 69 patients treated with preoperative oral neomycin and erythromycin developed a wound infection.

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Discussion

Dr. Oliver H. Beahrs (Rochester): I appreciate the opportunity to have read this paper prior to its presentation. Dr. Nichols and associates have done us a favor in reminding us once again that judicious use of antibiotics preoperatively in colonic surgery remains very important.

In the earlier part of the decade of the 1930's the mortality associated with colonic surgery was 20% or higher. Later in the decade after introduction of chemotherapeutic agents and subsequently the antibiotics, mortality was reduced to 5% or less. The single factor that stands out as a basis for this more favorable experience is the availability of these drugs: Sulfonomides and antibiotics.

This fact alone has prompted us to continue the use of antibiotics preoperatively for bowel preparation irrespective of reports that their use exposes the patients to risks especially that of entero-colitis. We did not want to reduce the occurrence of one complication only to be faced with other and previous problems of equal or greater magnitude.

Recognizing the etiology of entero-colitis, establishing the diagnosis early and managing it judiciously when it occurs has eliminated the risk or danger of this complication.

In 1956 we began to use neomycin and oxytetracycline (Terramycin) as suggested by Dearing for 36 hours preoperatively for bowel preparation prior to colonic surgery. With mechanical preparation and these agents, an almost sterile colon content is obtained.

Five hundred twenty cases have recently been reviewed. Eighty-three per cent received the standard preparation. In 17%, none or other drugs were used due to acuteness of the disease or sensitivities.

With the standard preparation the hospital mortality rate was 1.5%; in the other group 4.7%.

Wound complications in patients receiving neomycin and terramycin was 2.5% while in those not receiving these drugs it was 10%. In the latter group, mortality was experienced in several cases secondary to the wound complications. With the standard preparation 18 in 520 patients developed entero-colitis, all were treated successfully without mortality and in only one case was hospitalization prolonged.

Certainly many factors influence mortality, occurrence of complications and success of operation. It is our opinion that the preoperative and postoperative bowel management both with antibiotics and mechanical methods contributes to favorable results.

The authors in their study have shown that the use of neomycin and erythromycin preoperatively essentially eliminates wound infections, a serious complication which leads to morbidity and mortality when it occurs.

In this day and age with a wide variety of antibiotics and chemotherapeutic agents available, the surgeon has the opportunity and obligation to offer the patient safety in colonic surgery by judicious use of these drugs. Lack of their use leads to complications which can be prevented.

I would like to ask the authors if they encountered any occurrence of entero-colitis or other unfavorable complication due to the use of antiobiotics and whether they encouraged early oral food intake so that intestinal flora is restored.

Dr. William A. Altemeier (Cincinnati): I have enjoyed the opportunity of reading this paper before the meeting and compliment the authors on their careful work and their evaluation of the data.

There are several points which I want to emphasize, however. In the five-university hospital ultraviolet study, the incidence of infection for cecostomy and colostomy was 19.3%, colectomy with anastomosis 10.3%, and abdominal perineal resection 11.6% regardless of the type of bowel preparation or antibiotic therapy. (Slide)

For many years I have not used antibiotic bowel preparation, but have relied instead on the intravenous administration of penicillin and tetracycline as the factor of antibiotic protection for the patient, particularly in penetrating wounds of the abdomen and have insisted that this be administered preoperatively so that at the time the excision was made there was an antibiotic preparation bathing the tissues of the wound. The intravenous antibiotic administration has been continued intra- and postoperatively.

There are multiple studies by others, including Dr. John Burke, that substantiate the effectiveness of intravenous antibiotic therapy administered before operation in patients with contaminated wounds of various types.

In penetrating wounds of the abdomen in which there is no opportunity for preoperative bowel preparation of any type, our wound infection rate has only been 3% when the antibiotic is administered as part of the resuscitation preoperatively. When it has not been given until intra-operatively, the rate has jumped to 15%. If it has not been given until after the operation, the