Further Observations on the Clinical Use of Penicillin

W. E. Herrell

The Importance of the Cardiac Impulse in Determining the Size of the Heart

H. L. Smith

Recent Publications by Members of the Staff

FURTHER OBSERVATIONS ON THE CLINICAL USE OF PENICILLIN

W. E. Herrell, M. D., M. S., in Medicine, Division of Medicine: Penicillin, the antibacterial agent which was first reported by Fleming in 1929, is now being studied both experimentally and clinically. Penicillin appears to have received little attention for approximately eleven years after the report of Fleming. It remained for the Oxford investigators in 1940 (Chain, Florey and others) to prepare a highly concentrated and active preparation of penicillin suitable for clinical use. In 1941, Abraham and others reported on their investigative studies including clinical trials. Fortunately, penicillin, unlike many similar substances, has been found to be relatively nontoxic and at the same time bactericidal under certain conditions. It is well recognized that penicillin is not related to, nor does it behave like any of the chemotherapeutic substances now in use. It is not hemolytic. It is highly soluble. It does not behave as a detergent. Its action is not inhibited by the presence of para-amino benzoic acid nor by the products of tissue destruction.


Early in 1941, Heilman and I began our investigation of the antibacterial activity of penicillin. Using the tissue culture method, we were able to confirm, with minor differences, the observations made by the Oxford investigators. Other confirmations of these studies have been made by Hobby and associates. Subsequently, Meyer and others have prepared a potent preparation which appears the same as that studied by Abraham. An interesting report has recently appeared by Roberts and his associates which indicates that three different strains of Penicillium notatum, which had their origin in the strain isolated by Fleming, possess the ability to elaborate another form of penicillin. They ascribe to this second form of penicillin the name of “penicillin B.” Unlike penicillin which is extremely soluble and rather unstable under certain conditions, penicillin B is readily soluble in water but is insoluble in lipid solvents. Penicillin B in the dry state is stable. The potency of penicillin B is in the range of approximately 50,000 Oxford units per milligram. While penicillin B is active against certain gram-positive forms including the Staphylococcus aureus, it is also active against gram-negative bacteria. Unfortunately, penicillin B is toxic for mice when injected subcutaneously. The St. Louis University investigators indicate that 2.5 mg. (3,000 to 50,000 Oxford units) administered subcutaneously causes death of mice in three to twenty-four hours. Small repeated injections made over a period of time, however, make possible toleration of larger quantities. If this seemingly potent material can be freed of its toxicity, a more stable form of penicillin may become available for clinical use. At any rate, the product described by these investigators may prove useful clinically in spite of this toxicity. Because of its potency, its stability and its apparent polyvalent activity, it should prove valuable at least for local use.

The recent report by Meyer and his associates on the preparation of methyl and ethyl esters from the free acid of penicillin is

exceedingly interesting. These preparations appear to be fairly stable and highly protective for mice against lethal intraperitoneal doses of a highly virulent strain of hemolytic streptococci. The material was administered subcutaneously.

SELECTION OF CASES FOR TREATMENT

The clinical use of penicillin at the Clinic was reported briefly in 1942. Experience with the material in the treatment of severe infections owing to organisms susceptible to penicillin continues to be exceedingly gratifying. Because of the somewhat limited amounts of penicillin available, care should be taken in selection of the type of infection to be treated. It appears that penicillin is not indicated in the treatment of infections due to the commoner gram-negative organisms. Experimentally it is ineffective against Mycobacterium tuberculosis. While an occasional strain of green-producing streptococci is susceptible to the action of penicillin even in dilutions of 1:500,000, penicillin seems not to be indicated in the treatment of subacute bacterial endocarditis. The blood stream may be temporarily freed of these organisms, yet the problem of the valvular lesion, which serves as a continuing focus, still precludes the successful use of this or any other antibacterial agent. In our experience streptococci susceptible to penicillin will reappear in the blood stream within four to six hours after administration of penicillin is discontinued in this type of case. Treatment with penicillin should be reserved for severe infections owing to Staphylococcus aureus, Streptococcus pyogenes, susceptible strains of Diplococcus pneumoniae, Neisseria gonorrhoeae and Neisseria intracellularis. On the basis of experimental evidence it should prove useful in the treatment of infections associated with gas gangrene. Because of its activity against Actinomyces bovis, clinical trials are now being undertaken.

