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Advances in Antibiotic Therapy

Volume XX | Friday, January 7, 1949 | Number 11

BULLETIN OF THE
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INDEX

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

January 10 - 15, 1949

No. 230

Monday, January 10

8:00 -	Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.
9:00 - 9:50	Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
9:00 - 10:50	Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.
10:00 - 12:00	Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.
11:00 - 11:50	Roentgenology-Medicine Conference; Staff; Veterans Hospital.
11:00 - 11:50	Physical Medicine Seminar; E-101, U. H.
11:00 - 12:00	Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.
12:00 - 1:00	Physiology Seminar; No seminar meeting until Jan. 17.
12:15 - 1:20	Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.
12:30 - 1:20	Pathology Seminar; Haemachiromatosis; Sam Nerenberg; 104 I. A.
12:30 - 1:30	Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Class Room, Minneapolis General Hospital.
1:30 - 2:30	Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.
1:30 - 2:30	Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
4:00 -	Pediatric Seminar; Iron Metabolism; R. Engel; 6th Floor, Child Psychiatry, U. H.
4:00 - 6:00	School of Public Health Seminar; 113 MeS.
4:00 - 6:00	Kellogg Lecture; Postoperative Care of the Urinary Bladder; Donald Creevy; Powell Hall Amph.
5:00 - 5:50	Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.
5:00 - 6:00	Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

Tuesday, January 11

8:30 - 10:20 Surgery Seminar; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans' Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

2:00 - 4:00 Kellogg Lecture; Function Tests of Pulmonary Ventilation; John S. Gray; Todd Amphitheater.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference, Dr. Rigler and Staff; University Hospitals.

8:00 p.m. Pulmonary Hypertension; Richard Ebert; MeSc. Amph.

Wednesday, January 12

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans' Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:00 - 12:50 Radio Isotope Seminar; Measuring Instruments, Part II: Ionization Chambers; James Marvin; Rm. 216, Hospital Court, Temporary Bldg.

4:00 - 5:00 Infectious Disease Rounds; Medical Conference Room; Veterans Adm. Hospital.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. B. Visscher; Todd Amphitheater, U. H.

Thursday, January 13

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Craig Freeman and H. M. Stauffer; M-109, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hospital.

12:00 - 1:00 Physiological Chemistry Seminar; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Class Room, Minneapolis General Hospital.

4:00 - 5:00 Bacteriology and Immunology Seminar; Thermo Death Times of Organisms Occurring in Milk; Jos. Olson; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Roentgen Diagnostic Technique in Scandinavia; Jack Friedman; Todd Amphitheater.

Friday, January 14

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Non-Bacterial Pneumonias; J. T. Syverton; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, January 15

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, H. M. Stauffer, and Staff; Todd Amphitheater, U. H.

9:00 - 12:00 Neurology Conference; Powell Hall Amph.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 11:50 Urology Seminar; Sterility in the Male; Gordon Strom; E-101, U. H.

11:00 - 12:00 Anatomy Seminar; Progress in Neuroanatomy During 1948, A. T. Rasmussen; Experiments in Fixation and Staining of Sclerotic Nerve Cells, J. F. Hartmann; 226 I. A.

II. ADVANCES IN ANTIBIOTIC THERAPY

Ellard M. Yow
Wesley W. Spink

Introduction

In recent months progress in antibiotic therapy has been in three directions: one, a better understanding of certain fundamentals of the action of antibiotic substances when used alone or in combination with other chemotherapeutic agents; secondly, a wider experience with penicillin and streptomycin, with resulting clearer understanding of their uses in infectious diseases and some of the problems associated with their use; and thirdly, the experimental study and clinical trial of newer antibiotic substances.

Bacterial Resistance to Antibiotics

Experimental evidence is still lacking in the precise mechanism of action of the antibiotics. Recent findings are consistent with the theory that penicillin and streptomycin probably act by interfering with some essential phase of the metabolism of sensitive bacteria.[25,26,64,69,105,109] Progress has been made, however, in the knowledge of the origin of resistance of bacteria to antibiotic substances.

It was learned early in the investigations on penicillin that, among species of bacteria sensitive to this agent, there were some strains quite resistant to its action.[1] Demerec[38,39] proposed the theory that penicillin-resistant strains arise from resistant variants that occur naturally in every large population of a sensitive strain of bacteria. These resistant variants originate through mutation, independent of exposure to penicillin. He further believed that the property of resistance is an inherited characteristic and that penicillin acts as a selective agent which suppresses non-resistant bacteria. Thus, resistant mutants occurring at random in a small fraction of a bacterial population, survive when exposed to a certain concentration of penicillin which eliminates all sensitive bacteria.

Demerec based this theory on the observation that when a culture of Staphylococcus aureus was exposed to various concentrations of penicillin for the first time, most of the bacteria were eliminated by a penicillin concentration of 0.03 units per ml., but there were a few survivors resistant to concentrations as high as 0.15 units per ml. Colonies arising from the resistant variants contained organisms resistant to slightly higher concentrations of penicillin. By exposing the culture to gradually increasing concentrations of penicillin, the sensitive organisms were eliminated and the resistant variants survived; so that eventually a strain was developed that was extremely resistant to penicillin.

Demerec repeated this experiment, exposing a culture of Staphylococcus aureus to streptomycin. He found that the number of resistant survivors decreased rapidly between concentrations of 2.0 mcg. per ml. and 4.0 mcg. per ml., but more gradually between concentrations of 4.0 mcg. per ml. and 50 mcg. per ml. This work was expanded by other investigators[3,30,85,97,98,99,100,110,136,156,165] using very large bacterial populations of different gram positive and gram negative bacteria. They observed that, in contrast to the survival curve of penicillin, the streptomycin survival curve reached a plateau beginning at concentrations of approximately 100 mcg. per ml. and extending to concentrations between 1000 and 10,000 mcg. per ml.

The study of the survival of resistant variants is incomplete, but by combining the results of different investigators and our own studies on Brucella, hypothetical Penicillin and Streptomycin, survival curves may be plotted for the purpose of clarifying the discussion.

There is a marked difference clinically in the development of resistant strains of bacteria during penicillin

