Bile Peritonitis *

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THE HIGH MORTALITY RATE in bile peritonitis justifies any studies which may lead to a lowering of this mortality rate. Experimental studies of the cause of death in bile peritonitis date back to the 1700's, but even today there is no agreement on the major etiologic factor(s) in this condition. The results of this study have served to emphasize the importance of bacterial factors, even though most texbooks ascribe death to a "chemical peritonitis." Investigation of the role of antibiotics in the treatment of experimentally produced bile peritonitis began as a result of an accident which occurred in the course of other studies.[7] The collection of sterile bile from a dog receiving antibiotics was interrupted when a tube slipped out of the gallbladder and bile began to drain into the peritoneal cavity. To our surprise, the animal showed no apparent ill effects from this continuous drainage of bile into the peritoneal cavity. This survival was in marked contrast to the usually reported experience with continuous spillage of bile into the peritoneal cavity and led to these studies where antibiotics have been shown to prevent death in an otherwise fatal form of bile peritonitis.

Studies of bile peritonitis have generally ascribed death to one of three major areas: (1) toxicity of bile or bile salts; (2) fluid loss; or (3) bacterial factors.

Wangensteen's review of the extensive European literature on the dangers of bile in the peritoneal cavity remains the most complete discussion of this segment of the literature available to date.[30] The literature survey and experimental results led Wangensteen to conclude: "The leakage of sterile bile into the peritoneal cavity is not innocuous. The experimental animal dies of cholaemia due to the toxic action of the bile salts within a short time when well-functioning biliary fistulae from which bile escapes into the peritoneal cavity are established. . . . The more rapid death in the dog following the extravasation of bile lies partially in the explanation that dog bile is largely the more toxic taurocholic acid, whereas, human bile contains relatively more of the less toxic glycocholic acid."

The quantity of bile required to produce a lethal result has varied with the different experimental animals used and with the kinds of bile used to study bile peritonitis.[26] Bunting and Brown [5] found the MLD for rabbit bile to be between 0.25 and 0.5 ml./kg.; Helvestine [11] found 4 ml. necessary for uniformly lethal results in guinea pigs; Buckwalter and Joiner [4] reported 8 ml./kg. were necessary when dog bile was injected intravenously into normal dogs; and the MLD required following intraperitoneal injection in dogs has varied from 5 ml./kg.,[12] to an intermediate amount reported by Blalock,[3] to the 20 to 40 ml./kg. reported by Miles and Jeck.[19] Some of the

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discrepancy between these results may be explained by Johnson's study [16] which showed that the greater the concentration of bile salts, the greater the toxicity or the lower the MLD. This may explain some of the widely varying results reported by others who did not report the concentration of bile salts in their studies.

Bunting and Brown [5] found bile was toxic to any tissue with which it came in contact. This was in conformity with the hypothesis of Horrall and Carlson [15] that bile salts cause a dissolution of cells by diminishing the surface tension of the fats which form a part of the cell membrane, and of Manson and Eginton [17] that bile contained some "specific toxic or devitalizing action."

The toxicity of bile and its various constituents was evaluated by Horrall,[13, 14] Horrall and Carlson [15] and Still.[27] All agreed that the toxicity of bile was derived from bile salts and that bilirubin was nontoxic. This is in agreement with Mentzer's summary [18] of the literature: "Every constituent of bile has been considered by various experiments to be the cause of death in these animals but the work of Wangensteen, Horrall, and Ravdin, Morrison, and Smyth proves that bile salts are the only factors that can be responsible."

Death in bile peritonitis has also been attributed to shock due to fluid loss. The fluid lost into the peritoneal cavity has been considered by Harkins and coworkers,[1, 8-10] Moon and Morgan,[20] Manson and Eginton,[17] Thoren [28] and Trusler, Reeves, and Martin [29] to be the major cause of death, and each has thought that adequate fluid replacement might be sufficient to prevent death in this condition.

Bacteria have been considered by other investigators to play a role of varying importance in the cause of death in bile peritonitis. Most of these experiments have been conducted by injecting bile intraperitoneally into normal animals, or else by opening the gallbladder and allowing its contents to drain into the free peritoneal cavity.

