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

## Streptomycin

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INDEX



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I.

# UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
## CALENDAR OF EVENTS

November 23 - November 29, 1946

No. 134

Saturday, November 23

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

8:30 - 11:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G Rigler, and Staff; Todd Amphitheater, U. H.

10:00 - 12:00 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 - Anatomy Seminar; The Bone Marrow Pattern in Brucellosis; R. D. Sundberg; 226 I. A.

11:00 - Medicine - Roentgenology Conference; Veterans' Hospital.

Monday, November 25

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; Interns' Quarters, U. H.

12:15 - 1:15 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:30 - 1:20 Pathology Seminar; Congenital Leukemia; Norlene Eckles; 104 I. A.

12:15 - 1:30 Pediatrics Seminar; Irvine McQuarrie and Staff; 6th Floor Seminar Room, Eustis, U. H.

12:00 - 1:00 Physiology Seminar; Metabolism of the Brain; N. Lifson; 214 M. H.

Tuesday, November 26

8:30 - Surgery-Pathology Conference; N. K. Lufkin, John R. Paine, and Associates; Small Conference Room, Veterans' Hospital.

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

10:30 - Surgery Seminar; John R. Paine; Small Conference Room; Building I, Veterans' Hospital.

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

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

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

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

3:45 - 5:00 Pediatric Staff Rounds; I. McQuarrie and Staff; W-205, U. H.

4:00 - 4:50 Surgery-Physiology Conference; Pulmonary Edema; Allan Hemingway and Lyle Hay; Eustis Amphitheater, U. H.

5:00 - 5:50 Roetgenology Diagnosis Conference; At Veterans' Hospital.

Wednesday, November 27

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

8:30 - 10:00 Psychiatry and Neurology Seminar; Staff; Station 60 Lounge; U. H.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Uremia; E. T. Bell, C. J. Watson, O. H. Wangensteen, and Staff; Todd Amphitheater, U. H.

12:00 - 1:00 Physiological Chemistry Journal Club; Staff; 116 M. H.

4:00 - 6:00 Medicine and Pediatrics Infectious Disease Rounds; W-205 U. H.

Thursday, November 27 -- Holiday - Thanksgiving.

Friday, November 29

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

9:00 - 9:50 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

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

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

10:30 - 12:20 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department; U. H.

11:30 - 1:00 University of Minnesota Hospitals General Staff Meeting; Movies (Arranged); New Powell Hall Amphitheater.

1:00 - 2:00 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

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

# II. STREPTOMYCIN*

Wendell H. Hall
Abraham Braude
Wesley W. Spink

## Origin, Nature and Properties

Unlike the discovery of penicillin, which followed a chance laboratory observation by Fleming in 1929, the isolation pf streptomycin resulted from a deliberate search for an antibiotic capable of exerting a bacteriostatic and bactericidal effect upon gram-negative bacteria and Mycobacterium tuberculosis. This work involved extensive surveys, analyses and tests in which many investigators collaborated. S. A. Waksman, who initiated the studies in the Department of Microbiology of the New Jersey Agricultural Experiment Station, Rutgers University, was primarily responsible for its discovery.[1]

The ultimate objective was to find a substance not only having a bactericidal and bacteriostatic effect upon bacteria, but also one which was non-toxic, which was not inactivated by body fluids and which acted *in vivo* as well as *in vitro*. It is not surprising that a number of antibiotics were isolated during this project which possessed only some of these properties. These included:

*actinomycin* - a highly toxic compound,
*clavacin* - more active against gram-negative bacteria but also toxic,
*fumigacin* - not very toxic, but not very active,
*chaetomin* - non-toxic but inactive *in vivo*,
and *streptothricin* - satisfactory in most respects but being somewhat too toxic.

It had been found early in the work that Actinomycetes offered great potentialities as a source of antibacterial activity. Twenty to thirdy per cent of all these organisms tested possessed such properties to a marked degree, but only a few of the cultures contained substances of promise for use as chemotherapeutics.

Among the first of these substances was streptothricin. It was found to be active both *in vivo* and *in vitro* against gram-negative organisms but two serious limitations were found. Purified preparations exerted a delayed toxic effect on animals and certain gram-negative as well as gram-positive bacteria were found to be naturally resistant to high concentrations.

The shortcomings of streptothricin led to a widespread search among various groups of microorganisms for more satisfactory agents. Eventually an Actinomyces was found which produced a substance possessing most of the desirable pharmacological and antibacterial properties. This organism resembled very closely Actinomyces griseus, which had been isolated from the soil 28 years previously by Waksman. It produced an antibiotic very similar to streptothricin but posessed greater activity against gram-negative bacteria and certain sporeformers which were resistant to streptothricin. The new substance was named streptomycin on the basis of its isolation from an organism which belongs to the group of Actinomycetes called Streptomyces. The first two cultures of Streptomyces griseus from which streptomycin was isolated were obtained independently from a heavily manured field soil and from the throat of a chicken.