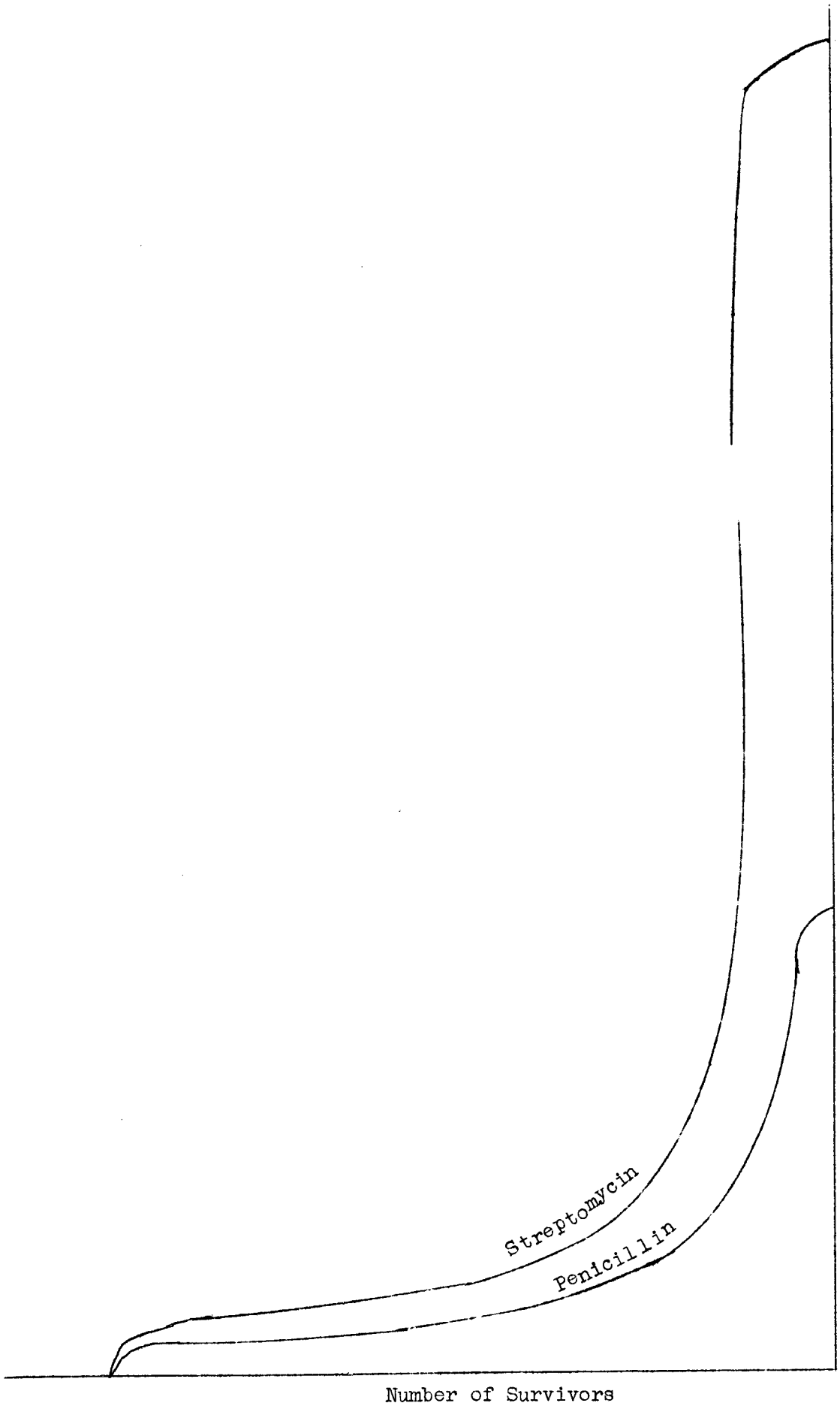

Fig. 1

Survival of Bacteria when Exposed to Penicillin and Streptomycin

therapy and the development of resistant strains during streptomycin therapy. The appearance of resistant strains during treatment with penicillin occurs rarely, and when it does occur, it develops slowly.[100] There is little evidence that penicillin-resistant strains of gonococci, meningococci, pneumococci, or group A hemolytic streptococci have been isolated from patients.[108] The development of resistance to streptomycin, on the other hand, is frequent and its rate of development is rapid.[100] Streptomycin-resistant strains developing during therapy of almost all streptomycin-susceptible species have been noted.[108]

Demerec's theory of the origin of bacterial resistance to antibiotics provides us with a basis for this difference in the development of penicillin- and streptomycin-resistant strains of bacteria clinically. In the first place, it is not difficult to attain a level of penicillin in the blood which will inhibit the most resistant variant in the original bacterial population, since this is only 0.15 units per ml. It may be impossible, on the other hand, to reach a streptomycin blood level above that required to inhibit the most resistant variant present, which may be resistant to a concentration as high as 10,000 mcg. per ml. In the second place, the marked difference in the degree of resistance between streptomycin-resistant variants and penicillin-resistant variants would provide an explanation for the difference in the rate of the development of resistant strains of bacteria. The variants markedly resistant to streptomycin could in one generation give rise to a population of the same resistance, while it would take a penicillin-resistant variant many generations to develop the same marked degree of resistance. The clinical development of bacterial resistance involves other factors than these, however; depending on the size of the bacterial population, the degree of resistance of the variants present in the individual strain, the concentration of the antibiotic actually coming into contact with the bacteria, and the ability of the host's defense mechanisms to dispose of those organisms surviving the antibacterial action of the drug.

Another very interesting development in regard to bacterial resistance is the observation of Miller and Bohnhoff,[97,98,99,100] that among streptomycin-resistant survivors there are bacteria that are not only resistant to streptomycin but grow only in the presence of the antibiotic. These are called streptomycin-dependent variants and have been demonstrated in cultures of staphylococci,[110] meningococci,[100] gram negative bacilli,[110] tubercle bacilli,[156] and in our own laboratory in cultures of Brucella. Whether these dependent variants play any part in infections in human beings is not known, but dependent strains have been isolated from throats of patients receiving streptomycin.[100] A fatal case of pulmonary tuberculosis has been reported,[60] in which a streptomycin dependent strain of Mycobacterium tuberculosis was isolated. When this strain was injected into guinea pigs, those treated with streptomycin died sooner and with more extensive lesions than those receiving no treatment.

The Synergistic Effect of Combinations of Chemotherapeutic Agents

Recent laboratory and clinical experience has demonstrated that when certain chemotherapeutic agents are used in combination, they may act cooperatively, so that the total effect is greater than the sum of the effect of the individual drugs taken separately. In the test tube and in experimentally infected animals, the synergistic action of the combination of penicillin and sulfonamides has been shown for Staphylococcus aureus, Streptococcus pyogenes,[85,155] Salmoenla typhosa,[85] Diplococcus pneumoniae,[85] and many gram negative bacilli.[81] The combination of streptomycin and sulfonamides has been shown experimentally to act synergistically against infections due to Klebsiella pneumoniae,[85] Brucella,[128] and Mycobacterium tuberculosis.[85] In rabbit syphilis, the combinations of penicillin and mapharsen, and penicillin and bismuth are more effective than the agents used separately.[90]

Clinical investigations indicate that combined sulfadiazine and penicillin is the treatment of choice in pneumococcal meningitis.[158] The combination of sulfadiazine and streptomycin has been recommended in the treatment of brucellosis,[49, 116, 137] influenzal meningitis,[2] salmonella and shigella infections, and in urinary tract infections due to Proteus vulgaris and Pseudomonas aeruginosa.[147] The sulfones have been used with streptomycin in treating tuberculosis and leprosy.[87]

The most logical explanation for this synergistic action is that of Klein and Kalter.[81,82,83] They suggested that the increased effect may be due to the reduction in the number of the bacteria by one agent, so that the other agent has a reduced number against which it must act. It has been found that in vitro the activity of an antibiotic agent is effected by the number of organisms to which it is exposed.[69] An agent which is only partially antibacterial in the presence of a large number of cells may become more active in the presence of a smaller number.[81] However, in order for agents to act synergistically, they must act by different mechanisms, and each must, to some extent at least, be active against the bacteria for which it is being used.

In view of the previous discussion on bacterial resistance, one would anticipate that the use of different antibacterial agents in combination would decrease the development of bacterial resistance during treatment. We have found that the number of streptomycin-resistant survivors of a Brucella culture can be markedly decreased in vitro by the addition of sulfadiazine or aureomycin. The chance of resistant variants surviving two chemotherapeutic agents is much less than its chance of surviving one, since each drug is active against the bacteria surviving the action of the other.[37]

There are other advantages in the use of antibacterial agents in combination in the treatment of infectious diseases. Although sulfadiazine is much more readily diffused throughout the tissues and across body membranes, it is inactivated in the presence of purulent or necrotic material. Penicillin and streptomycin, on the other hand, are not inactivated by pus, but they cannot always be depended upon to cross in therapeutic concentrations the meningeal or pleural membranes following intramuscular administration. Another need for combined therapy is that one often must begin treatment in seriously ill patients before the etiologic agent is isolated and identified. In other cases the infection may be caused by several species of both gram positive and gram negative bacteria, such as in peritonitis, wound infections, and chronic pulmonary infections.

The simultaneous administration of two or more drugs is, however, not without danger. There is the increased possibility of toxic manifestations. Although this is no major problem with the use of penicillin, it may induce a state of severe hypersensitivity which may persist and prevent the subsequent use of the antibiotic when it is needed. Both sulfadiazine and streptomycin may produce serious reactions. Another objection to the concurrent use of more than one chemotherapeutic agent, of less clinical importance, is that one may not be able to ascertain which of the agents is the most effective and least dangerous in a particular infection.

