

HEPARIN IN THE PREVENTION OF PERITONEAL ADHESIONS*

REPORT OF PROGRESS

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A PRELIMINARY REPORT,¹ recently presented, suggested that heparin, intra-abdominally administered, is effective in preventing the formation and re-formation of peritoneal adhesions in the rabbit and dog. Ten dogs, receiving 3,000 units of heparin in solution in single daily administrations at operation and on each of two postoperative days, presented an adhesion reformation rate of 26 per cent, whereas the corresponding rate was 157 per cent in the control group of 20 animals, in which either no solution, normal saline solution, or amniotic fluid concentrate was administered intraperitoneally. In other words, after heparin the count of adhesions was about one-fourth of the count at the time of injection of the substance; in the control group the adhesion count showed more than half as many again at the final stage as compared to the number of adhesions divided.† Some doubts were expressed in regard to the safety of intraperitoneal heparinization from the point of view of hemorrhage on the basis of three fatal hemorrhages in 24 dogs. This high incidence of bleeding was believed to be the result of inadequate hemostasis at the time of dividing the adhesions.

The present report of progress offers evidence on three phases of the general study: (1) Intraperitoneal dosage; (2) the danger of hemorrhage; (3) the effect of intraperitoneal heparin in the freshly contaminated abdomen.

METHODS EMPLOYED.—Dogs were employed throughout. The method for creating peritoneal adhesions was that used in the previous investigation.¹ Adhesions were consistently produced by perforating the appendix and smearing a small, measured quantity of its expressed contents over the terminal ileum and the adjacent cecum. In recent experiments, light, dry gauze scarification of the terminal ileum was an added technic preliminary to contamination. This procedure was found to localize the adhesions more successfully. The appendiceal perforations were not closed. Six weeks later the resulting

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† Since publishing the original paper, five additional control animals were studied similarly with papain made up in Hartman's solution in a concentration of 1-20,000, as recommended by Ochsner.² The animals treated with papain presented a reformation of adhesions of 117 per cent. The results with papain were numerically the best of the control studies, bringing the average rate of adhesion reformation down to 147 per cent. The papain employed was obtained through the courtesy of Parke, Davis and Co., Detroit, Mich.

adhesions were divided and heparin solution in varying doses was administered intraperitoneally. In some animals (Table 1) additional heparin was given by paracentesis on one or more subsequent days. A third operation was performed two weeks later, at which time the number of reformed adhesions was observed and recorded.* Powdered heparin was purchased from the Connaught Laboratories, at the University of Toronto, and was dissolved in sterile water at the time of use. Normal saline was originally employed as the vehicle but was discarded when the reformation results with saline solution alone were found to be the highest in the control series. A number of animals in these groups have been discarded on account of wound infections communicating with the peritoneal cavity as the result of an epidemic of contamination of the cages.

In the experiments dealing with the contaminated peritoneum, the heparin solution (3,000 units) was first introduced at the time of perforating the appendix rather than after adhesions had formed. Two additional doses were given by paracentesis on successive postoperative days.

RESULTS.—*Dosage Experiments:* Table I presents the results of the dosage experiments in which both the number of single daily administrations and the quantity of heparin per dose were varied. The figures indicate that more than two intraperitoneal doses are necessary, even when a relatively large number of units of heparin are administered, and that more than three doses do not improve the results. The number of reformed adhesions following two daily doses of 1,000 units each is appreciably greater than when 3,000 units are employed. When three administrations are made, the results of the 1,000 unit dose and the 3,000 unit dose are approximately equal.

TABLE I

REFORMATION OF ADHESIONS

Results Two Weeks Following Separation of Previously Produced Adhesions in the Dog After the Introduction of Heparin Solution Intraperitoneally by Paracentesis

Number of Dogs	Number of Daily Heparin Injections	Units of Heparin Given per Injection	Average Number of Adhesions Separated	Average Number of Adhesions Reformed	Average Per Cent of Adhesions Reformed
10	1	3,000	6.3	5.8	92
5	1	9,000	15.6	9.6	62
5	2	1,000	15.4	13.8	89
10	2	3,000	16.0	8.4	52
10	3	1,000	8.4	2.4	29
10	3	3,000	9.7	2.6	26
6	4	3,000	15.8	5.3	33

Hemorrhage.—In experiments to date with intraperitoneal heparin administration, no further intra-abdominal hemorrhages have occurred. There

* The attempt at a quantitative method of recording results is, of course, inaccurate. It offers, however, the only objective method available short of direct observation of the animals.

have been to date 75 consecutive introductions of heparin without hemorrhage, and only three hemorrhages in a present total of 101 dogs.

