

## INTESTINAL OBSTRUCTION IN THE RABBIT. I.\*

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Although an extensive literature has grown up concerning the cause of death in high intestinal obstruction, there appears to be as yet no unanimity of opinion on the subject. Even in the articles which have been published during the past year there is almost as wide disagreement as in the older literature. It seems desirable, therefore, to add the weight of the results of the experimental study here reported to that side of the controversy on which they lie.

In view of the recent summaries by Murphy and Vincent,<sup>1</sup> and by Hartwell and Hoguet,<sup>2</sup> it seems unnecessary to review the older literature on the subject. It may suffice to say that of the older theories as to the cause of death in intestinal obstruction but one has survived which has any standing among present investigators. The theory that the fatal effect of obstruction is due to a nervous reflex has been given up because of lack of evidence to support it, while the theory that death follows a general bacterial invasion of the peritoneum or of the blood stream has failed in the face of strong evidence against it. The surviving older theory is that death is due to the absorption of a toxin or of toxins from the lumen of the obstructed gut. That there is a toxic factor in high intestinal obstruction is accepted by the majority of those who have recently published on the subject, but it is accepted with various reservations and with points of difference as to the source of the toxin.

Maury<sup>3</sup> (Draper)<sup>4</sup> furnishes evidence in favor of the theory that the toxic substance is secreted by the duodenal mucosa, and that this substance in health

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<sup>1</sup> Murphy, F. T., and Vincent, B., *Boston Med. and Surg. Jour.*, 1911, clxv, 684.

<sup>2</sup> Hartwell, J. A., and Hoguet, J. P., *Am. Jour. Med. Sc.*, 1912, cxliii, 357.

<sup>3</sup> Maury, J. W. D., *Am. Jour. Med. Sc.*, 1909, cxxxvii, 725.

<sup>4</sup> Draper, J. W., *Jour. Am. Med. Assn.*, 1911, lvii, 1338.

is neutralized by secretions from the mucosa of lower segments of the intestine. In cases of obstruction he found that the animal's life may be prolonged by feeding it jejunal mucosa.

Stone, Bernheim, and Whipple<sup>5</sup> have demonstrated in the obstructed duodenal loop in dogs a toxic substance which is not injured by heating at 60° C. for long periods, which can not be filtered out of the fluid, can not be destroyed by autolysis, by pancreatic digestion, or by bacterial fermentation, and which they believe to be a secretion from the duodenal mucosa, though they were unable to obtain a similar toxic substance by any chemical action upon the normal mucosa.

Murphy and Vincent<sup>6</sup> conclude that the vital factor in the production of the symptoms of acute ileus is the interference with the circulation of the obstructed intestinal segment, particularly the interference with the venous outflow, while the acute symptoms are caused by the absorption of a toxic substance which they believe is purely of bacterial origin. They consider that death is due to the living bacteria with their endotoxins.

Hartwell and Hoguet<sup>7</sup> in their first paper emphasized injury to the intestinal wall as the vital factor in causing death, by permitting the absorption into the blood stream of such toxic substances, of whatever origin, as are normally present in the intestinal lumen, or as are formed after obstruction. In a more recent paper,<sup>8</sup> as the result of further experimentation, they have advanced a new theory, to the effect that "the important element in the development of the symptoms seen in intestinal obstruction in dogs is the loss of water due to the vomiting," and have given evidence to show that life in animals with obstruction may be prolonged by subcutaneous administration of salt solution.

The authors quoted, with the exception of Hartwell and Hoguet, agree that high intestinal obstruction is more rapidly fatal than low obstruction. Hartwell and Hoguet could find no difference, but maintain that double ligation with isolation of a loop is more rapidly fatal than a single ligation, as the injury to the mucosa is greater in the former case.

The series of experiments forming the basis of this paper was the outgrowth of class experiments on the effect of intestinal obstruction, and differs from the experiments reported by the majority of observers in that the animal used for study was the rabbit and not the dog. The rabbit is, from one standpoint, an unfavorable animal for these experiments, as it is impossible with any reasonable procedure to secure the animal with an empty stomach. On the other hand, it is a particularly satisfactory animal for the study of duodenal obstruction because of the long loop of duodenum

<sup>5</sup> Stone, H. B., Bernheim, B. M., and Whipple, G. H., *Bull. Johns Hopkins Hosp.*, 1912, xxiii, 160.

<sup>6</sup> Murphy, F. T., and Vincent, B., *loc. cit.*

<sup>7</sup> Hartwell, J. A., and Hoguet, J. P., *Am. Jour. Med. Sc.*, *loc. cit.*

<sup>8</sup> Hartwell, J. A., and Hoguet, J. P., *Jour. Am. Med. Assn.*, 1912, lix, 82.

