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Review of the literature on experimental peritonitis

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REVIEW OF THE LITERATURE
ON
EXPERIMENTAL PERITONITIS

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INTRODUCTION

In 1919 Hertzler (47) wrote that, "In no chapter in the study of the peritoneum is the state of our knowledge so unsatisfactory as that concerned with the cause of death in peritonitis. Perhaps it may be admitted that, broadly speaking, any fatal disease becomes so either through a failure of respiration or of the circulation. But this as it may, the avenues which lead up to either of such catastrophies remain unexplained in the case of peritonitis. Obviously enough knowledge of the sequential development of deleterious phenomena would be of vast importance in the formulation of a scheme of treatment if we possessed it. However, we have no such knowledge and once the disease has passed the stage of its focal origin, the surgeon is without a fundamental scientific basis for subsequent procedure."

It was the original purpose of the writer of this thesis to write a paper upon the cause of death in peritonitis but it was found upon a review of the literature that the cause of death in peritonitis was not known. Many theories were present in the literature: some of these theories were bases on animal experimentation, others on clinical observation and many of them appeared to be based upon a fertile imagination.

The writer came to the conclusion from these observations that a thesis based on fundamental, scientific knowledge -- animal experimentation -- might be of value in the study of peritonitis.

David and Sparks (27), in 1928, stated that, "Many complex problems present themselves in the study of peritonitis. In general they may be listed as : a better understanding of the absorptive powers of the peritoneum; the problem of development of paralytic ileus and its influence on mortality; and finally, the questions involved in the early circulatory failure so frequently observed in general peritonitis. The questions raised are far reaching and not easy of solution. Some progress, however, may be made by the study of isolated problems which make up the whole."

It was found, upon a review of the literature that much of the experimental work on peritonitis concerned itself with these problems and that most of the experimental work could be placed under one of the following headings: absorption from the peritoneal cavity, diffuse peritonitis, intestinal obstruction, bile peritonitis, and autolytic peritonitis. The writer decided to use these headings as the major divisions of this thesis.

The literature on experimental peritonitis and peritoneal absorption was so voluminous that the writer decided to include only the articles on the above subjects which he thought were pertinent. An effort was made to exclude from this thesis opinions and conclusions which were not based on animal experimentation.

The subject matter in the body of the thesis was arranged chronologically so that the various trends of experimental work

could be observed. In the summary at the end of each section the subject matter was grouped according to content of thought.

Since this thesis is based entirely on experimental peritonitis in animals, the writer believed that no attempt should be made to correlate this subject with clinical peritonitis.

PART I

ABSORPTION FROM THE PERITONEAL CAVITY

ABSORPTION FROM THE PERITONEAL CAVITY

In 1937 Mengle (64), stated that one of the most important, if not the principal, factor in peritonitis is the accompanying toxemia. Since the success or failure of treatment depends largely on measures designed either to neutralize the toxins as formed or to prevent their absorption into the systemic circulation, it is natural that a great deal of interest has been evinced in the manner in which these toxins enter the systemic circulation.

A survey of the literature reveals that the absorption from the peritoneal cavity is as yet not thoroughly understood. There are many factors which affect the rate of absorption, and there is more than one avenue of escape of material from the peritoneal cavity.

Since the original investigations of von Recklinghausen (102), in 1863, much work has been done on the absorption from the peritoneal cavity of dyes, both diffusible and colloidal, organic and inorganic substances in solution and supension and colloids, including bacteria.

Von Recklinghausen, using silver nitrate stains, stated that particulate material entered the lymphatics through definite openings or "stomas", between the endothelial cells.

Waterhouse (105), in 1891, observed that a considerable quantity of a virulent culture of the staphylococcus aureus might be injected into the peritoneal cavity without causing peritonitis. He believed that this was due to the rapid absorption of bacteria.

Buxton and Torrey (17), in 1906, injected nucleated erythrocytes and suspensions of living bacteria into the peritoneal cavity and timed their appearance in the blood and lymph streams. They found that absorption from the peritoneal cavity took place through the omentum and through the lymphatics of the diaphragm into the anterior mediastinal lymph nodes.

Danielsen (24), in 1907, concluded that while crystalloids were absorbed from the peritoneum through the blood stream, colloid substances were absorbed through the lymph channels.

In 1907 Achard and Gaillard (6) concluded from their experiments that the molecular weight was a great factor in the rate of absorption of organic materials from the peritoneal cavity. The higher the molecular weight, the lower the rate of absorption. The absorption of organic matter was in inverse proportion to the weight of the molecule.

In 1914 Thiele and Embleton (98) injected bacteria into the peritoneal cavity. These appeared in the thoracic duct within two to ten minutes. The bacteria were then found first in the heart muscle, next in the lung, and finally in the general circulation.

They also tied the thoracic duct at its termination, and drained the proximal end, following which they injected bacteria into the peritoneal cavity. They stated that bacteria did not appear in any of the organs mentioned nor in the blood. They

concluded that the lymphatics were the avenues of absorption from the peritoneal cavity and not the blood.

In 1914 and 1915 Dandy and Rowntree (22) studied the absorption of phenolsulfonphthalein from the peritoneal cavity. They found that it appeared in the blood stream in from two to four minutes, in the urine in from four to six minutes and in the lymph stream, thoracic duct, in from twenty to fifty minutes. They were also the first to point out that, whereas absorption takes place about equally from all parts of the cavity, certain areas do not absorb as readily as others. They studied the effect of posture on drainage and discovered that the rate and amount of absorption was about equal in all postures except with the pelvis down, in which position the absorption was uniformly about 15 per-cent less. They summed up the literature on absorption from the peritoneal cavity that had been published up to that time and concluded that most of the absorption took place through the blood stream and that this was true for both bacteria and toxins. All their studies were made on normal animals, i.e., in the absence of peritonitis.

Costain (20), in 1923, produced acute peritonitis in six dogs by tying the appendix and leaving it in situ. Within three days all developed the typical symptoms of peritonitis. In three of the animals, he drained the thoracic duct. He obtained positive cultures of bacteria common to the intestinal flora of the

dog through this opening; while the blood was sterile throughout. These animals recovered. The three dogs that were left to their fate gave positive blood cultures and died. He concluded that absorption of bacteria and toxins took place through the lymphatics and not through the blood stream. Costain later operated on a young girl for pneumococcus peritonitis. He drained the thoracic duct and the patient recovered.

In 1925 Steinberg (87) in a study of absorption from the peritoneal cavity in dogs, stated that drainage of the thoracic duct had no value in the treatment of peritonitis.

McGuire (71), in the same year, injected Bacillus prodigiosus intraperitoneally in dogs. He made the following conclusions from his experiments: (a) that the forementioned organisms could not be recovered from lymph from the thoracic ducts of these animals (b) that lymph from the thoracic duct in cases of peritonitis in dogs did not appear highly toxic and that comparatively large amounts produced no effect when injected intravenously in rabbits. (c) that dogs with experimentally produced peritonitis were not benefited by drainage of the thoracic duct. All of them died.

McGuire (71) in his paper discussed the great dissimilarity of views and the conflict in findings and conclusions of various observers and workers in this field. He stated that there could be little doubt that there was absorption from the peritoneal cavity directly into the subperitoneal capillories after reading the work of Starling and Tubby, Hamburger, Orlow, Dandy and Rowntree,

Clark, Bolton, and Putnam. He quoted the researches of Durham, Buxton and Torrey, Thiel and Embleton, and Shipley and Cunningham to support the thoery that the omentum played a part in absorption from the peritoneal cavity. He stated that the work of Muscatello, Durham, MacCallum, Buxton and Torrey, and Cunningham showed that lymphatic drainage from the peritoneal cavity also took place through the diaphragmatic lymphatics and thence to the anterior mediastinal lymph nodes. He wrote that only Beck, Thiele and Embleton and Costain found that absorption took place through the thoracic duct.

Klein (55), in 1925, after experimenting on animals concluded that solid particles were taken up by the omentum and were then found in the lymphatic glands and the thoracic duct. Diffusible dyes entered the blood stream first and that toxins and bacteria were absorbed by the lymphatics and enter the general circulation by way of the thoracic duct.

Klein also reviewed many of the previous articles on peritoneal absorption and formulated the following principles influencing the absorption of toxins from the peritoneal cavity:

a. The concentration of the substances introduced, that is its osmotic pressure.

b. The molecular weight of the toxin.

c. The osmotic pressure of the blood at that particular time.

d. The amount of toxins free in the peritoneal cavity.

e. The reaction of the peritoneum.

f. The length of time the toxin remained in the peritoneal cavity.

g. The part of the abdominal cavity into which the toxin entered.

h. The intraabdominal pressure.

i. The state of bodily rest and position.

Cunningham (21), in 1926, made an extensive review of the experimental work on absorption from the peritoneal cavity and made the following summerizations. "In general, then, we may summarize the work which has been done on the mechanism involved in the absorption of particulate matter from the peritoneal cavity in the following way. The earlier work all tended to establish the concept of the presence of actual preformed physical openings between the peritoneal cavity and the diaphragmatic lymphatics. This idea was gradually eliminated and in its place the concept of potential physical openings between the cells was offered. In turn this hypothesis is being replaced by one which assumes that most, if not all, of the particulate matter that is absorbed from the peritoneal cavity passes directly through the living cytoplasm of the mesothelial cells."

