Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Penicillin

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STAFF MEETING BULLETIN
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INDEX

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William A. O'Brien, M.D.

I. LAST WEEK

Date: October 22, 1943

Place: Recreation Room
Powell Hall

Time: 12:15 to 1:20 P.M.

Program: Surgical Treatment of Ulcer
Bernard G. Lannin
Ivan D. Baronofsky

Discussion: Leo G. Rigler
Cecil J. Watson
Macnider Wetherby
Owen H. Wangensteen

Attendance: 119

Alice Carlson,
Record Librarian

- - -

II. MEETINGS

1. ANATOMY SEMINAR

Saturday, October 30, 1943, 11:30 a.m., Room 226, Institute of Anatomy.

"Leukemia in Man and Animals"
(reticulo-endotheliosis)
Hal Downey

- - -

2. PHYSIOLOGY-PHARMACOLOGY SEMINAR

Wednesday, November 3, 1943, 12:30 p.m., Room 105 Millard Hall.

"Stilbene Compounds in the Treatment of Trypanosomiasis"
Louis D. Fink

- - -

3. BACTERIOLOGY SEMINAR

Thursday, November 4, 1943, 4:30 p.m., Room 129, Millard Hall.

"Jaundice"
Gerald Needham

- - -

III. BABIES

Dr. and Mrs. John Knutson, a boy on October 17, 1943.

Dr. and Mrs. Eugene McElmeel, a girl, October 21, 1943

CONGRATULATIONS!

- - -

IV. ALUMNI HOMECOMING - Friday, November 5, 1943

8:00 - 10:50 Surgical Clinic, West Operating Room--Department of Obstetrics and Gynecology.
John L. McKelvey and Staff.

8:00 - 9:50 Symptomatology of Rectal Diseases--Todd Amphitheatre--Department of Surgery
W. A. Fansler

8:30 - 9:50 Grand Rounds -- Department of Pediatrics
Irvine McQuarrie and Staff

9:00 - 10:20 Grand Rounds--Department of Neurosurgery--
William T. Peyton and Staff

9:00 - 9:50 Medical Case Presentations, Todd Amphitheatre--Department of Medicine
Cecil J. Watson and Staff

11:30 - 11:45 Annual Business Meeting Minnesota Medical Alumni Association--Eustis Amphitheatre.

11:45 - 1:15 Hospital Staff Meeting Complimentary Luncheon--Powell Hall--Carcinoma of Larynx--
L. R. Boise

1:30 - 2:50 Neurology-Radiology Conference, Todd Amphitheatre-- William T. Peyton, Leo G. Rigler, and Staff.

1:30 - 5:00 Surgical Clinic, Main Operating Room--Department of Surgery--Owen H. Wangensteen and Staff.

- - -

V. PENICILLIN

Wesley W. Spink

Published with the approval of the Committee on Medical Research of the National Research Council.

Introduction

The antibacterial agent, penicillin, was not sparked into being overnight, but like sulfanilamide, its application to clinical medicine pyramided a procession of shrewd scientific observations that extended over a period of years. Dubos pointed out in his Harvey Lecture[1] that in 1860 Pasteur stated that a mold Penicillium glaucum attacked the d-form of tartaric acid, but was inactive against the l-form. The specificity of microbiological activity was again emphasized by Pasteur in 1877 when he observed that microorganisms attacked and depressed the highly malignant anthrax bacillus. These observations, and those of others, were of little more than academic interest until the turn of this century when it was shown that soluble extracts of Pseudomonas pyocyanea, called pyocyanase, possessed highly antibacterial properties toward a group of unrelated microbial species.[2] Pyocyanase proved to be highly toxic but for years the material was applied locally for the treatment of human infections, such as the topical application of pyocyanase to the oral pharynx of carriers of the diphtheria bacillus. Later the observations of the British bacteriologist Twort, which were extended by the French physician, d'Herelle, were crystallized in the concept that bacterial growth produced a highly specific antimicrobial agent known as bacteriophage. In 1927, two Englishmen, Raistrick and Robinson, isolated a crystalline antibacterial substance from the mold Penicillium citrinum, which is known as "citrin."

One of the most spectacular discoveries took place at the Rockefeller Institute for Medical Research about 1931 when Reno Dubos found that a sporulating soil bacillus attacked the specific polysaccharide of type 3 pneumococcus, thereby stripping that microorganism of its invasiveness.[3] During the immediate succeeding years, Dubos and his associates extended these investigations, and in 1939,[4] he announced that upon lysis, a gram positive, spore-bearing, aerobic bacillus released a substance capable of destroying many species of gram positive bacteria but ineffective against gram negative microorganisms. The crude material was called tyrothricine, while from this substance, tyrocidin and gramicidin were obtained. The hopes that these substances would find widespread clinical application were dampened by the toxicity of the material. The crystalline material, tyrocidin, was found to be effective in vitro against both gram positive and gram negative bacteria but because of its toxicity and loss of activity in animal tissue, tyrocidin has not been utilized in the treatment of infections. On the other hand, while gramicidin remained too toxic for systemic use, the material has been successfully used locally in the therapy of human and animal infections. Gramicidin differs from the sulfonamides in that its antibacterial property is not inhibited by pus, autolysed tissue, dead bacteria, etc. Furthermore, it is effective against sulfonamide-resistant organisms. It has found successful application in the treatment of bovine mastitis caused by hemolytic streptococci, and in the therapy of human streptococcic and staphylococcic lesions such as skin ulcers, would infec-

tions, infected burns and infections of the pleural cavity.[5,6] Because of the limited mode of administration, gramicidin has not replaced the sulfonamides, and in the future it will verylikely be superseded by penicillin. Nevertheless, the original studies of Dubos have stimulated many investigators to pursue the potentialities of other antibiotic agents.

History of Penicillin

In 1929, Dr. Alexander Fleming,[7] Bacteriologist in St. Mary's Hospital in London, was attracted by a biological phenomenon that must have been noted by others. After inoculation of the surface of an agar plate with staphylococci, he observed after several days that the surface of the agar had become contaminated by a green mold, and the colonies of staphylococci adjacent to the mold were undergoing degeneration into transparent, small colonies. The mold was later idntified as belonging to the species Penicillium notatum. Fleming prepared filtrates from broth cultures of this mold, and showed that this material inhibited the growth of gram-positive bacteria such as pneumococci, streptococci, and staphylococci; but of the gram negative group, only the gonococcus and meningococcus were affected. The growth of the influenza bacillus and colon bacillus was uninhibited. He proposed that the filtrate might be used as a local antiseptic and suggested the name penicillin.

The report of Fleming excited little further interest until the exigencies of war found the Australian-born Professor of Experimental Pathology at Oxford University in England, H. W. Florey, exploring the possibilities of penicillin with a highly trained personnel under the auspices of the Medical Research Council of Great Britain. The first publication of the Oxford group appeared in 1940.[8] They confirmed the observations of Fleming in that penicillin inhibited the growth of gram positive species of bacteria, but with the exception of the gonococcus and the meningococcus, gram negative organisms were not affected. They also noted that penicillin was remarkably non-toxic when administered to animals. In 1941, Professor Florey came to the United States, to enlist the efforts of certain governmental and private groups in furthering investigations of penicillin. Shortly thereafter, a second comprehonsive report by the Oxford workers appeared in which the results of the clinical use of penicillin in human beings was described.[9]

Early in 1942, a few commercial firms in this country began the slow and difficult task of preparing penicillin. In addition, the Committee on Chemotherapeutic and Other Agents of the National Research Council was given the responsibility of sponsoring and supervising clinical investigations with the meager supply. Once production problems were overcome, enough penicillin became available for the treatment of human infections, but the material has been and still is very limited. At the present time, all penicillin for experimental and clinical studies is released through the office of Dr. Chester S. Keefer, Chairman of the Committee on Chemotherapeutic and Other Agents of the National Research Council.

Only a few clinical reports have appeared in this country concerning the results of the treatment of human infections.[10,11,12] The most comprehensive report in this country is that published by the Committee on Chemotherapeutic and Other Agents.[13] On the other hand, the results of many basic studies have been published and will be referred to subsequently.

Preparation of Penicillin

Details concerning the present methods of preparation and purification of penicillin are not available, but a general idea concerning the procedures may be obtained from the published reports of the Oxford groups.[8,9] The mold, Penicillium notatum, is seeded to a relatively simple medium, such as Czapek-Dox medium, which is contained in large flasks so that ample surface area for growth is available at about 24 degrees C. After several days of growth, the active principle is to be found in the medium. The liquid is carefully removed and then concentration is carried out at low temperatures. Impurities are removed with

the aid of organic solvents. The solvents then must be separated from the active material. Impure penicillin is converted to a salt, usually a barium salt in large scale production, and then for clinical purposes calcium or sodium salts are prepared. The final result is a dried yellow extract which is hermetically sealed in ampules. The whole procedure is marked by many pitfalls which may destroy the active part. Some of the difficulties have been due to bacterial contamination, changes of pH which destroy the material, and the selection of strains of the mold which produce little or no active penicillin.

It soon became necessary to standardize the preparation for clinical use, and today the standardization is in Oxford units. Several methods have utilized in this standardization, but the dilution method is the basis of the Oxford units. Under these circumstances, an Oxford unit is that amount of penicillin which when dissolved in 50 cc. of meat extract broth just inhibits completely the growth of a test strain of S. aureus. In general, the material in use contains less than 500 units per mg. When one considers that the material will inhibit the growth of bacteria after being diluted several million times, and that the penicillin available contains only 10 to 15 per cent of pure penicillin, one can readily gain some idea concerning the extreme potency of this antibacterial agent.

