Intestinal Obstruction.

II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine.

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Obstruction to the passage of food through the intestine leads to adverse symptoms and complete obstruction causes death. Acute obstruction in the upper part of the small intestine is more rapidly fatal than in the intestine lower down. The symptoms are those of a severe, rapidly developing toxemia. Toxic substances accumulate in the obstructed intestine, which when injected intravenously in animals or absorbed from the abdominal cavity produce symptoms similar to those arising after acute obstruction. It has been shown by Stone, Bernheim, and Whipple (1), and later by Hartwell and his associates (2), and Murphy and Brooks (3) that the production of isolated closed loops of the intestine, with the reestablishment of intestinal continuity around the isolated loop, produces symptoms similar to those following complete obstruction of the intestine at the same level. There is an accumulation of toxic materials in these intestinal loops similar to those in the obstructed intestine. In a previous study (4) it was demonstrated that these toxic substances can be formed in such isolated closed intestinal loops, with resultant toxemia, after all food materials and digestive secretions have been previously removed by careful washing with water or salt solution. It was also shown that the secretions of the intestinal mucosa are not toxic and do not give rise to the symptoms of acute obstruction when absorbed directly from the abdominal cavity. Davis and Stone (5) have found that these secretions are not toxic even when injected intravenously in animals. This is in agreement with the observation of Murphy and Brooks. The presence of bacteria in the lumen of the intestine or in isolated closed intestinal loops is necessary for the production of the characteristic toxic substances. In the absence of bacteria, as in isolated closed intestinal loops previously rendered sterile by prolonged drainage into the abdominal cavity, many changes, even to autolysis of the mucosa through occlusion of the blood supply, may occur and no untoward symptoms result. The toxic substances can be apparently formed by the action of bacteria on the secretions of the intestinal mucosa, or on material from desquamated mucosa cells.
Davis and Stone noted that whereas normal fresh intestinal juice was not toxic, if it was kept free from preservatives and unheated, it rapidly became so, producing the same effects on intravenous injection as the materials from closed loops. A rapid and profuse growth of bacteria in this secretion was noted.

However, the presence of bacteria plus a suitable substrate either in the lumen of the obstructed intestine or in closed intestinal loops does not in many cases produce the characteristic acute toxemia unless there is some factor present permitting the absorption of these toxic materials into the general circulation. Absorption of toxic materials from the intestine occurs both in clinical and experimental obstruction and after the formation of closed isolated intestinal loops in the great majority of cases. The present study was undertaken to determine the factors involved in this absorption of toxic materials and to secure additional evidence as to the manner of their production.

The experiments were performed on dogs, under complete ether anesthesia and with strict aseptic precautions.

Isolated Closed Intestinal Loops Previously Washed with Water and Ether.

It has been demonstrated many times by different workers that the production of closed isolated loops of the small intestines in dogs, in the great majority of cases, gives rise to a quickly developing rapidly fatal toxemia in all respects similar to the symptoms of complete acute obstruction of the intestine in the same region. These closed loops in the duodenum or upper jejunum are more rapidly fatal than similar loops in the ileum or colon. In every case there accumulates in the closed loops a toxic material, similar to the material found in the intestine in experimental obstruction in animals or in acute obstruction in man. If these isolated intestinal loops are previously washed with sterile water and ether about 50 per cent of the animals survive indefinitely and display no toxic symptoms following the operation.