Penicillin

Further experimental investigations and wider clinical experience with the use of antibiotics have led to a more complete evaluation of their clinical application and have crystallized certain problems associated with their use. The conditions in which penicillin is likely to be effective have pretty well been defined after five years of its use in the treatment of infectious diseases. Penicillin is the drug of choice in the treatment of infections due to staphylococci, pneumococci, and streptococci, but it has not completely replaced the sulfonamides in meningococcal infec-

tions, urinary tract infections, bacillary dysentery, nor the use of certain sulfonamides in the preparation of the bowel for surgery.[52]

Table 1

Diseases in which Penicillin Therapy Is Indicated

Pneumonia	Cellulitis
Empyema (with drainage)	Tetanus (with antitoxin)
Tonsillitis	Gas Gangrene (with antitoxin)
Scarlet Fever	Wound infection
Otitis Media	Gonorrhea
Meningitis	Syphilis
Bacteremia	Rat Bite Fever
Bacterial endocarditis	Relapsing Fever
Diphtheria (with antitoxin)	Weil's Disease
Erysipelas	Ornithosis
Vincent's Infection	Pyogenic Infections

Table 2

Penicillin-Susceptible Species of Bacteria

Staphylococcus Pyogenes	Clostridium Tetani
Streptococcus Hemolyticus	Clostridium Welchii
Streptococcus Viridans	Borrelia Vincenti
Streptococcus Anhemolyticus	Treponema Microdentium
Diphococcus Pneumoniae	Spirillum Minus
Corynebacterium Diphtheriae	Leptospira Icterohemorrhagiae
Neisseria Gonorrhoeae	Borrelia Novji
Neisseria Intracellularis	Streptobacillus Moniliformis
Treponema Pallidum	Actinomyces Bovis
Bacillus Subtilis	Bacillus Anthracis

While the development of penicillin-resistant strains of bacteria in an individual patient is rarely a problem, there is evidence that there is an increase in the incidence of penicillin-resistant strains of staphylococci isolated from infections before treatment. This is particularly true in hospital wards and it is suggested by Barber[6] that it may be due to the elimination of sensitive strains with penicillin administration and the spread of resistant strains by "carriers" working with the patients.

There have been a few diseases in which the efficacy of penicillin has been established only after a lapse of a considerable period of time. The most important of these is syphilis.

Syphilis: Sufficient data have now been collected to compare the early results of penicillin therapy with those of the heavy metals in the treatment of syphilis, though exact dosage schedules have not been established.

In primary and secondary syphilis

there is evidence to suggest that treatment with penicillin alone is slightly inferior to metal therapy, when the latter is properly carried out.[118] It is difficult, however, to distinguish the "failures" from "reinfections" after penicillin therapy, since syphilis treated very early in its course with penicillin may leave the host without immunity and make reinfection possible.[118] Nevertheless, it is generally accepted that the risk of toxic reactions does not justify the possible advantage of arsenic and that it should be reserved for a second course of therapy, should this become necessary.[118,144]

Apparently the duration of therapy is more important than the total penicillin dose in early syphilis. Results have been just as satisfactory following the administration of 2,400,000 units as with 10,000,000 units.[118] The optimum length of treatment is difficult to access, but it is probably eight to fifteen days.[144,146] It does not appear essential that demonstrable penicillin levels be present consistently in the blood,[43] but on the other hand, the optimum time interval between injections has not been established. The U.S. Public Health Service recommends in primary and secondary syphilis a schedule of 50,000 units of crystalline penicillin G in aqueous solution be given every two hours for a total of 4,800,000 units.[144] Thomas[149] has reported using 300,000 to 600,000 units daily for fifteen days of penicillin in oil and beeswax with results similar to those using more frequent injections of aqueous solutions of penicillin. A regime now being investigated is the use of 1,200,000 units of procaine penicillin in one injection weekly for two weeks or 600,000 units twice weekly for three weeks.[149]

In latent syphilis, in which the diagnosis is based only on the positive serologic test for syphilis, therapy is more difficult to evaluate. So far as the reduction of the titre of the serologic test is concerned, penicillin therapy is no more effective than treatment with arsenic and bismuth.[144] In benign late and visceral syphilis, involving the skin, mucous membranes, bones, liver, and lungs, results with a total dose of 2,400,000 to 4,800,000 units of penicillin are as favorable as following treatment with heavy metals.

Penicillin has been almost 100 per cent effective in the prevention of prenatal syphilis, especially if given before the eighth month.[144] Penicillin therapy in early congenital syphilis appears to be superior to any previous method of treatment, but its value in late cases remains to be evaluated.[75]

Penicillin exerts a very favorable influence on the spinal fluid abnormalities when used in early and late asymptomatic neurosyphilis. In most cases normal values are found six months after beginning treatment, but in later cases, the reversal of a positive Wassermann test is slower.[133] The response of the clinical manifestations of symptomatic neurosyphilis to penicillin therapy has been more favorable than that following treatment with heavy metals and the serologic and clinical relapses have been less frequent. The additional use of induced amalaria has not yet been evaluated, but it is advisable in patients with neurosyphilis entailing a serious threat to vital function, such as dementia paralytica or taboparesis, unless it is otherwise contraindicated.[144]

The occurrence of the Jarish-Herzheimer reaction is common in the treatment of all types of syphilis with penicillin.[144] The reaction is seldom severe enough, however, to prevent continuation of penicillin therapy. Although available evidence indicates that it cannot be avoided by initiating therapy with small doses of penicillin, the U.S. Public Health Service recommends that in cardiovascular syphilis it be withheld until after preparatory treatment with heavy metals has been given.[144] Moore,[103] on the other hand, states that the possibility of therapeutic paradox in cardiovascular syphilis has been greatly exaggerated.

The advantages of penicillin in the treatment of syphilis, then, are fewer toxic reactions, ease of administration, and the much shorter period of time required for a course of therapy. While precise schedules of doses remain to be worked out, acceptable schedules are presented in Table 3.

Table 3

Acceptable Penicillin Schedules in the Treatment of Syphilis

Primary Secondary Latent Late manifest Late congenital Prenatal	Aqueous solution of penicillin 50,000 units every 2 hours for 8 days or Penicillin in oil 600,000 units daily for 10 days
Early congenital	Aqueous penicillin 100,000 - 400,000 units per kilogram over period of 8-15 days.
Neurosyphilis: Asymptomatic Acute meningeal Diffuse meningovascular Gumma Vascular Paresis) Tabes) Primary optic atrophy)	6,000,000-10,000,000 units of aqueous penicillin over period of 8-10 days. 10,000,000-20,000,000 units units of aqueous penicillin over period of 10-20 days + malaria
Cardiovascular	Results inconclusive - probably should be prepared for several weeks with Bismuth, then 6,000,000-10,000,000 units of penicillin over 15 or more days.

*From U.S. Public Health Service.

Gonorrhea: Although one occasionally reads about the problem of penicillin-resistant cases of gonorrhea, there have been no strains of Neisseria gonorrhoeae isolated resistant in vitro to penicillin. Of 3000 individuals referred to the Hot Springs Medical Center as cases of penicillin-resistant gonorrhea, 2821 were culturally diagnosed as gonorrhea and bacteriologically cured with two or three injections of penicillin in oil and beeswax at twenty-four hour intervals. The remaining 226 patients were cases of "non-specific urethritis."[113] Hughes and Carpenter[74] state that many cases of relapses following penicillin therapy may be instances of reinfection. DuCondroy[42] emphasizes the importance of recognizing the "non-specific prostatitis" that often follows acute gonorrhea.