Chemistry of Penicillin

Since penicillin is so extremely active against certain species of bacteria, and the labored methods of preparation yield relatively small quantities containing large amounts of impurities, strenuous efforts have been and are being made to synthesize penicillin. There have been a few reports giving the empirical formula of penicillin but they are contradictory. The Oxford group have put forth the provisional formula of $C_{24}H_{32}O_{10}N_2Ba$.[14] Meyer and his associates (15) in this country conclude that penicillin is $C_{14}H_{19}NO_6$ or $C_{14}H_{17}NO_5 - H_2O$. Another group (16) have offered $C_{24}H_{34}O_{11}NSr$. Though the results are conflicting, it is not unlikely that the precise nature of penicillin will be determined and synthesis will take place in the near future.

Properties of Penicillin

Penicillin is extremely soluble in water. It is readily oxidized, and thus rendered inactive, by contact with the air and by a number of oxidizing agents. It is inactivated by reducing agents. Changes in pH result in inactive material. Its activity is reduced or destroyed by heat, heavy metals and alcohols. All the foregoing factors must be taken into consideration when penicillin is being utilized by clinicians. Meyer and his group[17] have shown that penicillin may be stabilized by the preparation of esters of penicillin.

Action of Penicillin

It is now generally agreed that penicillin exerts both an in vitro bacteriostatic (inhibitory) and bactericidal (killing) effect against microorganisms. While the precise nature of this antibacterial action is not clear, Hobby and her associates[18] have shown that penicillin will destroy hemolytic streptococci only if multiplication is taking place. Gardner,[19] working with the staphylococcus, stated that the bacterial cell grew in the presence of penicillin forming large spherical bodies, but that division and separation of the cell does not follow. Similar confirmatory evidence has been offered by Smith and Hay.[20] Rammelkamp and Keefer[21] have studied the antibacterial effect of penicillin upon hemolytic streptococci and staphylococci in human whole blood and serum. Hemolytic streptococci were completely destroyed, but a large inoculum of staphylococcus was not completely sterilized indicating to them that the remaining organisms had ceased to multiply and therefore were not susceptible, or the organisms had become penicillin-resistant. This observation may have an important relationship to the therapy of staphylococcic infections with penicillin. In fact, Rammelkamp and Keefer, suggest that a combination of sulfadiazine or sulfathiazole with penicillin might be more effective in the treatment of staphylococcic infections than either one alone.

Reference has already been made to the microorganisms sensitive to the action of penicillin. This statement may be elaborated by the following tabulation of susceptible and insensitive strains based on the studies of Hobby, Meyer, and Chaffee[22]:

Susceptible	Insusceptible
Pneumococcus	Hemophilus influenzae
Streptococcus hemolyticus	Escherichia coli
Staphylococcus	Bacillus typhosus
Meningococcus	Bacillus dysenteriae
Gonococcus	Bacillus proteus
Streptococcus viridans	Bacillus paratyphosus A
Bacillus subtilis	Bacillus enteritidis
Clostridium welchii	Bacillus pyocyaneus
Vibrion septique	Bacillus fluorescens
Clostridium histolyticus	Bacillus prodigiosus
Bacillus sporogenes	Friedländer's bacillus
Bacillus oedematiens	Staphylococcus albus--1 strain
Bacillus sordelli	Micrococcus albus--1 strain
Lactobacillus	Monilia kruzei
Cryptococcus hominis	Monilia candida

In general, gram positive strains are inhibited by penicillin, whereas gram negative strains are quite resistant. The gonococcus and meningococcus are two species of gram negative organisms whose growth is markedly inhibited by penicillin. Attention is called to the fact that strains of some species usually considered penicillin-sensitive may possess a natural resistance to penicillin. This is particularly applicable to some strains of staphylococcus.[23,24] Using a standardized dilution method, we have studied the in vitro sensitivity of 72 strains of coagulase-positive staphylococcus isolated from 65 human subjects with different types of staphylococcic infections, and we have encountered 7 strains that were quite resistant. There are also some species of streptococcus that are highly resistant, notably the enterococcus or streptococcus fecalis group. It is not known what the mechanism is whereby some species of gram-positive organisms resist the action of penicillin. Abraham and Chain[25] have shown that E.coli is resistant because this species produces a cellular enzyme which destroys penicillin. They have called this enzyme penicillinase.

Microorganisms susceptible to the action of penicillin may be rendered insensitive to penicillin by exposure of the organisms to increasing concentrations of the material.[23,26] This problem of acquired penicillin-resistance is of considerable importance from the clinical point of view. There is some evidence that penicillin-resistant pneumococci are less virulent than the sensitive parent strain.[26] Our own observations indicate that strains of staphylococcus which have acquired resistance to penicillin are less virulent. Strains of organisms resistant to the action of penicillin may still be sensitive to the sulfonamides, and the opposite holds true; namely: sulfonamide-resistant bacteria may be susceptible to the action of penicillin. This phenomenon indicates that the fundamental antibacterial activity of the sulfonamides and penicillin differ. It is of interest that we have under investigation 2 strains of staphylococcus which have been rendered resistant to both penicillin and the sulfonamides. It should be pointed out that the action of penicillin is not inhibited by exudate, necrotic tissue, dead bacteria and, most important, by para-aminobenzoic acid.

Administration and Fate of Penicillin in Human Subjects

There are two properties, among several, which make penicillin an ideal therapeutic agent. They are its extreme solubility in aqueous solutions and its low toxicity. The absorption, distribution and excretion of pencillin were studied by the Oxford investigators[9] and more recently by Rammelkamp and Keefer in this country.[27] Penicillin is not therapeutically effective when given orally. The active principle is apparently destroyed in the stomach. On the other hand, there is rapid and adequate absorption when penicillin is

placed directly into the duodenum through an indwelling tube. When given intravenously in aqueous solutions, there is a rapid rise in the blood level, but which is followed by a rapid diminution in the level. Very little penicillin penetrates the erythrocytes, the greater majority being present in the plasma. Penicillin is also rapidly absorbed when given intramuscularly, and more slowly when administered subcutaneously. Very little is absorbed when placed in the rectum. When given parenterally, penicillin does not appear to enter the spinal fluid. Penicillin introduced into the subarachnoid space, however, is excreted in the urine indicating some absorption into blood stream. Penicillin has not been found present in tears or sweat. Following parenteral injection, penicillin enters the serous cavities such as joint spaces and the pleural cavity slowly. Likewise, there is slow absorption from these spaces when penicillin is introduced locally into one of them. The majority of administered penicillin in excreted in the urine, though a considerable percentage of the active material remains unaccounted for. There is some evidence that penicillin acts as a diuretic increasing the output of urine. Rammelkamp[28] found that the excretion of penicillin was similar to diodrast.

Briefly, the trend in penicillin therapy indicates that the sodium or calcium salts of penicillin should be administered either intramuscularly or intravenously in physiologic solutions for systemic infections. Subcutaneous infusions are associated with some local irritation and absorption is slower. Solutions of penicillin may be introduced directly into joint spaces, the pleural and pericardial cavities, and may be applied directly to surface infections in the form of ointments and solutions. In the treatment of meningitis, it is advisable to inject the material directly into the spinal canal, and in instances of bacteremia, directly into the blood stream.

Dosage schedules with penicillin will undoubtedly undergo revision in the future. At present, the dose in units depends upon the infection being treated. Thus instances of severe staphylococcic bacteremia will require relatively large doses for comparatively a long period of time. On the other hand, cases of sulfonamide-resistant gonorrhea appear to require relatively small doses. In their report on the treatment of 500 cases with different types of infection, the Committee on Chemotherapeutic and Other Agents[13] has made the following tentative recommendations which is being quoted directly:

Dosage Schedule in Various Infections

"A. In Serious Infections Due to the Hemolytic Streptococcus, Staphylococcus Aureus or Pneumococcus with or without Bacteremia.--An initial dose of 15,000 to 20,000 Oxford units should be given, with continuing dosage as follows:

"1. Five thousand units every hour injected into the tubing of an inlying intravenous set or

"2. Constant intravenous injection of a solution at a rate designed to deliver 5,000 to 10,000 units per hour.

"3. After the temperature has returned to normal, the total dose in a twenty-four hour period may be reduced by half, but it should be continued for at least 7 days after the temperature is normal.

"B. In Chronically Infected Compound Injuries Such as Infected Compound Fractures or Septic Infections of the Soft Parts.--An initial dose of 10,000 Oxford units should be followed by 10,000 units every three hours parenterally, with local treatment as indicated. This schedule may have to be increased or decreased, depending on the seriousness of the infection and the response to treatment.

"C. Sulfonamide Resistant Gonorrhea. --The minimum dosage schedule has not been worked out completely; 10,000 Oxford units every three hours intramuscularly or intravenously for twelve doses has been used with success. It is not unlikely that the same effect may be obtained with 20,000 units every three hours for five doses. The results of treatment

should be controlled by culture of the exudate.

"D. Empyema--Streptococcic, Pneumococcic and Staphylococcic.--Penicillin in isotonic solution of sodium chloride should be injected directly into the empyema cavity after aspiration of pus or fluid. This should be done once or twice daily, using 30,000 or 40,000 units depending on the size of the cavity, the type of infection and the number of organisms. Penicillin solutions should not be used for irrigation. It requires at least six to eight hours for a maximum effect of penicillin, so that continuous action is needed.

"E. Menigitis-Staphylococcic, Pneumococcic and Streptococcic.--Penicillin does not penetrate the subarachnoid space in appreciable amounts, so that it is necessary to inject penicillin into the subarachnoid space in appreciable amounts, so that it is necessary to inject penicillin into the subarachnoid space or intracisternally in order to produce the desired effect. Ten thousand units diluted in isotonic solution of sodium chloride in a concentration of 1,000 units per cubic centimeter should be injected once or twice daily, depending on the clinical course and the presence of organisms. Intravenous or intramuscular injections should be carried on at the same time.

"F. Pneumonia.--The dosage schedule for pneumococcic pneumonia has not been worked out satisfactorily, but for the present it is well to give between 60,000 and 90,000 units a day for three to seven days. Recovery has followed with smaller doses, but the foregoing schedule seems necessary, at least in some cases."