He also concluded that, "It now seems wholly settled that solutions which are absorbed from the peritoneal cavity pass in large part directly into the blood stream. It is, however quite probable that a small amount of this material is also absorbed

through the lymphatic vessels. The chances are, however, that this quantity is small since it is probable that the rate of absorption is dependent to a great degree upon the rate of flow through the blood vessels. Since the rate of flow is so greatly in excess of the rate of flow of the lymphatics only a small amount can possibly escape by way of the latter vessels." (21)

In another section of his review he concluded, "Thus it seems indicated from the more recent and more exact work, that there is a small part of the absorption which takes place from the serous cavities which cannot be explained on the basis of the known physical laws of osmosis and diffusion. There seems to be two possible explanations of the machanism involved in this absorption of isotonic solutions. The first of these is that the active force is in some way bound up in the metabolic activities of the mesothelial cells and is therefore controlled by laws similar to those active in other cellular functions. That this activity is less in amount than the activity found in the lining cells of the intestine, or in the secreting cells as such organs as the pancreas, may be related, at least in part, to the differences in the cytoplasmic extent of these different type of cells. The second possible explanation of the absorption from the peritoneal cavity of isotonic solutions is that the force active is mechanical, i.e., abdominal pressure, respiratory movements, etc., and that the isotonic solution is gradually forced into the lymphatics

or blood vessels by pressure. It does not seem probable that this part of the absorptive activity of the peritoneum can be due simply to the pressure of mechanical openings since there is no evidence of any equalization in types of colloidal content other than what can be explained on the basis of diffusion through the walls of blood vessels." (21)

In 1927 Drinker and Churchill (28) wishing to make intra-vital studies of the capillaries, tried a great many kinds of dyes, inks and colloidal graphite base for printer's ink. The latter, when neutralized and diluted with a saline-acacia solution, gave the best results. He believed that since the particles were smaller than erythrocytes, there was not the tendency to plug the lymphatics by clumping, as other inks do, or to diffuse out into the perilymphatic tissues spaces, an objection he had against the use of the soluble dyes.

Florey (35) in 1927, also used hydrokollag 300 and declared it to be far superior to many other substances which he had used. As a result of his experiments, he concluded that intra-abdominal pressure, as affected by the activity of the animal and by the rate and depth of respiration, played a big role in the removal of particulate material from the peritoneal cavity. He also made the suggestive remark that experiments performed on the relative rates of absorption through the lymphatics in anesthetized animals gave a far from accurate picture of what really happens in

the normal animal.

In the same year Higgins (48) after studying the absorption of particulate material from the peritoneal cavity of dogs, found five routes through which particulate material might be removed: (a) the sternal route --- the most important --- which traverses the substernal aerolar tissue and empties into the lymph nodes between the first and the second rib and thence into the thoracic duct or the right lymphatic duct just at or before the venous confluence; (b) the pulmonary route, consisting of lymphatics and nodes in the anterior mediastinum and bronchial nodes at the base of the lungs; (c) the thoracic duct itself; (d) the retroperitoneal route, and (e) the direct peritoneal route.

He credited the sternal route with transmission of about four-fifths of the entire amount of the particulate material.

In 1927 David (25) after producing peritonitis in dogs by means of the Bacillus coli made the following conclusions; (a) evidence was presented that Bacilli coli passed directly into the blood stream as well as into the lymphatics from the normal peritoneum; (b) a well developed plastic peritonitis prevented the passage of Bacillus coli from the peritoneum into the blood stream or into the lymphatics emptying into the thoracic duct; (c) lesser grades of peritonitis prevented the passage of Bacillus coli into the blood stream but did not prevent its passage into the lymphatics; (d) Bacilli coli injected into the peritoneum which contained a transudate, passed rapidly and in great numbers into the chyle from the thoracic duct and directly into the blood

stream; (e) by analogy he assumed that in a well developed general infectious peritonitis bacteria did not pass directly into the blood stream or into the lymphatics draining into the thoracic duct, and that the major problem in peritonitis did not concern itself with the development of a septicemia.

In the same year Steinberg and Goldblatt (94) also did experiments in dogs concerning the passage of bacteria from the peritoneal cavity into the lymph and blood. They found that both blood and lymph of normal dogs were bacteria-free whether the animals had been fed or had fasted. Following the intraperitoneal injection of B. coli suspended in physiologic sodium chloride, a large number of these organism were found in the lymph, thoracic duct, and a relatively smaller number in the blood. Dogs, with the thoracic duct intact, after receiving intraperitoneal injections with saline suspensions of B. coli, rapidly developed a severe bacteremia but practically always survived. They injected B. coli suspended in gum tragacanth and found that a smaller number of the organisms appeared in the lymph, thoracic duct, and that none appeared in the blood stream. They found that although these animals did not have a bacteremia, they invariably died. They concluded their article by stating that bacteremia was not responsible for the death of dogs in acute B. coli peritonitis and that the rapid passage of bacteria from the peritoneal cavity into the blood was associated with the recovery of the animal.

Brown (12) in 1927 reported experimental work in dogs and cats which seemed to show that lymphatic drainage of the diaphragm was only subsidiary to the removal of the material by the venules of the omentum and mesentery. He expressed the belief that lymphaticostomy, which had been advocated as a method of preventing toxins from entering the circulation, was of no value in spreading peritonitis.

Morton (69) in 1927, summarized his experiments on rabbits and dogs by stating that phenolsulphonephthalein was absorbed at essentially the same rate from the inflamed and the normal peritoneum, both in mechanical and bacterial peritonitis. An exception noted was that an adhesive type of peritonitis greatly lessening the peritoneal area did seem to retard the rate of absorption slightly. He further concluded that the presence of hypertonic solution of sugar in the peritoneum did not retard the absorption of dye.

In 1928 David and Sparks (27) studied peritoneal absorption in dogs by injection of Diphtheria toxin into the peritoneal cavities of dogs. They concluded that Diphtheria toxin passed promptly in considerable amounts directly into the blood stream as well as to the peritoneal lymphatics from the normal peritoneum of the dog. Also, that intraperitoneal transudate favored the prompt passage of Diphtheria toxin from the peritomeum. Working with peritonitis, they found that a plastic peritonitis markedly, if not completely, interfered with the passage of diphtheria

toxin from the dog's peritoneum. They assumed as a result of their experiments that when a plastic exudate was formed in the peritoneum, the passage of bacteria and toxin from the peritoneum was markedly interfered with.

In 1928 Mann (68) stated that Herrmann's experiments suggested that while dyes absorb in animals with peritonitis perhaps as readily as in the normal animal, this was not true of bacteria.

Buchbinder, Heilman and Foster (16) in 1929, produced diffuse experimental peritonitis in dogs and made the following conclusions: (a) Rapidity of absorption in the largest measure governed the prognosis of acute, diffuse peritonitis; (b) fibrin was the most important factor in controlling the rate of absorption: (c) fibrin was diminished or absent in the more virulent cases because of dilution of the exudate; (d) the streptococcus was most commonly identified with this abudndant exudate and the accompanying virulent course of the disease; (e) the addition to such an inflammatory exudate of a transudate produced by the intraperitoneal injection of hypertonic dextrose solution produced a more rapid spread of the infection and insured the lethal outcome.

Poynter (76 & 77), in 1927 and 1929, discussed his experiments on peritoneal absorption and compared his results with those which had been reported in previous papers.

He believed that particulate matter, as well as solutions, reached the blood stream by the same routes and in a very short time. He reported that when particulate matter, India ink, was injected into a normal peritoneal cavity, it rapidly found its way to the under surface of the diaphragm. Posturing the animal only slightly delayed the process. As soon as the dye came in contact with the peritoneum it found its way through the peritoneal surface to enter the small lymph radicles in the subserous layer. (76) He stated that these small channels were arranged in irregular radiating nets which tended to produce an etched pattern on the diaphragm covering all of the region occupied by muscle. These small channels joined to form two main pathways on each side, one ventral and the other dorsal, which are known as the parasternal and paravertebral lymphatic channels. The channels extended upward and after passing through the superior mediastinal lymph nodes emptied into the great veins in the root of the neck. Poynter and his colleagues were impressed by the rapidity of the process; from three to five minutes being sufficient for the dye to reach the blood stream after interperitoneal injection. (76)

Poynter stated that the lymphatics were not the only paths of peritoneal absorption but both particulate matter and solutions were taken up by the omentum and passed directly to the portal circulation.

In studying the absorption from the acutely inflamed

peritoneum, they repeatedly induced peritonitis in animals and, at various intervals in the process, examined their reaction to absorption. They found that the paths were the same and the absorption rate did not materially differ from the rate for the normal membrane. They did find that absorption was slightly freer in early severe infection and was definitely less in old fibrinous processes. They suggested that it was possible that the interference with circulation of fluids within the cavity in the latter case was responsible for the difference. They also found that after two or three days the bacteria disappear from the blood stream in experimental peritonitis and a very little later the peritoneal contents was also sterile even when the gross appearance was still one of acute peritonitis. (76)

Poynter disagreed with the experimental work which tended to show that the thoracic duct acted as a channel to convey materials absorbed from the peritoneal cavity. He stated that while the superior mediastinal portions of the lymph channels on the left frequently joined the thoracic duct before it entered the veins, he and his colleagues had never found dye in the thoracic portion of the duct. (76)

Kennedy (52), in 1931, stated that the former view was that the peritoneum was studded with small openings called stomata which were supposed to be the real beginning of the lymphatic vessels. He believed that stomata as real openings

did not exist and that the blood vessels, not the lymphatic vessels were probably the true absorbents of the peritoneal cavity. He did not believe that there was any one portion of the abdominal cavity richer in absorbents than any other.

In 1932 Menville and Ani (66) studied the absorption of thorotrast, a colloidal thorium dioxide, from the peritoneal cavities of albino rats. Their experiments were undertaken to visualize, if possible in the living rat by means of the roentgen ray, the routes of absorption by the lymphatic system form the peritoneal cavity to the right and left lymphatic ducts. They injected three, healthry, albino rats intaperitoneally with .5 cc of thorotrast. Twenty-four hours after injection and again two weeks after injection they made roentgenograms which showed very fine striations in the abdomen which closely resembled lymph vessels. The diaphram showed an increased density, suggesting some absorption of thorium in that region by lymphatics. They reported that chest films showed clearly the intercostal vessels with the right and left lymphatic ducts, also the drainage system of the lymphatics from the peritoneal cavity, diaphragm, intercostal nodes and vessels into the lymphatic ducts. In one animal they noted an apparent connection between the two lymphatic ducts; whether this was but a branch of a duct, they did not decide.

Steinberg (90), in 1936, repeated earlier experiments (94) and again found that gum tragacanth successfully retained injected

bacteria within the peritoneal cavity. He used this observation as a basis for attempting to establish artificial peritoneal immunity.

Mengle (64), in 1937, performed experiments to show that in normal animals and those with either local or spreading peritonitis the greatest stimulation to lymphatic absorption was produced by the anestetics which most stimulated the activity of the diaphragm.