Table 4

Penicillin Therapy in Gonorrhea*

Acute Gonorrhea	Penicillin in oil 300,000 units or Aqueous penicillin 100,000 units every 2 hours x 3
Relapse	Penicillin in oil 300,000 units daily for three days or Aqueous penicillin 100,000 units every 3 hours for three days

*From U.S. Public Health Service

Diphtheria and tetanus: There has been adversity of opinion about the use of penicillin in those diseases in which the causative organism is sensitive to penicillin, but in which the damage is done by the exotoxin of the bacteria; such as gas gangrene, tetanus, and diphtheria. Although penicillin has no effect on the toxins of these diseases, its use is recommended in conjunction with the specific antitoxin in an attempt to remove the source of the toxin.[34,66] It is no substitute for debridement in tetanus and gas gangrene.[39]

Administration of penicillin: Although the indications for penicillin therapy have, in general, been well established, there remain the problems of the optimum doses and the best method of its administration. Much attention has been given to the relative value of intermittent blood levels as opposed to constant blood levels, temporary high blood levels as compared to sustained blood levels, and systemic administration alone as against systemic administration with supplementary intrathecal therapy. Various preparations to decrease the absorption of penicillin and other agents to decrease the excretion of penicillin have been introduced.

The fact that penicillin was the first actively bactericidal agent that could be administered by parenteral injection to human beings to kill the invading bacteria with minimal injury to the host has made necessary the re-evaluation of some of the principles applicable to therapy with drugs prior to penicillin.[134]

One of these principles that must be reconsidered is the relationship of the constancy of the blood level to the therapeutic effect of an antibiotic agent. With the sulfonamides it was well established that a constant level of the drug should be maintained in order to prevent the multiplication of bacteria and to permit the defense mechanisms of the patient to destroy the invading organisms.

Is this principle of sulfonamide therapy applicable to treatment with penicillin? There is evidence that constant blood concentrations of penicillin are not necessary in most infections. In the first place, penicillin has been found to be actually bactericidal in its action against most bacteria in concentrations ordinarily obtained in the tissues.[13,45,68,69] Chain and Duthie[26] demonstrated, by measuring the oxygen uptake of suspensions of bacteria and performing viability counts, that penicillin acted by rapidly killing staphy-

lococci under conditions favorable for their growth. Bigger[13] also observed that bacteria were killed *in vitro* by penicillin only when they were actively multiplying and suggested that constantly maintained penicillin blood levels may fail to kill those organisms that happen to be in a resting state. While it has never been proven that in the human body constant blood levels are less effective than intermittent levels, it has been shown that intermittent levels, in most infections at least, are just as effective.

The interval between injections of an aqueous solution of penicillin is variable. It is governed by the size of the dose, the sensitivity of the organisms to penicillin, and the rate of multiplication of the bacteria. Detectable blood levels following the intramuscular injection of 1,000,000 units of an aqueous solution of crystalline penicillin G may be maintained for 10 to 12 hours, after 300,000 units for 6 to 8 hours, and after 100,000 units for 4 to 6 hours. Eagle[45] has expressed the levels in terms of three time periods: first, the length of time the penicillin is present in the maximally effective concentration, and during which the organisms are killed at the maximum rate; secondly, the time during which penicillin is present in lower concentrations and is more slowly antibacterial; and thirdly, the period during which the concentration of penicillin has fallen below the level established *in vitro* as being necessary to kill the organisms, but during which the organisms continue to die at a rate more rapid than the rate of their multiplication. The last period may be extended for varying periods, during which no penicillin can be detected in the serum. The explanation of this is yet open to question, but Eagle suggests several possibilities: the penicillin may persist in the tissues longer than in the blood, the organisms may be killed *in vivo* by a concentration less than that required *in vitro*, or the organisms may be disposed of by the body's defense mechanisms during the period in which they are recovering from the toxic effects of penicillin and before they again begin active multiplication. The work of Parker[112] indicates that this latter possibility is an important one.

The efficacy of infrequent intermittent injections of penicillin has been studied both in experimentally infected animals and in patients. White and associates[116] found that an aqueous solution of crystalline penicillin G given intramuscularly at 12-hour intervals was just as effective in streptococcal infections in mice as injections given at two-hour intervals, provided the total dose was the same. Zubrod[167] made similar observations. In experimental pneumococcal infections, Gibson[55] showed that results were as good when penicillin was administered at infrequent intervals as when given every 2 to 3 hours.

In human infections, Jersild[78,79] reported the use of intramuscular injection of an aqueous solution of penicillin in doses of 90,000 to 150,000 units given twice daily for six days in 2,000 cases of scarlet fever treated since 1945 at the Blegdam Hospital, Copenhagen, Denmark. The nose and throat cultures became negative within 48 hours and there were no recurrences in the period during which they were followed. The average febrile period was 4.5 days, as compared to 7 days in sulfonamide-treated patients. None of the suppurative complications of scarlet fever developed after penicillin was begun. Davies[36] treated patients with carbuncles and hemolytic streptococcal tonsillitis with the same dosage schedule and reported "striking results." Sixty-eight patients with scarlet fever were treated with the same regimen by Ward[157] with satisfactory results. Jawetz[77] treated 81 patients with hemolytic streptococcal pharyngitis by different routines and concluded that results were just as satisfactory with infrequent penicillin doses. Tompsett[152] reported favorable results in 26 patients with pneumococcal pneumonia treated with injections of 300,000 units at 12-hour intervals.

Table 5

Penicillin Dosage Schedules in
Infections Due to the Most Penicillin-Sensitive Bacteria

Diplococcus Pneumoniae Streptococcus Hemolyticus Neisseria Gonorrhoeae Fusospirochaetes	200,000 units of an aqueous solution of crystalline penicillin G every 12 hours or Procaine penicillin 300,000 units every 24 hours.

Is there any advantage in maintaining constant levels of penicillin in the blood? Because of the shortage of nursing personnel in hospitals and because of the large number of patients that must be treated outside of the hospital, preparations delaying the absorption of penicillin have been used widely. The first of these to be introduced was a suspension of penicillin in a mixture of beeswax and sesame oil.[122] This preparation has proved effective in treating syphilis and gonorrhea on an outpatient basis and some mild infections in the home. Whether this combination is more effective than similar doses of crystalline penicillin in aqueous solution given once or twice daily is unknown since comparative studies are lacking. Local and systemic reactions have occurred more frequently with the suspension of penicillin in oil and wax than with aqueous penicillin.[52,86]

Recently, several other preparations which delay the absorption of penicillin have been introduced. These have been prepared by chemically combining a molecule of penicillin with a molecule of procaine or an aluminum salt,[17,65,145] forming a crystalline substance only slightly soluble in water and slowly absorbed when injected intramuscularly. Their administration is facilitated by suspension in peanut oil. Levels of penicillin are maintained longest in the blood after administration of procaine penicillin G in peanut oil with 2 per cent aluminum monostearate of the small particle type. After the intramuscular injection of 300,000 units, effective levels are present in 92 per cent of the patients at 48 hours and in 86 per cent at 96 hours.[150] Higher blood levels can be obtained with these crystalline repository penicillin preparations, in contrast to the beeswax and oil suspension, by increasing the dose administered. The possibility of sensitivity to procaine must be considered before administering procaine penicillin, but in clinical use thus far, reactions have apparently been infrequent.[67,86]

While the use of repository preparations of penicillin may be a convenient way to administer the antibiotic under certain circumstances, there is no evidence that the resulting sustained low penicillin level is any more effective than higher intermittent levels from the periodic injection of aqueous solutions of penicillin. As discussed above, infections due to the most sensitive organisms to penicillin can be effectively treated with two injections of an aqueous solution of penicillin daily. In infections due to less sensitive organisms, such as the staphylococcus and Streptococcus viridans, intermittent levels are still just as effective, but the interval between injections must be shorter.