In treating an initial group of severe infections at the University Hospitals we followed the original recommendation of the Committee, namely, 10,000 units was given intravenously every four hours until the infection was under control, and then 5,000 units every four hours for several more days. In the light of our experience, this apparently was insufficient in some cases. More recently, we have used an initial intravenous injection of 50,000 units, which was repeated in two to three hours. Then subsequently we have employed one of two procedures. One method employed was to give intravenously every two to three hours 10,000 units until the infection was under control, and then 5,000 units in 1 cc. of physiologic saline every four hours for several more days. The second method utilized after the initial large doses was to give 50,000 units contained in a liter of physiologic saline solution or in distilled water with 5 per cent glucose, permitting the material to drip in intravenously at a rate of 25 to 30 drops per minute. This method was then continued with a rest period of 2 hours between the completion of the infusion of each liter. In other words, two 50,000 unit doses were given in each 24-hour period as a continuous intravenous drip. After the infection was brought under control, 5,000 units were given intramuscularly every four hours.

In the treatment of small infants with severe infections, an initial dose of 25,000 to 50,000 units has been given intravenously and repeated in two to three hours. Then 5,000 units in 1 cc. of physiologic saline has been injected intramuscularly every three to four hours until the infection is well under control.

We have had too little experience with the local use of penicillin on surface infections. Clark and his associates[29] in England treated successfully a group of burns with sodium and calcium salt made up in a base of lanette wax SX and castor oil. The concentration of penicillin in the cream was 120 Oxford units per gram. Florey and Florey[30] treated a large group of eye infections locally as often as every hour with an ointment prepared by dissolving penicillin in distilled water and then mixing the solution with vaseline giving a resultant strength of 600 to 800 units per gram. This strength of ointment did cause burning. An aqueous solution of 600 to 800 units per 1 cc. of water was also used.

At present, there is no simple chemical test for measuring the concentration of penicillin in the tissues and body fluids. Methods available for quantitating penicil-

lin are based on microbiological assays utilizing a standard of penicillin and a standard species of bacteria.[31,32]

Combined Use of Penicillin and the Sulfonamides

The question might well arise whether penicillin therapy and a sulfonamide should be administered simultaneously. As far as is known, there is no contra-indication, and inadvertently, the combination has been used at the University Hospitals without apparent ill effects. One might well conceive of an individual suffering from a mixed infection where one or more of the etiologic agents might be unaffected by penicillin, but sensitive to a sulfonamide, and, yet the major offender might be penicillin sensitive. Obviously, in an attempt to evaluate a therapeutic agent, evaluation of a combination would require a large number of cases treated under controlled circumstances. Rammelkamp and Keefer[27] have introduced evidence recently, which might indicate that staphylococcic bacteremia could be controlled more effectively by a combination of penicillin and sulfadiazine or sulfathiazole, rather than by penicillin alone.

Penicillic acid, Penicidin, Penicillin B, and Penatin

It is desirable to point out that several other anti-bacterial substances have been obtained from extracts of the mold, Penicillium, which appear to differ from penicillin. Penicillic acid has been isolated in crystalline form from the species Penicillium cyclopium.[33] It is relatively easy to prepare and inhibit the growth of both gram positive and gram negative bacteria. There is no information available concerning its clinical possibilities. Penicidin is another product of Penicillium which has been isolated and inhibits both gram positive and gram negative organisms.[34] Penicillin B also prepared from Penicillium notatum is quite inhibitory for both gram positive and gram negative organisms, especially in the presence of glucose.[35] It is much more toxic than penicillin. Penatin[36] produced by Penicillium notatum also inhibits gram positive bacteria and gram negative species not susceptible to penicillin.

Clinical Evaluation of Penicillin at the University of Minnesota

In 1941 we were asked to cooperate with the Committee on Chemotherapeutic and Other Agents of the National Research Council in the clinical evaluation of penicillin. However, it was not until the middle of 1942 that the material became available. Penicillin was administered to the first patient at the University of Minnesota Hospitals on July 11, 1942. Since that time, a total of 41 patients have received the material under our direction. At the onset, we were particularly interested in evaluating penicillin in the treatment of patients having staphylococcic infections. Previous experience at the University Hospitals indicated that the sulfonamides were of definite value in the therapy of this type of sepsis, but the end results over a period of four years were not too satisfactory.[37] In accordance with the desires of the Committee on Chemotherapeutic and Other Agents other types of bacterial infections were also elected for treatment such as hemolytic streptococcic bacteremia, subacute bacterial endocarditis, pneumococcic meningitis, sulfonamide-resistant pneumococcic pneumonia, and sulfonamide-resistant gonococcic infections.

While a total of 41 patients have received penicillin, this report is concerned with the results in 38 patients. Data have not been completed in the remaining three patients. The penicillin was supplied in the form of a sodium salt contained in sealed ampules. This salt is a yellow material having a bitter taste. The contents of the ampules contained between 5,000 to 100,000 Florey or Oxford units. The material has been given either intravenously or intramuscularly in an aqueous solution. When penicillin has been applied locally or injected into cavities, freshly prepared physiologic saline solutions were used.

A summary of the types of infections treated with the material is given in Table 1. In every instance, repeated attempts were made to identify the causative

Table 1

Summary of Types of Infections Treated with Penicillin

Disease	No. of Patients
1. Acute staphylococcic bacteremia without osteomyelitis	9
2. Acute staphylococcic bacteremia with osteomyelitis	4
3. Severe staphylococcic sepsis without demonstrable bacteremia	3
4. Chronic staphylococcic osteomyelitis	5
5. Staphylococcic pyoderma (local application)	2
6. Acute hemolytic streptococcic bacteremia	3
7. Subacute bacterial endocarditis	3
8. Pneumococcic meningitis	2
9. Sulfonamide-resistant pneumococcic pneumonia	1
10. Sulfonamide-resistant gonorrhea	3
11. Gonococcal Arthritis and Tenosynovitis	2
12. Pneumonia (?etiology) and E. coli peritonitis	1
Total	38

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microorganism. Bacteremia was demonstrated by culturing venous blood in brain broth, and the degree of bacteremia was quantitated with triplicate blood-agar pour plates. In this manner, the effect of penicillin upon the bacteremia was quantitated. The coagulase test was carried out with all strains of staphylococci isolated from the patients. The comparative in vitro sensitivity for sulfathiazole and penicillin of many of the strains isolated from the patients was determined. These and other investigations with penicillin will form the basis of other reports.

Results

Acute Staphylococcic Bacteremia without Osteomyelitis

The outstanding features in the therapy of 9 patients is summarized in Table 2. In order to give a more comprehensive picture of the nature of the infection and the results, a brief abstract of each of the cases follows:

Table 2

Penicillin Therapy in Patients having Acute Staphylococcic Bacteremia Without Osteomyelitis

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford units)	Results
1. 78 M.	Postoperative prostatitis; thrombophlebitis left saphenous vein	16 days Sulfathiazole orally and parenterally 9 gm. in 3 days	Blood culture- 39 cols./cc. coag.-pos.staph. Same type of organism in urine	2 courses: 1)140,000 in 9 days 2)100,000 in 4 days	Died
2. 25 M.	Acute sinusitis Sulfadiazine oliguria	15 days Sulfadiazine orally 20 gm. in 5 days	Blood culture- 4,700 cols./cc coag.-pos.staph.	40,000 in 5 hours	Died
3. 43 F.	Furunculosis; Exfoliative dermatitis (sulfathiazole)	36 days Sulfathiazole orally 2 weeks	Blood culture- Coag.-pos.staphy. 8x	290,000 in 5 days	Recovery
4. 55 M.	Diabetes; acute staphylococcic endocarditis (mitral)	8 days Sulfadiazine - 16.5 in 5 days	Blood culture- 400 to 2000 cols./ cc. coag.-pos. staph.	350,000 in 2 days	Died
5. 72 M.	Postoperative prostatitis; multiple pulmonary abscesses.	16 days Sulfadiazine- 19 gm. in 5 days Sulfathiazole- 22 gm. in 5 days	Blood culture- 15 to 250 cols./ cc. coag.-pos. staph.	120,000 in 2 days	Died
6. 16 M.	Acute staphylococcic endocarditis (tricuspid);multiple pulmonary abscesses	38 days Sulfathiazole and Sulfadiazine orally for 12 days	Blood culture- 40 to 800 cols./ cc. coag.-pos. staph.	340,000 in 4 days	Died
7. 9 mos. F.	Severe stomatitis	8 days Sulfathiazole and sulfadiazine - total amounts not known	Blood culture- 250 cols./cc. coag.-pos.staph.	150,000 in 5 days	Recovery
8. 9 M.	Tetanus; bronchopneumonia; Staphylococcic bacteremia and staph. in local lesion	1 day Sulfadiazine, 4 gm. surgical excision of foot. Tetanus antitoxin locally and parenterally	Blood culture- Coag.-pos staph. culture of local lesions, staph.	140,000 in 2 days	Died
9 16 M.	? perinephritic abscess	About 6 weeks Sulfadiazine - orally - 16 gm. in 5 days.	Blood culture- Hem. staph. aureus 2 x	520,000 in 8 days	Recovery

Patient 1. - .,78, male - entered the hospital for a transurethral prostatic resection and two resections were necessary within a period of 9 days. Within 24 hours after the second operation he developed chills and fever. Seven blood cultures showed coagulase-positive staphylococci to be present with a maximum colony count of 39 colonies per cubic centimeter. At the time of this colony count there were 5.5 mgs. of free sulfathiazole in the blood stream. After 5 days of penicillin therapy, the blood culture remained sterile. At the same time, there was marked improvement in his general condition. He left the hospital apparently recovered, but a pyuria persisted, which is a common occurrence after transurethral resection. Ten days after leaving the hospital, he had a recurrence of chills, fever and dysuria. Coagulase-positive staphylococci were isolated from the blood and urine. There was an unavoidable delay in obtaining a further supply of penicillin. He rapidly became progressively worse. He developed a thrombophlebitis of the left saphenous vein. On the day treatment with penicillin was started, there were so many staphylococci in the blood culture that an accurate colony count could not be made. However, within 60 hours of penicillin therapy, the colony count dropped to one per cubic centimeter. Although the bacteremia was under control, the patient expired. An autopsy was not permitted.