The mucosa of such loops when examined at varying intervals after the operation is normal in appearance. Since it has been demonstrated that the presence of bacteria in closed intestinal loops is necessary for the production of toxic materials it would appear that the ether washing of these loops previous to closure must have either
inhibited the growth of bacteria and so prevented the formation of toxic substances, or it must have changed conditions so that toxins present were not absorbed. It is conceivable that the ether may have affected conditions in any of the following ways: (1) The specific bacterium causing the elaboration of the toxic product in the closed loop may have been removed or its growth inhibited. The bactericidal property of the ether itself may have been sufficient to destroy the bacteria or the hyperemia incited by the ether as an irritant may have been instrumental in aiding phagocytosis. (2) The substrate upon which bacteria act to produce the toxic product may have been washed out by the ether. Thus the ether-soluble lecithin, a constituent of bile and animal tissues generally, is split by putrefactive intestinal bacteria giving rise to the exceedingly toxic choline and neurine. (3) The secretory activity of the mucosa may have been sufficiently depressed to prevent the accumulation of enough fluids to distend the intestine to the point of rupture or to occlude its blood supply. The recovery of the cells from the effects of the anesthetic may have been sufficiently gradual to permit the establishment of an equilibrium between the amount of secretion into the lumen of the intestine and the amount of absorption. There is a possibility that the absorptive properties of the cells of the washed loop may have been increased through the removal of the lipoid envelope of the cells by the ether. (4) The ether may have inhibited the formation of toxic substances within the cells of the mucosa of the closed loop, or produced some change in a possible harmful internal secretion of the mucosa of the intestine. (5) The ether may have decreased the absorption of substances from the intestine.

Experiments to Determine the Factors Involved in the Production of the Poisons of Obstruction.

It was found that if isolated intestinal loops were washed with water and ether previous to closure many animals survived the operation, never displayed any toxic symptoms, and that these loops when subsequently removed and examined contained great numbers of bacteria. Ether does not sterilize these intestinal loops and the efficacy of the
ether in prolonging the life of closed loop dogs does not depend primarily upon its bactericidal properties. A large number of antiseptics, such as alcohol, lysol, phenol, cresol, formaldehyde, mercuric chloride, silver nitrate, and chloroform, was used to wash the intestinal loops previous to closure. These chemicals did, in many cases, prolong the life of dogs with closed intestinal loops. Their efficacy, however, was not proportionate to their bactericidal efficiency and none was so effective as ether. In no case did they afford a complete sterilization of the intestinal loop or permanently inhibit the growth of bacteria.

The following experiments were done to determine whether the growth of bacteria and the production of the usual toxic substances in closed intestinal loops were prevented by the previous use of antiseptics. A dog which had survived the production of an isolated closed loop of the upper jejunum, previously washed with ether, was subsequently opened and the contents of the closed loop were removed with a syringe. About 50 cc. of fluid were obtained which, when injected into the abdominal cavity of another dog, caused a severe toxemia and death in 6 hours. In another animal an isolated loop of the transverse colon was made, washed with sterile water and 70 per cent alcohol, the ends were closed, and the continuity of the intestinal tract was reestablished by end to end anastomosis. This animal displayed no untoward symptoms and after 28 days was opened and the isolated loop removed. It was greatly distended, containing 225 cc. of turbid chocolate-colored fluid. The mucosa was normal. 6 cc. of this fluid were injected intravenously in another dog, and produced a profound prostration and death in 10 hours. Both the jejunal and the colon loops contained large numbers of bacteria.

These experiments established the fact that it is impossible to sterilize even a short piece of the intestinal tract by the use of chemical antiseptics. They indicate that the part played by ether is not that of a bactericide and that it does not markedly inhibit the production of toxic materials in intestinal loops. The absorption of these toxic substances is for some reason prevented. It is possible for many times the lethal dose of these poisons to remain in closed loops of the jejunum or colon without the production of toxic symptoms.
Experiments to Determine the Factors Involved in the Absorption of Poisons from the Obstructed Intestine.