ABSORPTION FROM THE PERITONEAL CAVITY

SUMMARY

SUMMARY

The great dissimilarity of view and the conflict in finding and conclusions of various observers on this subject is striking. An effort will be made to summarize the principal view points in the following paragraphs.

Thiel and Embleton (98), Costain (20), Klein (55), and Steinberg and Goldblatt (94) believed that the thoracic duct was one of the principal avenues of absorption from the peritoneal cavity. Dandy and Rowntree (22) and Higgins (48) believed that the thoracic duct played a minor role as an avenue of absorption. Steinberg (87), McGuire (71) and Brown (12) were against such a concept. Poynter (76) concluded from his experiments that the thoracic portion of the thoracic duct did not serve as an avenue for absorption.

Cunningham (21) and Poynter (76) believed the lymphatics of the diaphragm played an important part in absorption from the peritoneal cavity. Brown (12) decided that the lymphatic drainage of the diaphragm was subsidary to the drainage from the omentum.

Thiel and Embleton (98), Klein (55), Drinker and Churchill (28), Florey (35), Higgins (48), Steinberg and Goldblatt (94), David and Sparks (27), Menville and Ani (66) and Mengle (64), believed that, in general, the lymphatic system was the principal system by which absorption took place from the abdominal cavity. Danielson (24) believed that only colloids were absorbed from the peritoneal cavity by this route. Cunningham (21) conceded that

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small amounts of solutions were absorbed in this manner while Poynter (76) and David and Sparks (27), believed that the blood stream was equally important.

Dandy and Rowntree (22), and Kennedy (52 believed that the blood stream was the main avenue of absorption. Danielson (24) believed that only crystalloids were absorbed by this route. Klein (55) concluded that diffusible dyes entered the blood stream first. Cunningham (21) decided that the greatest part of solutions injected into the peritoneal cavity was absorbed directly into the blood stream. Steinberg and Goldblatt (94) believed that only a small number of organisms injected into the peritoneal cavity was absorbed directly into the blood stream while Costain (20) did not believe that absorption took place directly into the blood stream.

Buxton and Torrey (17) and Brown (12) believed that the omentum was an important avenue of absorption. Klein concluded that solid particles were absorbed primarily by the lymphatics of the diaphragm and were then collected by the thoracic duct. Poynter (76) concluded that the omentum absorbed particulate material which was then carried to the portal circulation. He believed the omentum and the lymphatics of the diaphragm were the two principal avenues of absorption from the peritoneal cavity.

Higgins (48) believed that in a well developed general

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peritoneal infection bacteria did not pass directly into either the blood stream or the lymphatics. Morton (69) concluded that and adhesive type of peritonitis lessesned absorption. Buchbinder, Heilman and Foster (16) believed that fibrin diminished peritoneal absorption. Poynter (76) concluded that absorption was slightly more free in early severe cases but was less in old fibrous processes.

Cunningham (21) believed that abdominal pressure, respiratory movements, etc., might play an important part in gradually forcing an isotonic solution into the into the lymphatics or blood vessels. Florey (35) also concluded that the intra-abdominal pressure, as affected by the activity of the animal and by the rate and depth of respiration, played a big role in the removal of particulate material from the peritoneal cavity. Mengle (64) concluded that stimulation of diaphragmatic cavity stimulated lymphatic absorption from the peritoneal cavity.

David and Sparks (27) believed that intraperitoneal transudate favored the absorption of toxins while plastic peritonitis interfered with the absorption of both bacteria and toxins.

PART II

DIFFUSE PERITONITIS

SUMMARY

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DIFFUSE PERITONITIS

In 1891, Waterhouse (105) in a series of twelve observations on dogs concluded that a considerable quantity of a virulent culture of the staphylcoccus aureus could be injected into the peritoneal cavity without causing peritonitis. Also, when staphylococcus was mixed with an untried medium it caused no disturbance if the mass could be readily absorbed. He implied then, that in dogs rapid absorption of organisms from the normal peritoneum would prevent the development of peritonitis.

Durham (29) in 1896 studied the cellular changes which occured after peritoneal infections in guinea-pigs and recognized the following stages:

(a) Preliminary stage lasting from five to seven minutes.

(b) Leucopenic lasting about one hour.

(c) Mecroxphil lasting to the fourth or seventh day or later.

(d) Macrophage lasting to the fourth or seventh day or later.

(e) Return to normal.

Whipple (106) in 1916, after experimenting with animals felt confident that there was a definite proteose intoxication in general peritonitis, either septic or sterile, and in intestinal obstruction and allied conditions, and in acute hemorrhagic pancreatitis. He believed that proteose intoxication was the most important factor in the general intoxication noted

in these conditions. From his experimental work, he decided that proteose was derived from the tissues or tissue proteins of the host. Wipple did not deny that there might have been other substances present that might have contributed to the general intoxication noted in the above named conditions, but he believed that proteose was the most important factor.

Steinberg and Goldblatt (94), in 1927, injected B. coli into the peritoneal cavities of dogs and made the following conclusions: (a) dogs, with thoracic duct intact, after receiving intraperitoneal injections with saline suspensions of B. coli, rapidly developed a severe bacteremia but practically always survived; (b) when dogs with the thoracic duct intact received intraperitoneal injections of B. coli susupeneded in gum tragacanth, they did not have bacteremia; yet these animals invariably died; (c) dogs practically always survived following the intraperitoneal injection of broth cultures of B. coli containing aleuronat; (d) when large numbers of virulent B. coli suspended in gum tragacanth were injected intraperitoneally into dogs, the animal always died, and the outcome was not altered by direct drainage of the thoracic duct.

Steinberg and Goldblatt (94) further concluded that bacteremia was not responsible for the death of dogs in acute B. coli peritonitis and that the rapid passage of bacteria from the peritoneal cavity into the blood was associated with the recovery

of the animal.

David (25), in 1927, presented evidence, from his experimental work on dogs, that colon bacilli passed directly into the blood stream as well as into the lymphatics from the normal peritoneum but that, a well developed plastic peritonitis prevented the passage of B. coli from the peritoneum into the blood stream or into the lymphatics emptying into the thoracic duct. Lesser grades of peritonitis prevented the passage of B. coli into the blood stream but did not prevent their passage into the lymphatics. He stated the colon bacilli, injected into the peritoneum which contained a transudate, passed rapidly and in great numbers into the chyle from the thoracic duct and directly into the blood stream. He assumed, by analogy, that in well developed general infectious peritonitis bacteria did not pass directly into the blood stream or into the lymphatics draining into the thoracic duct, and that the major problem in peritonitis did not concern itself with the development of a septicemia. It is also possible to conclude from his experiments that in the normal peritoneum and in the lesser grades of peritonitis B. coli entered the blood stream and a bacteremia was present. (25)

In 1928, David and Sparks (27), injected Diphtheria toxin intraperitoneally into the peritoneal cavities of dogs. Their work and results has been previously described under Absorption. They felt from their experiments that in the early hours of

peritonitis the factors of absorption of toxins and bacteria into the circulation directly and via the lymphatics was the dominant factor of danger, while later absorption from the peritoneum became less important and local conditions, such as paralytic ilieus gained the ascendancy in the picture. They also concluded that the very severe toxemia associated with general peritonitis must be caused in some degree by absorption of bacterial toxins from the peritoneum.

Herrmann (46), in 1928, concluded that peritonitis was a defensive reaction to bacterial infection, and depended for its development on the presence of basic immunity. Such immunity was apparently local peritoneal immunity and could be produced by the intraperitoneal injection of vaccines. They decided that Streptococci and Bacilli coli, growing symbiotically, probably represented the most important pathogenic components of the fecal flora of dogs. Their work tended to show that intraperitoneal vaccination with these organisms confered a high degree of resistance to subsequent fecal soiling.

Mann (58) discussed Herrmann's experiments and stated that two hypotheses were given for death in peritonitis; either death was caused by the absorption of bacteria and toxins, or the peritoneal reaction and plastic exudate produced stasis of the gastro-intestinal tract and death resulted in intestinal obstruction. He did not believe that plastic exudate prevented

absorption from the peritoneal cavity because experimental peritonitis in animal had demonstrated that with a thick plastic exudate many of the dyes would pass from the peritoneal cavity as readily as in a normal animal. He stated that Dr. Herrmann's experiments suggested that while dyes were absorbed in animals with peritonitis perhaps as readily as in the normal animal, this was not true of bacteria.

In 1929, Steinberg and Snyder (96) concluded from their experiments in dogs that active immunication with living colon bacilli, followed by fecal peritonitis, resulted in the first twenty-four hours in a cellular reaction which was predominantly polymorphonuclear. The bacteria in the peritoneal cavity were phagocytosed largely by polymorphonuclears, and the phagocytosis was practically complete at the end of the first eight hours after the onset of peritonitis. The polymorphonuclears, evoked by colon bacillus immunization, acted as phagocytes of other bacteria in the peritoneal exudate than B. coli. The difference in the cellular reaction the the peritoneal exudate, the peripheral blood and the tissue between a non-immune and an immune animal, under the conditions of these experiments, was quantitative. They concluded that the immune animal mobilized polymorphs more rapidly and mobilized a far greater number of them than the non-immune animal. They demonstrated that the factor in the colon bacillus that evoked this cellular activity was destroyed entirely

by formaldehyde.

Steinberg and Snyder (96) also stated that the presence of white cells in the peritoneal exudate of immune animals with peritonitis apparently represented a local manifestation of a general mobilization of these cells. The polymorphs in the general circulation were apparently the first cells to appear at the point of bacterial invasion, and therefore they probably represented the first line of cellular defense against the bacterial infection.

Buchbinder, Heilman and Foster (16), in 1929, stated that there were two mechanisms in wide-spread peritonitis, either one of which could produce death: obstruction through ileus, and toxic absorption from the inflamed peritoneal surface and the contained exudate. They believed that in the absence of ileus, it might be assumed that the toxemia resulted from the bacteria and their products, and that the resorption of the exudate itself played a powerful, if not a leading role, in the production of the toxemia.