Manson and Eginton [17] evaluated the importance of bacteria by comparing the survival of untreated animals with biliary fistula to those treated with welch antitoxin. Unfortunately, the untreated series had a patent common duct, while the treated series had the common duct ligated, so that all bile had to drain into the peritoneal cavity in these animals, thus lowering their chances for survival. In addition, the work reported here shows the difficulty in determining the correct amount of antitoxin that should be used in such experiments.

Horrall [12] drained the gallbladder contents into the peritoneal cavity in dogs and then closed the gallbladder, with survival in all cases. However, if the gallbladder edges were sewn open, death occurred uniformly within 24 hours. This led to an evaluation of the minimum lethal dose of bile injected intraperitoneally, which was found to be 5 ml./kg. for dogs. Since both the bile in the gallbladder and the bile injected intraperitoneally were almost uniformly bacteria-free, he concluded that bacteria were not essential to the lethal outcome in bile peritonitis in the presence of sufficient bile.

More recently Miles and Jeck [19] produced bile peritonitis by injecting bile into the peritoneal cavity of normal dogs. Infection was reported to be of prime importance in bile peritonitis, but sterile bile was fatal when 20 to 40 ml./kg. were used, and the early death following the injection of sterile bile was attributed to cholemia.

The most significant contributions to the study of the role of bacteria in bile peritonitis are by Rewbridge and associates. These authors showed that bile draining into the peritoneal cavity was lethal and that the intraperitoneal injection of pure, bacteria-free bile salts produced an identical picture.[23] All cultures of the peritoneal fluid at death revealed a bacillus similar

to, if not identical with, *Cl. welchii*. It was concluded that this organism was responsible for the infection which caused death in bile peritonitis. Sterile bile salts in the pelvis, the chest, or the subcutaneous tissues produced uniformly lethal results, and cultures were positive for *Cl. welchii* in the injected area.[2] This showed that sterile bile could produce its effects through tissue damage which permitted growth of organisms previously dormant in the tissues. This again emphasized the importance of bacteria and specifically of the welch organisms. Careful bacteriological studies [22] showed that the organism identified as *Cl. welchii* was found in the peritoneal fluid of all animals with bile peritonitis, even though the bile obtained at the original operation was sterile. On the basis of these three studies, it was concluded that bile peritonitis in dogs was an infection, and that *Cl. welchii* invaded the peritoneal cavity, presumably as the result of permeability changes produced by the local action of the bile salts in the peritoneal cavity.

The advent of antibiotics has permitted an extension of these observations which form the basis of this report.

Methods

Bile peritonitis was produced by an aseptic surgical technic in unselected dogs weighing between seven and 24 kg. The fundus of the gallbladder was opened, and the mucosa sutured in eversion to permit continuous drainage of the animal's own bile into the peritoneal cavity (Fig. 1). This aided in maintaining patency of the biliary fistula since it prevented contact of the serosal surfaces of the gallbladder and also prevented adhesions of the small intestinal loops to the gallbladder. The omentum and the spleen were removed to prevent them from sealing the open end of the gallbladder. The common duct was not ligated.

At the beginning of the operative procedure the bile was aspirated from the gall-