(twenty-five to thirty-five centimeters) lying between the entrance of the bile duct and that of the pancreatic duct. This gives opportunity for cutting out these secretions and thus for the study of the unmixed secretion from the isolated duodenal mucosa.

In conducting the experiments the operative procedure was carried out under ether anesthesia, which, as a rule, had a total duration of about twenty minutes. Uniform and careful surgical technique was employed and we were successful in preventing any complication from infections. The agent used to produce obstruction was a coarse, soft, twine ligature, carefully applied so as to produce complete obstruction with the least injury to the intestinal wall or to the blood vessels. In order to secure this latter point, the ligature was passed between the intestine and the vascular loops lying in the mesentery close to the intestinal wall. To the majority of animals operated upon no food was given for twenty-four to forty-eight hours previous to operation, and water only was given subsequent to the operation, as it was found early in the work that continued feeding led to an earlier lethal result, and in some cases to such accidents as perforation of the stomach.

The preliminary set of experiments showed that in the rabbit, as in the dog, there was a striking difference in the time ensuing between operation and death, in animals in which the obstruction was produced at different levels. Duodenal obstruction with the ligature twenty-five centimeters from the pylorus produced death in less than twenty hours, while after obstruction in the upper ileum, 100 centimeters from the pylorus, the animal survived practically forty hours, and with the ligature placed below the cæcum, the animal lived eleven days. The short interval between obstruction and death in the animal with duodenal ligation seemed to indicate that bacteria played no part in the fatal result, at least in an infectious way, but that death was due to a toxin of some nature.

As the work of Bunting and Brown,<sup>9</sup> in this laboratory, had shown that rabbit bile was extremely toxic when reabsorbed from the peritoneal cavity, it seemed necessary to rule out this secretion as a factor, especially as at the time these experiments were begun the published articles had not settled the point. The rabbit stands

<sup>9</sup> Bunting, C. H., and Brown, W. H., *Jour. Exper. Med.*, 1911, xiv, 445.

well the ligation of the bile duct, surviving a month if there be no leakage of bile into the surrounding tissues. It was a simple matter, therefore, to rule out the bile as a factor in the process by ligation of the duct previous to the obstructing operation. In rabbit 5 of the series the duct was ligated seven days previous to the duodenal obstruction, and death followed the latter in about twenty-two hours. In rabbits 21, 22, and 25, ligation of the bile duct was done on the day previous to the obstruction and the fatal result followed in each case in less than twenty-four hours. In many of the subsequent experiments the bile duct and pylorus were occluded by a single coarse ligature in order to secure the duodenal secretions freed from gastric contents and bile, and in no case was the course of the subsequent duodenal obstruction modified.

That the pancreatic secretion plays no part was shown easily in the rabbit, on account of the position of the duct. In practically the entire series of duodenal obstructions the ligature was placed above the duct, thus causing no confinement of that secretion. Experiments had also shown that a rabbit in which the pancreatic juice pours directly into the peritoneal cavity through a severed duct may survive for a week.

The effect of ligation of the pylorus was next studied and it was found that, in the rabbit, obstruction at that point will cause death constantly in from thirty-six to forty-eight hours. The reabsorption of gastric secretion and the products of digestion have a sharp toxic effect (rabbits 17, 19, and others). Death from pyloric obstruction is never so prompt, however, as that following duodenal obstruction, or as that following the combined pyloric and duodenal obstruction.

The experimental results which had been secured up to this point indicated that in the rabbit there was a very striking and interesting relation between the position of the intestinal ligature and the interval elapsing between operation and death. The series was extended further and this point came out even more sharply. Indeed it may be said that in a series of about forty animals operated upon, the results as summarized below have been constant; that is, in animals weighing about 2,000 grams and deprived of food for from thirty-six to forty-eight hours previous to operation. It seems to

be unnecessary to record the details of operations, as the technique followed in each case has already been indicated.

The results of the series are as follows: (1) Obstruction of the pylorus in the rabbit is followed by death in from thirty-six to forty-eight hours, unless perforation of the stomach ensues, in which case death will occur sooner (rabbits 17, 19, and 20). (2) Obstruction of the duodenum between the pylorus and a point about eight centimeters below is followed by death in from thirty-six to forty-eight hours (rabbits 31, 32, 53, 56, and 58). (3) Obstruction at a point from eight to ten centimeters below the pylorus will cause death in approximately twenty-four hours (rabbits 4, 5, 52, and 61). (4) Obstruction of the duodenum below this point will be followed by death in less than twenty-four hours, often in less than fifteen (rabbits A, 1, 2, 21, and others). (5) Obstruction of the jejunum to a point approximately ninety centimeters below the pylorus will result in death in about twenty-four hours (rabbits 27 and 65). (6) Obstruction of the ileum may cause death in from thirty-six to forty-eight hours, although when the ligature is placed close to the cæcum life may be prolonged for a week (rabbits 28, 30, 66, 67, 74, and 75). (7) With obstruction below the cæcum, the animal may survive still longer (rabbit C, eleven days).