Heparin in the Contaminated Peritoneum.—Table II presents the results of the introduction of heparin into the freshly contaminated peritoneum in 17 dogs as compared with the results in a group of 100 consecutive control animals in which the peritoneum was contaminated for the creation of adhesions for later study. Whereas 43 per cent of the control animals died of peritonitis, 53 per cent of the heparin dogs succumbed to this complication. In the animals that survived, however, the average number of adhesions formed in the heparin dogs was less than one-third of that formed in the controls.

TABLE II

HEPARIN AND CONTAMINATION

Results Following the Intraperitoneal Introduction of Heparin at the Time of Perforation of the Appendix

Group	Number of Dogs	Mortality Rate	Average Number of Adhesions in Living Dogs
No solution	100	43%	9.4
Heparin	17	53%	2.9
3,000 units at operation and two additional doses			

DISCUSSION.—The absolute figures furnished by the present experiments confirm the earlier conclusion that heparinization of the peritoneal exudate in dogs inhibits the reformation of divided intra-abdominal adhesions. The suggestion of a curve dependent upon dosage, as presented in Table I, adds further evidence of a definite heparin effect. To this may also be added the low numerical incidence of adhesions in the surviving dogs, presented in Table II.

The study of dosage is as yet incomplete. The method of attack is necessarily slow and final conclusions may be delayed. Furthermore, for reasons to be discussed below, the ultimate determination of the optimum dosage of heparin given intraperitoneally may not be pertinent. Certainly, for the moment, it is clear that more than two intraperitoneal doses are necessary, and that four daily doses do not present improved results over those following three daily doses. The minimum effective dose per day for three administrations has not yet been determined.

The freedom from further occurrence of hemorrhage has paralleled greater operative attention to hemostasis. It is probable, therefore, that the earlier explanation of the cause of the trouble at first encountered, namely, inaccurate hemostasis, is correct. We now feel that hemorrhage is not a danger, if bleeding can be completely controlled before introduction of the heparin solution.

In the earlier experiments with rabbits,¹ it was surprising that 100 per cent

of recoveries occurred when heparin was introduced into the peritoneum at the time of perforation of the appendix. It might have been expected that all such animals would die of general peritonitis on account of the assumed absence of fibrinous adhesions. In the present group of dog experiments, almost equally surprising results occurred. It had been supposed that at least 90 per cent of the dogs in which heparin had been introduced at the time of perforation would die of peritonitis. In contrast to this expectation, only 53 per cent died, a mortality not strikingly different from that among the controls. This seems to indicate that heparin may not materially increase the danger of peritonitis when the peritoneum is soiled. We are not yet ready to suggest a modification of the traditionally accepted ideas of peritoneal defense against infection as at least partially effected through fibrinous adhesion about the source of contamination. We feel, however, that these results indicate the possible usefulness of heparin in the contaminated peritoneum provided the source of contamination is not still present, as for instance following intestinal suture. Further experiments in this connection are contemplated.

The studies so far prosecuted do not yet permit of clinical application. We are convinced of the effectiveness of heparin and of its safety. The method of administration and the optimum dosage are still undetermined. It must be pointed out that repeated daily intraperitoneal administration is not well adapted to clinical use. Postoperative paracentesis in patients may be uncomfortable and may present danger. Three other methods of administration are now under investigation: (1) The first is based on the possibility that an intraperitoneal exudate may be uncoagulable if the blood plasma from which it is derived is first rendered relatively uncoagulable by subcutaneous or intravenous heparinization. In these studies heparinization of the animal is begun by these routes as soon as the operation for division of adhesions is completed. (2) The second method combines intraperitoneal administration of heparin at the time of division of adhesions (as in the present experiments) with subcutaneous or intravenous heparinization in an attempt to prolong the local effect. (3) The third attack is a study of intraperitoneal drip heparin administration through an inlying rubber tube introduced at operation.

Until the best method has been worked out in the dog application to the clinical case must be delayed. As stated in the earlier report the possible success of the method in clinical surgery must, at least for a long period, be judged on laboratory rather than clinical evidence.