As it became more and more definitely established that penicillin was a relatively non-toxic drug, a tendency developed to use larger and larger doses. Usually this increase in dosage is un-

Table 6

Penicillin Dosage Schedules in Infections Due to Less Sensitive Bacteria

Staphylococcus Pyogenes Streptococcus Viridans Neisseria Intracellularis Corynebacterium Diphtheriae Clostridium Tetani Clostridium Welchii Bacillus Anthracis Actinomyces Bovis Spirillum Minus Borrelia Novji Streptobacillus Moniliformis	100,000 units of an aqueous solution of crystalline penicillin G every 3 hours.

necessary and wasteful, but there are certain indications for large penicillin doses. In infections due to relatively resistant strains of staphylococci and streptococci, large doses of penicillin may be required. It has been found clinically that in large doses, penicillin may be a valuable aid in certain infections due to gram negative bacilli, such as peritonitis and some cases of urinary tract infections. High blood levels increase the diffusion of penicillin across body membranes and into relatively avascular areas, such as walls of abscesses and bacterial vegetations on cardiac valves.[52]

Table 7

Dosage Schedules in Infections Due to Bacteria Relatively Resistant to Penicillin

Streptococcus Viridans Streptococcus Anhemolyticus Leptospira Icterohemorrhagiae Some gram negative bacilli	300,000 - 1,000,000 units of crystalline penicillin G every 2-3 hours (caronamide in doses of 4.0 grams every 4 hours may be added)

Various drugs have been used to produce prolonged high penicillin blood levels by inhibiting the secretion of penicillin by the renal tubules. The most satisfactory of these drugs is caronamide (4 - carboxy-phenolmethane-sulfonanilide). It has been demonstrated by Collins, Seeler and Finland[33,127] that with an oral dose of 2.0 gms. of caronamide every hour in patients over 60 years, and in doses of 4.0 grams every 4 hours in patients under 60, that 6 hours after injecting 1,000,000 units of penicillin intramuscularly, the blood level is ten times that when caronamide is not used, and after 12 hours the level was twenty times as high. The indications for caronamide are limited,

however, being most valuable in cases of subacute bacterial endocarditis and in bacteremias due to relatively resistant organisms. Since the diffusion of penicillin across body membranes and into cavities is related to the height of the blood level, caronamide may be of value in treating meningitis and "walled-off" infections.[94]

There is no doubt that penicillin is effective in purulent meningitis due to pneumococci and staphylococci. There is some difference of opinion as to whether penicillin should be introduced intrathecally in order to insure adequate concentrations in the cerebrospinal fluid. Penicillin, when given intramuscularly in large amounts, will appear in the subarachnoid space, particularly if the meninges are inflamed. While it is true that the central nervous system may be irritated by penicillin, this probably does not occur unless high concentrations are present.[146] In suppurative meningitis one is desirous of not only curing the patients, but doing so as quickly as possible, so that the residual damage to the nervous system is minimal or absent. Therefore, it is recommended by some that in the treatment of suppurative meningitis one should not depend upon parenteral therapy alone, but should introduce from 10,000 to 20,000 units of crystalline penicillin in 10 cc. of normal saline solution directly into the subarachnoid space every 24 to 48 hours.

Recently, Lowrey and Quilligan[88] reported the treatment of 17 patients with pneumococcic meningitis without intraspinal penicillin with 14 recoveries. Dowling, Sweet, and Hirsch[41] used 1,000,000 units of penicillin intramuscularly every two hours in 8 patients with pneumococcal meningitis, only two of which received any intrathecal penicillin. Five or 27.5 per cent of these patients recovered as compared to 40 per cent of 53 patients with both systemic and intrathecal penicillin.

In an extensive review of the treatment of pneumococcal meningitis, Waring and Weinstein[156] concluded that since the overall mortality rate with the most intensive therapy is 40 per cent, the risk of local irritation from intrathecal therapy is "preferable to any compromise in antibacterial therapy."

Table 8

Penicillin Therapy in Meningitis

Neisseria intracellularis (Meningococcus)	Sulfadiazine 3-4 grams initially, followed by 1.0 grams every 4 hours + Intrathecal and intramuscular penicillin if response to sulfadiazine is not prompt.
Diplococcus Pneumoniae Streptococcus Pyogenes Staphylococcus Pyogenes Neisseria Gonorrhoeae	Intramuscular penicillin 100,000 units every 3 hours + Intrathecal penicillin 20,000 units every 24 hours (for at least one dose)

The oral administration of penicillin has been used satisfactorily in uncomplicated streptococcal pharyngitis, pneumococcal pneumonia, and acute gonorrhea.[52,121] In order to obtain the same concentration of penicillin in the blood and tissues as that following parenteral injection of penicillin, approximately five times the parenteral dose must be given when prescribed orally. Absorption is maximum when given before meals or on an empty stomach.[50] The simultaneous administration of alkali is not necessary. Patients seriously ill should not be treated only by the oral route, especially in the initial stages of their illness.

Penicillin blood levels following oral administration may be enhanced by the simultaneous administration of caronamide, but the resulting blood levels are more erratic than those following intramuscular administration.[33] Pencillin absorption is apparently better in infants than in older children and adults.[32]

Streptomycin

Three years of clinical experience with streptomycin have established its value in the treatment of infections due to that group of bacteria largely unaffected by penicillin, such as the gram negative bacilli and Mycobacterium tuberculosis. The most striking effect of streptomycin is attained in the treatment of tularemia and it has aided greatly in decreasing the mortality rate of influenzal meningitis. It is of definite value in some forms of tuberculosis and in urinary tract infections, bacteremias and pulmonary infections due to gram negative bacilli. Results have not been encouraging in enteric infections and when used alone in brucellosis.

Table 9

Bacteria Susceptible to Streptomycin Therapy

Pasteurella Tularensis	Shigella Dysentariae
Escherichia Coli	Aerobacter Aerogenes
Klebsiella Pneumoniae	Proteus Vulgaris
Mycobacterium Tuberculosis	Pasteurella Pestis
Brucella	Streptococcus Pyogenes
Hemophilus Influenzae	Neisseria Intracellularis
Hemophilus Pertussis	Neisseria Gonorrhoeae
Salmonella Choleraesuis	Corynebacterium Diphtheria

Table 10

Diseases In Which Streptomycin Therapy Is Indicated

Tularemia
Hemophilus Influenzal Meningitis
Meningitis due to other Susceptible Bacteria
Bacteremia due to Susceptible Bacteria
Urinary Infections due to Susceptible Bacteria
Friedlander's Pneumonia
Pneumonia due to other Susceptible Bacteria
Tuberculosis
Peritonitis
Penicillin- resistant infections
Brucellosis, in combination with Sulfadiazine

While streptomycin has been most effective in infections due to gram negative bacilli, the antibiotic is also indicated in some infections caused by gram positive and gram negative cocci, especially in those diseases due to penicillin-resistant cocci.

Methods of administration of streptomycin are, in general, similar to those of penicillin. It does not cross the meningeal or pleural barriers in reliable amounts and intramuscular administration should be supplemented by local instillation in meningitis and empyema. Streptomycin differs from penicillin in two important ways, with respect to absorption and excretion. First, streptomycin is more slowly excreted than penicillin. Following the intramuscular injection of 0.5 grams, significant levels of streptomycin may be maintained for 8 to 12 hours, and after 1.0 gram, for 12 to 18 hours. Second, practically no streptomycin is absorbed from the gastro-intestinal tract when administered orally. Tables 11 and 12.

Tuberculosis: The evaluation of the use of streptomycin in the treatment of tuberculosis has been slow, because of the nature of the pathologic process of the disease. While it has been shown to be strikingly beneficial in some phases of the disease, results have been equivocal or insignificant in others.

