It will be seen that, as the potency of the penicillin in units per mg. increases, the first tube to show growth is one step higher in the series. As has been shown, when a potency of 1,600 units per mg. is reached the phenomenon no longer occurs, growth occurring simultaneously with all the higher concentrations.

Further evidence that inhibition with high concentrations of penicillin is due to impurities was obtained by inactivating in the autoclave a solution of penicillin containing 100,000 units in 5 ml., or 20,000 units per ml., and inoculating with one loopful of staphylococcus broth culture. No growth occurred in 7 days, though it occurred in lower concentrations.

Speculation about the nature of any unknown inhibitory substances and their possible therapeutic action is beyond the scope of this paper.

Failure of growth at the very low concentrations of penicillin must be a phenomenon quite distinct from that observed at the other end of the scale and is much more difficult to interpret. In an attempt to elucidate it the following experiment was done:

To four tubes of broth each containing 195 units of penicillin were added the corresponding concentration of penicillinase and one loopful of staphylococcus broth culture. They were incubated for three days; no growth occurred. They were then treated as follows:

Tube 1: excess penicillinase added. Tube 2: one loopful of staphylococcus broth culture added. Tube 3: excess penicillinase and one loopful of staphylococcus broth culture added. Tube 4: no additions. All were incubated at 37° C. with a broth control.

The results were:—Tube 1: +, 24 hours; tube 2: +, 4 hours; tube 3: +, 4 hours; tube 4: 0, 7 days. Control: +, 24 hours.

Tube 1 shows that the original inoculum was still living, but that the original amount of penicillinase added was not sufficient to inactivate the penicillin. Tube 2 indicated that the penicillin had been sufficiently reduced in activity to allow a fresh inoculum to grow; tube 3 is thus redundant, in view of the results with tubes 1 and 2. Tube 4 confirms that the penicillin had not been inactivated by the original addition of penicillinase. The extremely rapid growth in tubes 2 and 3—full growth with maximum turbidity in 4 hours—is difficult to explain. It seems to be analogous to the very rapid growth, noted above, with high concentrations diluted to fall within the critical range of concentration. Both these observations seem to indicate that treatment of penicillin with penicillinase at sub-maximal levels for several days increases the susceptibility of the medium to growth of staphylococcus when the conditions are altered sufficiently to allow growth to take place. That the alteration is in the medium and not in the inoculum seems clear from tubes 2 and 3, where the inoculum was fresh.

Discussion

The observations here reported are, apart from any academic interest, of practical importance for sterility-testing of penicillin.

This laboratory is frequently called upon to test for sterility dried penicillin in phials containing up to 1,000,000 units. In the light of the observation here reported it is clear that to make certain of getting growth of sensitive contaminants the final dilution in the test medium should be related to the potency of the sample in units per mg. With potencies of less than 1,000 units per mg. it should be of the order of 1:100. However, with penicillin of recent manufacture, potencies of at least 1,400 units per mg. are usual, and it should not be necessary with such samples to employ volumes of test broth larger than those normally used for sterility testing. Where very low concentrations of penicillin are to be tested for sterility care must be taken to add gross excess of penicillinase, of the order of 10 times the equivalent quantity, whatever the potency of the sample. This does not normally arise in practice.

Apart from the above practical considerations, the phenomenon described is interesting from several points of view. Inhibition by high concentrations suggests that impurities in penicillin exert on staphylococci an inhibitory effect that is not a true penicillin effect, for it does not occur with "pure" penicillin. Inhibition at the low end of the scale is more difficult to understand. It would seem that penicillinase does not act proportionately to its concentration—that the relationship of penicillinase activity to concentration of penicillin is in fact

not linear. Consequently the value obtained by the method of assay described holds good only for a limited range of penicillin unitage—round about 4,000 units. The quantitative relationship of penicillinase and penicillin may have a bearing on the generally assumed enzymic action of penicillinase.

The extremely rapid growth of staphylococci (full growth from a single loopful in 3 to 4 hours at 37° C.) after reducing to a normal dilution a concentrated penicillin solution in which growth has so far failed to occur is a most striking phenomenon and difficult to explain. So also is the similar rapid growth in very dilute penicillin in broth after excess penicillinase has been added to a tube in which no growth has so far occurred. Such rapid growth has never previously been observed in this laboratory: it would seem to merit further study.

Summary

Staphylococci are inhibited by penicillin above a certain concentration, notwithstanding that the penicillin is shown to have been inactivated by penicillinase.

This does not occur with "pure" penicillin, suggesting that the inhibition is due to impurities.

Similar inhibition occurs in penicillin dilutions in broth below a certain concentration. In this instance the inhibition is due to the penicillinase having failed to inactivate.

In both instances, if the penicillin in broth is rendered capable of supporting growth by diluting the high concentrations or by adding excess penicillinase to low concentrations, growth of staphylococci occurs with extraordinary rapidity.

The implications of the observations are discussed from the point of view of sterility-testing of penicillin.