Patient 2.

- 25, male, developed a sudden upper respiratory infection associated with a sinusitis. This was followed by chills, high fever, pain over the frontal region, and recurrent epistaxes. He was given sulfadiazine, and oliguria ensued after the ingestion of 20 gm. in 5 days. His condition became worse, and he was hospitalized. The patient was practically moribund when a continuous intravenous drip of penicillin was started. There were 4,700 colonies of coagulase-positive staphylococci in a blood culture taken just before penicillin was started. The patient expired after receiving 40,000 units of penicillin within 5 hours.

Patient 3.-

, 43 - female, had a vaginal hysterectomy for uterine fibroids. Three weeks postoperatively, or 5 weeks before entry to the University Hospitals, she developed chills and fever. Six consecutive blood cultures revealed the presence of staphylococci and sulfathiazole was administered for 2 weeks. At the end of this time, she developed a severe exfoliating type of generalized dermatitis and edema. Although she had improved, she still had chills, fever and a bacteremia associated with furunculosis. At the University Hospitals, a total of 9 blood cultures revealed coagulase-positive staphylococci in two. Following the administration of penicillin the fever subsided and the furunculosis cleared up without operative interference. This case is regarded as one of low grade bacteremia and furunculosis definitely benefited by sulfathiazole but not entirely controlled. Penicillin finally controlled the infection.

Patient 4. -

55 - male, developed chills and fever about 10 days after an undiagnosed type of pain occurred in the perineal region. The patient in addition to being a diabetic exhibited petechial hemorrhages in the mucous membranes of the eye, mouth, and skin over the trunk, extremities, palms and soles. There were no cardiac murmurs. He was stuporous, resisting anterior flexion of the neck; the Kernigs were positive; and bilateral Babinskis were elicited. The original working diagnosis was meningococcemia and ? meningococcic meningitis. Blood cultures were consistently positive for coagulase-positive staphylococci. Penicillin was given intravenously without any demonstrable effect on his clinical course or his bacteremia, and the patient expired after 24 hours of penicillin therapy. Autopsy revealed a small ulcerating vegetation on a normal mitral valve; myocardial abscesses; and abscesses of the kidney.

Patient 5. -

, 72 - male, had a routine transurethral prostatic resection

without incident. The first day post-operatively he was febrile, and a small patch of pulmonary consolidation was elicited at the right base. Sulfadiazine was given followed by improvement, but the drug was poorly tolerated. Abdominal distention and listlessness were prominent features. Because of an exacerbation of his fever and an increase in the pulmonary findings, sulfathiazole was administered. Again, the drug was tolerated poorly. Blood cultures showed the presence of 15 to 250 colonies of coagulase-positive staphylococci per cubic centimeter. Penicillin was given 20 hours before death without benefit. Antopsy revealed multiple pulmonary abscesses.

Patient 6.-

, 16 - male, had felt below normal physically for about a month. He then developed a sudden onset of chills fever and prostration. Staphylococci were isolated from his blood stream and sulfathiazole and sulfadiazine were given for 12 days without benefit. Eighteen days after the febrile onset the patient had an enlarged heart with a systolic murmur heard over the apex, and a whistling systolic murmur over the pulmonic area. There was evidence of pulmonary infiltration at the right base. No petechiae were present. Eight consecutive blood cultures revealed coagulase-positive staphylococci with a maximum colony count of 800 per cubic centimeter. It was the opinion that this patient had an acute staphylococcic endocarditis with multiple pulmonary abscesses but because of his desperate condition a therapeutic trial with penicillin appeared justified. He was given 340,000 units over a period of four days with no improvement in his condition. His condition deteriorated rapidly and he expired on the 48th day of his illness. Autopsy revealed a massive bacterial vegetation of the tricuspid valve withoue involvement of the other valves. The lungs were riddled by pulmonary abscesses, some of which had coalesced.

Patient 7. -

. 9 months - female, had been ill for a week with an initial lesion involving the oral mucosal surface of the lip. The lesion became progressively worse in spite of the use of a sulfonamide. On entry to the hospital, the upper lip was markedly swollen with black thick crusts on the outer surface. The skin revealed erythematous areas covered with yellowish crusts over the left sole, abdomen, chest, right arm, and left ear. The left cheek had a reddened and ulcerated area about 2 cms. in diameter. The buccal mucosa of the right cheek was ulcerated and covered with gray exudate. Coagulase-positive staphylococci were cultured from the mouth lesions, and from the blood. Sulfadiazine had been administered, and a blood culture taken just before penicillin was given showed no growth. Nevertheless, the child was desperately ill. The improvement following penicillin therapy was dramatic. The swelling of the mouth and the ulceration of the cheek subsided rapidly. The other skin lesions cleared. The child left the hospital 14 days after entry completely recovered.

Patient 8. -

, 9 - male, was well until two weeks previous to admission when he injured his left foot by stepping on a rusty barbed wire in a pig pen. The day before entry he had difficulty opening his mouth, biting his tongue several times. There were neck rigidity and slight opisthotonus, but generalized spasms could not be induced. The lesion of the foot was incised, following which he was sedated and a total of 320,000 units of tetanus antitoxin was administered, locally and parenterally. On the fourth hospital day, his temperature became elevated and evidence of pneumonia appeared. Staphylococci were isolated from the local lesion and from the blood stream. Because of these bacteriologic findings and his desperate condition, penicillin therapy was instituted. He became progressively worse, developing respiratory embarrassment, and expired on the 7th day of his illness. Penicillin was without effect.

Patient 9. -

., 16 - male, was treated in cooperation with Dr. J. L. Lapierre. About 4 weeks before admission to the

hospital the patient squeezed several pustules on his face. Shortly thereafter he began to have intermittent chills and fever. The day after hospitalization he developed tenderness over the area of the right ischial tuberosity. Staphylococcic bacteremia (Hem. staph. aureus) was established by two blood cultures. Sulfadiazine was given with some improvement but the bacteremia persisted. Penicillin therapy was instituted and the patient progressively improved. The second day after penicillin was started, a blood culture remained sterile, as did four subsequent cultures. He was given a total of 520,000 units of penicillin intravenously, mostly as a continuous intravenous drip with 40,000 units being given over a ten hour period in one liter of solution. On discharge, he complained of some pain in the right hip on walking. A diagnosis of perinephritic abscess was made also, which apparently subsided.

Comment:

The end results in the foregoing patients show that 6 of the 9 patients died. Therefore, a brief explanation is in order. Patient 1 received too little penicillin, which was given intermittently. This was due to the limited supply available. Patients 2 and 5 were given the material shortly before death. Patients 4 and 6 had an acute staphylococcic endocarditis, and penicillin is apparently ineffective when this complication is present. Patient 8 expired because of respiratory failure due to tetanus.

Acute Staphylococcic Bacteremia with Osteomyelitis

The following cases have been separated from the preceding instances of staphylococcic bacteremia without osteomyelitis since it has been recognized for years that the group with osteomyelitis have a better prognosis. Pertinent information concerning this series of patients is presented in Table 3. The essential features of the illness of each of these individuals is briefly abstracted.

Patient 10. -

, 7 - female, sudden onset of headache, abdominal pain, chills, fever and pain in region of left knee. The maximum temperature was 105.8 F. which was followed by convulsions and delirium. She was desperately ill on entry, having been sick for 96 hours before receiving penicillin intravenously. Staphylococcic bacteremia was demonstrated on 6 occasions with a maximum count of 68 colonies per cubic centimeter of blood. Dramatic improvement occurred within 48 hours after receiving penicillin, and the blood was sterilized in 5 days. In the next two weeks, the pulmonary lesions cleared. Although her general condition improved, the osteomyelitis in the distal end of the femur progressed to involve the shaft. Four weeks after initiating penicillin therapy, new bone formation was present, but the destructive process was still apparent. After an elapse of four months, a pathologic fracture of shaft of femur was reported. Nine months after treatment, union of the fracture had occurred with good callus formation. Within the area of the fracture there were two small abscesses with sequestra within them, and there was also a small sequestrum lying lateral to the shaft. Otherwise the osteomyelitis was quiescent and repair was in evidence.