Streptomycin production, in contrast to that of streptothricin, was found to be markedly effected by the composition of the medium. Whereas streptothricin was readily obtained from simple media, streptomycin production was found to depend greatly on the presence in the medium of a certain organic material supplied by meat extract. Similar methods, however, can be used to isolate the two antibiotics from the medium. This involves separation of the mass of growth of the organism by centrifugation or filtration, adsorption of the antibiotic

*The streptomycin used in the treatment of the majority of the patients included in this report was provided by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

onto charcoal from the filtrate, elution from the charcoal with acid alcohol, and concentration by removing the alcohol with ether. Streptomycin in this form is a yellow-, brown-, or red- colored aqueous concentrate. A solid preparation is obtained by desiccation or precipitation with acetone. Further purification and crystallization results in the formation of an insoluble reineckate which occurs after the addition of the Reinecke salt to the water soluble amorphous fraction. The insoluble reineckate is converted in turn to a soluble hydrochloride or sulfate.

Streptomycin activity was first made quantitative by the arbitrary definition of a unit in terms of the amount of material which, when present in 1 ml. of nutrient medium, just inhibited the growth of a given strain of E. coli. When crystalline products became available, a new standard was established based on the weight of the pure material. One microgram of streptomycin base is equal in activity to one unit.

Waksman and his associates have demonstrated that streptomycin is a much more stable compound than penicillin.[1] The crystalline form withstands months of refrigeration without loss of potency and solutions can be heated for 10 minutes at 100° with less than 50% inactivation. They also pointed out that it is not destroyed by microorganisms. Chemically it is composed of the hydroxylated base, streptidine, and the disaccharide, streptobiosamine.[2] The inactivation of streptomycin by the addition to media of acids or acid precursors, such as glucose and phosphates, may be attributed perhaps to neutralization of the basic portion of the molecule. This property of streptomycin appears to be responsible for the important clinical observation that the drug is far less effective in acud urines than in alkaline urines. Streptomycin activity is also reduced *in vitro* by cysteine, cevitamic acid and certain ketone agents.[3] This may be related to their chemical combination and subsequent blockade of a group in the streptomycin molecule.

That inactivation of streptomycin also occurs *in vivo* was suggested by Manwaring[4] following experiments in which 15 million units were given orally to patients with typhoid fever. In spite of the fact that over 60% was recovered in the stool after oral administration, E. typhosa was cultured from the feces of these patients. This survival of the organisms could not be explained by the development of streptomycin resistance as they could be killed *in vitro* by 6 units per cc.

Table 1 shows the number of micrograms of streptomycin required to produce a bacteriostatic effect upon various organisms *in vitro*. Higher concentrations are bactericidal. Certain gram-negative, gram-positive and acid-fast organisms are susceptible, whereas spore-forming anaerobes and fungi are resistant. The effectiveness of streptomycin against both gram-negative and gram-positive organisms serves to emphasize the objection offered by Kobacher and Mehlin[5] against the customary procedure of classifying bacterial response to therapy on the basis of whether or not the gram stain is retained. The susceptibility of organisms is not necessarily related to their staining properties.

Furthermore, the resistance to streptomycin is not constant for any given species of bacteria. It varies with strains within the species and is increased by exposure to streptomycin in doses that are not bactericidal.

Demonstration of the readiness with which resistance develops was given by Knop[6] who employed organisms isolated from urine cultures. After first determining the initial sensitivity of the organisms, she cultured them in broth containing varying concentrations of streptomycin. Those cultures which survived the maximum concentration were transferred every 48 hours up to a concentration of 1000 micrograms/cc. In this manner, all the bacteria tested quickly developed a high degree of resistance. It was found that Strep. faecalis and Pseudomonas aeruginosa developed resistance after the fewest transfers, whereas the strains of A. aerogenes, Proteus and E. coli required several more. Equally significant was her demonstration that none of the resistance was lost after a period of growth in broth to

Table 1.

Range in Sensitivity
to the Bacteriostatic Action of Streptomycin[9]

| | Micrograms per Cubic Centimeter | |
|---|---|---|
| **Gram-Negative Organisms** | | |
| Aerobacter aerogenes | 0.5 | 64.0 |
| Bacillus anthracis. | 0.375 | |
| Brucello abortis | 0.5 | 3.75 |
| Brucella melitensis | 0.5 | |
| Brucella suis | 0.5 | |
| Eberthella typhi | 1.0 | 37.5 |
| Erysipelothrix muriseptica | 2.5 | |
| Escherichia coli. | 0.3 | 3.75 |
| Escherichia communior | 1.0 | 4.0 |
| Hemophilus influenzae | 1.56 | 5.0 |
| Hemophilus pertussis | 1.25 | 3.0 |
| Klebsiella ozogenes | 0.375 | 1.5 |
| Klebsiella pneumoniae | 0.625 | 256. |
| Malleomyces mallei | 10.0 | 10.0 |
| Neisseria gonorrheae | 5.0 | |
| Neisseria intracellularis | 5.0 | |
| Pasteurella lepiseptica | 0.5 | 2.5 |
| Pasteurella pestis | 0.75 | 1.5 |
| Pasteurella tularensis | 0.15 | 0.3 |
| Proteus vulgaris | 0.4 | 3.2 |
| Pseudomonas aeruginosa | 2.5 | 25.0 |
| Salmonella aertrycke | 4.0 | 10.0 |
| Salmonella enteritidis | 0.5 | |
| Salmonella schottmülleri | 2.0 | |
| Salmonella suipestifer. | 60.0 | |
| Shigella paradysenterise | 0.25 | 3.75 |
| Vibrio comma | 6.0 | 37.5 |
| **Gram-Positive Organisms** | | |
| Actinomyces bovis | 3.75 | |
| Clostridium butyricum | 8.34 | |
| Clostridium septicum. | 105. | |
| Clostridium sordelli. | 105. | |
| Clostridium tetani. | 104. | |
| Clostridium welchi. | 104. | |
| Corynebacterium diphtheriae | 0.375 | 3.75 |
| Diplococcus pneumoniae. | 8.0 | |
| M. tuberculosis, var. hominis | 0.15 | |
| Staphylococcus aureus | 0.5 | 16.0 |
| Streptococcus fecalis | 50.0 | |
| Streptococcus hemolyticus | 2.0 | 16.0 |
| Strept. lactis. | 4.0 | |
| Strept. salivarius | 5.0 | 25.0 |
| Strept. viridans. | 16. | 120. |