METHODS OF ADMINISTRATION

Penicillin which is not pyrogen free may be administered locally in the treatment of infections owing to susceptible organisms. On the other hand, other germicides of similar antibacterial activity are easily available for local use. Among these substances are sulfonamides, gramicidin and synthetic quaternary ammonium compounds, such as phemerol and zephiran. Penicillin may be administered by mouth; however, it must be protected against the acid phase of the stomach which renders the substance impotent. It is doubtful that this method of administration is of great value. Nonpyrogen-free material may be administered subcutaneously in small amounts without difficulty.

It is my opinion that the continuous or nearly continuous intravenous administration of pyrogen-free penicillin is the most suitable method of treating severe infections of the types considered previously. The material rapidly disappears from the blood stream into the surrounding tissues and is rather rapidly excreted in the urine. The continuous intravenous administration, therefore, insures a more uniform and continuous contact between the antibacterial agent and the bacteria invading the blood stream than any other method of administration. Periodic intravenous injections of relatively large amounts of penicillin followed by an interval during which the amount of the material in the blood is almost negligible may do much to encourage the development of so-called penicillin-resistant or penicillin-fast pathogens.

For the treatment of moderately severe or severe infections
30,000 to 40,000 Oxford units per twenty-four hours is in my opinion an adequate amount of penicillin. Half of the twenty-four hour dose is dissolved in 1 liter of physiologic solution of sodium chloride. If for any reason the administration of physiologic solution of sodium chloride is undesirable, penicillin may be administered in a 5 per cent solution of glucose in triple distilled water without any loss of activity of penicillin. Initially between 100 and 200 c.c. of the material is administered intravenously at a fairly rapid rate. Following this the rate of injection is regulated to between 30 and 40 drops per minute. The second liter containing penicillin may be attached to the continuous intravenous system eight to ten hours later. Repeated venipunctures may be avoided by allowing the solution of glucose to drip in slowly during the interval in which penicillin is not being administered. A simple arm splint is applied to keep the arm in position. This is tolerated well by the patient and renders the continuous intravenous administration possible and not uncomfortable. When pyrogen-free penicillin has been used, no toxic reactions have been observed. The solution containing penicillin is made up immediately before use. There is no evidence of loss of potency of the material which is kept in the closed system and is administered in the manner described.

**CLINICAL RESULTS**

The present report is based on the clinical experience in ten cases in which penicillin has been used. The remainder of the clinical material will appear in a subsequent report. The entire group of cases are summarized briefly in table 1. The organism of infection in eight of these cases was the Staphylococcus aureus. In one case the organism isolated was a nonhemolytic streptococcus, and in the tenth case the organism of infection was a green-producing streptococcus. In two cases of this group penicillin was administered locally and in one subcutaneously. In the remaining seven cases it was administered
intravenously. In eight of the ten cases severe overwhelming infections occurred. In the two cases in which the material was used locally the infection was of a chronic nature.

Cases 1 and 2.—These patients suffered from chronic ulcers of the lower extremities, one of which was associated with an underlying osteomyelitis. In both cases the organism of infection was the Staphylococcus aureus. Penicillin was applied locally to these wounds and in both instances cultures became negative and clinical improvement occurred.

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Infecting organism</th>
<th>Blood culture†</th>
<th>Days treated</th>
<th>Total penicillin units</th>
<th>Administration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic ulcer and osteomyelitis</td>
<td>Staph. aureus</td>
<td>0</td>
<td>10</td>
<td>16.8</td>
<td>2,100 Local</td>
<td>Good</td>
</tr>
<tr>
<td>2</td>
<td>Chronic ulcer</td>
<td>Staph. aureus</td>
<td>0</td>
<td>7</td>
<td>16.8</td>
<td>2,100 Local</td>
<td>Good</td>
</tr>
<tr>
<td>3†</td>
<td>Facial and orbital cellulitis</td>
<td>Staph. aureus</td>
<td>+</td>
<td>9</td>
<td>1160</td>
<td>160,000 Intravenous</td>
<td>Recovery</td>
</tr>
<tr>
<td>4</td>
<td>Multiple encapsulated abscesses</td>
<td>Staph. aureus</td>
<td>+</td>
<td>34</td>
<td>4,200</td>
<td>Subcutaneous</td>
<td>Recovery</td>
</tr>
<tr>
<td>5</td>
<td>Extensive facial cellulitis</td>
<td>Staph. aureus</td>
<td>+</td>
<td>12</td>
<td>1110</td>
<td>196,000 Intravenous</td>
<td>Recovery</td>
</tr>
<tr>
<td>6</td>
<td>Acute postoperative pyelonephritis</td>
<td>Staph. aureus</td>
<td>0</td>
<td>7</td>
<td>850</td>
<td>200,000 Intravenous</td>
<td>Recovery</td>
</tr>
<tr>
<td>7</td>
<td>Extensive cellulitis of mouth and tongue</td>
<td>Nonhemolytic streptococci</td>
<td>0</td>
<td>4</td>
<td>320</td>
<td>64,000 Intravenous</td>
<td>Recovery</td>
</tr>
<tr>
<td>8</td>
<td>Infected postoperative wound</td>
<td>Staph. aureus</td>
<td>0</td>
<td>5</td>
<td>440</td>
<td>88,000 Intravenous</td>
<td>Recovery</td>
</tr>
<tr>
<td>9</td>
<td>Severe facial and nasal cellulitis</td>
<td>Staph. aureus</td>
<td>0</td>
<td>6</td>
<td>561</td>
<td>132,000 Intravenous</td>
<td>Recovery</td>
</tr>
<tr>
<td>10</td>
<td>Subacute bacterial endocarditis</td>
<td>Green necrotizing streptococci</td>
<td>+</td>
<td>6</td>
<td>640</td>
<td>128,000 Intravenous</td>
<td>Failure</td>
</tr>
</tbody>
</table>