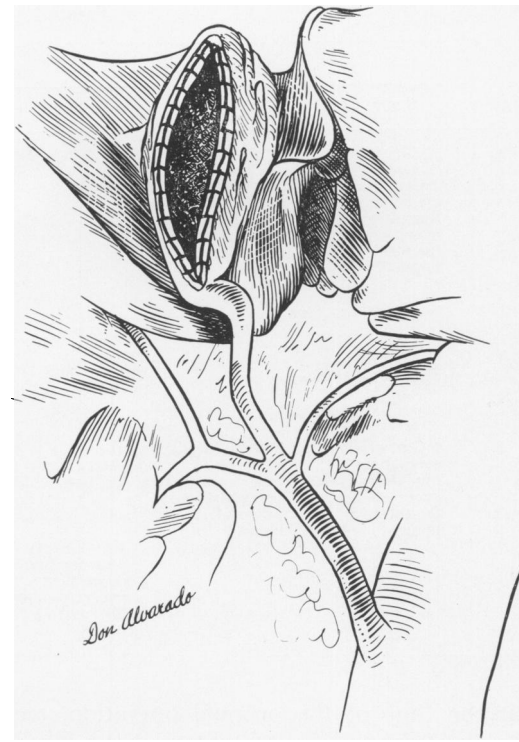

FIG. 1. Diagram of operative procedure. The gallbladder wall is divided, and the mucosa sutured in eversion to permit continuous drainage of bile into the free peritoneal cavity.

bladder into a sterile syringe, and at the end of the operation this same bile was injected into the peritoneal cavity. If this step were not carried out bile spilled into the peritoneal cavity during the operative procedure might be removed inadvertently prior to the end of the operation. An initial insult of one ml. of bile per kg. body weight was found to be essential to provide uniform results. If the gallbladder did not contain enough bile to provide the initial insult, then sterile bile from other animals was added to make this minimum amount.

All animals received the same treatment with the exception of the course of antibiotic therapy that might have been utilized. Animals that died were autopsied and those that survived the experimental procedure were ultimately sacrificed to determine what changes had taken place. Cultures were obtained from the bile taken

TABLE 1. *Antibiotic Therapy*

Series	Preoperative			At Operation		Postoperative	
	Neomycin	Tetracycline	Kanamycin	Pencillin	Tetracycline	Pencillin	Tetracycline
1.	No Antibiotic Therapy						
2.	1 Gm. orally every hour for four doses then every six hours for total 72 hours	200 mg. orally every hour for four doses then every six hours for total 72 hours		800,000 units I.M.	100 mg. I.M. 500 mg. I.V.	800,000 units I.M. every 12 hours for four days	100 mg. I.M. every six hours for four days
3.				800,000 units I.M.	250 mg. I.M.	800,000 units I.M. every 12 hours for four days	250 mg. I.M. every 12 hours for four days
4.				800,000 units I.M.	500 mg. I.M.		
5.	1 Gm. orally every hour for four doses then every six hours for total 72 hours	200 mg. orally every hour for four doses then every six hours for total 72 hours or	1 Gm. every hour for four doses then every six hours for total 72 hours				

at the time of the original operation, and from the peritoneal fluid and blood at death. All cultures were studied by aerobic and anaerobic technics. Reports on cultures obtained at autopsy are included only if the autopsy was performed immediately after death.

In spite of all precautions to prevent sealing of the bile fistula, there were a number of experiments where this did occur. These experiments have been discarded and are not included in the final tabulations since these do not represent true instances of bile peritonitis.

The experimental work was divided into six series of animals, the only differences being in the form of antibiotic therapy used (Table 1).

Series 1. Controls. No antibiotics used at any time.

Series 2. Preoperative, operative, and postoperative antibiotics.

Series 3. Operative and postoperative antibiotics.

Series 4. Operative antibiotics only.

Series 5. Preoperative antibiotics only.

Series 6. Gas gangrene antitoxin control, no antibiotics.

Series 1

The animals in Series 1 served as controls and received no therapy of any kind. Of the 19 animals with patent biliary fistulas, one died at 37 hours, four between 25 and 29 hours, and all others died between 17 and 22 hours after creation of the biliary fistula. At autopsy there were between 95 and 900 ml. of a foul-smelling, noncoagulable, bile-stained fluid in the peritoneal cavity. There were minimal adhesions between the gallbladder and the adjacent viscera. The peritoneal surfaces were inflamed and discolored, but continued to present the shiny, smooth appearance that characterizes normal peritoneum. The hemorrhagic, edematous appearance was also noted on the serosal surfaces of the gastro-intestinal tract, its mesentery, and on the peritoneal coverings of the pancreas and kidneys. There was generally congestion of liver and kidneys, and the entire gastro-intestinal tract usually had a hemorrhagic mucosal surface.

