

THE USE OF CITRATE SOLUTIONS IN THE PREVENTION OF PERITONEAL ADHESIONS.*

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A BETTER title for this paper would be: An experimental study in the prevention of peritoneal adhesions, working upon the hypothesis that fibrous exudates in the peritoneal cavity depend upon the same principles that apply to the formation of fibrin in blood clots; *i.e.*, before a fibrous exudate can form in the peritoneal cavity with its resultant plastic agglutination, there must be the liberation of that hypothetical ferment, thrombokinase, its activation of prothrombin in the presence of calcium and the production of thrombin.

Thrombin as an active enzyme converts soluble fibrinogen into fibrin.

If then, we are to attempt to influence the production of fibrin deposits or peritoneal adhesions in the abdominal cavity, we must by some method inhibit the process of ferment activity. We must either inactivate thrombokinase or bind the calcium in the serous exudate.

In the Research Laboratory of the Medical Department of the University of California I have done a series of some sixty experiments on rabbits (these animals have all been under ether narcosis).

To determine first, whether or not there was an active thrombin element in the normal peritoneum, a rabbit was carefully opened, the peritoneum gently everted, covering the edges of the abdominal incision. An artery in the flank was cut and allowed to bleed freely into the abdominal cavity. Clotting occurred at the site of bleeding in 5 minutes, which is about the normal time for rabbits. Blood, running over the surface of this clot and gravitating to the region about the kidney where neither air had entered nor any trauma had been inflicted, remained fluid and unclotted for 15 minutes.

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Rabbit No. 2 was similarly opened, the peritoneum roughly scrubbed with a gauze sponge, a mesenteric vessel cut and allowed to bleed. Clotting occurred in 3 minutes.

Rabbit No. 3 was opened, the contents of the ileum and jejunum smeared over the intestines and an artery in the mesentery severed. Blood flowing outside the peritoneal cavity clotted in four minutes, while blood in the soiled peritoneum was mainly fluid at the end of 15 minutes.

These findings are paralleled by clinical experience. It is a common phenomenon to observe that during abdominal operations, where the peritoneum is abraded and traumatized extensively, there is an abundant formation of clots. While after intra-abdominal wounds which cause little trauma, but sever large blood-vessels, the abdomen may be found filled with fluid blood. It is also no uncommon thing to find laked, unclotted blood where the intestinal or gastric contents have escaped into the abdominal cavity following perforating or lacerating wounds of these viscera.

From this evidence we may assume first of all that there is not an active thrombin element in the normal, untraumatized peritoneal cavity. Second, that trauma to the endothelium of the peritoneum, even exposure to the air, causes the liberation of an active thrombin ferment, supposedly thrombokinase. Third, that the presence of intestinal or gastric juice with its ferments retards or abolishes the action of thrombokinase.

It is, of course, a fact that pepsin, trypsin and other powerful enzymes will inactivate thrombokinase. It is also a physiologic law that thrombokinase only is active in the presence of a calcium salt. And this salt may be bound or neutralized by citrates, oxalates or sulphates.

These experiments have been conducted to ascertain if this hypothesis in any way helped to elucidate the problem of peritoneal exudates, and the production or prevention of peritoneal adhesions. Heretofore, apparently all our preventive measures have assumed the rôle of lubricants or protectives, as if the abdominal organs were a collection of lead pipes, pistons, filters and valves,—a purely mechanical conception.

In this work, therefore, the direct experimental method,

the empirical testing of measures only vaguely suggestive, and the control, or comparative measures, have been combined. Because our interest is mainly centred in that phase of peritoneal adhesions found in the surgical problems of the abdomen, I have applied my endeavors to the prevention, if possible, of post-operative adhesions.

To mimic those conditions which most surely are productive of strong fibrous adhesions, the colon of the rabbit was scarified throughout its length with multiple scratches about an inch long, possibly four or five hundred in number. These were deep enough to cause oozing of blood, to expose the muscularis, but avoided active bleeding and puncture.

In control rabbits at the end of a week an abdomen thus treated is a mass of agglutinated intestine, hemorrhagic exudate, fibrous lymph and many plastic adhesions. In order to tabulate the results of these various experiments two general headings have been made, designated as exudate and adhesions, and their degree marked by the plus or minus sign. In some instances a quantitative estimation of the albumin output was made and recorded. This was done by implanting little glass tubes in the abdominal cavity and at the end of a week estimating by means of phosphotungstic acid, the albumin content. It was hoped by this device to be able to gauge the relative inflammatory reaction present. But the method was found too uncertain to warrant putting any confidence in it.

The following tabulation shows the average result of repeated experiments. The variations in these repetitions were so small that no indecision arose over the markings. In each case the scarification of the colon was followed by pouring into the abdominal cavity one-half ounce of the sterilized solution in question. The incisions were closed with silk.