* †Negative; ++Positive
†Previously reported
In this type of case penicillin appears to be only an adjunct to the usual surgical procedures, such as drainage and skin grafting.

Case 3.—This patient suffered from an extensive cellulitis of the face and orbit complicated by septicemia owing to Staphylococcus aureus. The blood stream was free of bacteria twenty-two hours after the intravenous administration of penicillin was begun. During nine days he received a total of 160,000 Oxford units (1,160 mg.) by the intravenous drip method. Recovery was uneventful.

Case 4.—The patient was a white man, twenty-four years of age, who, on treatment with sulfa-thiazole, had partially recovered from septicemia caused by Staphylococcus aureus. He had multiple cystlike lesions of the scalp and neck which contained fluctuant material from which the Staphylococcus aureus could be repeatedly identified on culture. These cystic lesions were aspirated and penicillin injected into them. All of these lesions disappeared within forty-eight hours after the injection of penicillin. The solution injected contained 100 Oxford units per cubic centimeter of physiologic solution of sodium chloride.

Case 5.—The patient, a girl, aged four years, was admitted to the hospital after an illness of four days. The past history contained no significant data. The father related that on several occasions shortly before the child's illness she had bitten the inside of her left cheek. Four days before admission redness and swelling appeared on the left side of the jaw and progressed rapidly. Dysphagia as well as increasing difficulty in breathing followed. The temperature had risen to 104° F. The child was unable to sleep for twenty-four hours before admission and progressive obstruction to breathing and swallowing occurred.
On examination the tongue was fixed, edematous and nearly frozen to the hard palate. Necrosis was present in the left alveolar lingual region. Shortly after admission the lesion was drained surgically by means of a simple stab wound. A small drain was introduced. Extensive necrosis was present which extended through the floor of the mouth. The next day the child was critically ill (fig. 1a and b), breathing was labored, and there was evidence of cyanosis together with pneumonia in the right lung. Laboratory studies revealed a leukocyte count of 4,500 per cubic millimeter of blood with a differential count of 37 per cent neutrophils, 62 per cent lymphocytes and 1 per cent monocytes. The concentration of hemoglobin was 60 per cent of normal; the erythrocyte count was 3,900,000 per cubic millimeter of blood. Blood cultures were obtained and intravenous administration of penicillin was instituted. The blood cultures were reported as showing 25 colonies of a hemolytic type of Staphylococcus aureus per cubic centimeter at the end of twenty-four hours.

Twelve thousand Oxford units (87 mg.) of penicillin was dissolved in 1 liter of physiologic solution of sodium chloride and continuous intravenous drip was begun. For the next five days the patient received between 20,000 and 30,000 Oxford units of penicillin daily. Thirty-six hours after initiation of treatment blood cultures were sterile and remained so throughout the patient's recovery. Roentgenograms of the thorax thirty-six hours after institution of treatment with penicillin revealed definite pneumonia of the upper lobe of the right lung which was assumed to be staphylococcal in origin although no sputum examination was obtainable. Within ninety-six hours after the beginning of treatment (fig. 1c) the child was again able to swallow, was having little difficulty in breathing and could take a liquid diet by mouth without difficulty. By the fifth day she was able to eat semi-solid and solid foods. On the sixth
day the rectal temperature was 100° F. By the ninth day (eleventh day in hospital) the temperature was normal. Figure 2a is a photograph of the child taken at this time. Treatment with penicillin was discontinued three days later. In figure 2b and c the child is shown shortly before her dismissal from the hospital. The erythrocyte and leukocyte counts and doses of penicillin are given in table 2. It is significant that the leukocyte count, which was 4,500 when treatment was begun, increased progressively as the patient improved (fig. 3 upper left).