They concluded from their experimental work on dogs that the rapidity of absorption, in the largest measure governed the prognosis of acute, diffuse peritonitis and that, fibrin was the most important factor in controlling the rate of absorption. They believed that fibrin was diminished or absent in the more virulent cases because of dilution of the exudate. They

demonstrated that streptococci were most commonly identified with this abundant exudate and the accompanying virulent course of the disease. They concluded that the addition to such an inflammatory exudate of a transudate produced by the intraperitoneal injection of hypertonic dextrose solution produced a more rapid spread of the infection and insured the lethal outcome. They decided from their experiments that an abundance of thin exudate served to prevent ileus by mechanical isolation of intestinal loops. (16)

In 1931 Steinberg (88) stated that of the several current conceptions regarding the cause of death in acute diffuse peritonitis, that of toxemia was the most commonly accepted. He wrote that until 1926 no experimental evidence was offered to substantiate such a conception. At that time Steinberg and Ecker (93) produced the death of rabbits following the intraperitoneal injection of broth cultures of B. coli. They stated that rabbits that received colon bacillus antiserum intravenously, in addition to the broth culture of colon bacillus intraperitoneally, survived. However, Steinberg later demonstrated (88) that the introduction of broth culture of colon bacillus into the peritoneal cavity of rabbits and dogs might result in the death of the animals, but not necessarily in peritonitis. He believed that since the inflammatory peritoneal lesion was either absent or doubtful and the value of the colon bacillus antiserum was still questioned,

the experiments of Ecker and himself were merely suggestive but by no means conclusive of a bacterial toxin being responsible for death in peritonitis.

Steinberg (88) stated that a second experimental evidence supporting toxemia as being the cause of death in acute diffuse peritonitis, was offered by Williams (107) who administered B. welchii antitoxin to patients with clinical evidences of a severe peritonitis. Williams obtained a large percentage of survivals in patients thus treated. He found a proliferation of B. welchii in the small intestine of patients with a low intestinal obstruction and a similar picture in the small bowel of dogs with an experimentally obstructed bowel. Williams hypothecated that death in intestinal obstruction and peritonitis was at least partially due to the absorption of B. welchii toxin from the stagnant bowel. Again Steinberg (88) believed that these experiments were suggestive but were inconclusive. Steinberg believed that the patients might have recovered without treatment with B. welchii antitoxin. Furthermore, he stated that William's patients had peritonitis secondary to intestinal obstruction, and consequently other factors might be present that were not found in primary peritonitis.

Steinberg (88) stated that the nature of the toxic action was a matter of much speculation. He wrote that the theory that a bacterial toxic substance paralyzed the medullary vasuclar

centers received an additional stimulus by the work of Manenkow. (59) This investigator injected cultures of staphylococcus into the serosa of the stomach of rabbits with a resulting diffuse peritonitis and death of the animals. Similar amounts of a culture of staphylococci introduced into the serosa of the colon resulted in a localized peritonitis and survival or prolongation of the life of the animals. Manenkow assumed that since the stomach has a direct nerve-lymphatic connection, death was due to the passage of the toxin along the lymphatics of the nerve with the subsequent action on the medullary centers. Kirschner (56) pointed out that the fall in blood pressure in peritonitis occurs only a short time before death, and he doubted that the medullary vascular centers were affected by the toxins.

Steinberg (88) stated that among other theories for which there was little or no evidence there was one of the peritoneal cavity with injury and stagnation of the portal circulation.

Steinberg (88) also reviewed some of the literature on the conception that the intestinal paralysis was a deciding factor in the fatal outcome in diffuse peritonitis. This will be further mentioned in the division of this thesis dealing with intestinal obstruction.

Steinberg (88) concluded from his experiments on dogs that in acute diffuse peritonitis under the conditions of his experiments, death was due to the toxin produced by the bacteria

present in the peritoneal cavity. Intestinal paralysis, intestinal stasis and intestinal bacteria, under the conditions of his experiments played no part in the death of the animal. He concluded that the administration of the corresponding antitoxin averted death in acute diffuse peritonitis. He believed that in the absence of an antitoxin that was capable of neutralizing the toxin, two factors were responsible for the survival of the animal with peritonitis: (a) rapid phagocytosis; (b) a sufficient large number of polymorphonuclears to cope with the invading bacteria. He assumed that in the presence of these two factors, the formation of toxin by bacteria was prevented and the death of the animal was averted.

He also concluded that the bacterial toxin had no inhibitory effect on the number or on the rapidity of appearance of the polymorphonuclear leukocytes. However, he did believe that the toxin interfered with complete phagocytosis of the bacteria by the polymorphonuclear leukocytes. (88)

In 1932 Steinberg (89) after experimenting with dogs concluded that protection against peritonitis could be obtained by intraperitoneal injection of B. coli which was greater with heat-killed organisms. He did not believe that it was a true immunity but rather a hyperleukocytosis and phagocytosis due to coincident presence of polymorphs at the site of infection.

In 1933, Rademaker (78) experimented in animals with the

effect of blood in experimental peritonitis. It would seem that from his results that blood injected with organisms not only gives no predisposition to peritonitis but offers a moderate degree of protection against it, at least in the case of the colon bacillus. The control animals receiving a minimal lethal dose all died, yet only two of sixteen receiving a minimal lethal dose with varying amounts of blood died from peritonitis, and these animals received a small amount of blood. That this effect was not the result of mechanical dilution was later proven by the addition of broth in varying quantities to minimal lethal doses of bacteria without affect. Peritoneal smears also indicated that blood seemed to hasten the disappearance of bacteria from the peritoneum. He thought that this might be by reason of greater rapidity of absorption or by increased rapidity of destruction of the bacteria. He concluded that this power of protection was not sufficiently great, nor could anology be drawn with sufficient clarity to human peritonitis to justify its clinical application in anyway at present.

In 1933, Steinberg, Kobacker and Russell (95) experimented with dogs to see what part functional heart failure played as a cause of death in peritonitis. They observed that the changes in the electrocardiograms in fecal and B. coli peritonitis were identical and indicated myocardial damage. Histological sections of the peritoneum revealed dilated capillaries engorged with

blood. This marked dilation and engorgement became apparent within one hour after the onset of the infection. He stated that in a former article they demonstrated that the cause of death in peritonitis was due to liberation of soluble bacterial toxic substances within the peritoneum. With the observation of dilated and engorged peritoneal capillaries, the cause of the cardiovascular collapse was suggested, by them, to be due both to the toxic action of the soluble toxins and a local peritoneal stagnation of blood.

David and Loring (26), in 1933, stated that probably the most serious types of peritonitis were those in which not only virulent micro-organisms were present in the peritoneal cavity, but in addition, culture material for the micro-organisms to develope on. They believed that this set of conditions was seen in various types of perforative peritonitis or in lesions accompanied by the death of tissue, such as postoperative peritonitis or peritonitis with strangulated hernia. They attempted to produce this type of peritonitis in dogs by the introduction of bacteria on culture mediums into the tissues of dogs and obtained a severe type of infection which they thought was due not only to the bacteria introduced but also, to secondary invaders, chiefly B. welchii. They presented experimental evidence which indicate that the secondary invading bacteria were already present in the tissue in an avirulent state but were activated to growth by the

infection introduced. They gave the following practical significance of these observations: (a) the importance of the death of tissue in surgical procedures acting as a favorable culture medium for the development of bacteria already present in the tissue or introduced at the time of the operation; (b) the suggested mechanism of the development of some secondary infections; (c) the increase of the virulence of B welchii when growing in symbiosis in living tissue with pus-producing bacteria.

In 1934, Harmon and Harkins (42) stated that there was little experimental work to substantiate the clinical belief that death from peritonitis was due to vasomotor collapse incident to absorption of toxins from the peritoneum. It occurred to them that the vaso-motor system of the host might be less sensitive than that of a normal animal to the toxic substances developed in the peritoneal cavity. Experimenting on dogs, Harmon and Harkins found that in those cases where a significant drop in blood pressure was obtained upon injection of the peritoneal washings into a normal dog there was a heavy growth of Escherichia coli with or without a growth of an obligate anerobe resembling Clostridium welchii.

Meyer (67) stated, in 1934, that Wegner was the first to study the reactions of the peritoneum in a comprehensive way. He credits Wegner with demonstrating that the peritoneum absorbed with impunity a considerable quantity of putrefying material and that he also showed if such material in sufficient amounts could

be introduced, death by intoxication might result before the defensive functions of the peritoneum could be mobilized. If, for any reason, absorption of non-fatal doses was delayed, time might be had for the bacteria to multiply and the peritoneum thus become the site of a rapidly developing colony.

Meyer (67) believed that Wegner set forth several fundamental factors; the possibility of death by absorption of toxins before reactive factors could be set into action, that is, before peritonitis could develop; that small doses of bacteria might be destroyed before they could do harm; also, that stagnating fluid in the peritoneal cavity would favor the development of bacteria.

Meyer (67) experimenting on dogs came to the conclusion that retroperitoneal tissues were less resistent to the invasion of organisms than was the peritoneum. If this is true, spread of the infection from the peritoneum to the retroperitoneal space would probably be a factor in the cause of death from peritonitis.

Bargen and Dixon (7), in 1935, reviewed the experimental work on certain phases of experimental peritonitis and made the following statement, "Peritonitis has been one of the feared causes of death following operations upon abdominal viscera, or following perforation or other injury of an abdominal viscus. Recent experimental studies have raised the question whether it is peritonitis, as such, that we should fear, or a toxemia in which peritonitis is only the evidence of a defensive mechanism of the

peritoneum. If all the defensive mechanisms of the body are available, spilling of intestinal contents in the abdominal cavity may not be the serious affair we have been led to believe. If the defensive mechanisms are not all available, such spilling, even if minute, may be the instigator which sets in motion the necessary development of a fatal toxemia associated with peritonitis. Bacteria, such as the streptococcus and colon bacilli, are always present in the walls of the intestine about a neoplasm which has invaded the wall of that portion of the intestine. These bacteria multiply and spread rapidly in the absence of adequate defence, and cause the real damage. If unusual dissemination of these bacteria with resulting peritoneal irritation occurs, and if adequate cellular reaction if not at hand, splinting and distention of the intestine, and retention of toxins follow. Elaboration of poisonous toxins then ensues, and if the process cannot be reversed in time, death associated with peritonitis will follow."