Five of the animals in this group were more closely followed for changes in hematocrit, white blood cells, serum bilirubin, blood urea nitrogen, and serum amylase. These studies demonstrated a rise in white blood cells between six and 12 hours followed by some decrease at the time of death, a decrease in serum amylase, and a terminal elevation of blood urea nitrogen. The other values were not significantly altered.

Culture of the bile removed at operation and injected into the peritoneal cavity was negative in all but two of the eighty experiments in this entire study. *E. coli* were found in one of these and bacteroides in the other.

Peritoneal fluid cultures were obtained immediately after death in 11 experiments. Ten of these were positive for clostridia, staphylococci, or both, and the remaining one was positive for bacteroides. Blood cultures, obtained in ten experiments, were negative in eight and positive for staphylococci in two.

Series 2

The animals in this series received preoperative bowel antisepsis with neomycin and tetracycline, and received intramuscular penicillin and tetracycline at the time of operation and for four days postoperatively. Seven of the eight dogs in this series either died or were sacrificed from eight to 23 days following creation of their biliary fistula, and all had a patent fistula at autopsy. The remaining animal died at 20 hours. The animals surviving for the longer time periods all had clinically marked ascites. The amount of peritoneal fluid in these animals varied between 1,450 and 4,800 ml., and it was deeply bile stained in all. In none of these animals was the ascitic fluid foul-smelling as it had been in the control series. This fluid was usually turbid and sometimes "muddy" due to the deposit of bile solids. Congestion of the viscera was not generally noted in these animals in contrast to those in the control series. The serosal surfaces of the gastrointestinal tract were not so hemorrhagic, but there were deposits of bile-pigmented material on all peritoneal surfaces. Bilirubin determinations, the highest of which was 4.74 mg. per cent, indicate that absorption of bilirubin was not of sufficient magnitude to alter the outcome. Similarly, there were no major changes in BUN or chlorides.

Cultures of bile at operation were all negative. Cultures of the peritoneal fluid at death or sacrifice were negative in two experiments and positive only for yeasts in one.

Series 3

The animals in this group received intramuscular penicillin and tetracycline at the time of operation and for four days subsequent to operation. Of the nine animals in this series with patent fistulas, all survived from six to 20 days. The clinical and autopsy findings in this group were quite similar to those in the preceding group.

Series 4

These animals received antibiotics only at the time of operation, and at that time received a single intramuscular injection of penicillin and one of tetracycline. Of the 11 animals in this series, nine survived from 13 to 30 days, while two died at 27 and 32 hours. The clinical and autopsy findings in this series were similar to those in previous groups that survived. It is interesting to note that the dramatic change in survival from the controls was achieved with only a single injection of antibiotic.

Elevation of serum bilirubin was the major chemical change observed in this series. Three of the highest values in this entire study were noted here: 4.65, 7.85, and 40.75 for direct bilirubin and 6.7, 10.7, and 51.00 for total bilirubin during the survival period in three animals.

Cultures of the bile at operation were negative. The peritoneal fluid at death or sacrifice was negative in four and contained only staphylococci in one.

Series 5

In this series the animals received only oral antibiotics in the preoperative period in an attempt to determine the effect of reduction of the gastrointestinal flora on bile peritonitis, since it was assumed that some of the bacteria in the peritoneal fluid at death might have come from the gastrointestinal tract. The first animals in this series received neomycin and tetracycline, while the second group of animals received only kanamycin when it was realized that significant blood levels of tetracycline resulted from its oral administration. Bile levels in two animals were 4.2 and 1.8 mg. per cent of tetracycline and 0.4 and 2.0 mg. per cent of neomycin. In one animal the serum levels were 3.2 mg. per cent of tetracycline and 2.2 mg. per cent of neomycin. These are comparable to the levels that would be achieved if the drugs were administered at surgery, and indicated the value of changing to a drug such as kanamycin where absorption from the gastro-intestinal tract would be negligible. Thus, any changes noted with kanamycin were solely the result of reduction of the organisms in the gastro-intestinal tract. The results of these two subgroups are comparable and will be discussed together. The six animals with patent fistulas survived from 20 to 114 hours with an average survival of 58 hours. Both the maximum and the average survival times were increased over those of control animals. The autopsy findings were more closely related to those found in the various groups of animals that survived rather than in the control series.