The fact that closed loops of the upper jejunum in dogs are rapidly fatal, in the great majority of cases, while identical loops previously washed with ether are compatible with life in approximately 50 per cent of cases, is significant and affords an opportunity for the study of the factors involved in the absorption of the poisons of obstruction. Washing with ether does not prevent the formation of toxic materials in closed intestinal loops but it does prevent the absorption of these materials in many instances. If closed loops of the upper jejunum, untreated with ether, are made, the animal usually dies in from 1 to 5 days with symptoms of an acute toxemia, appearing only from 10 to 24 hours before death. At autopsy there is usually a perforation of the loop and a general peritonitis. Many animals, however, die and the autopsy discloses an intact loop, in most cases enormously distended, discolored, with a necrotic mucosa, but no peritonitis. It is noteworthy that these closed loop dogs display no adverse symptoms until shortly before they die at a time when apparently the accumulation of secretions in the loop has caused sufficient distention to occlude the blood supply to the mucosa. It seemed possible that ether may have prevented the onset of toxemia in closed loop dogs by preventing this distention of the loop.

Ether acts as a local narcotic causing a coagulation of the cell protoplasm. This coagulation might at least temporarily depress the secretion of intestinal juice. If this is the important factor then other substances with strong astringent but without bactericidal properties should be equally effective.

Isolated loops of the upper jejunum were made in eight dogs, flushed with water and subsequently with 8 per cent alum (aluminum potassium sulfate), the ends infolded and closed, and the continuity of the intestinal tract was reestablished by end to end suture. Two of these dogs survived the operation and remained in good health 6 months later. Six of the dogs died within the first 5 days with a perforation of the loop and a general peritonitis. Similar isolated jejunal loops were made in fourteen dogs, but a 6 per cent solution of tannic acid was used to flush the loop instead of alum. Of these dogs four con-
continued in perfect health for months after the operation; the remainder died after periods varying from 6 to 20 days.

Apparently, simple astringents with no germicidal properties are just as effective in preventing the symptoms of toxemia in dogs with closed intestinal loops as are the antiseptics. It was evidently the astringent properties of the ether and the other chemicals rather than their bactericidal properties that account for the results produced.

The factor of distention in short closed intestinal loops is of paramount importance in the production of the toxemia, since if the distention is prevented in the majority of cases toxemia does not occur.

It has been emphasized by Hartwell and his associates and by Murphy and Brooks as well as by ourselves that toxic materials are not rapidly absorbed through the normal mucosa. This fact is well illustrated in the following experiments. Three dogs, which had survived the production of closed ether-washed loops of the upper jejunum for several weeks, were subsequently reopened. Into the closed loop of one dog the contents of a normal intestine with its bacterial flora, into the loop of the second the contents of an obstructed intestine, and into the loop of the third the evaporated ether washings of an isolated jejunal loop, containing a possible bacterial substrate, were injected. None of the animals displayed any unusual symptoms after recovering from the laparotomy and continued in good health. It has been noted before that dogs may survive the production of closed loops of the jejunum and may continue in perfect health although the loop may contain many times a lethal dose of toxic substances. This we believe is due to a protective function on the part of the intestinal mucosa which is able to inhibit or diminish the systemic effect of poisonous substances found in the alimentary tract. It is dependent upon the capacity of the mucosa cells for physiological selection by which these cells, while they absorb certain substances (in apparent defiance of physical laws) that diffuse with difficulty, do not, on the other hand, permit others to pass which may be more diffusible. This protective capacity, however, has a limit, or intoxication from the alimentary tract could not occur. Indeed it has been our experience that if long (1 to 6 feet) closed loops of the intestine, previously treated with ether, are made, no symptoms may be apparent for 2 weeks, but shortly thereafter a slowly developing toxemia may ensue and death.
occur in the course of 5 or 6 days. The mucosa of these loops may be perfectly normal to both gross and microscopic examination. With short loops any poisons which may have found their way through the mucosa were apparently removed from the circulation or detoxified by the liver. With the long loops, however, the liver was not able to cope with the large quantity of toxic substances and toxemia resulted.

