

THE RELATION OF THE WELCH BACILLUS TO APPENDICITIS AND ITS COMPLICATIONS*

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TEN years ago we began a study of the relation of Welch bacillus infection to gangrenous appendicitis and peritonitis and of the possible clinical value of the antitoxin available at that time. In 1923 and again in 1925 we reported our results up to that time which appeared to indicate some value in the use of the serum and suggested the possibility of its usefulness in intestinal obstruction and as a prophylactic in perforating wounds of the bowel and in operations on the intestinal tract.

It may not be out of place to summarize briefly the contents of these previous papers before discussing subsequent experience in this field.

It seemed evident that in gangrenous appendicitis and peritonitis we have to do with a faecal infection due in part, at least, to the activity of the Gram-positive anaërobes that normally infest the gut and whose presence in war wounds was so regularly associated with gas gangrene. We had seen occasionally infection of the abdominal wall after operation for appendicitis in which gas gangrene had supervened and a few similar cases associated with retroperitoneal emphysematous oedema. These cases were unusual. They were all highly toxic in their course and all were fatal. In a few cases we had been led to suspect the presence of the bacillus aërogenes capsulatus of Welch and to verify its presence by cultivation and animal inoculation. We considered, at that time, however, that these were rather rare infections. We had no therapeutic measures with which to combat the disease and the difficulties of routine anaërobic bacteriological study hampered further investigation. This was before the war.

There are several things in the picture presented by a case of gas gangrene of the extremities in his last hours that singularly resemble that of one dying of peritonitis. The low temperature, the rapid, feeble pulse, the dusky flush and cyanosis, the dyspnoea, the dilated pupil, the euphoria. The similarity is more than suggestive.

When we returned to civil practice we found one American antitoxin serum—a mixed antitoxin for tetanus and perfringens—available, and its use in a series of gas gangrene infections seeming to establish its value, it appeared worth trying in appendicular peritonitis.

I shall not repeat here the résumé of the literature made in 1923. That dealing with the Welch bacillus is massive but discussion of the activity of that organism in surgical conditions within the abdomen is not very rich. I would, however, refer once more to the monograph of Heyde of Friedrich's

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clinic in Marburg, published in 1911 and devoted to a study of the anaërobes in appendicitis. I know of but one subsequent study of equal analytic scope, to which I shall refer later. He attempted to answer the following questions:

- 1.—What anaërobic types are found?
- 2.—How often do they occur?
- 3.—Do particular forms predominate at different stages of appendicitis?

His investigations were painstaking and time consuming. He found that from one to two months were necessary for a complete study of the isolated strains from any given case. His findings are not without interest even now. He found the greatest obstacle to his study in the presence of the *B. coli* which by its rapid growth obscured and distorted the true bacteriologic conditions present. He did not believe that within the animal body the *B. coli* is able to split up proteid with the formation of putrid products but thought that this supposition, which has been so widely held, was due to overlooking the existence of anaërobes which were present at the same time. *Bacillus coli* showed none of that ability to form foul-smelling products credited it by so many authors. He listed seventeen varieties of anaërobes isolated, concluded that anaërobic bacteria were present in one hundred out of one hundred and two cases studied and that they were present in greater profusion than aërobes in all stages of appendicitis and peritonitis and attributed to them the direct causation of inflammation, of gangrene and of toxæmia. He found that the perfringens group—*B. Welchii*—outstripped all others in rapidity of growth.

Simonds, however, in his classical monograph, "Studies on *B. Welchii*, with Special Reference to Classification and to Its Relation to Diarrhœa," noted, in 1915, that the relation of anaërobes in general and of *B. Welchii* in particular to appendicitis was still unsettled. There are, however, some more recent contributions that deserve notice.

Gas bacillus infection of the abdominal wall has been noted and reported by Beer, Winter, Russell, Ochsner, Dayton and others. These spreading gangrenous processes are rare but a milder and comparatively harmless involvement of the fascia and subcutaneous tissue is present in many drained cases. The Welch bacillus can be regularly recovered from such cases by proper anaërobic methods.

Our problem was to study the occurrence of the Welch bacillus from the lumen of the appendix in cases of appendicitis and attempt to evaluate the use of an antitoxin in cases in which we found it in the peritoneal fluid. This we did as follows: We made

1. Anaërobic cultures of the contents of appendices removed at operation.
- 2.—Anaërobic cultures of specimens of tissue taken from the wall without invasion of the lumen of appendices removed at operation.
- 3.—Anaërobic cultures of the fluid removed from cases of peritonitis secondary to gangrenous appendicitis.