Series 6

Certain observations made by others and in these experiments suggested the lethal effects might result from *Cl. welchii* toxins acting in the peritoneal fluid. Accordingly, antitoxin was administered to six animals subjected to bile peritonitis. The amount of antitoxin used varied from one to four vials given at operation. The survival ranged from 16 hours to 84 hours, with all but one of the animals dying within 28 hours. This indicates that antitoxin administered in the dosage and time schedule used here did not protect against the effects of this form of experimental bile peritonitis.

Discussion

Survival in experimental bile peritonitis in the dog was significantly increased by the administration of antibiotics, almost regardless of the route and time of antibiotic administration. Certain routes of antibiotic administration gave better results, but almost any method of antibiotic administration improved survival over that obtained in untreated controls. Speculation as to the explanation for these effects of the antibiotics is interesting.

If one compares the survival of the control animals with those treated with preoperative intestinal antisepsis only it is obvious that there are major differences in minimum, maximum, and average survival times (Fig. 2). This suggests that the improved survival is due in part to the preoperative control of the gastro-intestinal bacteria. Precisely why control of this flora affects the ultimate outcome of these animals is not known, and further study of this phenomenon is underway.

The maximum survival in the control group was 37 hours. To compare this with the survivals in the other series, a time well beyond the maximum survival in this control series was arbitrarily selected, and five days was chosen as the basis for survival or nonsurvival (Fig. 3). Using this criterion, all animals in the control group and all animals receiving only preoperative antibiotics succumbed to the experimental procedure. However, the mortality rate was

reduced to 20 per cent when antibiotics were administered before and after operation and there was *no* mortality when antibiotic therapy was limited to the operative and postoperative period. Of interest was the mortality rate of only 20 per cent when antibiotic therapy was limited to that administered during the operative procedure. Just as there is speculation about the precise role of antibiotics when limited to the preoperative period, so there must be some speculation about how antibiotics can be so effective when their administration is limited to that given at the time of operation.

Bile removed from the gallbladder at the time of the original operation was sterile in all but two experiments. Since this represents a study of over 80 unselected

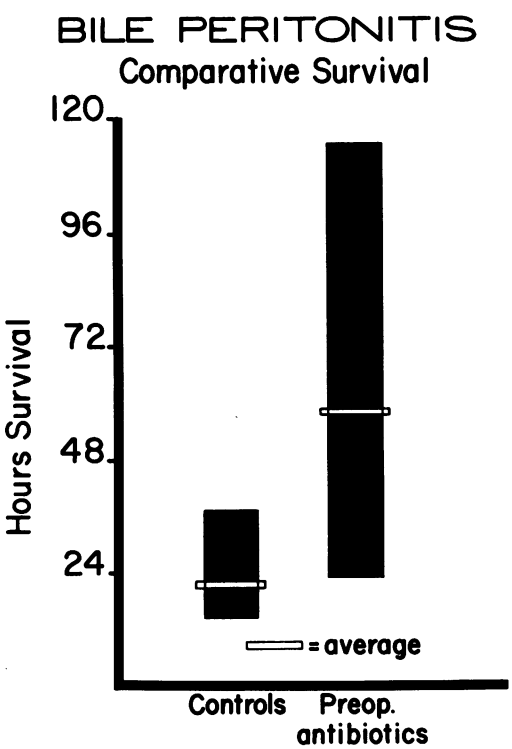

FIG. 2. Comparative survival time of the control series and the series that received preoperative intestinal antisepsis only. The height of the bar is the longest survival, the bottom of the bar is the shortest survival, and the cross bar is the average for the series.

