

Prevention of Postoperative Adhesions in Rabbits with Streptococcal Metabolites.* (18278)

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In the past, investigators have used various drugs in attempts to prevent postoperative adhesions, but without success. Rea and Wangenstein(1) introduced defibrinated ox blood, amniotic fluid, sodium ricinoleate, ether and normal saline into the peritoneal cavity; Totten(2) used hypertonic glucose; Merkle (3) and Gepfert(4) instilled amniotic fluid intra-abdominally. Ochsner and Garside(5), Donaldson(6), and Ward(7) tried proteolytic enzymes such as papain to digest deposits of fibrin. The work of Lehman and Boys(8), and Van Dyk(9) have suggested that the incidence and extent of postoperative adhesions may be reduced by the introduction of heparin into the peritoneal cavity at the time of operation and in the early postoperative period. However, Bloor and his associates(10) reported a series of experiments in rabbits in which they concluded that heparin did not prevent the formation or reformation of intraperitoneal adhesions or the deposition of fibrin. In the investigations of White(11), heparin and dicumarol appeared

to be effective in decreasing but not preventing postoperative peritoneal adhesions in dogs. The method by which healing and hence adhesion formation takes place is well known and will not be reviewed here. Suffice it to say that fibrin must be present before scar tissue can be formed. The amount of fibrin formed varies with the irritant and with the individual. In serous cavities fibrinous inflammation is common. In all types of fibrinous inflammation, variable numbers of polymorphonuclear leucocytes are entangled in the threads of fibrin. Sherry *et al.*(12) have accumulated evidence that a considerable amount of nucleo-protein, which is not fibrin or its denaturation product, is present in inflammatory exudates. Tillett, Sherry and Christensen(12) have indicated in their reports that desoxyribose nucleoprotein, together with deposits of fibrin, account for the gelatinous and stringy coagulum present in purulent exudates.

It has been demonstrated that some hemolytic streptococci elaborate, during their growth in broth cultures, both a fibrinolytic principle (streptokinase) and a potent desoxyribonuclease, (streptodornase)(12). When streptococcal concentrates are added to whole samples of inflammatory exudates *in vitro*, the rapid lysis of both fibrin and desoxyribose nucleoprotein occurs. Because of this action on fibrin and inflammatory exudates, a logical application for these streptococcal metabolites presented itself, namely, in experimental postoperative adhesions.

* The Streptokinase and Streptodornase used in these studies were supplied by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

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TABLE I. Summary of Results with Streptokinase-Streptodornase in the Prevention of Postoperative Adhesions in Rabbits.

Animals	No. of rabbits	Form of drug	Results		
			No. with adhesions to scarified area	No. with adhesions to infected sutures	No. with no adhesions
Control	25	0	23	6	2
Treated	6	Powder	0	6	0
	19	Solution	0	4	15

Materials and methods. Fifty male rabbits, weighing from 2½ to 3½ kg were used in these experiments. They were divided into a control and an experimental group of 25 animals each. The latter group received streptokinase and streptodornase intraperitoneally at the time of operation. In all groups, surgery was performed under intravenous sodium nembutal anesthesia. A mid-line incision was made and an area of peritoneal wall, measuring 1 x 2 inches, on either side of the midline, was abraded with a scarifier. The scarifier was made by cutting a one-inch square from a large vegetable grater. The scarification procedure was standardized by using five strokes per area. Slight oozing of the abraded areas was produced intentionally in all cases. In one group of 8 control and 8 experimental animals, segments of the ileum and colon were also scarified, but ample adhesions were found to result simply from the abrasions of the peritoneal wall. The latter procedure was carried out in all subsequent experiments. Streptokinase and streptodornase were both contained in the same preparation and the dosage used varied from 600,000 to 1,400,000 streptokinase units per animal and from 180,000 to 350,000 streptodornase units per animal. The first 6 animals received the powdered drug, whereas in the remaining nineteen animals the drug was diluted in 10 cc of normal saline before instillation. In this series, the drug was administered intra-abdominally only at the time of operation. A laparotomy was performed on all animals 14 days after the initial operation and the number and extent of the adhesions were noted.

Experimental results. Fifty rabbits survived operation and scarification. A summary of the results is shown in Table I. Twenty-three control animals developed extensive adhesions to the areas of scarifications and to the suture line. A typical result is shown in Fig. 1. In the treated group, the 6 rabbits which received powdered streptokinase and streptodornase had been repaired with through and through silk sutures and all of these animals developed adhesions, varying from slight to dense, to the infected suture line. All of the remaining treated animals received the drug in solution and were closed in layers. Four animals in this group had slight to medium adhesions to the infected suture line, while 15 had no adhesions at all. None of the treated animals developed adhesions to the area of scarification. All of the control animals with adhesions had them at the scarification site. In each case the abraded areas of the treated animals had healed within the observation period (Fig. 2). It is interesting to note that the animal receiving the highest dosage of drug, 1,400,000 units of streptokinase and 350,000 units of streptodornase, failed to form adhesions at the incision even though there was a massive infection of the suture line. No signs of irritation or toxicity due to the drug were seen in any of the treated animals.

The results of these experiments demonstrate rather conclusively the usefulness of



FIG. 1.
Control animal showing omentum adherent to site of scarification.



FIG. 2.
Treated animal showing no adhesions to site of scarification.

streptokinase and streptodornase for preventing postoperative intra-abdominal adhesions in rabbits due to trauma. It should be emphasized that in all of the treated animals with adhesions, the bands were adherent to the infected suture line, not to the area of scarification. The last series of experiments, in which no infection was found at the suture line, revealed no adhesions in the treated animals. Of the 10 treated rabbits with adhesions, 6 were closed with through and through sutures, and all of these animals had extensive infections at their suture lines. Inas-

much as the drug was administered only at the time of operation, it is conceivable that the enzymes were no longer active as the relatively slowly progressing infection extended from the suture line. It is interesting to note that wound cultures taken from infected suture lines revealed predominantly fecal organisms. In the present report, the optimum dosage was not determined. However, the results were found to be much better when the drug was placed in solution prior to use than when used in the dry form.

Conclusion. The results in this series of animals were sufficiently encouraging as to justify the further investigation of streptokinase-streptodornase in the prevention of experimental postoperative adhesions.

Addendum: Preliminary work in dogs has indicated so far that the drug does not prevent the formation of postoperative intra-abdominal adhesions in this animal. This may be due, however, to a variety of factors such as insufficient dosage, animal inactivators or inability of streptokinase and streptodornase to activate dog's serum. Kiser's(13) experiments have shown that *in vitro*, streptokinase and streptodornase fail to activate dog's serum except in very high dosage.

13. Kiser, J., personal communication.

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Effects of a Transient Vitamin A Deficiency on Subsequent Resistance to Cold.* (18279)

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It is becoming increasingly apparent that malnutrition may cause residual effects that

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persist long after dietary deficiencies have been corrected and the gross manifestations of nutritional disease have been ameliorated (1). Recent findings by Best and Hartroft (2) are pertinent in this regard. These work-

Communication No. 274 from the Department of Biochemistry and Nutrition, University of Southern California.

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