In 1936 Steinberg (90) reported on his work with B. coli and gum tragacanth. He deducted from his experiments that gum tragacanth successfully retained the bacteria within the peritoneal cavity. This retention resulted in a local outpouring of a large number of polymorphonuclear leukocytes within three hours following the introduction of B. coli suspended in gum tragacanth. When viable, virulent bacteria which produce peritonitis were introducted intraperitoneally or the appendix was ruptured and feces

smeared over the peritoneum, under the conditions of his experiments, the offending bacteria were rapidly phagocytosed by the polymorphonuclear cells. He assumed that the rapid bacterial phagocytosis was responsible for the large percentage of survivals of the animals from an otherwise lethal peritonitis. He believed the difference between a normal, non-protected, and protected animal in withstanding a peritoneal infection was largely a quantitive leukocytic factor. In the surviving animals the phagocytosis was accomplished rapidly prior to the production of soluable toxic substances, which were assumed to cause abnormal changes in the vascular system and possibly other organs and death.

In 1937 Harmon and Harkins (43) stated that one of the common hypotheses of the cause of death from peritonitis was that of vasomotor collapse incident to the absorption of toxins from the peritoneum. They stated that it had long been assumed that causative micro-organisms were the source of the toxins, with the peritomeum acting merely as an absorptive membrane.

Harmon and Harkins (43) experimented with dogs and demonstrated the presence of a vasodepressant toxin occurring in the peritoneal cavity coincident with the development of suppurative peritonitis. Their earlier experiments in this series demonstrated that a definite time was required for the development of this toxic product. The toxins or toxin seemed to appear earlier when the open intestinal segment was placed high in the gastro-

intestinal tract, where opportunity was greatest for soiling the upper portion of the abdomine. The nature of the experiments was such as to rule out effectively the possibility of inherent toxicity of the pancreaticoduodenal secretion. No similar substance was demonstrated in the exudate of bile peritonitis prior to death, or in the normal peritoneum or the soiled peritomeum without diffuse suppruative inflammation.

The picutre of shock produced by these toxic peritoneal fluids was a primary type of shock, since the blood pressure was often low while the bleeding volume approximated that of normal animals.

Harmon and Harkins (43) in the same year experimented with dogs in an effort to determine the nature of this toxic vasodepressant substance. They concluded that the toxic vasodepressant substance that was present in the peritoneum in many instances of experimental suppurative peritonitis was non-protein in nature and occurred in greatest concentration in extracts prepared from the centrifuged sediment obtained from peritoneal washings.

They further concluded that the soluable toxic substance present in bacteria free filtrates of colon bacillus produced a powerful vasodepression after an incubation period following its injection. The toxic substance from this organism was similarly active after intraperitoneal injection in some instances. (43)

By the bleeding volume method and by observations on cellular and hemoglobin concentration in the blood, the shock syndrome

produced by administration of toxic filtrates of the colon bacillus was found to be a primary type, analogous to that produced by the experimental injection of other vascular poisons such as histamine.

Vasodepressant substances with an almost immediate time of action were also produced by the staphylococcus, by strains of streptococci and by cultures of the Clostridium welshii and Clostridium sporogenes.

Harmon and Harkins (43) stated that the exact role that these substances played in an actual instance of peritonitis was not elucidated in their experiments. They thought it not inconceivable that they could contribute to the final, fatal decline in this disease.

In 1938 Steinberg and Dietz (92) experimented with albino rats and dogs on the inflammation of serous surfaces. They concluded that there was no apparent relationship between the cell sequence and the hydrogen ion concentration of the inflammatory exudate produced under the conditions of their experiment. They demonstrated that the body tended to bring to its usual concentration of hydrogen ions the concentration of hydrogen ions of injected fluids whether these were more alkaline or more acid. They believed that this occurred whether the tissues were normal or subject to an inflammatory process of short or long duration. They thought that there is a variability of the pH of the normal peritoneum. This variability was either inherent in the peritoneum

and due to the individual differences in the members of the same animal species or dependent on the technical equipment and methods. The range of variability was, however, smaller in the animal with an inflammatory process in the peritoneum than in the normal animal.

Steinberg (91), in 1938 demonstrated that the polymorphonuclear leukocytes produced in the peritoneal or pleural cavity of one animal (dog) might be transferred to the peritoneal cavity of another animal of the same species or another species (rabbit) with preservation of the phagocytic function. The phagocytic function of the transferred leukocytes was capable of preventing death from an otherwise fatal peritoneal infection as was produced in this experiment. He concluded that constituents other than intact polymorphs in the exudate played little or no part in the preservation of life in these experiments.

Coller and Brindman (18), in 1939, experimented with dogs to see whether or not the peritoneum of the dog could be made immune, that is, was it protected by preliminary surgical intervention. They concluded that under the conditions of their experiments, and judged on the basis of complete recovery or survival time, there was an enhanced resistance to infection resulting from the surgical manipulations in the peritoneal cavity. This was insufficient to protect the animal against a severe form of peritonitis. On the basis of their observations, it was their opinion that survival was related to the character

and degree of the cellular response in the peritoneum. They concluded that phagocytosis in the peritoneal cavity was an important factor in survival of the dogs with diffuse acute peritonitis. The polymorphonuclear leukocyte seemed to be the important cell in the phagocytosis and consequent recovery.

In their experiments none of the dogs survived in which the organisms did not disappear within twenty-four hours after infection. In some of the dogs the organisms disappeared in a shorter time, but they did not survive. They assumed in these dogs that death was due to toxemia resulting from the overwhelming toxin injected with the organisms and that death was not due to toxins liberated as a result of bacterial proliferation. However, since only those dogs in which there was a rapid disappearance of organisms survived, and since this occurred only in those with a relatively good cell response in the peritoneal cavity, it was assumed that phagocytosis was an important factor in the survival of these animals. Furthermore, on the basis of percentages of cell types found in the peritoneal exudate, it was assumed that the polymorphonuclear leukocytes were of prime importance in spite of the fact that the few mononuclears present showed a greater capacity for phagocytosis as evidenced by the relatively greater number of engulfed organisms. (18)

In 1940, Altemeier and Jones (2) treated a group of fourty-two rabbits with approximately ninety percent of an erythema dose of X-ray and then innoculated the rabbits intraperitoneally with

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with equal amounts of mixed highly virulent bacterial culture. They found that the degree of protection of the treated animals rose sharply three weeks after irradiation and reached its maximum between the fourth and sixth week. They state that a study of their own experiments and a review of the literature failed to explain the manner in which the above protection was brought about.

SUMMARY

Most of the work on diffuse peritonitis has been experimental work on the cause of death in peritonitis. All of the work presented in this thesis is based on animal experimentation. The ideas of the various authors summarized below are all based on experimental work. Since a more detailed statement and the results of each author's experimental work are contained in the body of the thesis, only a short resume will be given here.

David and Sparks (27) concluded from their work that in the early hours of peritonitis, absorption of toxins and bacteria was the dominant factor in death from peritonitis, but as the infection progressed, paralytic ileus became a more dominant factor in the cause of death. Mann (58) concluded that death was due either to bacteria and their toxins or to intestinal obstruction. Buchbinder, Heilman and Post (16) believed that death resulted from a toxemia due to an absorption of bacteria and their products or resorption of exudate. They also believed obstruction due to paralytic ileus to be a factor.

Steinberg (90) believed that the primary cause of death was a failure of the polymorphs to phagocytose the invading bacteria before bacteria could produce toxic substances. Wagner (67) believed that death by absorption of toxic bacterial products could take place before reactive factors could be set into action. Bargen and Dixon (7) thought that death resulted from the absence of adequate cellular defense which allowed

bacteria to elaborate poisonous toxins. Coller and Brindman (18) believed that survival was related to the character and degree of cellular response. The polymorphonuclear seemed to be the important phagocytic cell.

Whipple (106) concluded that the main cause of death was proteose intoxication. Harmon and Harkins (42) believed that the production of a non-protein vasodepressant substance which caused a primary type of shock was an important factor leading to death.

Steinberg, Kobacker and Russell (95) believed that death was due to the liberation of a soluable bacterial toxin within the peritoneum with accompanying cardiovascular collapse. Manenkow (59) believed that death was due to passage of toxins along the lymphatics of nerves with subsequent action on the medullary centers.

Williams (107) concluded that death was due to B. welchii toxin from the stagnated bowel. David and Loring (26) concluded that in perforative peritonitis secondary invaders chiefly B. welchii played an important part.

The following authors gave opinions concerning the protection of the animal from peritonitis. Steinberg and Goldblatt (94) believed that rapid absorption of invading organisms was associated with recovery. Herrmann (46) believed that peritonitis was a defensive reaction and depended upon local peritoneal immunity. He demonstrated that he could vaccinate dogs with

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streptococci and B. coli and develop in dogs a high resistance to fecal soiling. Steinberg and Snyder (96) believed that an adequate polymorphonuclear response would prevent peritonitis in dogs. Buchbinder, Heilman and Foster (16) concluded that rapidity of absorption governed the prognosis in peritonitis in dogs. Rademaker (78) demonstrated that varying amounts of blood injected with a minimum lethal dose of B. coli prevented death. Altemeier and Jones (2) concluded that roentgen rays could be used to protect rabbits from peritonitis.

PART III

INTESTINAL OBSTRUCTION

Whipple (106), in 1916, experimented with dogs and decided that there was a definite proteose intoxication in intestinal obstruction and allied conditions, in general peritonitis, either septic or sterile, and in acute hemorrhagic pancreatitis. He believed that proteose intoxication was the most important factor in the general intoxication noted in these conditions. He thought that the proteose was derived from the tissues or tissue proteins of the host.

In 1925 Budde (14) published an article illustrating the device with which the eventurated loop of mouse intestine was kept functioning while laved with fluid. He thus tested the peritoneal exudate from thirty patients with peritonitis. A primary paralysing action on the bowel wall was apparent only in cases in which in addition to the colon bacillus infection there was a profuse anaerobic flora. With purely aerobic infection, the paralyzing action seemed to proceed from toxic injury to the vasomotor centers.