In this series of exudates none presented a worse appearance than the experiment with camphorated oil. Here there is a thick creamy deposit, masses of fibrous lymph, large plaques of camphor adherent to the mural peritoneum and under the diaphragm, and dense resistant adhesions throughout the entire abdomen.

TABLE I.

	Exudate.	Adhesions.
Control	+	++
Tr. Iodine	++	++
Camphorated oil	+++	+++
Olive oil	++	++
Petrolatum	++	++
Butter	++	++
Sugar 50 per cent. solution	+	++
Citrated sugar	+	+
Egg albumen	+	+
Citrated egg albumen	++	+
Milk	+	+
Peptonized milk	+	—
Ringer's solution	—	++
Salt solution, normal	—	+
Ammonium oxalate 1 per cent. } Salt solution. }	—	+
Citrate of soda 1 per cent. } Salt solution }	—	—
Sodium citrate 2 per cent. } Sodium chloride 4 per cent. } in water.....	—	— —
Citrate of soda solution 2 per cent. } Salt solution 3 per cent. }	—	— —

Petrolatum gives a slimy, greasy emulsion appearance, with quantities of opaque lymph and isolated firm adhesions between the intestines. The abdominal incision is poorly healed, its edges are insecurely agglutinated and appear poorly vascularized.

The only death occurring in this series of experiments resulted from the use of iodine in the abdomen. Apparently it was due to the toxic effect of iodine plus a septic peritonitis.

As you see from the table, citrate of soda in salt solution gives the best results. After an impartial scarification, which under normal circumstances at the end of a week would give a nasty peritoneum, with the addition of citrate solutions we have an abdomen practically free from exudate, no adhesions, sometimes the endothelium shows no sign of insult past a hazy opacity and thickening.

These findings are so striking in contrast to all others that they seemed incredible. If it were possible to show by

photographs this difference, the case would be clearly proved; but we must content ourselves with description.

It was apparent from the first that the citrate of soda—2 per cent.—with hypertonic salt solution—3 per cent.—was the best medium used. It was found that hypertonic solutions remained longer in the abdomen than normal solutions. A hypertonic solution colored with methylene blue gave traces of its presence after 48 hours, while normal solutions disappeared in half this time.

At the beginning of this *arbeit* the following questions arose:

First, are we not trying to prevent a natural protective process?

Second, will not capillary hemorrhage be encouraged?

Third, will not infection result, from an interference with the local immunity?

Fourth, will not these solutions be absorbed so rapidly that no good will result from their use?

Fifth, may these solutions themselves be toxic?

The first is the most difficult to answer. But we may change the question by asserting that Nature does not always work best alone and we are assisting rather than interfering.

To answer the second, two experiments were tried in which citrate solutions were employed after voluntarily severing many small vessels of the intestinal subserosa. No evidence of hemorrhage was found at autopsy one week later.

For the third question it must be said that rabbits are very resistant to abdominal infection and that we lost but one animal in the entire course of some 60 laparotomies, even in the face of rather indifferent asepsis.

The fourth question is answered by our success. In peritoneal post-operative inflammation, the height of the storm is past in 48 hours. The solution is present when most needed. When the insulted, traumatized endothelium is pouring out plastic exudate, with a large content of fibrin ferment, it is met by the inhibitory action of citrate of soda.

To test the toxicity of citrates and oxalates five grains each

in one-half ounce of salt solution were injected intravenously in two rabbits. It had no apparent effect on these animals.

It is conceded that probably the best medium for carrying the citrate solution has not been found, and that I have not taken into account the problem of colloids. It is quite likely that further investigation with these questions in view will throw much light upon the subject. Another feature of the work is that upon the introduction into the abdomen of these hypertonic salt solutions with or without citrates, there is always a marked peristalsis with an accompanying contraction of the abdominal muscles, which often rouses the animal from anæsthesia, and seemingly is painful. This quickly passes, and there is no evidence of local irritation—in fact, reddened and ecchymosed intestines become less vascular and more normal in color.

It is not assumed that citrate solutions will prevent adhesions where large denuded areas of the peritoneum are exposed. These should be treated by omental grafts or mesenteric plication. These laboratory results seem applicable only as a mild preventive measure during abdominal operations, which ordinarily tend to leave more or less agglutination and troublesome post-operative adhesions.

It is *not* suggested that large quantities of solution be left in the abdominal cavity, although in the absence of pus it probably is not detrimental so to do, but that the usual operating room solutions of normal salt have added to them a one or two per cent. of citrate of soda.

For the past month, Dr. Terry has employed a 3 per cent. salt with a 2 per cent. citrate solution in all abdominal work done at the University Hospital. It is not easy, of course, to determine how much good this does as a preventive, but from all visible signs in the laboratory, it certainly seems not only theoretically correct and far superior to any means hitherto employed, but is unquestionably of marked practical advantage.