Patient 11. -

, 51 - male, who was known to have had diabetes mellitus for 17 years. He developed ulcers of the right great toe and second right toe two weeks before entry to the hospital Eighteen months previously he had had amputations of the right fifth toe and metatarsal because of osteomyelitis. Seven months before the present illness he had an amputation of the left small toe because of osteomyelitis. Both extremities healed completely. After the present admission to the hospital, the 5th great toe was amputated. Sulfonamides prescribed orally and locally failed to control the osteomyelitis. He developed chills, fever and evidence of staphylococcic bacteremia. Seven blood cultures

Table 3

Penicillin Therapy in Patients having Acute Staphylococcic Bacteremia with Acute Osteomyelitis

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford units)	Results
10. ____ 7 F.	Pulmonary abscesses, osteomyelitis left femur	96 hrs. 4 gm. sulfathiazole orally	Blood culture-68 cols./cc coag.-pos.staph.	252,000 in 15 days	Recovery
11. 51 M.	Diabetes mellitus. Osteomyelitis; rt. foot; tabes dorsalis (nonluetic).	61 days. Amputation rt. great toe; sulfathiazole-urea locally; sulfadiazine orally - 24 gm. in 7 days; sulfathiazole orally 48 gm. in 11 days.	Blood culture-20 cols./ cc coag.-pos.staph. Same type organism from local lesion.	520,000 in 15 days	Recovery
12. 12 F.	Osteomyelitis of both tibiae; acute thyroiditis	11 days. Sulfamerazine orally 44 gm. in 8 days	Blood culture-30 col./cc coag.-pos.staph. Same type organism from local lesion.	785,000 in 25 days	Recovery
13. 10 M.	Osteomyelitis left femur; acute staphylococcic endocarditis (mitral)	19 days. 36.5 gm. sod. sulfadiazine in 14 days 200,000 units staph. antitoxin	Blood culture-15 to 225 cols./cc. coag.-pos. staph.	498,000 in 6 days	Died

showed coagulase-positive staphylococci with a maximum of 20 colonies per cubic centimeter of blood. At the time this colony count was made, there were 3.4 mgs. of free sulfathiazole in the patient's blood. Pyuria then developed with staphylococci being cultured from the urine. Penicillin therapy was given which was followed by marked improvement in his condition. After 9 days of penicillin therapy, the blood cultures remained sterile, and the local lesion showed definite improvement. Roentgenologic examination of the right foot revealed marked destruction of the bones, including the ankle joint. He had no pain in the extremity because of severe tabes dorsalis, diabetic in origin. The osteomyelitis failed to regress, and because of the patient's age, the lack of sensation of pain in the extremity, and the danger of reinvasion of the blood stream by staphylococci, the surgical staff amputated the right leg just above the knee. The amputation had remained free of infection six months after surgery.

Patient 12. -

., 12 - female, sudden onset of illness five days before admission with emesis, which was followed in the next two days by fever, and swelling and pain over the right tibia

and left ankle region. She became irrational and disoriented. Seven blood cultures showed the presence of coagulase-positive staphylococci with a maximum of 30 colonies per cubic centimeter, which occurred in the presence of a blood sulfamerazine concentration of 14.4 mgs. per 100 cc. The patient received penicillin intravenously with a coincident improvement in her condition, and sterilization of the blood within 48 hours of treatment. The osteomyelitis of the distal end of the left tibia and of the proximal end of the right tibia progressed during and following penicillin therapy. Four months later, the outstanding finding was the considerable diminution in bone destruction with new bone formation and sclerosis. In addition, this patient developed an infiltrative type of lesion in the right subclavicular region at the level of the second interspace. The tuberculin test was positive. Two months after detection, the lung process began to show some fibrosis. The patient is being watched and treated as an instance of early tuberculous pulmonary infiltration, but the diagnosis still remains in doubt.

Patient 13 -

, 10 - male, entered the hospital four days after onset of a febrile illness associated with pain in the right leg, fatigue and malaise. On entry his temperature was 105 and he was delirious. There were skin pustules; evidence of pulmonary infiltration of the right base posteriorly; no cardiac murmurs were heard; and pain and swelling of the left inguinal region. Coagulase-positive staphylococci were isolated from the blood stream. He was given sodium sulfamerazine and staphylococcic antitoxin but his condition became worse. The pulmonary infiltration increased, but at no time was there x-ray evidence of bone destruction in the left hip. Because of the persistent bacteremia, penicillin therapy was instituted. There were 225 colonies of staphylococci per cubic centimeter of blood just before the administration of penicillin. Following penicillin therapy, the blood stream became sterile for the first time. Shortly thereafter, he developed a systolic and diastolic murmur over the mitral area. It was obvious that the patient had an acute bacterial endocarditis. Nevertheless, penicillin therapy was continued without further benefit. He expired on the 24th day of his illness having received 498,500 units of penicillin. Autopsy revealed an acute staphylococcic endocarditis of the mitral valve; extensive pulmonary abscesses; and a purulent osteomyelitis of the neck of the femur.

Comment: The foregoing group includes another instance of acute staphylococcic endocarditis which penicillin failed to control. It is of interest that in two of the patients (10 and 12) with acute osteomyelitis and staphylococcemia, penicillin cleared the blood stream of organisms, but from a roentgenological point of view the bone lesions progressed. While the final outcome of these patients was favorable, it was necessary to observe and to control the activities of the patients for a long period of time. In this connection, the conclusions of Florey and Florey[30] are of importance. They also observed the same progressive rarefaction of bone by radiological methods, but concluded that if left alone the bones will recalcify. They state that acute staphylococcic osteomyelitis, if treated early with adequate amounts of penicillin, will cease to be a surgical condition. We would like to make the recommendation that the affected extremity be immobilized in a plaster cast until recalcification is well established.

Severe Staphylococcal Infections Without Demonstrable Bacteremia

The following group of patients undoubtedly must have had a staphylococcal bacteremia during the course of their illnesses because of the nature of their lesions, but because bacteriologic evidence of a bacteremia is lacking these patients are considered in a separate group. Essential data on these patients are given in Table 4, and the outstanding features of their clinical course are as follows:

Patient 14 -

, 9 - female, this patient was treated in cooperation with Dr. Erling Platou of Minneapolis eighteen days before

Table 4

Penicillin Therapy in Patients having Severe Staphylococcal Infections without Demonstrable Bacteremia

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford units)	Results
14. 9 F.	Acute osteomyelitis, right tibia. Purulent pericarditis with effusion. Empyema left pleural cavity.	20 days Sulfonamide - probably sulfadiazine amount not known.	Coag.-pos. staph. from pericardial & pleural cavities, and from osteomyelitic lesion.	1,195,000 in 29 days. (70,000 into pericardial cavity; 20,000 into left pleural cavity.	Recovery
15. 30 F.	Diabetes mellitus. Osteomyelitis right thumb. Epidural abscess with meningitis.	14 days Local heat to spine.	Coag.-pos. staph. from epidural abscess	260,000 in 10 days.	Recovery
16. 41 F.	Chronic pyoderma of left buttock and thigh.	15 mos. Debridement, Sulfonamides, Transfusions, Vaccine.	Staph.,non-hem. strept. and proteus bacillus from local lesion.	500,000 in 6 days.	Improvement.

entry, the patient became febrile, which was followed by a painful and swollen right ankle. She was given a sulfonamide--?sulfadiazine. The swelling progressed involving the foot and the leg. An abscess over the right ankle was opened and coagulase-positive staphylococci cultured from the purulent material. Her condition became progressively worse. On entry, the patient was extremely ill. She was cyanotic, dyspnoeic, orthopneic and quite irritable. The temperature was 103.4, pulse 146, and respiratory rate 30. There was evidence of a pericarditis with a large effusion, and signs of an effusion of the left base posteriorly. The right leg was swollen, hot and tender with a draining wound in the area of the external malleolus. Seventy-five cc. of purulent material was removed from the left pleural cavity, and 240 cc. from the pericardial cavity. These exudates contained coagulase-positive staphylococci. Blood cultures remained sterile. Penicillin was administered intravenously, and 70,000 units were introduced into the pericardial cavity and 20,000 units into the left pleural cavity. Five days after starting penicillin therapy, exudate removed from the left pleural space remained sterile, while attempts to aspirate material from the pericardial cavity were unsuccessful. She gradually improved, but there was a persistent elevation of her temperature. This was associated with a progressive destructive process in the left tibia. Three weeks after entry, Dr. Leo Rigler interpreted a roentgen film of the tibia as follows: "there is new bone formation extending all along the shaft from one epiphysis to the other and the amount of destruction is relatively minor." Six weeks later, the amount of new bone formation had greatly increased, while the destruction was minimal. Kymographic studies of the

heart shadow revealed a normal sized heart with no evidence of constrictive pericarditis ten weeks after beginning treatment with penicillin.

Patient 15 -

, 30 - female, known diabetic for four years. Osteomyelitis of right thumb for two months. Two weeks before entry she had an onset of back pain extending from the tenth thoracic to third lumbar vertebra. Four days before admission, she developed acute back pain with a stiff neck, and complete loss of sensation below the waist associated with inability to move the legs, and incontinence of the rectum and bladder. Lumbar puncture revealed staphylococci in the cerebrospinal fluid. On entry, the patient had diabetic acidosis. Coagulast-positive staphylococci were isolated from the epidural abscess. The day following the first administration of penicillin, Dr. William T. Peyton carried out a hemilaminectomy extending from 7T to 12T. The entire length of the exposed cord was bathed in purulent exudate which had compressed the dura. The exudate was aspirated and following this there was a space of 0.5 to 0.75 cm. about the dural sac. The neurosurgeons expressed grave doubt as to the chances of this patient surviving the acute illness. Penicillin was administered postoperatively, and improvement was prompt. The diabetes was readily controlled. At the time of leaving the hospital, 31 days after entry, sensation and some movement in the lower extremities were present.

Patient 16. -

41, - female, had an onset of a hard, indurated area over the left buttock in June 1942. The area was incised subsequently, following which the lesion involved the left buttock and proximal part of the thigh. Sloughing with profuse drainage then occurred. Sulfonamides were administered systemically and locally without effect. Tubercle bacilli were said to have been observed in preparations of the exudate. She then was transferred to Glen Lake Sanatorium, but a tuberculous etiology could not be confirmed. Cultures revealed staphylococci, nonhemolytic streptococci and proteus bacilli. Treatment consisted of debridement, sulfonamides and autogenous vaccine. There was little improvement. Penicillin therapy was instituted on September 17, 1943. She received a total of 500,000 units intravenously over a period of 5 days. After two days of therapy, staphylococci were not found, but the proteus bacillus persisted. At the end of the period of penicillin therapy the drainage was less profuse and not so malodorous. But the improvement was not too striking. In view of the limited supply of material, further treatment with penicillin was not carried out.