Williams (107), in 1926, stated that he believed that the similarity between the general clinical manifestations of cases of acute peritonitis and acute obstruction was widely admitted. He believed that it was paralytic obstruction which produced the characteristic clinical aspects in the later stages of most fatal cases of acute peritonitis. Also, that taking the features common to the two conditions, though there is variation in individual intensity, collectively they bore a striking resemblance

to the clinical features of the toxemia associated with gas gangrene.

He hypothesized that the toxemia in cases of intestinal obstruction, whether organic or secondary to peritonitis, resulted, in part at least, from the absorption of the toxin of B. welchii, due to the proliferation of this anaerobe in the stagnant contents of the small intestine.

Williams (107) supported his theory by experiments with human subjects and dogs. He concluded that there was proliferation of B. welchii in the small intestine in cases of intestinal obstruction and peritonitis in human subjects and in these diseases experimentally produced in dogs. He also tended to show that B. welchii toxin was present in the small intestine in intestinal obstruction and peritonitis in human subjects and in these diseases experimentally produced in dogs. He did not find the toxin in the normal small intestinal contents, nor in contents of the large intestine, even when obstructed, in human subjects. The occurrence of hemolysis, the microscopical changes in the heart and liver of the fatal cases and the clinical aspect of his experimental cases, he thought, was compatible with the absorption of B. welchii toxin. Williams made clinical tests with B. welchii antitoxin and concluded that he obtained an improvement of the general mortality rate in each series of cases.

Orr and Haden (74), in 1928 experimented with the chemical changes in the blood of the dog in experimental peritonitis.

They had previously recorded the chemical changes in the blood occurring in pyloric and intestinal obstruction and since distension of the intestine paralytic ileus are often associated with general peritonitis, they thought that a study of the blood chemistry of general peritonitis might be valuable. They concluded that the changes in the blood chlorides, urea nitrogen and non-protein nitrogen resembled those observed in pyloric and high intestinal obstructions, but in the latter two conditions an alkalosis developed which was not observed in general peritonitis. They stated that, as a whole, the similarity between the chemical changes of high intestinal obstruction and general peritonitis suggested that the cause of death might be, at least in part, the same in the two diseases.

Morton and Stabins (70), in 1928, reported experimental evidence that the antitoxin of B. welchii has a specific action in the relief of intestinal obstruction in dogs.

Copher, Stone and Hildreth (19), in 1929, concluded from their experimental work on dogs that B. welchii antitoxin should be given a clinical trial as an adjuvant in the treatment of general peritonitis.

In 1930 Alvarez (3) after experimenting with rabbits and cats concluded that certain forms of paralytic ileus might perhaps be due to a blockage by toxins or by nervous inhibition of the synapses between the conducting neurones in Auerbach's plexus. Tonic contraction rings which sometimes produce intestinal

obstruction might well be produced by a loss of function in another group of neurones which presumably were attached directly to the muscle.

Scott and Wangensteen (84), in 1932, wrote that the lethal factors in strangulation obstruction were believed by most workers to be due to the absorption of toxins which were elaborated within the lumen of the strangulated loop or within its walls. If this was the case, they decided that any toxemia that might result would be secondary to the absorption of these toxins into the general system. This implied either absorption through the mesenteric lymphatics draining the loup, the mesenteric veins or else transperitoneally. However, Scott and Wangensteen thought that there was little evidence that in a strangulation of any magnitude the veins or lymphatics from the strangulated loop were still capable of absorbing fluids or other products. They decided if there was any absorption, it must be transperitoneally.

Scott and Wangensteen (84) concluded from their experiments that the peritoneal fluid obtained from dogs dying of strangulation obstruction was non-toxic, when injected intravenously into normal dogs provided the strangulated loop was not ruptured or about to rupture and the fluid did not give off a foul odor. They did not deny that the peritoneal fluid might contain toxic products, but they were not demonstratable, at least, on injection into other dogs, until rupture of the loop.

In 1934 Gatch, Trualer and Lyons (37) concluded from their

experiments that the normal content of the bowel in dogs and in human subjects was always toxic when injected intravenously into animals. They admitted the presence of many substances which might contribute to this toxic property, but they thought that the chief source of the toxin appeared to be the pancreaticoduodenal secretion. They believed that the content of the obstructed bowel or of an isolated obstructed loop was less toxic than the normal intestinal content, unless the obstructed segment received and retained in concentrated form the pancreaticoduodenal secretions, in which case its toxicity seemed to exceed or equal that of the normal contents.

Bargen and Dixon (7), in 1935, referred to the work of Dragstedt of Chicago, and of Burget of Portland, Oregon. These investigators isolated loops of intestine in the dog, closing off both ends and fastening the lips to the anterior abdominal wall. The lumen of the intestine, from which such a loop was isolated was reestablished by end to end anastamosis. The continuity of the fecal stream was thus maintained but a portion of the intestine was isolated in such a manner that the portion which was formed in this loop could not be evacuated by the animal. Within a short time after such a loop was emptied and following the recovery of the dog, it filled up with a dirty, grey-brown material which contained innumerable bacteria. If nothing was done about this material, a severe toxemia developed, and the dog died. If the loop was emptied periodically by needle aspiration through the

abdominal wall, complete relief of all symptoms of toxemia resulted, and the dog remained well.

Among the numerous factors which have been considered significant in the death from acute intestinal obstruction, the nervous system has been alluded to recently by Herrin and Meck (45) and by Taylor, Weld and Harrison (97). These investigators claimed to have prolonged the survival time of dogs, dying from distention of an intestinal loop by denervation of the adjoining mesentery.

In 1937, Fine, Rosenfeld and Gendel (33) worked on this problem and concluded that the survival time of cats with obstruction and gaseous distention of the small intestine was inversely proportional to the level of the pressure in the lumen of the bowel. Preliminary exclusion of the extrinsic nerve supply of the gastro-intestinal tract did not influence the survival time of such animal. They did not believe that fluid accumulation in the intestinal lumen, bowel wall and peritoneal cavity in these animals was sufficient to account for their rapid death. They reported that extrinsic denervation of the gastro-intestinal tract did not significantly alter the fluid volume in the intestine or peritoneal cavity.

Aird (1), in 1938, experimented with intestinal obstruction in dogs. He concluded that in high intestinal obstruction there was at the time of death a reduction in blood volume and in plasma volume due apparently to the dehydration and which with

demineralization, was the dominant factor in causing death. In low small intestinal occlusion death occured without reduction of the blood volume. If, however, the animal lived until dilatation and congestion of the obstructed bowel supervened, then the blood volume was often markedly reduced at the time of death, but not sufficiently reduced to be solely responsible for death. The reduction in blood volume seemed to be partly due to loss of whole blood into the congested intestinal vessels, and partly due to dehydration, since the plasma loss was greater than the cell loss.

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The work on experimental intestinal obstruction in animals has not been extensive. Most of this experimentation has been done in conjunction with experimental peritonitis. All of the conclusions reported here are based on animal experimentation. Most of the experimental work in this field has centered around the cause of death in intestinal obstruction. A short summary of most of the articles presented in this section of the thesis is given below.

Wipple (106) believed that a proteose intoxication was the cause of death in intestinal obstructional absorption of B. welchii toxin from the intestinal content of dogs and man. He supported his view by extensive experimental research.

Williams (107) concluded that death was due to absorption of B welchii toxin from the intestinal content of dogs and man. He supported his view by extensive experimental research.

Hargen and Dixon (7) believed that death resulted from absorption of toxic material from the lumen of the obstructed intestinal loop.

Aird (1) concluded that in high intestinal obstruction death was due to demineralization and dehydration. He also concluded that in low, small intestinal obstruction this factor played a lesser part in causing death.

Scott and Wangensteen (84) were of the opinion that if there was any absorption from an obstructed bowel, it must occur

transperitoneally. Their experiments on dogs showed that the peritoneal fluid of dogs dying from strangulation obstruction was non-toxic when injected intravenously provided that the strangulated loop had not ruptured.

Gatch, Trualer and Lyons (37) concluded that the contents of the obstructed bowel were less toxic than the normal contents unless the obstructed segment retained, in concentrated form, the pancreaticoduodenal secretions.

Fine, Rosenfeld and Gendel (33) demonstrated that the survival time of cats with gaseous distention of the small intestine was inversely proportional to pressure in the lumen of the bowel. They did not believe that preliminary exclusion of the extrinsic nerve supply influenced the survival time.

The following authors did not attempt to explain the cause of death in intestinal obstruction in animal, but they did report interesting findings from their experimental work on intestinal obstruction.

Budde (14) using peritoneal exudate from patients with peritonitis demonstrated a primary paralyzing action on the bowel wall of mouse intestine in cases in which both B. coli and a profuse anaerobic infection was present. He showed also, that a purely anaerobic infection seemed to damage the vasomotor centers.

Orr and Haden (74) noted a similarity between the chemical

changes in the blood in high intestinal obstruction and general peritonitis. He believed that the cause of death might be the same in both conditions.

Morton and Stabins (70) and Copher, Stone and Hildreth (19) believed that the antitoxin of B welchii had a specific action in the symptomatic relief of intestinal obstruction in dogs.

Alvarez (3) worked on rabbits and cats and came to the conclusion that paralytic ileus might be due to the action of toxins.

PART IV

BILE PERITONITIS

BILE PERITONITIS

Manson and Eginton (60), in 1938, stated that, "although bile peritonitis is relatively uncommon, the mortality rate is excessively high, usually given around fifty percent; it has been shown that it accounts for a significant number of deaths following operations upon the biliary tract. As soon as the importance of this hitherto rarely recognized condition was demonstrated, numerous experimental attempts were made to ascertain the mechanism of death in bile peritonitis."

There was little American and English experimental work done on bile peritonitis until 1926. At that time Wangensteen (103) did some experimental work on the escape of sterile bile into the peritoneal cavity.

Wangensteen (103) justified his work by stating that the ominous import of the discharge of infected bile into the peritoneal cavity following perforations in the inflamed extra-hepatic bile passages was generally conceded. He gave numerous case reports showing the high mortality in this condition.

He continued by showing that the significance of the escape of sterile bile into the peritoneal space was not so generally agreed upon. Some of the early writers on this subject believed that the escape of bile into the peritoneal cavity was regularly followed by a fatal outcome. He believed that more recent observations would lead us to believe that the leakage of bile into the peritoneal cavity is attended with no great danger.