The following experiment emphasizes the importance of the protective action of the normal intestinal mucosa. An isolated loop (12 cm. in length) was made in the jejunum, washed with water and ether, both ends were closed, and the continuity of the alimentary tract was reestablished by end to end anastomosis around the loop. The animal quickly recovered and displayed no subsequent toxic symptoms. 1 month later a second laparotomy was done, the isolated closed loop filled with a 25 per cent solution of magnesium sulfate, dropped back, and the abdomen closed. 3 days later the animal died with the usual symptoms and autopsy revealed a perforated loop with a general peritonitis. It was demonstrated before that ether washing of the loop previous to closure does not prevent the formation of toxic materials. It is well known that a strong solution of magnesium sulfate will attract fluids into the lumen of the intestine acting through the alteration of osmotic pressure conditions. Evidently the distention of the closed loop produced by the attraction of liquids was the immediate cause of the toxemia and death. The animal was able to survive the production of a closed jejunal loop which contained more than a lethal dose of toxic materials without symptoms but died when this loop was distended. The conclusion seems inevitable that the injury to the mucosa produced by the distention has deprived these cells of their protective function and permitted an overwhelming amount of toxic material to enter the blood stream. Evidence obtained from the other workers in this field as well as from our own experiments indicates that the distention of the intestine injures the mucosa by occluding its blood supply. Once the protective layer of intestinal epithelium has been functionally destroyed absorption takes place as from the peritoneal cavity whose serosa exerts no selective action.
It is not probable that simply an irritation of the mucosa by retained substances in the obstructed intestine is the factor which damages the cells, destroys their power of selective absorption, and permits the absorption of the toxins of obstruction. There is no evidence that the toxins of obstruction are qualitatively different from the toxic materials present in the normal digestive tract and if simply an irritation of the mucosa were the important factor in their absorption a pronounced toxemia should occur in any enteritis.

Experiments to Determine the Possibility of a Non-Bacterial Origin of the Poisons of Obstruction.

In view of the fact that some of the workers, who have done a great deal of experimental work on the problem of intestinal obstruction, hold to the view that the poisons responsible for the toxemia arise independently of the intestinal bacteria, it is necessary to detail the experiments which have forced us to reject these theories. It has been postulated by a number of workers and considerable experimental and clinical evidence has been adduced to show that the toxemia incident to obstruction of the intestinal tract is due to the absorption of poisons formed in the intestinal mucosa. These poisons may be either normal products of the lining cells which, because of the obstruction, are abnormally absorbed or they may be the results of an abnormal activity on the part of the intestinal mucosa induced by the condition of obstruction. Thus Draper (6) holds that the toxemia in intestinal obstruction is due to an aberrant activity of the duodenal and probably the pancreatic cells. Whipple, Stone, and Bernheim (7) believe that death in these cases of obstruction is due to the absorption directly into the blood stream of a perverted secretion of the duodenal or upper jejunal mucosa. They assume a disturbed physiological balance of the mucosa by which abnormal products are formed and secreted into the blood stream. This toxic secretion is a proteose and, it is stated, can be formed in a mucosa in which there is no gross evidence of disturbance. Thus both of these theories exclude the intestinal bacteria as an important factor in the production of the toxic materials. A number of experiments were done to obtain evidence on this point and in no case do we believe
that the experimental evidence warrants the assumption of a non-
bacterial origin of the poisons concerned in obstruction.

In our first study (4) the following points were brought out: (a) Open isolated
loops of the duodenum, the jejunum, or the ileum do not give rise to a toxemia
when their secretions are drained directly into the abdominal cavity. South and
Hardt (8) had independently found that animals could survive the production of
open isolated loops of the small intestine, and this has been abundantly confirmed.
(b) Closed isolated intestinal loops previously washed with ether may produce
no symptoms in 50 per cent of cases. (c) Closed isolated intestinal loops pre-
viously rendered sterile by prolonged drainage into the abdominal cavity pro-
duce no untoward symptoms. (d) Sterile closed intestinal loops produce no
adverse symptoms even on complete autolysis of the mucosa through occlusion
of the blood supply. (e) An ether-washed closed intestinal loop (not sterile),
which had caused no symptoms, produced the typical toxemia and death on
occlusion of its blood supply.