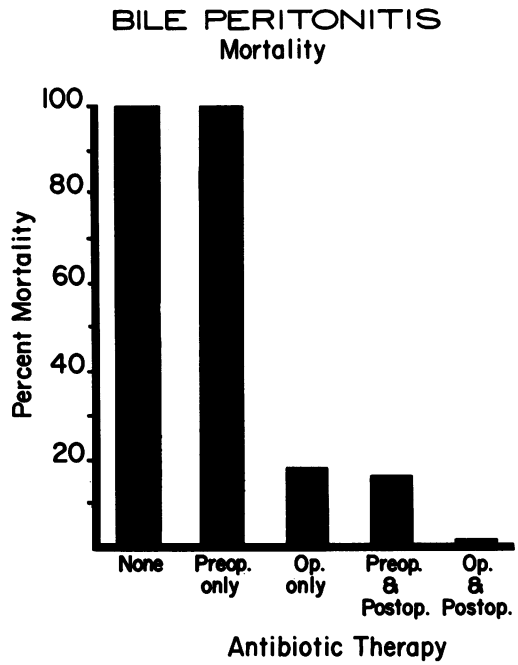

FIGURE 3.

dogs, it must be concluded that dog bile is usually sterile, and that antibiotic effects could not be ascribed to an action on the bile in the gallbladder at the time the biliary fistula was created.

Since antibiotics alone significantly altered the course of this type of experimental bile peritonitis, it seems that bacteria play a major role in bile peritonitis in the dog. This is in contradistinction to much of the currently accepted writing in this field, where a chemical peritonitis due to bile salt intoxication has come to be the accepted cause of the ill effects in bile peritonitis. Since even a single injection of antibiotics administered at the time of operation was sufficient to completely alter the course of this process, it may be assumed that antibiotics were exerting some specific type of antibacterial activity. The precise manner in which antibiotics rendered this uniformly lethal condition nonlethal is not yet known. Studies in our laboratories have shown that the simultaneous intraperitoneal injection of bile and

antibiotics into mice does not alter the lethality of bile. The intraperitoneal injection studies need to be extended and repeated in the dog, since the results reported for experimentally produced bile peritonitis indicate the important role of antibiotics.

If bacteria are so important in this condition, and if the initial bile found in the gallbladder and sprayed into the peritoneal cavity is sterile, then it would be interesting to know where the organisms in the peritoneal cavity come from and how they get there. Several possibilities come to mind. Passage of bacteria through the biliary tract as a reflux from the duodenum is a distinct possibility. However, if this can occur at all, it would seem that it should occur occasionally in an animal with an intact biliary tract, and this should lead to an occasional experiment in which the initial bile was already contaminated. Yet such has not been our experience. The bacteria could come through the wall of the gastro-intestinal tract in response to the irritation of the bile on the serosal surface. That bacteria can migrate through a bowel wall that has no gross perforation has already been shown,[6, 24, 25] but these migrations have usually been through a bowel wall that is already the seat of some extensive pathologic process, whereas the bowel wall in these experiments was only subjected to the irritation of bile on its serosal surface. Since the normal muscles and viscera of dogs are known to harbor bacteria, these organisms may have come from their normal habitat in response to the noxious stimuli of bile in the peritoneal cavity. However, it seems unlikely that a single injection of antibiotic at the time of operation should control this mass migration.

In the face of some of these unsolved problems it is well to consider the importance of some other factors in bile peritonitis. Bile salts are toxic, but the large collections of biliary ascites in many of these animals—amounting to 4,800 ml. in one animal—show that large peritoneal accumulations of biliary fluid cannot be the only problem to be considered. Consideration should be given to whether the combination of bile and bacteria have any effect on one another with regard to stimulation of bacterial growth, influence on production of toxins or enzymes, or alteration in the toxicity of the bile.[21] Thus further studies of various combinations of bile, antibiotics, and bacteria are indicated to more completely understand the various factors that may enter into the toxicity of bile peritonitis and thus provide better understanding of the picture of bile peritonitis.

Conclusions

A technic has been described for the production and study of bile peritonitis.

Antibiotics will prevent a lethal outcome in experimental bile peritonitis.

The role of bacteria and other factors in the lethal outcome in bile peritonitis has been discussed.

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