Streptomycin therapy has been most effective in acute cases of tuberculosis or in early spreading of the disease in older cases, such as acute tuberculous pneumonia, superficial ulcerations, and in the acute stages of dissemination. The beneficial action of streptomycin is limited by the extent of caseous necrosis present. Caseous lesions of soft tissues, prostate and epididymus usually respond very poorly to treatment. The more superficial type of caseous necrosis of the larynx, bronchi, intestine, bladder and skin respond more readily than those lesions in the deeper structures, such as the lungs and kidneys.[4]

The treatment of miliary and meningeal tuberculosis with streptomycin has been discouraging because of the tendency for relapses to occur, even after an interval of a year. Bunn[22] reported the results in 100 cases of acute miliary and/or meningitis treated by the Veterans Administration. In this group, acute pulmonary dissemination of miliary tuberculosis proved most responsive to streptomycin, but 37 per cent of the patients with meningitis survived. At the time of the initial report, 40 of the 100 patients treated were living, having been followed for periods varying between 4 and 14 months. A follow-up 8 months

Table 11

Streptomycin or Dihydrostreptomycin
Dosage Schedules

Tularemia	0.5 gram intramuscularly every 8 hours
Friedlander's Pneumonia	0.5 gram intramuscularly every 8 hours
Bacteremia	0.5 gram intramuscularly every 6-8 hours
Urinary Infection	0.5 gram intramuscularly every 8 hours + Sulfadiazine 1.0 gram every 6 hours
Peritonitis	0.5 gram intramuscularly every 6 hours + Penicillin 200,000 units every 2 hours + Sulfadiazine 1.0 gram every 4 hours
Brucellosis	Streptomycin 0.5 gram every 8 hours + Sulfadiazine 1.0 gram every 4 hours for 10-14 days

later revealed that 24 patients were alive, only 15 of whom were free of evidence of active disease. These 15 patients included 7 patients with miliary tuberculosis, 7 with meningitis, and 1 with both. Ten of the 24 patients still alive had severe labyrinthian dysfunction, 1 was deaf, and 3 had other neurological sequellae. Only 1 patient in whom miliary dissemination was followed by meningitis was still alive, and he was undergoing a fourth course of therapy.

A series of 63 cases of tuberculous meningitis was reported from the pediatric clinic at the University of Athens, 13 of whom also had miliary tuberculosis.[28] Of the 50 patients with meningitis alone, 21 were well approximately one year after therapy was started. Two of the patients with both miliary and meningeal tuberculosis remained well after therapy.

These two studies differed in two important respects; first, the duration of symptoms before therapy with streptomycin was begun, and secondly, the schedule of therapy. The patients reported by Bunn had had symptoms of tuberculosis meningitis for an average duration of 2.9 weeks, while most of the children in the Athens group had had symptoms less than 14 days. The method of the administration of streptomycin

Table 12

Streptomycin or Dihydrostreptomycin Therapy in Meningitis

Influenzal Meningitis	0.125 gram every 4 hours intramuscularly + 0.025 gram intrathecally daily + Sulfadiazine 0.065 gm / lb / 24 hrs. + In severe cases, specific antiserum
Meningitis due to other gram negative bacilli	0.5 gram intramuscularly every 6-8 hours + 0.025-0.050 gram intrathecally every 24-48 hours + Sulfadiazine 1.0 gram every 4 hours
Tuberculous Meningitis	0.5 gram intramuscularly every 12 hours + 0.025-0.050 gram intrathecally every 24-48 hours

by the Veterans Administration varied a great deal from patient to patient. All of the patients received intramuscular streptomycin, but the dose varied from 1.0 to 4.0 grams daily. With few exceptions, intrathecal streptomycin was given in doses from 0.02 to 0.2 grams daily for an average number of 80 instillations. The Athens group used total daily injections of 0.5 gram intramuscularly and 0.01 to 0.05 grams intrathecally. This was continued for 4 to 6 weeks, followed by a rest period of 5 to 10 days. Treatment was then resumed for 10 to 15 days or as long as a month in severely ill patients, followed again by a rest period, alternating for six to nine months. At three month intervals during the first year they were given intramuscular treatment for 10 days. These workers emphasized the importance of temporarily discontinuing intrathecal therapy where signs of acute hydrocephalus appeared.

In the general problem of the use of streptomycin in the treatment of tuberculosis, it has been strongly emphasized that antibiotic therapy is no substitute for the established principles of treatment. Because of the development of resistant strains of Mycobacterium tuberculosis, the value of streptomycin may be limited to a period of one or two months in many cases. Streptomycin should, consequently, be used as strategically as possible, with the long term plan of treatment in mind.

Bacterial Resistance to Streptomycin: The greatest limiting factor in the use of streptomycin in the treatment of infectious diseases is the rapid development of bacterial resistance. The development of resistant strains of almost all the bacteria susceptible to

streptomycin have been reported clinically. In tuberculosis, resistant strains begin appearing around the end of the first month of therapy and by the fourth month, 80 per cent of the strains isolated from patients receiving 1.0 gram of streptomycin daily are markedly resistant. Subsequent streptomycin therapy is probably of no value in these cases showing resistant strains. Organisms causing infections of the urinary tract become highly resistant to streptomycin very quickly, especially if there is improper drainage of urine.[51] The development of bacterial resistance has been the cause of failure of streptomycin therapy in brucellosis[61] and influenzal meningitis.[3]

Once streptomycin-resistant strains appear, they usually remain permanently resistant. There are certain steps that can be taken to reduce the incidence of resistance. These include such measures as maintaining an alkaline urine in urinary tract infections, prompt and adequate surgical drainage when indicated, and reserving streptomycin therapy until it is actually needed rather than using the drug prophylactically.

Streptomycin toxicity: A second limiting factor in the use of streptomycin is the frequent appearance of evidences of damage to the eighth cranial nerve. It has been shown by Tompsett[151] that with daily doses of 3.0 grams over a period of 42 to 120 days, 90 to 100 per cent of patients had objective evidence of impaired vestibular function. If 2.0 grams were given for 60 days, the incidence was 83 per cent and with administration of 1.0 gram for 42 to 120 days, 12 to 17 per cent of patients exhibited evidence of eighth nerve damage. Vestibular symptoms of streptomycin toxicity usually appear after the second week of therapy and are related primarily to the total daily dosages and secondarily to the duration of therapy. Although the vestibular damage is usually permanent, most patients learn to compensate for the dysfunction.

Dihydrostreptomycin: The incidence of eighth nerve damage will probably be decreased by the use of a reduced salt of streptomycin, called dihydrostreptomycin.[8,40] When this drug is given in doses of 3.0 grams or less a day, toxic manifestations have been rarely observed to date; but when administered in doses as high as 4.0 or 5.0 grams, the incidence of toxicity is about the same as that of streptomycin. Dihydrostreptomycin has approximately the same antibacterial activity as streptomycin and is active against the same species of bacteria. Strains of bacteria resistant to streptomycin are also resistant to dihydrostreptomycin and apparently the development of resistance to dihydrostreptomycin is encountered as frequently as with streptomycin. Dihydrostreptomycin offers another distinct advantage, in that in patients in whom streptomycin has had to be discontinued because of renal damage or skin eruption, dihydrostreptomycin may be given without difficulty. On the other hand, patients allergic to dihydrostreptomycin may tolerate streptomycin without reactions appearing.