Wangensteen (103) summarized his experimental work on dogs by stating that the leakage of sterile bile into the peritoneal cavity was not innocuous. The experimental animal died of cholaemia due to the toxic action of the bile salts within a short time when well functioning biliary fistulas from which bile escaped into the peritoneal cavity were established. He also believed that the escape of any considerable amount of sterile bile into the peritoneal cavity of man following subcutaneous rupture of the normal bile passages, unless removed, was always fatal. He stated that no instance of recovery in such an event had been recorded without removal of the bile by operation or puncture. He believed that the loss of bile from the intestinal tract was a contributing factor, but at the same time probably also accounted for the delayed death in untreated cases, through a diminution of bile salt production when bile failed to reach the intestine. He stated that the more rapid death in the dog following the extravasation of bile was partially due to the fact that dog bile is largely the more toxic taurocholic acid, whereas, human bile contained relatively more of the less toxic glycocholic acid.

In 1928, Horrall and Carlson (50) stated that it was well established that bile in sufficient quantities was toxic by the oral, the subcutaneous, the intravenous and the intraperitoneal routes. They wrote that the peritonitis and death that followed the introduction of large quantities of bile into the peritoneal

cavity had been ascribed to bacteria as well as to the toxic constituents in the bile itself. Horrall and Carlson (50) reviewed the literature and stated that on experimental evidence, toxic actions had been ascribed to the following bile constituents: the pigments, the cholesterol and the bile acids. They referred to the most recent of these reports stating that Bouchard (10) King and Stewart (54), King, Biglow and Pearce (53) and de Bruin (13) concluded that the pigment acted as the toxic agent in bile or was more toxic than the other constituents. On the other hand, Raywoch (79), Gilbert and Herscher (38) believed that if the pigment had any poisonous action at all it was very slight. They quoted Danilewsky (23) and Flint (34) as attributing a toxic action to the cholesterol. Fasciani (32) was unable to confirm this, even though he injected large amounts. Rohrig (83), Traube (99), de Bruin (13) and Sellard (85) attributed various poisonous actions to the bile acids. Landois (57), King and Stewart (54) and others concluded that the bile salts were either feeble poisons or non-poisonous. Boisson (9) thought that the toxicity of bile was due to "impurities" which could be removed by filtering.

Horrall and Carlson (50) made the following conclusions from their experiments on dogs: (a) Bile was toxic when injected intraperitoneally, subcutaneously and intravenously; (b) when bile was injected in sufficient quantity to cause death in

twenty-four hours, the presence of bacteria in the bile did not modify its toxicity; (c) the toxicity of bile was not modified by boiling or freezing; (d) bilirubin was non-toxic; (e) bile dialysate had the same toxicity as whole bile; (f) the non-sialysate portion of bile was non-toxic; (g) pure bile acids were non-toxic due to their insolubility; (h) the cholate portion of the salts of the bile acids, such as sodium glycocholate and sodium taurocholate, were toxic.

Horrall (49) in 1929, did further experimental work on dogs and concluded that bile from the gallbladder injected into the peritoneal cavity of dogs in amounts of five c.c. or more per kilogram of body weight caused peritonitis and death within twenty-four hours. Bacteria were not essential and did not modify the course of bile peritonitis when bile was present in a sufficient quantity to cause death within twenty-four hours.

In 1931, Rewbridge (80) disagreed with Wangensteen and Horrall and stated that experimental data shows that the cause of death in bile peritonitis was not due to the circulation of the bile salts in the blood at toxic levels because no increase of bilirubin or bile salts was found even though the dogs were moribund as the result of peritonitis. Rewbridge (80) believed that the cause of death must be due to the local action of the bile in the peritoneal cavity and the secondary changes produced by it. He experimented with bile peritonitis in dogs in an effort to prove this assumption and made the following conclusions:

(a) bile peritonitis in dogs was an infection; (b) Bacillus 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; (c) a peritonitis identical with bile peritonitis was produced by Bacillus welchii; (d) examination of the blood for bilirubin and bile salts was of no value in determining the amount of drainage of bile into the peritoneal cavity; (e) these conclusions were confined to the action of bile on the dog's peritoneum.

Mentzer (65), in 1934, experimented with bile peritonitis in dogs and made the following conclusions: (a) experiments showed that bile peritonitis in animals was not comparable to that in man; (b) diffuse, sterile bile peritonitis had rarely, if ever, been found as the cause of death in man; (c) extravasated sterile bile was rapidly encysted in man and then became relatively innocuous; (d) infected bile which had become spread diffusely over the peritoneal cavity proved fatal unless promptly drained by surgical measures. Death ensued from pyogenic rather than chemical peritonitis.

In 1935, Blalock (8) obtained bile, pancreatic juice, gastric juice, and duodenal secretion by cannulating the various structures. The juices were injected with a syringe and needle into the peritoneal cavities of other dogs. The following results were obtained from the injection of bile: (a) bile that was

recovered the first several days following the cannulation of the common duct exerted more ill effects when injected into the peritoneal cavity than that which was collected later. Bile apparently exerted more untoward effects than an equal quantity of pancreatic juice; (b) eleven experiments were performed in which equal quantities of uninfected bile and pancreatic juice were injected into the peritoneal cavity -- four of the animals died and it seemed quite definite that the combination of bile and pancreatic juice was more toxic than an equal volume of either of them; (c) studies on the cardiac output and blood pressure were performed before and following the injection of bile or pancreatic juice of both. Although results were not identical in all cases, the major early alteration consisted of a decline in the blood pressure, as is found in primary shock, and the subsequent change consisted of a greater drop in the cardiac output than in the blood pressure as is found in secondary shock.

Harkins, Harmon, Hudson and Anderson (39), in 1935, stated that Blalock, Underhill, Harkins, and others had shown that in burns, freezing, and intestinal trauma, a large factor in the production of the resultant shock and death was the loss of a large amount of plasma-like fluid from the blood stream. To test the hypothesis that the loss of a similar plasma-like fluid into the peritoneal cavity might be a large factor in the production of death in bile peritonitis they undertook a series of experi-

ments in dogs. They concluded from these experiments that the amount of plasma-like peritoneal exudate in experimental bile peritonitis indicated that the loss of this fluid from the blood stream was an important factor in the production of shock and death in that condition.

In 1936, Moon and Morgan (68) stated that the toxicity of bile had long been recognized. Either whole bile or the cholic salts producing severe systemic intoxication when injected and producing intense local irritation of the tissue at the site of injection. They quote Horrall and Carlson as having found that intraperitoneal injection of sterile bile produced severe illness characterized by vomiting, diarrhea, oliguria, albuminuria, bradycardia, low blood pressure and death in coma within twenty-four hours. Moon and Morgan (68) quoted them as describing edema, congestion and petechial hemorrhages of the lungs, brain, gastrointestinal mucosa, and marked congestion of the liver and kidneys as postmortem findings following bile peritonitis. Moon and Morgan (68) believed that these physiologic and pathological features were characteristic of shock whether occurring clinically or experimentally. With this idea in mind they injected bile or sodium glycocholate into dogs with the following results.

Intraperitoneal or intravenous injections of bile or sodium glycocholate produced the shock syndrome characteristically in dogs. This was accompanied by hemo-concentration as in shock otherwise

produced. Sublethal degrees of shock followed sublethal doses of the agents mentioned. These recovered or resulted in pulmonary edema, pneumonia and subsequent death. The postmortem findings were the same as those following shock otherwise produced. (68)

The evidence indicated that bile or its salts caused acute injury to the walls of capillaries and venules. This resulted in atony and increased permeability, whereby a disparity developed between blood volume and volume capacity of the vascular system. Such a disparity manifested itself in the shock sysndrome. (68)

In 1936 Harkins, Harmon and Hudson (41) wrote that once the importance of this hitherto rarely recognized condition was demonstrated, numerous experimental studies on the mechanism of death in bile peritonitis were made. These observations include the work of Horrall and others and center chiefly around the postulates that toxic action and anaerobic bacterial invasion are the chief two lethal factors in bile peritonitis. From other data similarly obtained by experiments, Harkins, Harmon and Hudson advanced the idea that secondary shock, in the sense of decreased volume of circulating fluid, was one of the most important lethal factors in this condition. They fully recognized that there were substantial differences between experimental and human bile peritonitis. However, they believed, that since the theories of the previous workers were obtained by experiment, refutation of

these theories might come from similar experiments. From their experiments on dogs they concluded that at least five possible lethal factors in experimental peritonitis due to bile or to implanted liver might be active, including: (a) local irritant action of the foreign substance producing local plasma loss and secondary shock; (b) local damage to body tissues with absorption of toxic products thereby produced; (c) absorption of toxic products from the foreign substance itself; (d) absorption of exotoxins produced by the action of organisms on the foreign substance present or the body tissues themselves; and (e) ability furthering secondary shock. (41)

They further concluded that the first of these factors, i.e., producing local plasma loss and secondary shock, seemed to be of relatively greater importance in bile peritonitis than in peritonitis due to implanted liver. (41)

Harmon and Harkins (44), in 1937, found a vasodepressant toxic substance in the exudate of experimental suppurative peritonitis but were unable to demonstrate a similar substance in the exudate of bile peritonitis prior to death.

Manson and Eginton in 1938 (60) stated that it was quite obvious that infected bile inundating the peritoneal cavity might engender a suppurative or pyogenic peritonitis, the same as perforation of an infected appendix; the malignant character of this type of bile peritonitis being conceded by most authors,

consequently the efforts of most investigators have been applied to determine the effects of sterile bile in the peritoneal cavity.

They place the controversial opinions of the various authors on this subject into two categories:

A. Sterile bile in the peritoneal cavity is innocuous. This opinion was supported by Noetzel (73), McWilliams (72), Orth (75), Sich and Fraenkel (86), Buchanan (15), Ritter (82), Fraenkel and Krause (36), and many others.

B. Sterile bile in contact with the peritoneal surface is harmful. They again classify opinions under this heading into several divisions.

(a) Death in choleperitoneum is due to the toxicity of one or more components of bile, especially the bile salts. Wangensteen (103), Horrall (49), Horrall and Carlson (50), Brand (11), and Rywosch supported this view.