- 4.—Anaërobic cultures of the blood in cases of proven *B. Welchii* peritonitis.
- 5.—Post-mortem studies in cases of death due to peritonitis and appendicitis.
- 6.—Clinical studies of the value of antitoxin in cases proved by culture to be infections with *B. Welchii*.

We found that cultures made from the contents of the lumen of appendices removed at operation showed the presence of *B. Welchii* in 90 per cent. of the cases.

In seven cases in which the appendix was acutely inflamed, thickened and œdematous but with no gross perforation, cultures made of portions aseptically removed in the operating room and so cut as to remove the peritoneal and muscular coats of the organ without invading its lumen also showed the presence of *Bacillus Welchii*.

In sixteen cases, localized pus collections with gangrene showed *B. Welchii* and in forty cases in which culture was made from free fluid in the pelvis or general peritoneal cavity, *B. Welchii* was found ten times.

The results of blood culture were, for the most part, negative. The studies of the blood made in cases of gas gangrene during the war showed that blood culture is negative at the beginning of gangrene. In cases fully developed Lardenois and Baumel found seven positive cases in forty-eight cultures. Weinberg and Segine found four positive cultures before death in twenty cases of hæmoculture. Delbet and Fiessinger found two positive in seven blood cultures made in the agonal period. It is evidently the general opinion that the passage of organisms into the blood occurs just before or after death as the antitryptic indexes alkalinity are lowered.

It seemed to us evident that the Welch bacillus was present in the lumen of most appendices and is frequently found outside of the gut in an actively growing form in appendicular abscess and in localized peritonitis and in a rather large number of cases in free peritoneal exudate, that in most cases its activity is cut short by operation with removal of the appendix but that this is not always the case and it is apparently an active factor, if not the most active factor, in the production of a fatal disease.

In the beginning of the work we were handicapped by the fact that culture made at the time of operation required from twelve to twenty-four hours for an available report. We found, however, that by making injections of the suspected material in the liver of the living guinea pig, killing the animal at the end of three minutes after injection, and placing the animal in the incubator, study of the liver, at the end of two hours, was an adequate clinical test. Smears were taken from the bloody peritoneal fluid, the liver itself and from the heart's blood. In positive cases the organism could be seen easily. According to our records there were 97 per cent. positive findings in animals after two hours compared with the positive anaërobic milk cultures. We felt, at that time, the desirability of an assured bacteriological diagnosis before ad-

ministering the antitoxin. It was, and is, expensive. The reactions when given by the intravenous route were quite severe and sometimes alarming and we were feeling our way. After using this routine for about four years we thought we could recognize, in the clinical appearance of the peritoneal exudate and by the examination of smears made at the table, the presence of the Welch bacillus sufficiently accurately for our purpose and described the cases thus.

The cases of diffuse peritonitis in which the anaërobes are present in numbers show a more or less typical clinical picture. The temperature is not, as a rule, much elevated, the pulse rate out of ratio, they are cyanotic and the pupil is dilated, a dusky flush may be present. At section the fluid may be foul or not, a dark colored or coffee-ground fluid is sometimes seen. One may find, in the region of the base of the cæcum, an emphysematous retroperitoneal cellulitis spreading and sometimes extending to the anterior abdominal wall. The progress of such a case may be quite favorable for from twenty-four to forty-eight hours when with comparatively little distention and little or no regurgitant vomiting the pulse becomes rapid and thready, cyanosis becomes more profound, the skin grows clammy, respiration more and more rapid and death occurs.

We then gave up the guinea-pig culture method which we felt we could do without but did not begin routine prophylactic injection until several cases of gangrene of the appendix with but slight peritoneal involvement apparent at the time of operation unexpectedly developed peritonitis on the third or fourth day, which went on to a fatal termination with the proven presence of Welch bacillus, missed by smears at the table and unsuspected. We had been considering the path of infection from the lumen of the appendix into and through its wall to the peritoneal cavity eventually, terminally, or post-mortem to the blood-stream. It had not occurred to us that after the removal of the appendix any large infected area of bowel wall might remain in the picture.

