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## MASSIVE DOSES OF PENICILLIN IN THE TREATMENT OF PERITONITIS\*

### *A Preliminary Report*

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The purpose of this report is to call attention to the fact that large doses of penicillin (100,000 units or more intramuscularly every two hours) exert a striking effect in controlling peritonitis arising from mixed flora of the intestinal tract. Penicillin, first in large doses and then in diminishing amounts for a week or ten days, will profoundly inhibit dissemination of peritonitis and will result in spontaneous resolution of many intraperitoneal abscesses. Large initial doses of penicillin and protracted therapy produce results far superior to those observed with the usual doses or the sulfonamides.

Early reports on the use of penicillin in peritonitis were equivocal and gave little promise that this drug would be superior to the sulfonamides.<sup>1</sup> At that time penicillin was scarce and expensive, and the average dose was not more than 30,000 units intramuscularly every three or four hours. Penicillin in these doses exerted a striking effect in controlling peritonitis from hemolytic streptococcal or staphylococcal infections, but appeared to do little to control mixed infections from perforated appendixes. Although peritonitis seemed less likely to spread and the patients were less sick, penicillin exhibited little advantage over the sulfonamides. Formation of intraabdominal abscesses was not prevented, and a prolonged febrile course with eventual suppurative complications was the rule.

During the past four months 30 patients with established peritonitis or with extensive contamination of the peritoneal cavity from rupture of intraabdominal abscesses were treated at the U. S. Naval Hospital, San Diego. There were 2 cases of spontaneous perforation of carcinoma

\*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

of the sigmoid, 1 of perforated diverticulitis of the sigmoid, 1 of peptic ulcer perforating into the free peritoneal cavity more than twenty-four hours before operation, 6 of perforated appendixes of from thirty-six hours to five days' duration and not operated upon, and 20 in which perforation of the appendix into the free peritoneal cavity was found at operation or in which a periappendiceal abscess ruptured during removal of an acutely inflamed appendix. Not included in this group was peritonitis from simple perforated ulcers or slight contamination incident to removal of an acutely inflamed appendix.

*In none of these cases did intraperitoneal complication occur.* Masses, when present, resolved spontaneously without drainage. After five days of treatment the temperature and pulse rate usually fell to normal and remained so. In this series the only complication was wound infection in 5 cases. It is interesting to note that these infections appeared late and were attended by only the mildest systemic reaction and practically no cellulitis.

In this study it soon became apparent that an initial large dose of penicillin maintained until the temperature was normal was not sufficient to control the infection permanently. If penicillin was withdrawn too soon, symptoms and signs of localized intraperitoneal suppuration recurred. In such cases resumption of full doses again controlled the infection and ultimately resulted in a permanent cure.

To prevent these relapses and still to economize as much as possible on penicillin, the dosage was decreased by one-half every two days. For the first two days 100,000 units was given intramuscularly every two hours, then 50,000 units every two hours for two days, 50,000 units every four hours for two days, and finally 25,000 units every four hours for two days, a total of 4,500,000 units in eight days. In 2 cases recurrence of signs and symptoms or development of localized abscess on decreased doses necessitated resumption of full doses for a few days.

The action of large doses of penicillin in controlling mixed infections which did not respond to usual doses is not clear. Cultures of pus at the time of operation have repeatedly shown *Bacillus coli* and other penicillin-resistant organisms, and usually in addition penicillin-sensitive gram-positive cocci. One interpretation of these observations and of the fact that wound infections are not always controlled, whereas intraperitoneal infections usually are, is as follows:

1. Usual doses of penicillin are not sufficient to overcome the penicillinase (anti-penicillin) effect of the *B. coli*.<sup>2</sup>
2. When larger doses are given, the penicillinase effect is overcome, and penicillin, although it does not inhibit the penicillin-resistant *B. coli*, becomes effective against the virulent gram-positive cocci.

3. *B. coli* and the majority of penicillin-resistant organisms are not virulent or invasive and are essentially saprophytes.

4. Tissues with high resistance, such as the peritoneum, are able to defend themselves against such organisms as *B. coli* if infection with virulent gram-positive cocci is controlled.

5. Areas of low resistance, such as a wound of the abdominal wall, are not equipped with the defense mechanism of the peritoneum, and saprophytic organisms resistant to penicillin are likely to gain a foothold in dead spaces, in exudate, or in devitalized tissue.

The effect of penicillin on fever is not so dramatic as that observed when a sulfa-sensitive infection is treated with a sulfonamide. Two or three days may elapse before the fever begins to subside, but the pulse tends to remain slow, abdominal tenderness disappears within forty-eight hours, distention is minimized, and the patient looks and feels remarkably well.

Without untoward effects 100,000 units of penicillin has been given every two hours for as long as six days. In fact, the upper limit of the safe dose of penicillin has probably never been reached. In 3 cases of this series hives developed, and in 4 cases fever as high as 102 F. was apparently associated with the administration of penicillin. As soon as the drug was withdrawn, the temperature fell to normal.

#### SUMMARY

1. Massive doses of penicillin exert a striking effect on peritonitis and, if maintained for a considerable period of time, will usually effect a resolution of intraperitoneal inflammatory masses.

2. Thirty patients with established peritonitis, intraabdominal inflammatory masses, or extensive contamination of the peritoneal cavity from ruptured abscesses were treated with 100,000 units of penicillin every two hours intramuscularly for two days and with diminishing doses for six more days. None developed intraperitoneal abscess or complications.

3. If symptoms and signs of intraperitoneal inflammation recur after the first course of treatment, a second course will probably again control the infection.

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