New Antibiotic Agents

Bacitracin: In 1945 Johnson, Anker, and Melaney[80] observed that in a mixed culture from a badly infected fracture, a strain of Bacillus subtilis was particularly antagonistic to the other species in the culture. From this strain they recovered an antibiotic substance, which they called bacitracin.[5,7] This antibiotic was shown to be effective in vitro against gram positive organisms and against Neisseria.[95] Animals could be protected against experimental infections due to Streptococcus hemolyticus, Cl. Welchii, Diplococcus pneumoniae,[95] and Treponema pallidum.[46,47] When used topically in human patients bacitracin is effective in infected wounds and pyogenic skin infections.[95,101] It can be used either in the form of an aqueous solution in a concentration of 100 to 500 units per cc. or in the form of an ointment in concentrations of 500 units per gram.[95,10]

Table 13

New Antibiotic Agents Being Tried Clinically

Antibiotic	Bacteria Susceptible in Vitro	Clinical Infections Susceptible	Administration	Toxicity
Bacitracin	Gram positive cocci Gonococcus Meningococcus Clostridia	Pyogenic skin infections Infected wounds and burns	Topically wet dressings or ointment 100 u/ml. 500 u/ml.	Renal damage when administered parenterally
Polymyxin Aerosporin	Gram negative bacilli	Pertussis Infections due to: Pseudomonas aeruginosa Klebsiella pneumoniae	Not established	Renal damage
Chloromycetin	Gram negative bacilli Gram positive cocci Some virus and rickettsia	Epidemic typhus Scrub typhus Typhoid fever	0.25 gm. orally every 2-4 hours	None reported
Aureomycin	Gram negative bacteria Gram positive cocci Some viruses Most rickettsia	Penicillin and streptomycin resistant bacterial infections Brucellosis Rocky Mount spotted fever Lymphogranuloma venereum Viral ocular infections	0.5 to 2 gm. orally every 6 hours	Mild nausea and vomiting

When given parenterally to mice or monkeys, bacitracin produced kidney damage. Patients receiving bacitracin parenterally have exhibited albuminuria and in some instances, other evidences of renal damage.[124,125,126] Since bacitracin is still a crude drug and since the renal toxicity is not proportional to its antibacterial activity, there exists the possibility of eliminating the nephrotoxic principle by further purification.

The drug is only slightly absorbed when given orally, but when given by this route, fecal streptococci and spore-forming anaerobes can be temporarily eliminated from the feces.[19] At the present time, however, the only indications for bacitracin therapy are in the topical treatment of wound and skin infections and some eye infections due to gram positive bacteria, particularly those resistant to penicillin and sulfadiazine.

Polymyxin and aerosporin: Polymyxin was isolated by workers in the laboratory of the American Cyanamid Company from the Bacillus polymyxa.[11,141] It is probably very similar, if not identical, to an antibiotic called aerosporin, which was isolated independently in England from a related organism, B. aerosporus.[1a] Polymyxin is active in vitro and in experimentally infected animals against many gram negative bacteria, including Salmonella enteritides, Salmonella typhosa, Hemophilus pertussis, Hemophilus influenzae, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Seven strains of Brucella abortus and one strain of Brucella suis were found in our laboratory to be resistant in vitro to concentration of 100 mcg. per milliliter of polymyxin or greater, though Brucella has been reported by others as being sensitive to polymyxin. It is equally effective against streptomycin-sensitive and streptomycin-resistant strains of bacteria. It is absorbed from parenteral routes only and appears to have a high renal threshold.[140,141,142,143]

Clinical trials with polymyxin have been limited because of evidence of renal tubular damage following parenteral administration. Beneficial effects have been reported, however, from the use of polymyxin in infections due to Pseudomonas aeruginosa, Klebsiella pneumoniae, Hemophilus pertussis, and Brucella abortus.[123] Enthusiastic results are reported with the use of aerosporin in 10 patients with pertussis.[145-a]

Chloromycetin: An extremely important step forward in the treatment of infectious diseases was taken when two new antibiotic agents were isolated which were found to be active against certain viral and rickettsial diseases and which were effective when administered orally. One of these antibiotics is called chloromycetin and was isolated by Ehrlich and associates[48] from a soil Streptomyces similar to the one which produces streptomycin.[29,58] Chloromycetin is quite stable over a wide ph range and resists boiling. Its solubility in water is low, but it is quite soluble in propylene glycol. It is active in vitro in fairly small concentrations against many gram negative and gram positive organisms and in higher concentrations against Mycobacteria. It is not effective against fungi, protozoa or rabbit syphilis.[129,130]

Chloromycetin is active against all the known rickettsia which cause human disease and against some viruses. In human infections it has produced quite spectacular results in epidemic typhus and scrub typhus.[129,130] It has been beneficial in the treatment of typhoid fever.[163] The oral dosage is 50 mg. per kilogram as an initial dose, followed by 0.25 gram every 2 to 4 hours. There have been no significant toxic effects observed.[27]

Aureomycin (Duomycin)

Another antibiotic effective when administered orally against some viruses and rickettsiae was isolated by Duggar from the mold Streptomyces aureofaciens. Generically, the agent is called aureomycin and the trade name is "duomycin". In contrast to chloromycetin, aureomycin is soluble in water, but it is not as

resistant to heat or changes in ph. Aureomycin is quite unstable in solution and is most active at an acid ph. It is effective in vitro and in experimentally infected animals against most gram negative and gram positive bacteria, some viruses, and all of the rickettsiae pathogenic to man.

Bacteriologic studies on aureomycin have been reported by Paine, Collins, and Finland.[111] They found that weight for weight, aureomycin was less effective than penicillin, but more effective than streptomycin against most cocci. Aureomycin was found to be about as effective as streptomycin against most gram negative bacilli. It was active against penicillin-sensitive and penicillin-resistant as well as streptomycin-sensitive, streptomycin-resistant, and streptomycin-dependent organisms. They further observed that the antibacterial activity of the antibiotic was influenced in vitro by the number of bacteria present, the phase of growth of the organisms, and the ph. of the test media. A number of strains of gram negative and gram positive bacteria showed no marked tendency to become resistant in vitro on repeated exposure to aureomycin.

Clinically, aureomycin has been found by Wright and others[164] to be effective in lymphogranuloma venereum. Braley and Sanders[20] reported excellent results when aureomycin was used locally in a 0.5 to 1.0 per cent borate solution, in such eye infections as staphylococcal, pneumococcal, influenzae and inclusion conjunctivitis; in dendritic keratitis, Moren's ulcer, and epidemic keratoconjunctivitis. Finland[53] reported the use of aureomycin in 100 cases of bacterial infection. Sixty-six cases of gonoccal urethritis were treated with results inferior to those obtained with penicillin. The results in patients with typhoid and salmonella infections were equivocal. In 16 cases of urinary tract infections the response was quite favorable. Infections due to Proteus vulgaris and Pseudomonas aeruginosa were not benefited by aureomycin therapy. The only evidence of toxicity in this group of patients was the occurrence of loose bowel movements when large doses were given by mouth. There was no evidence of the development of resistant strains of bacteria in any of these cases.

At the University of Minnesota Hospitals investigations have been undertaken to determine the action of aureomycin in vitro and in experimentally infected animals against Brucella; to evaluate the results of aureomycin therapy in patients with brucellosis; and to study the effect of aureomycin in the treatment of infections resistant to penicillin and streptomycin.

In vitro experiments have revealed that of 15 strains of Brucella abortus, 14 strains of Brucella melitensis and 1 strain of Brucella suis, all isolated from patients, growth of the organisms was inhibited by concentrations between 0.4 and 1.4 mcg./ml. of aureomycin. In these concentrations, aureomycin prevented the multiplication of the bacteria, while concentrations of between 50 and 100 mcg./ml. were required to actually sterilize the cultures. No aureomycin-resistant variants of Brucella were observed in vitro by exposing extremely large bacterial populations to aureomycin. Furthermore, repeated exposure of organisms to increasing concentrations of the drug did not result in aureomycin-resistant bacteria. Aureomycin was equally as effective against streptomycin-sensitive and streptomycin-resistant strains of Brucella.

The effect of aureomycin against all three types of Brucella infection in the chick embryo has been compared to that of streptomycin and sulfadiazine. When used alone, aureomycin prolonged the life of the embryos, but all those surviving were found to harbor viable Brucella when sacrificed 12 days after beginning therapy. In combination with sulfadiazine, aureomycin was about as effective as the combination of streptomycin and sulfadiazine in prolonging life, but less effective in sterilizing the tissues. In mice and guinea pigs infected with Brucella, aureomycin therapy appeared to prolong life and to reduce the severity of the lesions found at autopsy, but did not

sterilize the tissues.