The following case was enlightening:

CASE 729.22, a child of five years, showed a general diffuse peritonitis of seventy-three hours' duration with cyanosis, distension, feeble and thready pulse. At operation, free turbid fluid in the peritoneal cavity; a leaking abscess. Appendix showed terminal gangrene with a small perforation. One hundred cubic centimetres of perfringens antitoxin were given on the operating table; six hours after operation the radial pulse was imperceptible and more serum was given, 150 cubic centimetres in the vein, 200 cubic centimetres in the axilla, following which the little patient rallied a few hours; later another collapse was controlled by more serum. Altogether 970 cubic centimetres of serum were given, most of it intravenously. The patient rallied after each administration. Seven days after operation lobar pneumonia developed. In the meantime the abdominal distension continued extreme and never yielded to treatment. On the eleventh day the pulse became imperceptible, the skin cold and clammy, and she died. The cultures were positive for *B. Welchii*. At autopsy the last 12 inches of ileum were found gangrenous and adherent to the pelvic wall. The intestine above it was greatly distended—a complete obstruction. The general peritonitis had subsided but the local gangrenous process in the terminal ileum had gone on.

It was apparent, in this case, that the antitoxin had been sufficiently active to control the toxæmia of the peritoneal infection but that the local gangrenous process in the terminal ileum had produced an intestinal obstruction which proved fatal. We then observed particularly the condition of the terminal ileum in autopsies made on cases dying of gangrenous peritonitis and found in most of them a much thickened wall with diffuse hæmorrhagic ulceration and beginning gangrene. It was evident that this portion of the bowel was paralyzed by an inflammation approaching gangrene and would act at once as a passively obstructed segment and a source of absorption of toxic matter. This suggested inspection of the terminal ileum in cases in which this seemed safe at operation and we were interested to find, in practically every case, a greater or less degree, in many cases marked, of œdema, thickening and loss of peristaltic excitability.

It seems probable that many cases of so-called acute appendicitis are in reality acute inflammations of the terminal ileum and cæcum in which the appendix, on account of its terminal blood supply, offers less resistance than the other lymphoid structures. How important a factor this ileo-typhilitis is in the mortality of appendicitis our autopsy material does not allow us to infer, but it would seem to be not entirely negligible.

Williams made a therapeutic test of the value of *Bacillus Welchii* antitoxin in cases of general peritonitis and intestinal obstruction at St. Thomas' Hospital. Antitoxin was given to eighteen of the most severely ill of a series of 256 consecutive cases of appendicitis with a reduction of mortality from 6.3 per cent. in a parallel series to 1.17 per cent. His conclusions were: In cases of peritonitis with paralytic obstruction there was a marked clinical improvement as the result of administration of *Bacillus Welchii* antitoxin. In cases of organic obstruction similar effects were obtained but in individual cases it was as a rule impossible to differentiate between the effects of the serum and the effect of successful operative relief of obstruction.

Williams, however, reported no bacteriologic studies of appendices or of peritoneal exudate and his work was based on the assumption that death, in septic peritonitis, is the result of absorption from the paralyzed small intestine of the toxins of the *Welch bacillus*. His use of the antitoxin was directed to the neutralization of this poison. He does not discuss any intoxication save that from within the gut.

Copher, Stone and Hildreth made an experimental study of the value of antitoxin in intestinal obstruction and peritonitis in dogs. They report that life was prolonged in the experimental series of dogs having acute, general peritonitis and acute intestinal obstruction by the use of the *B. Welchii* antitoxin.

Bower and Clark reported the use of *B. Welchii* antitoxin at the Samaritan Hospital in Philadelphia. In eleven cases of acute diffuse suppurative peritonitis, nine cases of acute intestinal obstruction and five cases of acute suppurative cholecystitis, they were convinced of its value.

Morton and Stabins studied experimentally the effect of *B. Welchii* antitoxin in high intestinal obstruction in dogs. They conclude that their results support the contention that the toxin of *B. Welchii* has a bearing on the toxæmia of intestinal obstruction. In a large number of cases the antitoxin of the *B. Welchii* seems to be potent in combination with surgical procedures to relieve the obstruction in bringing about the recovery of dogs with obstruction—control dogs do not recover under similar circumstances.

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With regard to the use of Welch antitoxin in intestinal obstruction we have been disappointed. In several cases, remarkable but relief improvement has followed the administration of larger doses; in a few its use has apparently contributed to recovery. In most of the cases in which it has been used its value did not appear. It is in France, however, that the most advanced work has been done.

Michel credits to Paul Delbet at the suggestion of Weinberg the first employment of anti-gangrene serum in appendicitis. He reported thirteen cases at the twenty-ninth Congrès Français de Chirurgie with twelve recoveries.

Bérard and Cotte later reported nineteen cases with sixteen recoveries.