Chronic Staphylococcal Osteomyelitis

Five patients having an active but chronic osteomyelitis were given the benefit of penicillin. Coagulase-positive staphylococci were isolated repeatedly from the patients with the exception of patient 22. In his case, bacteriologic information obtained elsewhere indicated the staphylococcus as the etiologic agent. While the acute phase of each of their illnesses had been controlled in part by one or more of the sulfonamides, suppurative lesions persisted. Immobilization of the affected parts with prolonged periods of bed rest had also been carried out. Data pertaining to the treatment of these patients is given in Table 5. It is to be noted that in patient 20 the

Table 5

Penicillin Therapy in Patients having Chronic Staphylococcic Osteomyelitis

Patient	Nature and Duration of Illness	Previous Treatment	Active Bone Lesions	Penicillin Therapy (Florey or Exford Units	Results
17. 27 F.	Pneumonia, rt. 2½ years before Empyema rt. osteomyelitis ribs 1½ years	Sulfonamides in large amounts, no benefit.	10 and 11 ribs anteriorly with multiple sinuses.	290,000 in 13 days	No improvement. coag.-pos. staph. persistently present in draining sinus.
18. 12 F.	Staphylococcic bacteremia, 2½ years. Osteomyelitis left hip, left tibia, left humerus.	Surgical drainage sulfonamides - especially sulfathiazole, with control of bacteremia and some benefit for bone lesions.	Left humerus with draining sinus.	2 courses: 1)180,000 in 6 days 2)230,000 in 14 days.	Temporary improvement with complete healing of sinus; exacerbation necessitated saucerization.
19. 15 F.	Staphylococcic bacteremia 22 mos. ago. Osteomyelitis left ischium, left hip, head of left femur, rt. tibia.	Surgical drainage Sulfonamides- especially sulfathiazole with control of bacteremia and definite benefit of bone lesions.	Left hip and head of left femur with draining sinus	370,000 in 14 days	Temporary improvement. Decrease and sterilization of drainage. Exacerbation.
20. 32 F.	Carbuncle of scalp 2½ years ago. Staphylococcic bacteremia. Osteomyelitis 3,4, 5th lumbar vert. left ulna, left tibia, mastoiditis. Herpes zoster face, left.	Sulfonamides - especially sulfathiazole in large amounts with definite benefit. Tyrothricin locally. Mastoidectomy.	3, 4, 5th lumbar vert. with paravertebral abscess.	340,000 in 12 days.	Complete arrest of disease with no symptoms for 5 months. Disappearance of para vertebral abscess. Carrying on normal activities.
21. 42 M.	Chronic, recurring osteomyelitis both femora, tibiae, fibulae and both forearms for 30 years.	Sulfonamides - especially sulfathiazole in large amts.-with definite improvement.	Abscess left tibia; soft tissue inflammation over rt. femur.	1,000,000 in 10 days.	Improvement; too early to ascertain results.

infection appears to have been completely controlled for 10 months after penicillin was administered. Patient 21 is free of any evidence of activity of the disease but the intervening time between his having received penicillin is too brief to warrant definite conclusions. The two remaining patients had only temporary improvement. In fact, patient 17 was eventually found to have had a tuberculous involvement of the bone and tissues with the staphylococcus acting in the role of a secondary invader. The strain of staphylococcus isolated from patient 19 was found to be highly resistant to the in vitro bacteriostatic action of the sulfonamides.

Because the essential information concerning these patients could be readily tabulated, the clinica course of each of these patients is not given in any further detail.

Comment:

Although the number of cases of chronic staphylococcal osteomyelitis treated with penicillin is too small to warrant a conclusive statement, it would appear that the material may be of definite benefit in this type of case. It is not unlikely that much larger doses given at more frequent intervals for longer periods of time may be necessary. Another possible mode of attack is the simultaneous parenteral use of the material with excision of diseased bone and the local application of penicillin, or perhals a sulfonamide. Because of the limited supplies of penicillin available no further cases of chronic osteomyelitis are being treated.

Acute Hemolytic Streptococcal Bacteremia

Three patients having bacteremia due to streptococci with the beta type of hemolysis were treated with penicillin. All three had received one or more of the sulfonamides prior to receiving penicillin. The important clinical features of these patients is summarized in Table 6. The clinical course of each of these patients is as follows:

Patient 22. -

., 29 - female - had an appendectomy about 6 weeks before entry to the University Hospitals. The sixth postoperative day she developed an upper respiratory infection and in the third postoperative week a right otitis media. The following week, chills and fever occurred, and during the fifth week a complete post auricular mastoidectomy was carried out. Two days before admission a left facial paralysis and left hemiplegia appeared. Hemolytic streptococci were isolated from the blood stream on two occasions. Dr. Peyton believed the patient had a brain abscess arising from the mastoiditis. Sulfathiazole was givenwithout benefit because of the desperate condition of the patient. While receiving penicillin the patient developed a left pleural effusion and pericarditis. Exudate removed from the pleural space remained sterile. Her condition improved; the temperature became normal; and the blood stream remained sterile. On the 14th day of penicillin treatment, the right side of the brain was explored for a brain abscess. None was found. The infection was completely eradicated without defining the precise nature of the cause of the neurological disturbances. The hemiplegia persisted.

Patient 23. -

, 51 - female - developed an acute pharyngitis and cervical adenopathy about ten days before admission. She had a severe diarrhea of one day's duration. She continued to have a spiking temperature (103 - 104) and sulfathiazole was prescribed. Red, nodular lesions developed on her legs; a polyarthritis appeared; areas of cellulitis were present on the left arm and feet; and a severe dehydration type of uremia occurred. Hemolytic streptococci were isolated from the blood on two occasions. Her blood urea nitrogen was 124 mgs. and the creatinine 5.9 mgs. The dehydration was corrected but sulfathiazole

Table 6

Penicillin Therapy in Patients Having Acute Hemolytic Streptococcic Bacteremia

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford Units)	Results
22. 29 F.	Otitis media, rt. Mastoiditis, rt. ? thrombosis rt. middle cerebral artery. Left hemiplegia Pericarditis Empyema, left.	15 days mastoidectomy sulfanilamide-amt. not known Sulfathiazole-16 gm. in 3 days.	Blood culture-50 cols. hem. strept./cc. - (4.6 mgs. sulfathiazole in blood)	470,000 in 17 days	Blood stream sterile in 24 hrs. Recovery with residual hemiplegia.
23. 51 F.	Acute tonsillitis. Cervical adenitis. Cellulitis Erythema nodosum Polyarthritis Extrarenal uremia	10 days Sulfathiazole - amt. not known.	Blood culture-87 cols. hem. strept./cc. (6.22 mgs. sulfathiazole in blood)	1,130,000 in 11 days	Blood stream sterile in 24 hours. Uremia corrected. Improvement. Died. Autopsy did not clearly establish cause of death.
24. 5 F.	Acute pharyngitis; acute adenitis; ?lymphatic leukemia.	8 days	Blood culture-hem. strept.	200,000 in 7 days.	Recovery. Still has lymphadenopathy. Cardiac enlargement. Leukemia still questioned.

was given without benefit. Penicillin therapy was instituted with prompt clearance of the blood stream of organisms and temporary general improvement. However, she remained stuporous. Meningitis was excluded. Streptococcus antitoxin was given without benefit. The polyarthritis improved and the skin lesions faded. The cellulitis localized, and the exudate removed remained sterile. She expired, and a complete autopsy failed to explain the cause of this patient's death. There was no suppuration present in any organs or tissue.

Patient 24. -

- 5, female - was treated in cooperation with Dr. I. McQuarrie and Dr. Erling Platou. Three months prior to entry the patient had an onset of listlessness, pallor and anorexia which was associated with low grade fever. Five weeks before entry, she had a sudden and massive enlargement of the cervical nodes which quickly returned to normal. One week before entry, she developed an acute upper respiratory infection followed by cervical adenopathy, otitis media of the left

ear, a high fever and a generalized purpura. The child appeared extremely ill with a temperature of 105. She had hepatomegaly, splenomegaly and firm nodes in the cervical, axillary and inguinal regions. Her Hg. was 4.84 gm. with 1500 leukocytes, 5 per cent neutrophiles and 95 per cent immature lymphocytes. Hemolytic streptococci were isolated from the blood stream. Because of the desperate condition of the patient, penicillin was given. The blood stream became sterile and the temperature gradually returned to normal. Subsequently, the leukocyte picture reverted to a normal level and a normal differential count. Later she developed congestive failure and cardiac enlargement, the cause of which was not clear. She improved markedly following cardiac therapy. More recently, the lymphadenopathy has reappeared and lymphocytosis had developed again. This case represents an instance of atypical lymphatic leukemia complicated by hemolytic streptococcal bacteremia.

Comment:

Although only three cases have been treated, it would appear that penicillin is quite effective in the therapy of hemolytic streptococcic bacteremia and its complications.

Table 7

Penicillin Therapy in Patients with Subacute Bacterial Endocarditis

Patient	Cardiac Lesion	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford Units	Results
25. 31 F.	Mitral stenosis and regurgitation of rheumatic origin	2½ months sulfathiazole orally 60 gm. in 16 days.	Blood culture- strept. virid. 130 cols./cc.	591,000 in 15 days	Slight improvement following sulfathiazole. No improvement from penicillin.
26. 45 F.	Aortic regurgitation ?congenital bicuspid valves.	4 weeks. sulfathiazole orally 45 gm. in 9 days sulfadiazine orally 125.5 gm. in 31 days.	Blood culture- 20 cols.// of strept. virid.	410,000 in 11 days	Slight improvement following sulfonamide therapy, none from penicillin
27 65 M.	Bacterial endocarditis superimposed upon normal mitral valve.	78 days Large amounts of sulfathiazole and sulfadiazine; sulfapyridine and neoarsphenamine	Blood culture- 106 cols./cc of gamma strept.	610,000 in 12 days	No improvement following any therapy.

Subacute Bacterial Endocarditis

It is now generally accepted that the sulfonamides are of little value in the treatment of patients with subacute bacterial endocarditis. The compounds may cause temporary improvement, but it is a rare case in which the disease process had been arrested. In view of the unsatisfactory results in the treatment of this infectious disease, penicillin was administered to each of three patients. The salient clinical data are shown in table 7. Penicillin did not affect the clinical course beneficially in either of the three cases. All three patients expired because of their disease.