Aureomycin has been used clinically in the treatment of 24 patients with blood cultures positive for Brucella melitensis.[139] About half of these patients were seriously ill and required hospitalization--the others were treated as out-patients. There was a dramatic clinical improvement in all of the patients treated with aureomycin, though in 12 of the patients there was a spike in fever and a shock-like picture after the first oral dose of the drug. This "Herxheimer-like reaction" was seen less frequently when the initial dose was reduced. The patients treated have been followed for periods varying between four and six months and during this time there have been 5 bacteriological relapses, but only two of the patients had symptoms.

Two patients have been treated with brucellosis dud to Brucella abortus. They responded promptly to aureomycin and have remained bacteriologically and clinically well for three months in one case and 6 weeks in the other.

Aureomycin has also been used at the University Hospitals in a group of patients with various infectious diseases in whom therapy with the sulfonamides, penicillin, and streptomycin was not successful. Before treatment was begun, the etiologic organism was tested in vitro in each case for sensitivity to penicillin, streptomycin, and aureomycin. Those organisms found to be sensitive to aureomycin included Staphylococcus aureus, Streptococcus viridans, Escherichia coli, Aerobacter aerogenes, Salmonella typhosa, Hemophilus influenza, Brucella abortus, Brucella suis, and Brucella melitensis. Strains of Proteus vulgaris and Pseudomona aeruginosa were resistant to concentrations greater than the level of aureomycin found in the blood. The diseases responding favorably to aureomycin therapy include osteomyelitis due to Staph. aureus; bacteremia due to Staph. aureus, E. coli, and Aerobacter aerogenes; and recurrent urinary infections due to Aerobacter aerogenes and E. coli. One patient with typhoid fever was treated with some decrease in the severity of the disease, but the response to aureomycin was not striking.

Table 14

Comparative Sensitivity of Strains of Bacteria Isolated from Patients to Penicillin, Streptomycin, and Aureomycin

Bacteria	Disease from which Isolated	In Vitro Sensitivity*		
		PEN u/ml	SM mcg/ml	AM mcg/ml
Staphylococcus Aureus	Septicemia	19	10	0.8
Staphylococcus Aureus	Wound Infection	>25,000	>25,000	0.8
Staphylococcus Aureus	Wound Infection	> 2,500	>25,000	0.8
Streptococcus Viridans	Subacute Bacterial Endocarditis	3.1	156	0.8
Streptococcus Viridans	Subacute Bacterial Endocarditis	10	31	1.4
Hemophilus Influenzae	Septicemia	62	6,250	1.0
Proteus Vulgaris	Meningitis	> 5,000	1,250	12.5
Proteus Vulgaris	Abdominal Fistula	78	50,000	12.5
Pseudomonas Aeruginosa	Multiple Abscesses	> 5,000	> 5,000	12.5
Pseudomonas Aeruginosa	Urinary Infection	> 5,000	> 5,000	12.5
Brucella Abortus	Brucellosis	31	1.2	0.8
Brucella Abortus	Brucellosis	62	1.2	0.8
Brucella Suis	Brucellosis	8	1.2	0.8
Brucella Melitensis	Brucellosis	2	1.2	0.8
Brucella Melitensis	Brucellosis	> 20	1.2	0.8
Brucella Melitensis	Brucellosis	> 20	10,000	0.8
Brucella Abortus	Brucellosis	250	7,250	0.8

*Concentration of antibiotic necessary to inhibit growth.

Table 15

Cases Treated with Aureomycin

Case No. and Age	Diagnosis	Bacteriology	In Vitro Sensitivity*			Results
			Pen. u/ml.	SM mcg./ml.	AM mcg./ml.	
I - 11 mos.	Brain abscess with bacteremia	Staphylococcus aureus	312	> 50,000	0.8	Recovery
II - 9	Osteomyelitis	Staphylococcus aureus	312	> 50,000	0.6	Recovery
III - 16 mos.	Agranulocytosis with bacteremia	Staphylococcus aureus	> 50	> 50	0.6	Temporary improvement
IV - 4 mos.	Pulmonary fibrosis with infarction	Staphylococcus aureus	> 50	3.2	0.8	Slight improvement
V - 14	Osteomyelitis	Staphylococcus aureus	3125	4.0	1.0	Recovery
VI - 16	Subacute bacterial endocarditis	Streptococcus viridans	20	31	1.6	Relapse
VII - 32	Puerperal sepsis with bacteremia	Escherichia coli	78	39	0.8	Recovery
VIII- 27	Typhoid fever	Salmonella typhosa	--	--	1.0	Shortened course
IX - 8 mos.	Recurrent urinary infection	Aerobacter aerogenes	> 50	> 50	1.0	Recovery
X - 18	Recurrent urinary infection	Aerobacter aerogenes	>2500	>25,000	4.0	Recovery
XI - 18	Acute brucellosis	Brucella abortus	250	1.0	0.8	Recovery

*Concentration of antibiotic necessary to inhibit growth.

Comment

The introduction of these additional antibiotic agents has increased the necessity of a thorough knowledge of their specific indications, limitations, and methods of administration. It has emphasized the significance of a fundamental knowledge of the principles of therapy in infectious diseases and of establishing accurate etiologic diagnoses. It will be more and more difficult to find the drug of choice by trial and error and more difficult to give them all at once.

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III. MEDICAL SCHOOL NEWS

E. Starr Judd Lectureship in Surgery

Dr. Alton Ochsner, Professor of Surgery, Tulane University, will come to our campus to deliver the E. Starr Judd Lecture in Surgery, on Tuesday, January 18, at 8:15 p.m. in the Auditorium of the Museum of Natural History. Dr. Ochsner's subject will be "The Treatment of Postphlebitic Sequelae by Vasodilatation and other Measures." Dr. Ochsner will also give the Kellogg Lectures in clinical medicine on Monday, January 17. A surgery colloquium is also planned. The exact time of these presentations will be announced in the next issue of the Bulletin.

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New Minnesota Foundation Members

Dr. Donald B. Frane, 1214 - 42nd Ave. North, Minneapolis
Dr. Robert E. Friest, 302 Medical Arts Building, Minneapolis
Dr. George M. Tangen, 2640 Glenhurst Avenue, Minneapolis
Dr. B. J. Mears, 1267 Lowry Medical Arts Building, St. Paul
Dr. R.E. Risch, 1953 Benjamin St. N.E., Minneapolis
Dr. Julian F. DuBois, Sauk Center
Winona Clinic, Winona
Dr. Harold E. Miller, 5412 Irving Avenue South, Minneapolis
Dr. J. Dordal, Sacred Heart

Continuation Course in Obstetrics

More than 100 physicians of this area will attend a course in Obstetrics offered at the Center for Continuation Study on January 6, 7, and 8. The course has been arranged by Dr. John McKelvey, Professor and Head of the Department of Obstetrics and Gynecology.

The first day will be devoted to the problems of the cardiac patient during pregnancy. Dr. Curtis J. Lund, formerly a member of our faculty and at present Head of the Department of Obstetrics and Gynecology at Louisiana State University Medical School, will return to our campus from New Orleans to participate. Problems related to the Rh factor will be discussed during the second day of the course. Dr. Bettina F. Carter of Pittsburgh, Pennsylvania, will present her work on Rh haptenes. Many members of our own staff will also contribute as members of the faculty for this course.

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Dr. John S. Gray, Professor of Physiology, Northwestern University Medical School, will visit our campus on Tuesday, January 11. Dr. Gray will deliver the Kellogg Lecture on "Function Tests of Pulmonary Ventilation" at 2:00 p.m. in Todd Amphitheater.

Kellogg Foundation Lectures

The following lectures will be given during the week of January 10. All medical students, interns, nurses, technicians, dietitians, and physicians are cordially invited to attend these lectures. A special invitation is extended to University Fellows.

Dr. C. D. Creevy	The Postoperative Care of the Urinary Bladder	Monday, January 10, 4:00-6:00 p.m., Powell Hall Amphitheater
Dr. John S. Gray	Function Tests of Pulmonary Ventilation	Tuesday, January 11, 2:00-4:00 p.m., Todd Amphitheater, U. H.