Bouchez in his Thèse de Paris, 1920, discussed the use of anti-gangrene serum in infections of intestinal origin with successful animal experimentation.

Michel and his pupil Rakovatz report that serotherapy and surgery show a mortality of 15 per cent. in cases which he charges with an expected mortality of 70 per cent. treated by surgery alone.

Weinberg, Prévôt, Davesne and Renard present studies on the bacteriology and the sero-therapy of acute appendicitis—a most complete and satisfying investigation which should be read entire.

They conclude that work on the bacteriology of appendicitis may be divided into three epochs. In the first, the isolation of aërobic organisms; in the second, beginning with Vuillon and his collaborators the primordial rôle in the evolution of that infection was attributed to the anaërobes neglecting or relegating to a second place the aërobic organisms. In the third, in which they now struggle, the ideal is to assign to each germ in the often very complex flora of a given case the part played by it in the symbiosis. They describe many combinations but consider that the primordial rôle in appendicitis belongs to *B. coli* and *B. perfringens*. They advise the use of a mixed serum to which anti-*coli* serum is added. They are better provided with antigangrene sera than we are but it is evident that they consider the *perfringens* antitoxin as the most valuable constituent of them all. They advise, as does Michel, the delay of surgical intervention in advanced cases until the administration of antitoxin has had time to take effect. They go so far as to suggest its use in the medical treatment of early cases.

Antitoxin.—In the beginning of our work we gave antitoxin intravenously with severe reactions in many cases in spite of subcutaneous injection of small amounts of serum given an hour before for desensitization. Increasing subcutaneous doses were then used over several hours for the same purpose. A measure of success followed this procedure but reactions, some quite severe, continued to occur. A few were alarming and for the last five or six years we have found just as satisfactory results with the subcutaneous method. We now adopt the following routine:

In all cases in which gangrenous change is apparent in the appendix 100 cubic centimetres of antitoxin is added to 1000 cubic centimetres of normal salt solution and given by hypodermoclysis. Anaërobic and aërobic cultures are made from the peritoneal exudate in the immediate neighborhood and from the fluid found in the pelvis, and further administration of antitoxin is guided by the result of culture and by the course of the case. If the organism is present in the peritoneal fluid and if evidence of peritonitis appears, and especially if the patient shows a rapid pulse with cyanosis, repeated and larger doses are administered—200 cubic centimetres daily for two or three days. The immediate effect of the antitoxin is more dramatic when given by the vein, but its action, while slower, is more prolonged by

the subcutaneous method, with no reactions. From five to ten days after injection serum rashes regularly appear.

The actual value of such a method of treatment can be determined only by an extended use in routine by a number of men in several institutions. I have used it with some freedom in more than one but have thought it best to present fifty cases from one hospital and to compare this series with the mortality of a larger group.

In a series of 450 cases of acute appendicitis cared for by several operators at the Brooklyn Hospital in the last five years, 297 were suppurative or catarrhal; of these two died, a mortality of .67 per cent. One hundred fifty-three cases were gangrenous with more or less peritoneal involvement. Of these twenty-five died—a mortality of 16 per cent. Of this group ninety-eight were cases of localized gangrene or abscess, of which thirteen died, thirty-eight were classed as spreading peritonitis with six deaths, and seventeen as generalized peritonitis with six deaths.

In the group treated with antitoxin there were no simple or suppurative cases. The serum was used only in cases of gangrene and its sequelæ, often late, often sparingly.

There were, however, ten cases of localized gangrene and abscess with one death, fifteen cases of spreading peritonitis with three deaths and twenty-five cases of general peritonitis with six deaths.

In the first series, the deaths from general peritonitis showed a 35 per cent. mortality; in the second (with antitoxin), a rate of 24 per cent.

It will require a much larger series and a more consistent use of antitoxin early, before a true estimate of its value can be made. At present it is our feeling that it should be tried in all cases presenting gangrenous change in the appendix at operation and in cases showing evidence of any peritoneal involvement at that time, and that its use should be extended until the case is out of danger or beyond help. A more critical and complete bacteriological study of appendicitis and of intestinal sepsis and a clinical evaluation of its results are most evidently needed and a larger *materia medica* of antitoxin sera would seem from the French experience to be needed. It is to be hoped that both these needs may be supplied.