An infection of this type complicated by septicemia is almost universally fatal. Leukopenia at the height of an illness of this type is also usually considered of grave prognostic significance.

### Table 2

**SUMMARY OF INTRAVENOUS TREATMENT WITH PENICILLIN**

<table>
<thead>
<tr>
<th>Days after admission</th>
<th>Maximal rectal temp. (F.)</th>
<th>Cells per cu. mm. of blood</th>
<th>Dose of penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Erythrocytes (millions)</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>1</td>
<td>104.8</td>
<td>4.29</td>
<td>5,400</td>
</tr>
<tr>
<td>2</td>
<td>104.8</td>
<td>3.90</td>
<td>4,500</td>
</tr>
<tr>
<td>4</td>
<td>103.8</td>
<td>3.90</td>
<td>3,800</td>
</tr>
<tr>
<td>8</td>
<td>104.0</td>
<td>6.50</td>
<td>6,500</td>
</tr>
<tr>
<td>6</td>
<td>103.0</td>
<td>9.10</td>
<td>9,100</td>
</tr>
<tr>
<td>7</td>
<td>102.0</td>
<td>13.20</td>
<td>132</td>
</tr>
<tr>
<td>8</td>
<td>100.0</td>
<td>4.60</td>
<td>10,400</td>
</tr>
<tr>
<td>9</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>99.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>99.8</td>
<td>8.60</td>
<td>8,600</td>
</tr>
</tbody>
</table>

**Case 6.—**The patient was a man sixty-eight years of age who was suffering from a calculus in the left kidney. At the time of surgical removal of the stone there was definite evidence of moderately severe renal and perirenal infection. Twenty-four hours following the surgical procedure the patient was critically ill. The rectal temperature ranged between 105 and 106° F. The wound was definitely infected, and bacterial cultures of the draining material revealed Staphylococcus aureus. Pyuria, grade 4, on the grading basis of 1 to 4 was present and cultures of the urine revealed Staphylococcus aureus. There was evidence of atelectasis of the left lower lobe of the lung with considerable pulmonary congestion. For five days the patient received 16,000 Oxford units of penicillin in physiologic solution of sodium chloride intravenously twice per day. Because of evidence of urea retention, some of the material was administered in a 5 per cent solution of glucose. The patient's temperature gradually returned to normal by the fifth day. Clinical improvement continued,
and there is little doubt that penicillin was an important factor in the control of the severe, overwhelming infection present not only in the wound but in the urinary tract.

Case 7.—The patient, a woman aged twenty-two years, was admitted to the hospital after an illness of only thirty-six hours. On the morning of the day before admission the patient noticed that her tongue was sore and swollen. She thought that she had previously bitten it but could not be certain. A few hours after the onset of swelling of the tongue and floor of the mouth a chill, followed by fever, developed. By the afternoon of the first day of her illness she was unable to swallow. The swelling of the tongue increased as well as the swelling of the floor of the mouth. The afternoon before her admission the temperature had reached 104° F. At the time of admission she was unable to swallow and unable to move the tongue. The tongue was edematous and extremely red. It was nearly fixed to the hard palate. Edema and redness of the floor of the mouth were marked. The cervical glands were enlarged and tender. A diagnosis of acute cellulitis of the tongue and mouth was made. Although this patient was seen earlier, the lesion was similar to that reported in
The patient had received no previous treatment for ulceration. Within a few days the ulceration began to improve. Within the first week the ulceration had almost cleared up. The patient was discharged from the hospital on the 10th day after admission and was able to return to work in a few days.

Case 2—The patient was a woman aged 24 years.

The ulceration on the right side of the face was evident and the ulceration continued to improve. Within the first week the ulceration was almost cleared up. The patient was discharged from the hospital on the 10th day after admission and was able to return to work in a few days.

Case 3—The patient was a woman aged 24 years.