CONCLUSIONS

(1) Intraperitoneal heparinization in three daily doses of at least 1,000 units largely prevents the reformation of divided peritoneal adhesions in the dog.

(2) Hemorrhage following the intraperitoneal administration of heparin is not a danger if hemostasis is complete before the heparin is administered.

(3) Contamination of the peritoneum does not appear to be a contraindication to the intraperitoneal use of heparin.

REFERENCES

- ¹Lehman, Edwin P., and Boys, Floyd: The Prevention of Peritoneal Adhesions with Heparin: An Experimental Study. *ANNALS OF SURGERY*, III, 427-437, March, 1940.
²Ochsner, Alton: Personal communication.

DISCUSSION.—DR. HARVEY B. STONE (Baltimore, Md.): Every general surgeon, I think, must be greatly interested in any proposed method of diminishing abdominal adhesions, and I personally have been particularly interested in this because, many years ago, one of the earliest pieces of experimental work that I undertook concerned itself with measures designed to prevent adhesions—and I might say in passing, it was completely unsuccessful. So when Doctor Lehman's work came to my attention, naturally, I was immensely interested in it, because it seemed to me that it was the most logical and hopeful attack on the problem that I had personally ever heard of.

The purpose of my speaking at all now is to report very briefly some uncompleted work which is being carried on by Doctors Owings and Hewitt, two of the younger men connected with the Hopkins Clinic, which they have given me permission to speak about. They are working on the same issue, namely, heparin as a preventive of abdominal adhesions, but have purposely modified, in several directions, the technic employed by Doctor Lehman, in order to explore varieties of procedure which may increase the success of the method. They have used various means of inducing adhesions, and the one, at the moment, which they have found most effective and, in their judgment at least, most suitable for comparative studies, is the production of a chemical irritation by painting of serous surfaces with small amounts of ferric chloride. Their experimental animals have been cats instead of either dogs or rabbits. They have used a different preparation of heparin, or at least heparin from a different source from that employed by Doctor Lehman, so that from many aspects of detail, their series will give a comparable study to his. Their work is by no means completed; in fact, I am requested to say that they are not in a position to express any opinion as yet about the results but merely to say what they have done.

First, I might say they have had no hemorrhages at all in their series of animals as a result of the introduction of heparin. They have found, beginning with smaller doses than those employed by Doctor Lehman, for instance, a considerable series in which 250 units of heparin were employed, no recognizable benefit. They then increased the dose of heparin to 500 units, again with no demonstrable reduction in the amount or extent of adhesions. However, in a third series in which 1,000 units of heparin were employed as an initial dose and two successive similar doses given each succeeding day, so that, in all, the dog received 3,000 units intraperitoneally, they have obtained a beginning promise of result. Now, it will be noted that only in this last series is their dose at all comparable to the amount employed by Doctor Lehman in his very promising work. So that their first statement is, so far as they have gone, these smaller doses are ineffective.

They have reexplored one-half of their current series of cats in which three successive doses of 1,000 units have been employed, and out of a series of eight animals so explored, one showed notable reduction or absence in the amount of adhesions discovered at the second exploration. Now, that is as far as they are prepared to make any statement, and obviously no generaliza-

tions can be made from such fragmentary facts; nevertheless the work is so important, if successful, and so promising in theory, that we expect to go on with it, exploring different modifications, and we hope that Doctor Lehman has at last found a really effective solution of the troublesome problem of adhesions.

DR. J. ALBERT KEY (St. Louis, Mo.): I would expect that if heparin were present in sufficient amounts to prevent formation of fibrin, there would be some delay and difficulty in the healing of the wound and I would like to know whether that has been noted.

DR. EDWIN P. LEHMAN (University, Va., closing): The problem of wound hemorrhage following the use of heparin, which Doctor Key has inquired about, was, of course, in our minds. The experience of those who have used heparin extensively in vascular surgery, both in the laboratory and in the human being, has been that there has been no trouble with this complication. With intraperitoneal administration of heparin the animals showed a definite prolongation of the coagulation time, which lasted about 12 to 18 hours. The coagulation time is increased from a normal of three minutes to a maximum of about 12 minutes. In none of them did we have wound hemorrhage, or any disturbance of healing which could be attributed to bleeding.

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