MESENTERIC OCCLUSION

A REVIEW OF RECENT METHODS OF TREATMENT, WITH NOTES ON SIX INSTANCES

BY

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Mesenteric occlusion is one of the rarer abdominal disasters and one that is very difficult to diagnose pre-operatively, very difficult to treat, and recovery from which is most exceptional. Having had experience of six cases in the last four years, with three recoveries, my interest was aroused and I was stimulated to consult the literature.

The occlusion may be arterial or venous, and may be thrombotic or embolic. Venous thrombosis is usually a complication of a septic process within the peritoneum. Arterial emboli may arise from cardiac vegetations, whereas arterial thrombi are likely in blood disorders—e.g., purpura. The arterial architecture is very important. The small intestine is supplied entirely from branches of the superior mesenteric artery, dividing into a series of arcades. There is no marginal artery such as is found in the large intestine. When an occlusion occurs in the area of the small intestine it has been suggested by Litten (1875) that a violent spastic contraction occurs from the ligament of Treitz to the middle of the transverse colon. The last case described below is difficult to explain on an arterio-anatomical basis. The symptoms may be acute or sub-acute: constant pain is a regular feature, with only moderate or ill-defined tenderness. Vomiting is more likely if the upper reaches of the alimentary tract are involved. Constipation or diarrhoea may occur.

Diagnosis may be facilitated in subacute cases by a plain skiagram, where gas is seen as far as the splenic flexure and a barium enema reveals no obstruction. Prognosis is always grave, but patients have lived many years after operation.

Treatment must be decided after the state of affairs has been assessed at laparotomy. The appearances found vary considerably: the bowel affected may be black, and profuse haemorrhagic exudate may be present; in others a deeper cyanotic colour is seen, with ecchymoses and less heavily blood-stained exudate. If the affected length of bowel is not too great and the patient's condition is good enough, a resection can be undertaken and anastomosis performed. Ficarra (1944) describes fifteen cases, three of which were cured by resection: Atkins (1937) reports recovery by resection, exteriorization, and subse-

quent closure; D'Abreu and Humble (1946) describe cases where small intestine was removed successfully, and careful administration of heparin subsequently is emphasized as an important factor. In all cases of cure resection had been performed, except in a case of lymphatic leukaemia (Murrey Scott and Lissimore, 1944), where the only treatment was dicoumarol 0.05 g. on alternate days. In three of the cases quoted below it will be seen that recovery occurred without resection; in only one case was heparin used. The routine followed (after dismissing the possibility or advisability of resection) was to institute an intravenous glucose-saline drip and, when vomiting threatened, to aspirate the gastric contents through a Ryle's tube. Except in one slight case (No. 4) this was maintained for ten days, and then the bowels were opened by pituitrin 0.5 ml. and a turpentine enema.

Case Histories

Case 1.—Miss C., aged 80. The patient was an arteriosclerotic subject with some evidence of myocardial failure. She had diffuse abdominal pain for two days, constipation, and vomiting; and there was distension without localized tenderness. Laparotomy showed cyanosis and distension of almost the whole of the small intestine. Nothing could be done, and the abdomen was closed. The patient died a few hours later.

Case 2.—Captain P., aged 76, a stout man retired from seafaring life, had two days' abdominal pain—not localized; vomiting; and constipation. A few days before this he had developed a slight purpura. Examination showed a dry tongue and distended abdomen, with no localizing features; his general condition was good. The diagnosis was mesenteric occlusion. Laparotomy brought to light a mesenteric occlusion affecting about five feet (1.5 m.) of small intestine. Resection was immediately decided upon and rapidly performed with an end-to-end anastomosis. The patient's condition on return to bed was good; but he never recovered consciousness, dying twenty-four hours later. Evidence suggested death from cerebral thrombosis.

Case 3.—Mrs. C., aged 58, had two days' history of right-sided abdominal pain with profuse diarrhoea; temperature 99° F. (37.2° C.), pulse 92. Her previous health had been good. Examination showed a dry tongue, and the abdomen slightly distended, with marked tenderness in the right iliac fossa. The diagnosis was appendicitis. Operation revealed a normal appendix, but the bowel was cyanosed from a point just distal to the caecum to the upper part of the descending colon. This was considered too extensive to resect, and nothing was done. The clot was found in the right colic artery. The patient was put on an intravenous drip, which was continued for seven days, and then a rectal drip for three days. Complete starvation by mouth was ordered. At the end of ten days the patient—to my surprise being still alive—was given an injection of pituitrin 0.5 ml. and a turpentine enema, with an excellent faecal result and the passage of flatus. For several days things went smoothly, the bowels acted on alternate days with enemas, and she took a gradually increasing amount of food by mouth. On the sixteenth day abdominal pain and tenderness were felt just above the caecum; her temperature rose to 100° F. (37.8° C.) and a slow perforation with localization was suspected. She was put on penicillin for four days, when the temperature subsided and the abdominal pain abated. She vomited several times. At the end of a week she seemed out of danger. She took light invalid solid diet, and the bowels responded to liquid paraffin and cascara. The tender mass gradually decreased in size, and after a month she went home. The patient remains well after six months.