Pneumococcic Meningitis

While sulfonamide therapy is effective in ths treatment of this disease, the results have not been too satisfactory. At the University Hospitals, the mortality rate in patients treated with the sulfonamides had been approximately 60 per cent. An opportunity arose to treat with penicillin two patients having pneumococcic meningitis. The patients were not responding well to intensive sulfonamide therapy combined with specific antipneumococcic rabbit serum. Patient 28 was treated through the cooperation of Dr. E. J. Huenekens of Minneapolis, and patient 29 with Dr. W. R. Shannon of St. Paul. The results of therapy in these patients are summarized in Table 8. It is apparent that in these two patients, at least, penicillin did not provoke a favorable therapeutic response. This failure may be related, in part, to the observation that penicillin does not enter the cerebrospinal fluid when the material is given intravenously or intramuscularly.[27]

Table 8

Penicillin Therapy in Patients Having Pneumococcic Meningitis.

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford Units)	Results
28. $5\frac{1}{2}$ M.	Rt. otitis media	35 days. sulfathiazole orally 4.5 gm. sulfadiazine orally - 181 gm. in 32 days. Type VI antipneumococcic rabbit serum.	Cerebrospinal fluid - type VI pneumonococci	652,000 in 10 days.	Temporary improvement from sulfonamide therapy. No definite benefit from penicillin. Died.
29 10 M.	Skull fracture involving ethmoid sinus.	Sulfadiazine for 29 days; sulfapyridine 9 days Type XXXIII antipneumococcic rabbit serum.	Cerebrospinal fluid - type XXXIII pneumococci	912,300 in 28 days	Temporary improvement following sulfonamides. None from penicillin. Recovery following operative drainage of sinus.

Local Use of Penicillin

Only two patients have been treated in which fresh solutions of penicillin were applied directly to infected tissues. Patient 30, a 13 year old female, had chronic ulcerative colitis, complicated by an extensive infection of the skin with a coagulase-positive strain of staphylococcus as the predominating contaminant. Over a period of several weeks, under the direction of Dr. E. A. Strakosch, practically every type of chemotherapeutic agent, including the sulfonamides and tyrothricin, was used locally in attempt to eradicate the skin infection. All attempts resulted in failure. It was observed that the strain of staphylococcus was markedly resistant to the in vitro bacteriostatic action of the sulfonamides, but sensitive to penicillin. Penicillin was applied in the form of freshly prepared packs in concentrations ranging from 0.38 to 5 units per cubic centimeter. This was continued for 45 days. The number of staphylococci became significantly reduced, and at times, this bacterial species was not present in the cultures made from the tissues. There was temporary improvement in the skin condition, but attempts to skin graft the area failed. Interestingly enough, during the time when penicillin was being applied, cultures of the lesions showed a strain of gram negative bacillus to be present which was insensitive in vitro to penicillin. The child expired and autopsy showed the presence of ulcerative colitis and extensive hepatic damage.

Patient 31 - an 11 year male, had severe third degree burns of his lower extremities. The lesions appeared clean, but efforts to graft the areas with skin taken from the chest and abdomen resulted in infection of the donor sites and the burned areas. Several forms of local chemotherapy including the sulfonamides did not control the infection. The tissues appeared to be infected by a coagulast-positive strain of staphylococcus. Penicillin packs were applied locally to a control area of infected tissue for a period of 17 days. While the number of staphylococci was reduced, the flora was replaced by gram negative organisms, and therapy with penicillin did not affect control of the infection. The infection was gradually controlled by other therapeutic means.

Comment: Although the foregoing method of employing penicillin failed to produce a satisfactory response, further investigations are warranted with the use of higher concentrations of penicillin in selected localized infections. Penicillin had certain advantages over the selection of the sulfonamides for topical application. Its action is not inhibited by tissue debris, purulent exudate and other sulfonamide inhibitors. Penicillin also appears to have little or no toxic effects on the tissues.

Sulfonamide-Resistant Pneumococcal Pneumonia

We have had the opportunity of treating of only one patient with a pneumococcal pneumonia, mainly because the sulfonamides have been effective. Pertinent data pertaining to this patient are presented in Table 9. Because of the unusual historical events in this patient's past and present illness, a brief summary follows:

Patient 32 - , 22 - male - entered the University Hospitals in a state of diabetic coma with a CO_2 combining power of 10.7, blood sugar of 617 mgs., and 4+ acetone and diacetic acid in the urine. His temperature was 103. This was his eighth entry to this Hospital in four years. His past illnesses included a bilateral otitis media in 1940 due to type VIII pneumococci. In 1940, he also had a type I pneumococcal pneumonia, bacteremia and encapsulated empyema treated with specific antipneumococcus serum and sulfathiazole. A rib resection for

Table 9

Penicillin Therapy in Sulfonamide-Resistant Pneumococcal Pneumonia

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (in Florey or Oxford Units)	Result
32. . . 22 M.	Diabetic coma; type I bacteremia and empyema	6 days sulfadiazine, 15 gm. oxygen	Type I pneumococcus from sputum; blood and empyema exudate	735,000 in 12 days.	Recovery

the treatment of empyema was necessary. In 1941, he entered because of an abscessed tooth. A short time later, he returned with a Type I lobar pneumonia successfully treated with specific serum and sulfathiazole. He had two subsequent admissions--one in 1941 and one in 1943 because of diabetic acidosis associated with upper respiratory infections.

Up until June 1943, he had an indwelling catheter in the left pleural cavity. At that time, the tube fell out and the wound healed over. He was symptom-free until a few days before entry when he was struck across the posterior left chest. This was followed by pain and tenderness. Four days before entry he developed pain in the left chest, cough, chills and fever. He then became drowsy and remembered little until after he had been in the hospital several hours.

He had dullness to flatness over the left chest posteriorly. An aspiration of the left pleural cavity revealed 5 cc. of exudate which contained Type I pneumococci. In addition, Type I pneumococci were obtained from his sputum and blood. His diabetes was controlled. He was placed in an oxygen tent and given sulfadiazine. The pneumonia spread to involve the left lower, right lower, right upper and possibly the right middle lobes. Although his blood stream became sterile, his condition became desperate. His leukocyte count dropped to 5400. Penicillin therapy was started on the sixth day of his illness, or fourth day in the hospital. Coincident with the administration of large doses of penicillin--735,000 units in 12 days--his condition improved in a remarkable way. Further efforts to aspirate material from the left chest were unsuccessful. It is our impression that the patient had a residual, subclinical type I pneumococcal empyema, which was reactivated by trauma, resulting in recurrent pneumonia and empyema.

Sulfonamide-Resistant Gonorrhea

Although the sulfonamides are quite effective in the therapy of acute gonorrhea, an occasional patient does not respond to sulfonamide therapy--and the number of cases appears to be increasing. Three patients in this category have been treated with penicillin with the essential details tabulated in Table 10. The outstanding feature in all three cases is that large amounts of one or more sulfonamides were given for a period of several

Table 10

Penicillin Therapy in Sulfonamide-Resistant Gonorrhea

Patient	Complications	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Florey or Oxford Units)	Results
33. 28 M.	None	7 weeks 147 gm. sulfadiazine orally; 80 gm. sulfathiazole orally	culture of urethral exudate - gonococci	115,000 in 3 days	"Cured"
34. 26 M.	Acute prostatis; acute epidydimitis	57 days complete course of sulfathiazole, sulfadiazine and sulfanilamide over period of 8 weeks	Culture of urethral exudate - gonococci	150,000 in 4 days.	"Cured"
35. 19 F.	Pregnancy	8 weeks Sulfathiazole, sulfadiazine, and sulfanilamide - total of 154.5 gm.	Culture of urethral exudate - gonococci	150,000 in 4 days	"Cured"

weeks, but clinical and bacteriological evidence of a gonococcal infection persisted. A further feature observed in these patients was the speedy diminution of the exudate and rapid disappearance of gonococci from the exudate as determined by cultural methods. These phenomena occurred within 24 to 48 hours.

Penicillin was administered in various doses to these individuals. Patient 33 was given an intravenous injection of 10,000 units every four hours for three doses, and then 5,000 units every four hours for 17 doses. Patient 34, who had a complicating epidydimitis was given 20,000 units intravenously as an initial dose. He was then given 40,000 units over a period of 10 hours in a liter of saline solution. After a rest period of two hours, this procedure was repeated. He was then given 80,000 units in a continuous ten hour intravenous drip, and then 25,000 units intravenously in 10 cc. of saline solution for three doses every four hours. Patient 35 was given 25,000 units intravenously in 10 cc. of saline solution, and then 50,000 units as a continuous ten hour intravenous drip in 1 liter of 5 per cent glucose and saline. The same dose was given again in 1 liter of saline solution, and finally 25,000 units in 10 cc. of saline solution.