The ulceration on the right side of the face was evident and the ulceration continued to improve. Within the first week the ulceration was almost cleared up. The patient was discharged from the hospital on the 10th day after admission and was able to return to work in a few days.
neutrophils, and one basophil. The next morning treatment with penicillin was begun. Studies made on the evening of the second day in the hospital revealed 7,100 leukocytes per cubic millimeter. There were 50 per cent lymphocytes, 35 per cent monocytes, 10 per cent neutrophils and 5 per cent metamyelocytes. On the second day of treatment the leukocyte count was 8,100; the differential count revealed 44 per cent lymphocytes, 16 per cent monocytes, 36 per cent neutrophils and 4 per cent metamyelocytes. Treatment with penicillin was discontinued on the sixth day and at this time the differential count revealed the presence of 22 per cent lymphocytes, 3 per cent monocytes and 74 per cent neutrophils with 1 basophil. On the sixth day the patient's temperature was normal (fig. 3 lower right); the swelling, edema and nasal obstruction had practically subsided and the drainage of purulent material from the right side of the nose had ceased. During the six days of treatment the patient received 132,000 Oxford units (561 mg.) of penicillin. The patient recovered.

Case 10.—The patient, a woman aged forty-four years, was admitted to the hospital with a diagnosis of subacute bacterial endocarditis. She gave a history and definite evidence of rheumatic endocarditis. Blood cultures revealed the presence of 50 colonies of green-producing streptococci per cubic centimeter. The patient's present illness was apparently of only two months' duration. A study of the organism isolated from the blood revealed that its growth could be inhibited in the presence of penicillin in dilutions of 1:500,000. In view of this finding and the good general condition of the patient, she was treated with penicillin in spite of the fact that penicillin has not been considered effective in this type of case. Within six hours after institution of treatment by the continuous drip method, cultures of the blood were negative and the patient was afebrile. For a period of six days she was treated with penicillin. As long as penicillin therapy was continued negative bacterial cultures could be obtained. Within a period of four to six hours after penicillin therapy was withdrawn bacterial cultures of the blood would again show a few colonies of green-producing streptococci per cubic centimeter.

Here again is emphasized the fact that the problem of treating bacterial endocarditis is not one of obtaining an antibacterial agent effective against certain strains of the green-producing streptococci. The ineradicable focus in the heart valve, as always, seems to re-implant the pathogens into the circulating blood stream.

COMMENT

The absence of any toxic manifestations attributable to the continuous or nearly continuous intravenous administration of penicillin in seven cases of severe sepsis is gratifying. Likewise, toxic
manifestations were not observed when penicillin was administered either subcutaneously or locally. For reasons which have already been mentioned, treatment with penicillin probably should be reserved for severe and systemic infections. While blood cultures were positive in only four of the cases reported, it does not seem unreasonable to state that the infections in the remaining cases were of such severe nature that if penicillin therapy had not been undertaken early, invasion of the blood by the organism present in the infection would have been likely to occur. Satisfactory results were obtained in all of the cases reported except in the infection associated with subacute bacterial endocarditis.

In several of the cases of severe infections associated with moderate leukopenia, the leukocyte counts rose during penicillin therapy and usually this increase paralleled recovery. In one instance (case 9) in addition to leukopenia there was complete absence of polymorphonuclear leukocytes in the patient's blood shortly before institution of treatment with penicillin. As improvement occurred, the neutrophils progressively increased.

SUMMARY

Penicillin continues to prove an exceedingly effective antibacterial agent in the treatment of clinical infections due to organisms susceptible to its action. The continuous or nearly continuous intravenous method of treating severe infections is advocated. This method permits a more constant level of the antibacterial agent in the blood and tissues, a definite advantage over methods which permit large amounts of the material to be delivered in a short period followed by a long period during which the level must obviously be comparatively low. When pyrogen-free penicillin is administered by the method described, no toxic manifestations have occurred.

The results obtained in the treatment of ten patients with penicillin have been presented. In eight of the cases in which the organism of infection was the Staphylococcus aureus, results were satisfactory. In one case the organism of infection appeared to be a strain of nonhemolytic streptococci. The result was satisfactory. In one instance, penicillin was used in the treatment of subacute bacterial endocarditis. Although the blood stream could be temporarily freed of the green-producing streptococcus by using penicillin, withdrawal of the therapeutic agent resulted in a recurrence of the infection.

To insure the best results in using penicillin, care must be taken in the selection of the type of case for treatment. Only through the selection of infections attributable to organisms susceptible to penicillin can unfavorable results be prevented.