ILLUSTRATIVE CASES

CASE I.—W. D., Jr., a boy of ten years, who had been sick for a week, was admitted with a rigid and somewhat distended abdomen with a tender mass in the right iliac fossa. Cyanotic, dilated pupils. Temperature 102°, pulse 140, respirations 40. Operation showed a generalized purulent peritonitis, a gangrenous appendix hanging over the pelvic brim, which contained foul, brown fluid. Appendectomy and drainage. Antitoxin immediately—100 cubic centimetres by clisis, repeated once on the second day. Pulse reached normal on the third day, temperature, on the sixth, after which a good recovery. Culture—B. Welchii and colon.

CASE II.—D. J., a child of eight years, admitted after two weeks of fever with a mass in the right lower quadrant size of a grapefruit. Temperature 104°, pulse 140, respirations 40. Operation showed an appendicular abscess which contained about 3 ounces of foul pus. There was some spreading peritonitis present. Antitoxin, 100

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cubic centimetres, was given on the day before operation by clysis and this was repeated two days later. The cyanosis did not disappear until after the second injection. A moderately stormy convalescence was established by the seventh day.

Note the early subcutaneous use of serum.

CASE III.—S. S., aged forty-five years, admitted forty-eight hours after the beginning of her third attack. Her pain began in the right lower quadrant which persisted in spite of castor oil and enemas, and at the time of admission to the hospital was general. She vomited thirty-eight hours after the beginning of the attack. Her abdomen was moderately distended and generally tender, the right side more than the left. Her entire right side was markedly rigid. There was moderate rigidity on the left side, more marked below. Her temperature was 102°, her pulse 120, her respiration 40; 17,000 leucocytes, 8,070 polymorphonuclears. She was somewhat cyanotic. She was operated on immediately and a gangrenous appendicitis with general peritonitis, foul, free pus, creamy brown, foul, surrounded the purple and inflamed coils of small intestines. The pelvis was full of foul pus; there was more pus in the right kidney fossa.

An appendectomy was performed and a drain inserted to the pelvis and to the appendix stump. She received 100 cubic centimetres of perfringens antitoxin intravenously on the second day and another 100 cubic centimetres by clysis on the third. Her convalescence was stormy with repeated vomiting, approaching faecal in character, a low temperature and a high pulse rate, which reached ninety on the seventh day, after which she made an uninterrupted recovery. Culture of the peritoneal fluid gave *B. Welchii* in pure culture.

CASE IV.—D. P., admitted with a history of vomiting and abdominal pain for twelve days; the pain in the main, suprapubic. Temperature 100°, pulse 100, respirations 20; leucocytes 14,400, polymorphonuclears 82 per cent. A large, rounded mid-line mass between the navel and the pubes. Operation showed the whole lower abdomen filled by an inflammatory mass; finger dissection, after walling off, opened a cavity containing about a quart of foul-smelling, thin pus. A counter incision and drain in left inguinal region and rubber tube drains to the cavity in the pelvis. No attempt to find the appendix. A faecal concretion was found in the cavity. He did not receive any antitoxin until the first day after operation when he was given 500 cubic centimetres in the vein. This was repeated in the next two days until he had 1,000 cubic centimetres in all. A temporary improvement was not maintained. An overwhelming intoxication carried him off by death on the fifth day.

CASE V.—F. R., a girl aged sixteen years. Pain in the epigastrium two days before admission; vomited repeatedly the next day and pain shifted to the right lower quadrant. On admission, marked right-sided rigidity, most pronounced below. Rectal examination revealed a mass in the right upper pelvis, very tender to touch. Temperature 100.2°, pulse 160, respirations 40; leucocytes 23,600, 90 polymorphonuclears.

At operation four ounces of opaque yellow fluid escaped. The omentum fastened to the base of the caecum from which an appendix, 3½ inches long, ran straight down from the brim to the bottom of the pelvis. The distal half was gangrenous and perforated with free faecal matter surrounding it. The appendix was removed and a 5⁄8-inch tube with raffia to the bottom of the pelvis, a smaller soft tube to the base of the caecum.

One hundred cubic centimetres *B. Welchii* antitoxin was given eighteen hours after operation and repeated every twelve hours until 600 cubic centimetres had been given. The pulse rate fell to 100 on the second day and remained there. The temperature reached normal on the eleventh day. She suffered from marked distention and vomited faecaloid material on the third and fourth days. Lavage was not needed after the fifth and she made an uncomplicated recovery.

Culture *B. Welchii* and colon bacillus.

The faecal peritonitis, the immediate response of the pulse rate to antitoxin, the continued fever and peritonitis, the critical period of the fourth and fifth days and the associated colon infection are noted.

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