These relations seem to be constant unless modified by continued feeding, when the interval is shortened, especially in high obstructions, or by some physiological or pathological process, such as an existing pregnancy or an infection. No difference in time reaction has been noted between the use of a double ligature isolating a loop, and that of a single ligature.

In studying the series of experiments it appears that obstruction of the duodenum holds a peculiar position by reason of the great rapidity of the onset of symptoms and the short interval before death. The animal appears to be overwhelmed by a toxin. Lethargy, muscular twitchings, and a rapid fall of temperature to a point in the neighborhood of 90° F., or even lower, are seen just before death. Pulse rate and respiratory rate are both decreased toward the termination. It has been suggested that in cases of obstruction these symptoms might be due to the lack of an internal duodenal secretion. This can be disproved not only by excision of

the duodenum, but by the positive results obtained with injections of the duodenal contents. In simple excision of the duodenum, with ligation and cauterization of the pyloric and jejunal stumps, and without gastro-enterostomy (a somewhat difficult procedure in the rabbit), the animal will live for the same length of time as with a simple pyloric obstruction, that is, about forty to forty-eight hours, and the course of symptoms is in no way different from that in simple obstruction. Injection experiments have shown that the fluid in a closed duodenal loop is toxic, and while a report of the experiments concerning the nature of the secretion and its pathological effects is reserved for a subsequent paper, it may be stated that a closed duodenal loop will be distended within three hours after placing the ligature, by a fluid which is clear, slightly straw colored, of about the same alkalinity as the pancreatic juice, and containing considerable mucin. Intravenous testing of the fluid is impractical because instant death follows the injection of small amounts. The autopsy, made immediately after death, shows soft agglutinative clots in the right heart. The intraperitoneal injection of about twenty cubic centimeters kills a rabbit weighing 1,000 grams in less than twenty hours, causing before death the rapid fall of temperature, the muscular twitching, and the slowing of the heart seen in the obstruction cases.

This toxin seems to be a secretion from the duodenal mucosa. The poverty of this portion of the intestine in bacteria, combined with the appearance of toxicity in the fluid so shortly after ligation, seems to weigh against the bacteria present having anything to do with the process. It seems also improbable that constant symptoms as seen in obstruction would follow the action of the variegated flora found in the animal's intestine.

Assuming then that a toxic secretion is present,—and every evidence from our series is in favor of this point of view,—it seems apparent from the time relations given above, that a certain length (about ten centimeters) of duodenum must lie above the ligature before the toxic dose secreted rises to the point necessary to kill in twenty-four hours or less. And further, that with the ligature below the duodenum, a certain length of intestine (about 100 centimeters), as suggested by Draper (Maury),<sup>10</sup> must be allowed to act

<sup>10</sup> Draper, J. W., (Maury), *loc. cit.*

upon this toxic secretion before its tendency toward a rapid fatal effect can be overcome.

Withdrawal of fluid from the body by vomiting can not be a factor in the rabbit. Vomiting does not follow obstruction in the rabbit except as an agonal occurrence. As was stated above there is a rapid secretion of fluid into the intestine in rabbits with obstruction, but in low obstruction, with all loops of intestine distended to the utmost, there is obviously much more fluid withdrawn from the tissues than in obstruction of a ten centimeter length of duodenum, and in the former case life may last a week, in the latter less than a day.

One should be able to save the life of an animal with obstruction by duodenostomy, and although Stone, Bernheim, and Whipple<sup>11</sup> have succeeded in the dog, our efforts with the rabbit have been successful only in prolonging life in duodenal obstruction by duodenostomy to forty-eight hours instead of the usual twenty hours or less. The result is probably due to a faulty technique, perhaps to absorption of secretion through the wound edges, as a similar duodenostomy without obstructing ligature gave the same fatal effect in forty-eight hours.

The import of this series of experiments is to the effect that the reabsorption of a toxic secretion from the lumen of the duodenum is the important factor in causing the rapid death of rabbits after high intestinal obstruction.

<sup>11</sup> Stone, H. B., Bernheim, B. M., and Whipple, G. H., *loc. cit.*