Gonococcal Arthritis and Synovitis

Two patients were treated. Before treatment with penicillin was instituted, it was appreciated that the material does not diffuse readily into the joint spaces. But both patients had tenosynovitis as quite a prominent feature. Both patients benefited markedly from therapy. Table 11 presents the salient clinical features, and the following discussion amplifies the tabulated material:

Patient 36. - , 40 - Indian female, had a sudden onset of pain in the left foot and ankle five days before entry. This was rapidly followed by

Table 11

Gonococcal Arthritis and Tenosynovitis

Patient	Lesion	Duration of Illness and Previous Treatment	Bacteriology	Penicillin Therapy (Oxford or Florey Units)	Results
36. , 40 F.	Cervicitis; vaginitis; tenosynovitis and arthritis both ankles and both wrists and hands	4 days	Gonococci cultured from cervical and vaginal exudate	114,000 in 6 days	"Cured" some residual tenderness of left wrist.
37. , 54 M.	Urethritis; severe arthritis and tenosynovitis rt. foot and ankle.	7 weeks	Gonococci cultured from urethral exudate	345,000 in 6 days	"Cured" Residual tenderness and immobility of rt. foot.

involvement of the right foor and ankle, and both wrists and hands. There was a history of exposure. This acute illness was preceded by an upper respiratory infection of two weeks' duration. It is of interest that she had polyarthritis as a child, and later chorea, but without subsequent demonstrable cardiac involvement. On examination, the outstanding features were edema, swelling, and redness of the dorsum of both feet and ankles; and a similar appearance of the dorsal region of both hands. There was exquisite pain elicited on pressure or movement of the involved extremities. Cultures of the cervical exudate revealed the presence of gonococci. Penicillin therapy was started on the ninth day of her illness. She received an initial intravenous dose of 30,000 units in 10 cc. of saline solution, and three hours later 20,000 units, followed in three hours by 10,000 units. She was then given 5,000 units intramuscularly every three hours for 13 doses and then 5,000 units every four hours for 12 doses. Within 12 hours after instituting penicillin therapy there was marked improvement in her condition. From then on there was rapid diminution in the pain and swelling of the extremities. Forty-eight hours after instituting therapy, cervical cultures revealed no gonococci. At the conclusion of penicillin therapy -- 6 days -- there was slight residual tenderness of the left hand and wrist.

Patient 37. -

., 54 - Male - developed gonococcal urethritis about seven weeks before entry to the University Hospitals. At first he was given continuous sulfonamide therapy for one month at home without improvement. He was then hospitalized elsewhere for six weeks and had four different courses of sulfonamide therapy in addition to local therapy. There was slight improvement. About one week before entry the right foot and ankle became swollen, reddened and extremely painful, and two days before admission the right testicle became enlarged, reddened, and very tender. He had lost about 70 lbs. in weight during his illness. Roentgenological examination of the foot revealed extensive and severe destruction of the joints. The ankle joint had only a minimal involvement. Fever therapy was contraindicated because of the uncertainty

of his cardiac status. A pure culture of gonococci was obtained from the urethral exudate. He was given an initial intravenous dose of 50,000 units in 10 cc. of saline solution, followed at three hour intervals by 40,000, 30,000 and 20,000 units. He was then given 10,000 units intramuscularly every three hours for 11 doses and then 5,000 units every four hours for 19 doses. Within the first 24 hours of treatment, the urethral exudate diminished markedly and no gonococci were recovered. His epidydimitis subsided slowly, but completely. The pain, edema and tenderness in the right foot diminished more slowly and at the conclusion of treatment he was able to move the ankle and toes voluntarily, but edema and redness was still present.

Comment: While the foregoing cases of gonorrhea treated with penicillin represent a successful application of the drug, the number of cases is too small from which to draw final conclusions. However, the report of the Committee on Chemotherapeutic and Other Agents[13] includes a much larger series and emphasizes the fact that penicillin is quite effective as a therapeutic agent in gonorrhea. It should be emphasized that the sulfonamides are still a means of controlling the majority of cases of gonorrhea.

Whether penicillin will prove to be a satisfactory agent in treating acute gonococcal arthritis will depend upon observations in a larger group of cases. As far as we know, no clinical reports have appeared in the literature on this subject.

Pneumonia (?etiology) and E. coli Peritonitis

Patient 38 - 25, female, developed small bowel obstruction nine days before entry to the hospital. The illness was complicated by pregnancy of 5 months. Operative interference for the obstruction was necessary and a look of small bowel was resected which was complicated by a perforation of the gut. Peritonitis ensued, although at operation 8 gram of sulfanilamide was placed in the abdominal cacity and 2 gram of sulfathiazole in the abdominal wound. Sulfathiazole was also given parenterally. On the fifth postoperative day, she developed signs of pulmonary consolidation on the left followed by a pleural effusion. Sulfamerazine was given parenterally. Attempts to identify the etiology of the chest pathology gave conflicting results. One sputum revealed gram positive diplococci which could not be typed by indirect and direct methods. A second specimen of sputum showed organisms consistent with Friedlander's bacillus; while a third contained coagulase-positive staphylococci. Two blood cultures were sterile. The peritoneal drainage abated, but in order to give her the benefit of further chemotherapy for the pneumonia, she was given penicillin by means of a continuous intravenous drip. She received a total of 390,000 units over a period of five days. This resulted in only slight and temporary improvement. Ten days after operation 600 cc. of bloody fluid was aspirated from the left pleural cavity. This remained sterile. The patient's condition became worse and she expired 12 days after surgery or on the 24th day of her illness. Autopsy revealed generalized peritonitis, and pneumonia and atelectasis of the left lung. The bowel obstruction was due to subacute enteritis (? regional) with perforation.

Toxic Manifestations

One of the most remarkable features in the foregoing group of cases is the lack of toxic reactions induced by penicillin. The drug appeared to provoke manifestations in only one case (patient 16). This patient had a thrombophlebitis of the vein into which penicillin had been injected, and according to one observer, she had flushing of the face coincident with the administration of the material.

Summary

1. A brief review of the literature on penicillin is presented.

2. The sodium salt of penicillin has been evaluated at the University Hospitals in the treatment of 38 patients with various types of bacterial infections.

3. Penicillin rapidly sterilizes the blood streams of patients having acute staphylococcal and hemolytic streptococcal bacteremias. While staphylococcal bacteremia may be controlled, associated bone lesions may appear to progress during and after therapy. Nevertheless, the bones appear to recalcify without a demonstrable residual infection. It is recommended that in the treatment of individuals with acute and chronic staphylococcal osteomyelitis large parenteral doses should be used at frequent intervals for a prolonged period of time.

4. Penicillin was remarkably effective in the treatment of 5 cases of gonorrhea. Two of the 5 patients had a complicating tenosynovitis and arthritis which was controlled with penicillin.

5. Although only one patient was treated, penicillin produced a remarkable therapeutic effect in an instance of pneumococcal bacteremia and empyema refractory to sulfonamide therapy.

6. Penicillin was without effect in the treatment of 3 patients with subacute bacterial endocarditis, and 2 patients with pneumococcal meningitis. The local use of penicillin in two patients with staphylococcal skin lesions produced only temporary improvement. This mode of therapy merits further investigation.

7. The treatment of 38 patients with penicillin was uncomplicated by toxic manifestations with the exception of one patient who developed a thrombophlebitis at the site where the material was injected, and also a flushing of the face.

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VI. GOSSIP

Paul VanDyne Newland, chief of staff, Clifton Springs Sanatorium and Clinic, New York was a hospital visitor this week. Member of 1935 class, University of Rochester, School of Medicine and Dentistry, he renewed many acquaintances here.....There will be a special course of lectures, demonstrations and discussions for inspectors who supervise food handling in eating and drinking establishments, November 18, 19 and 20 at Coffman Memorial Union. It is a combined offering of Minnesota Department of Health, Minnesota Department of Agriculture, Dairy and Foods, Department of Preventive Medicine and Public Health, League of Minnesota Municipalities and United States Public Health Service. Food sanitation problem is becoming critical as one may observe by casual inspection of public eating establishments. In ordinary times sufficient intelligent help supervised practices and kept establishments clean.. ..Grey Ladies of the American Red Cross will take qualifying tests to determine those best suited for diversional service for bedridden patients in general hospitals. This region is short of Occupational Therapists. Hospitals have been slow to accept Occupational Therapy as one of their obligations. Original purpose of Grey Ladies was to help patients with personal problems; Nurses Aides were trained to help the nurses. Hospital personnel becomes so short that Grey Ladies have been helping everywhere. Under new plan a certain number will be trained for diversional duty for special cases.... Minneapolis Public Library will conduct series of panel discussions on November 3, 4, and 5 at 7:45 p.m. on Problems of Youth, Postwar Economic Problems and Library and Its Public Relations. The roster is studded with names of interesting people including several members of University Staff. Public is invited.... At Michael Dowling Parent-Teachers Association Annual dinner this week most of the children came because there was no one to stay with them at home. This school cares for handicapped children from pre-school age through eighth grade. Busses bring them in morning and take them home at night. Bus driver and matron service is arranged for each area of city. At entrance a varied assortment of wheel chairs and movable desks receive children unable to walk. Bus attendants carry in those unable to help themselves and children who can get around after a fashion wheel their less fortunate mates to their places. Rule is to do things for yourself as much as possible. School population consists of those who have been victims of accidents, cerebral palsy, rheumatic and congenital heart disease, muscular dystrophy, bone and joint infections, infantile paralysis and miscellaneous conditions. Missing in recent years is the steady influx of those with defects following poliomyelitis. The reason is apparently the current interest in preventing these deformities through physical therapeutical means: also of interest in the same connection is the shrinking demand on the brace funds because of the same program. Largest number of children now are spastics. All pupils carry regular school program and 2-hour rest and treatment period. They have a fine swimming pool, good gymnasium, and excellent occupational therapy facilities. Parents represent a varied group and have little in common except disabled children. The teachers are outstanding and Miss McAlister, the principal, is an educator in the best sense of the term. The mothers tend to do too many things for the children at home and to dramatize themselves in public especially when the child is along (but they are realists). Fathers are poor realists and either try to push the youngster and force him to do things beyond his capacity or they reject the child trying to hide their feelings by running away from the situation. Most parents, however, make a conscientious effort to understand and to accept the fact that their child will be limited. Physicians who deal with these problem children enjoy unique opportunity of helping both parents and the child get the most out of the situation. The list of crippling conditions in childhood which responded to better care include accidents osteomyelitis, meningitis, rheumatic fever, tuberculosis and poliomyelitis. The group which remain consists largely of conditions present at birth....Dean C. Sidney Burwell of the Harvard Medical School will address staff and students at 11:00, Saturday, October 30, in the Medical Science Amphitheatre, on "Constrictive Pericarditis,"....