A consideration of these experiments indicates the improbability
of a toxic secretion of the mucosa cells. It has been amply demon-
strated that the normal secretions of these cells are not toxic when
absorbed from the abdominal cavity or injected intravenously. The
production of closed intestinal loops does not always cause toxic
symptoms if the factors of bacterial growth and distention of the loops
are controlled. If the toxemia were dependent upon toxic secretions
of mucosa cells it should uniformly occur when closed loops are made,
and furthermore one would expect a slowly developing toxemia from
the time of production of the loop instead of a fulminant toxemia coinci-
dent with distention of the loop and occlusion of its blood supply.
It might be conceived that distention of the intestinal loop is a neces-
sary stimulus to the mucosa cell to produce its toxic product. But if
bacteria have been previously excluded from such a closed loop it may
distend to the point of rupture, or its blood supply be occluded by
ligation and no toxic symptoms result. However, if bacteria are
present, either of these procedures will cause typical symptoms and
death. It might then be conceived that bacteria are a necessary
stimulus to the production of a toxic secretion by the mucosa. How-
ever, if bacteria are present in a closed loop but the distention of the
loop is prevented by substances which inhibit intestinal secretion, no
toxic symptoms result. It would be too far fetched to assume both
the presence of bacteria plus a distention of the intestinal wall as a
stimulus to dying cells to produce a specific toxic secretion. We know
that intestinal bacteria acting upon proteins or their split products can
elaborate poisons which produce symptoms identical with those of
obstruction, and all the evidence we have obtained points to these
substances as the important constituents of the toxins of obstruction.

It might be conceived also that obstruction and accompanying
injury to the intestinal mucosa may have thrown out of function an
organ essential to life. Several workers have stated, from experi-
mental evidence, that the mucosa of the upper duodenum has a specific
vital function, aside from the secretion of succus entericus and the
manufacture of secretin, and that disturbance of this function rapidly
causes death.

S. A. Matthews (9) reasons, from experiments in which the entire duodenum
in dogs was resected, that the duodenal mucosa is as necessary for life as the
adrenals or parathyroids probably through some hormone function other than
that concerned with the elaboration of secretion. A. P. Matthews (10) states
that if experiments are made so that the duodenal juice (succus entericus) is
drained to the exterior through a fistula, the animals die with apparently the
symptoms of complete extirpation of the duodenum. He suggests that death
may be due to the rapid excretion of some necessary substance through the
duodenum to the exterior or to the loss of some substance normally elaborated
by the duodenum which is necessary to the function of the intestine lower down.

It has long been known that resection of varying lengths of the jejunum, ileum,
or colon, and even a complete removal of the stomach may produce no symp-
toms other than can be accounted for as a result of the loss of a digestive and
absorptive organ. It has also been quite generally recognized that surgical inter-
ference with the duodenum is an extremely dangerous procedure and that excision
of even parts of the duodenum is usually fatal. The symptoms produced in
dogs after complete extirpation of the duodenum, as described by S. A. Matthews,
and those produced by drainage of duodenal juices, as described by A. P. Mat-
thews, were so much like those produced by simple occlusion of the upper intes-
tine, that it was considered advisable to repeat their experiments. A complete
account of our work has been published in another paper (11) and accordingly
only a brief summary need be given here. It was found that removal of varying
lengths of the jejunum and ileum produced no other effect than some nutri-
tional disturbance, attributable to the loss of an important digestive and ab-
sorptive organ. The mucosa of the combined jejunum and ileum does not se-
crete or manufacture a necessary substance and animals can survive for months
after the removal of the small intestine, the duodenum and colon remaining
intact. A dog was kept living 3 months after a complete removal of the pyloric
part of the stomach, the entire duodenum, and the upper jejunum. This was confirmed by Grey (12), who was able to keep a dog 9 1/2 months after complete removal of the duodenum.