Case 4.—Mr. H., aged 70. Hitherto a fit man requiring no medical attention, he had two days' history of abdominal pain, vomiting, and constipation. Examination showed a dirty tongue, slight distension of the abdomen, and localized tenderness over the right iliac fossa. Blood pressure was 230/120. A diagnosis of appendicitis was made. At operation the appendix was found normal; there was free blood in the peritoneal cavity, and ecchymoses of the caecum and a short length of ascending colon pointed to local occlusion of a mesenteric vessel. The abdomen was closed and an intravenous drip set up. Heparin was used in the drip, which was continued for three days, and complete starvation by mouth was insisted upon. Pituitrin 0.5 ml. and a turpentine enema resulted in a good bowel movement and passage of flatus. Light food by mouth was now taken, and the patient rose from bed on the eleventh day. He made normal progress as from a laparotomy.

Case 5.—Miss T., aged 74. This case is most interesting, as the patient had two attacks. The first ended in complete recovery (following laparotomy) for thirteen months. At the second attack there was partial recovery, but death resulted from a subsidiary cause. Originally she complained of abdominal pain with vomiting for four days. There was vague tenderness in the centre of the abdomen, but no disturbance of temperature or pulse, and the bowels responded to enemas. Laparotomy disclosed an extensive

occlusion affecting the upper two-thirds of the small intestine. Nothing operative could be done, so the abdomen was closed and an intravenous drip established. No food or drink by mouth was allowed, and a Ryle's tube was left *in situ* for several days, with frequent aspirations of stomach contents. This was continued for ten days. Pituitrin 0.5 ml. and a turpentine enema were given, and faeces and flatus were passed. The Ryle's tube was withdrawn and the drip discontinued. Liquids by mouth, and then solids, were allowed. Gradually recovery ensued; the abdominal distension slowly subsided, and the patient was as well as she had been for years.

After thirteen months the symptoms returned and were an exact repetition of the previous attack: vague abdominal pain with persistent vomiting. She went to a nursing home, and, being confident of the diagnosis, I did not advise laparotomy. She was treated as before with a Ryle's tube (which sometimes withdrew up to four pints (2.3 litres) of faecal matter), and an intravenous drip (later replaced by a rectal drip owing to difficulty with her available veins). After ten days the pituitrin and a turpentine enema produced a good result. She began to take fluids by mouth, but this time her convalescence was much impeded by vomiting and tremendous distension of the abdomen. Unfortunately she developed an ulcerative stomatitis with cervical lymphadenitis and parotitis. She was given penicillin, which controlled the accompanying fever, and pus was aspirated from the abscess that formed in the submaxillary region. She made a gallant fight for seven weeks, and seemed to be definitely better, with no vomiting for the last two weeks. Then she suddenly died from heart failure, apparently due to toxæmia. Post-mortem examination showed the same area of the bowel to have been affected—the upper two-thirds of the small intestine. It was still distended to twice the normal calibre, and the walls were cyanotic and thin. No accurate estimate of the state of the vessel could be obtained as examination was very difficult.

Discussion

In two cases (Nos. 3 and 4) the area affected was the large intestine, and one can understand how an anastomosis could be established by collateral vessels. In Case 5 a great length of small intestine was involved; on both occasions of occlusion recovery took place, although the intestine as seen at necropsy was still poor in appearance and performance. How did the length of bowel recover? In both the large-intestine cases the diagnosis made beforehand was appendicitis, presumably because of the localized tenderness over the distended caecum. In Case 2 and Case 5 mesenteric occlusion was diagnosed before laparotomy.

The choice of treatment at laparotomy would seem to be along the following lines. In large-intestine cases, if the intestine is not too gravely affected, expectant treatment is justified even if resection be thought practicable. In small-intestine cases resection should be carried out unless the amount of intestine involved is too great or the patient's condition makes it impossible. As much as 19 ft. (5.85 m.) of small intestine has been successfully removed.

Summary

The case reports of five patients with mesenteric occlusion are discussed. The possibility of the success of expectant treatment, particularly when the large intestine is affected, is emphasized.

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To secure the full use of the services of all available specialists, in view of the needs of the National Health Service, the Secretary of State for Scotland has informed the principal hospital authorities concerned that he is willing to meet the cost of additional full-time specialists at salaries up to £1,000. The approval of the Scottish Department of Health is to be obtained in each case. The Secretary of State will expect hospital boards to co-operate with the post-graduate organization of the appropriate university in making an appointment. The Department's approval will be given on the understanding that each appointment and the conditions attached to it are subject to review once the National Health Service is established. These arrangements are a development of the scheme set up by the Scottish universities and the Department of Health, under which ex-Service doctors training as specialists are appointed to special training posts in hospitals with salaries paid by the Department.