(b) Death is due to endogenous infection; that is the bacterial factor, especially Clostridium welchii. Rewbridge and Hrdina (81), Andrews, Rewbridge and Hrdina (5), and Dvorak (30) are quoted as supporting this view.

(c) Shock from fluid loss is the chief lethal factor according to Harkins and Harmon, Hudson and Andrews (39), Trusler and Martin (100) and Moon and Morgan (68).

Manson and Eginton (60) after a series of experiments on dogs concluded that there were at least two factors operative in

the causation of death in choleperitoneum; that is, the primary injury to the peritoneum by the toxic bile salts, and the secondary shock from loss of fluid from the vascular system. The toxic effect of absorbed bile and the bacterial factor might be of importance but, if so, they were probably only contributory to the lethal outcome.

BILE PERITONITIS

SUMMARY

BILE PERITONITIS

SUMMARY

For a summary of the experimental work in bile peritonitis, the reader is referred to a recent article by Manson and Eginton (60), in 1938. These authors have made an excellent, comprehensive summary of the experimental work in bile peritonitis up to that date. There has been little, if any, experimental work in bile peritonitis in the last several years so the writer of this thesis felt that he was justified in using their summary. They have included not only the American and English literature, but also, French, Italian and German literature, as well, in their review. This summary is found on pages 62 and 63.

AUTOLYTIC PERITONITIS

AUTOLYTIC PERITONITIS

Mann (58) observed in his experiments with hepatectomy in dogs that when small pieces of liver tissue were left behind in the peritoneal cavity, the dogs invariably died of a severe peritonitis in less than twenty-four hours. He also noted that the animals were more apt to die than when the liver was completely removed.

In 1925 Mason and his coworkers (62) confirmed Mann's observations. They studied the blood chemistry in such dogs, and found that saline extracts of autolized dog's liver injected intravenously proved very toxic. If the liver was not autolized, no toxic reactions were observed. They described the typical picture of dogs dying following deposition of pieces of dog's liver into the peritoneal cavity. One to three-hundred cc. of a serosanguinous fluid was usually present and the peritoneal surfaces were reddened. After twenty-four hours, liver placed into the cavity could hardly be identified except as a friable, mushy mass which contained gas. They concluded that the rapid death of the animals was due to absorption of toxic substances produced from intraperitoneal autolysis of the liver material. They pointed out the close correlation between their findings and those reported by Cannon in his investigation on traumatic shock.

In the same year these authors (62) also reported that, when the spleen was separated from its blood supply and left free in the peritoneal cavity, death occurred in fifty percent of the animals studied and was accompanied by an outpouring of fluid

into the peritoneal cavity similar to that found in liver autolysis. In general, spleen acted similarly to liver but did not produce death so easily or so soon.

Wangensteen (103), in 1928, showed the relative non-toxicity of rat's liver and adult dog's kidney compared to adult dog's liver. He also showed the existence of a quantitative tolerance of dog's liver, introduced into the rat's peritoneal cavity, the rat usually not dying till fifteen grams of dog's liver per kilogram of body weight of rat had been exceeded.

In 1930 Ellis and Dragstedt (31) indicated that an anaerobic gas forming bacillus commonly found in the dog's liver was responsible for death in liver autolysis in vivo. They identified this organism closely with the Bacillus welchii.

In the same year Andrew and his associates (4) performed experiments that differed from those of Dragstedt in one important respect. Whereas the latter had found that sterile autoclaved liver was non-toxic, Andrews reported that if such sterile liver was ground into fine bits, it produced an autolytic peritonitis accompanied by gas forming organisms similar to that produced by fresh liver. Andrews also reported that muscle or bile salts would produce a similar fatal peritonitis.

Andrews, Rewbridge and Hrdina (5), in 1931, pointed out that Ellis and Dragstedt in their experiments had used large, hard masses of cooked liver which presented little surface for autolysis.

Andrews and his coworkers ground the livers with sand and found that they would still produce the toxic syndrome even though sterile. They experimented further with animals and came to the conclusion that the cause of death in autolytic peritonitis was due to an overwhelming toxemia. They stated that the infecting agent was the Bacillus welchii. They also believed that this organism lay dormant in the tissues of the dog and could be stimulated to produce a fatal infection by intraperitoneal autolysis of sterile liver and bile salts.

In 1932 Mason and Lemon (61) experimented with dogs and concluded that liver tissue that underwent autolyis within the peritoneal cavity liberated a substance which caused a chemical peritonitis which was accompanied by a marked increase in permeability of the abdominal viscera. They believed that free fluid was always present in the peritoneal cavity of dogs dying from autolysis of liver tissue. The amount of free fluid usually being equal to one-third to one-half of the total blood volume. Accompanying the migration of free fluid into the peritoneal cavity, they observed a marked blood concentration. They believed that the fluid loss was sufficient to cause circulatory disturbances but that the failure of fluid administration to prolong life was due to the enormous increase in permeability of the abdominal viscera.

Dvorak (30), in 1932, experimented with dogs in an effort to determine whether or not the bacteria and their toxins are

solely responsible for the death of the animal or whether other toxic products peculiar to liver tissue itself as contended by Andrews also played a significant role in the death of the animal. He concluded that anaerobic bacteria or their toxic products were responsible for death in autolysis of dog's liver in vivo and that no toxic product was found in the liver responsible for death which was inherent to liver tissue and independent of bacterial activity.

Mason and Nau (63), in 1935, reported marked degenerative changes in the liver and kidneys of dogs subjected to the intraperitoneal introduction of sublethal amounts of fresh liver tissue. They concluded that these changes were caused by the absorption of toxins liberated from autolyzing liver fragments.

Trusler, Reeves and Martin (101), in the same year, in a series of papers made a special study of the anaerobic bacteria found in experimental liver autolysis and bile peritonitis. They found that these organisms did not produce exotoxins and were similar to those recovered from normal dog liver and muscle. The authors did not classify them as Clostridium welchii. They found that sterile autoclaved liver or bile salts did not cause invasion of the peritoneal cavity by anaerobic organisms if contamination by touching the muscle of the abdominal wall during the process of insertion was avoided. These authors noted that the various incubated preparations of liver and sterile bile salts caused an intense irritation of the peritoneal surfaces with much extravasa-

-tion of blood and fluids, and they believed the death of the dog to be associated with shock.

In 1936 Harkins, Harmon and Hudson (40) concluded from their experiments on dogs that at least five possible lethal factors in experimental peritonitis due to bile or to implanted liver might be active, including: (a) local irritant action of the foreign substance producing local plasma loss and secondary shock; (b) local damage to body tissues with absorption of toxic products thereby produced; (c) absorption of toxic products from the foreign substance itself; (d) absorption of exotoxins produced by the action of these organisms on the foreign substance present or the body tissues themselves, and; (e) ability furthering secondary shock.

They believed that the first of these factors, i.e., producing local plasma loss and secondary shock, seemed to be of relatively greater importance in bile peritonitis than in peritonitis due to implanted liver. (40)

Iesu (51), in 1937, after experimenting on dogs concluded that anhydremia following the implantation of pieces of liver in the abdominal could not be regarded as a constant cause of death, for in his work, he showed, first in rabbits and then in dogs, that under identical conditions the rabbits died in the same length of time as the dogs even when there was so little fluid in the peritoneal cavity as to preclude anhydremia as a factor in

the cause of death.

In the same year Trusler and Martin (100) after extensive animal experimentation concluded that the parenchymal elements of the liver were relatively non-toxic. When they separated these elements from the blood vessels, bile ducts, and connective tissue portions of fresh dog liver, seventy grams of the parenchymal tissue suspension caused neither death nor shock. However, fifty grams of the connective tissue suspension caused both shock and death.

They also reported that cultures taken from the parenchymal suspensions had consistantly shown that this fraction of liver harbored the dog liver anaerobe. Nevertheless, smears and cultures of peritoneal exudate removed from dogs subjected to the intraperitoneal introduction of parenchymal suspensions of liver showed that these animals rapidly sterilized the peritoneal cavity, even in the presence of large amounts of contaminated liver substance. (100).

They reported that the dogs that received the liver connective tissue suspensions rapidly died of shock and bacterial peritonitis, while the dogs that received the parenchymal liver suspensions survived and remained well. They concluded that this interesting observation merited further investigation. (100)

AUTOLYTIC PERITONITIS

SUMMARY

SUMMARY

Death from liver autolysis in vivo is a subject which has received a great deal of attention since 1925. Most of the investigators in this field have felt that death was due to the absorption of toxic products from the abdominal cavity but they have not agreed as to the nature or the source of this toxic substance. A short summary of the different view-points on this subject is given in the following paragraphs.

Mason and Nau (63) believed that death, in dogs, was due to toxins liberated from the autolyzing liver fragments.

Ellis and Dragstedt (31) concluded from their experiments that an anaerobic, gas-forming organism, closely resembling B. welchii, was responsible for death from liver autolysis in vivo. Andrews, Rewbridge and Hrdina (5) also believed that death was due to an overwhelming toxemia produced by the Bacillus welchii. They believed that this organism lay dormant in the tissues of the dog.

Dvorak (30) concluded from his experiments that there was no toxic product inherent to liver tissue which caused death in autolysis of liver in dogs. He believed that anaerobic bacteria or their toxic products were the cause of death in autolytic peritonitis.

Other men thought that shock might play some part in death from autolysis of liver in vivo.

Mason and his coworkers (62) concluded that the rapid death of animals was due to the absorption of toxic substances produced

by autolysis of liver. They thought that shock might be a factor in the causation of death. Trusler, Reeves and Martin (101) believed that death in autolysis of the liver was associated with shock. The anaerobic organisms that they found to be present did not produce exotoxins. They believed that the source of these organisms was contamination by the operator from the muscles of the abdominal wall. Harkins, Harmon and Hudson (40) believed that death was probably due to absorption of toxins from bacteria and from the liver itself. They believed that secondary shock was an important factor. Iseu (51) concluded from his experiments on dogs that anhydremia was not a constant cause of death in liver autolysis.

Trusler and Martin (100) recently performed experiments which showed that connective tissue portions of dog's liver caused shock and death while parenchymal portions, although they harbored the dog liver anaerobe, caused neither shock nor death.

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