Moorhead and Landes\(^1\) state that they have a dog in good health and gaining weight 3 months after the removal of the entire duodenum. Thus the mucosa of the alimentary tract does not possess a function comparable with the adrenals and parathyroids. Dogs were kept living 10 and 12 days after the establishment of a fistula which drained the entire duodenum. There is no evidence that the duodenum excretes in the succus entericus any substance necessary for life, or for the function of the intestine lower down.

DISCUSSION.

It has been definitely determined that death resulting from acute obstruction of the intestine is due to a toxemia and that the responsible toxic substances are formed in the obstructed intestine. These toxic substances can be formed even if all food materials, end-products of digestion, and the secretions of the stomach, liver, and pancreas have been carefully excluded. The secretion of the intestinal mucosa is not toxic either when absorbed from the abdominal cavity or injected intravenously. The mucosa of the alimentary tract (stomach, duodenum, jejunum, ileum, or colon) does not elaborate an internal secretion which is necessary to life, or which could be disturbed by the conditions of acute obstruction so as to account for the symptom complex of that condition. The presence of bacteria in the lumen of the intestine is necessary for the production of the characteristic toxic substances and in their absence these substances do not form. They are produced by the action of the intestinal bacteria on proteins or their split products. In the absence of food, gastric juice, bile, or pancreatic juice, these bacteria can produce the characteristic toxic substances from the intestinal juice or from the proteins of desquamated mucosal cells. The important poisons will not provoke the appearance of immune bodies when injected in experimental animals (13) and we were not able to demonstrate that an animal can become immune to the toxemia of acute obstruction (14). Toxic amines are produced

\(^1\) Moorhead, J. J., and Landes, H. E., personal communication.
by the action of various intestinal bacteria on amino-acids and the evidence more and more points to these substances as the important agents in the toxemia of acute intestinal obstruction.

The toxic substances arising in the lumen of the obstructed intestine are not readily absorbed through a normal mucosa, a point emphasized by Hartwell and his associates and by Murphy and Brooks. Nor are they absorbed to any great extent through the mucosa of a closed intestinal loop until this mucosa has been injured by the distention of the loop and the consequent interference with the blood supply. If this distention is prevented by any means absorption of poisons in quantities greater than can be cared for by the liver and other tissues does not occur. Thus it appears that the injury to the mucosa cells, either as a result of the sudden distention brought about by conditions of obstruction or by any other factors which interfere with the blood supply to the mucosa (strangulation, etc.), is an important factor in the absorption of toxic substances from the intestine. There can be no doubt that necrosis of the mucosa greatly facilitates the absorption of intestinal poisons; but it is incorrect to say that intestinal poisons, i.e. those found in obstruction, cannot be absorbed through a normal mucosa. The protective action of the intestinal mucosa exercised through its properties of selective absorption is not absolute, but that it is of great significance is shown by the fact that an animal can take care of the amount of poisons absorbed through the normal mucosa of a short closed intestinal loop, which has been treated with astringents, but that as soon as this mucosa becomes necrotic an overwhelming amount of toxic materials gains entrance to the blood stream, with toxemia and death occurs. The absorption in these cases cannot be different from absorption from the peritoneal cavity.

CONCLUSIONS.

1. It is impossible to sterilize the intestine by the use of chemical antiseptics even when these are applied directly to the mucosa of isolated segments.

2. The mucosa of the alimentary tract does not elaborate an internal secretion which is necessary to life, or a secretion which could be disturbed by the conditions of acute obstruction so as to account for the symptom complex of that condition.
3. The substances responsible for the toxemia in acute obstruction are produced by the action of intestinal bacteria on proteins or their split products.

4. An injury to the intestinal mucosa, particularly that resulting from disturbances of the blood supply to the intestine, greatly facilitates the absorption of these poisons. The work of Hartwell and his associates and that of Murphy and Brooks on this point are confirmed.

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