which no streptomycin had been added.

The same phenomenon has been observed *in vivo* during treatment of human infections. Finland[7] reported cases of urinary tract infections in which organisms with an initial sensitivity of 25 micrograms per cc. were found to have developed resistance to 50,000 micrograms per cc. after 5 days of treatment. Buggs[8] found a wide variation in sensitivity in the strains of bacteria isolated before treatment and the development of resistance in many of these strains after treatment. There is the possibility that these resistant strains existed prior to treatment and were not discovered. Both reports, however, described efforts to recover all strains before treatment so that there is good reason to believe that originally sensitive strains developed great resistance. The previously described *in vitro* results add to the evidence in favor of such a contention. These observations emphasize the importance of using adequate doses of streptomycin. Not only must the sensitivity of the pathogen be known, but enough of the drug must be given to produce levels in the tissues and body fluids well above the minimum effective concentration. Keefer[9] recommends that these levels be four to five times as great as the *in vitro* sensitivity level because of the reduction in streptomycin activity upon addition of serum.

Administration, Absorption, and Distribution

The intelligent use of streptomycin is based on a number of pharmacological principles. These may be simply enumerated as follows:

(1) Parenteral administration results in adequate blood levels.

(2) Urinary excretion is rapid. 60-80% is said to be accounted for in this manner in 24 hours.

(3) Good penetration into pleural fluid, peritoneal fluid, bile, aqueous humour and the fetal circulation occurs.

(4) Significant penetration into the cerebro-spinal fluid from the blood takes place only if the meninges are inflamed.

(5) There is essentially no absorption from the stomach or bowel. Only traces appear in the urine after oral administration.

(6) None is absorbed into the blood after nebulization.

No rigid rules can be given for establishing certain levels in any of these fluids. Zintel, Flippin, Nichols, Wiley and Rhoads[10] found in a study of 10 patients that intravenous injection of a single dose of 0.6 Gm. streptomycin produced an average blood level of 32.8 micrograms per cc. in 15 minutes, following which it fell gradually to 4.9 units at 6 hours. The same dose injected intramuscularly produced an approximate blood level of 17 micrograms per cc. in an hour, and this concentration was maintained for 3 hours thereafter, whereupon a less gradual decline occurred than with the intravenous method. When 3 Gm. of streptomycin in 3,000 cc. of 5% glucose was given by continuous intravenous drip daily, blood levels of 20 to 60 micrograms per cc. resulted. The same blood concentration was achieved by giving 3 Gm. daily intramuscularly in divided doses at 3 hour intervals.

The values for blood concentration obtained by these workers for intermittent intramuscular injection are higher than those given by Keefer[7]. This can be seen by examining Table 2.

Table 2.[9]

| I.M. dose q.3 H. | Expected mean conc. in blood for 3-hour period |
|---|---|
| 0.1 Gm. | 2 - 3 mcgm./cc. |
| 0.2 Gm. | 5 - 6 " |
| 0.3 Gm. | 6 - 8 " |
| 0.5 Gm. | 9 -10 " |

It is possible that the figures listed are lower than might be expected in many cases. The Surgeon General's report[11] states that a mean blood level of 16 micrograms per cc. can be obtained with

intermittent intramuscular use of 0.4 Gm. every 4 hours. At any rate, the intramuscular route is recommended as the preferred method of administration. Solutions containing 0.1 Gm. per cc. of normal saline may be used, and may be given with 1 cc. of 1% procaine to avoid pain.[12]

It appears that adequate concentrations in some of the body fluids may be obtained with the same dosages used to produce satisfactory blood levels. Buggs[13] examined the peritoneal fluid in 4 patients operated on for perforated peptic ulcer and found concentrations of 14.9 to 25.5 micrograms per cc. within one to two and a half hours after intravenous injection of 0.5 Gm. Zintel[10] demonstrated that parenteral administration for more than a few hours produced approximately equal blood and peritoneal streptomycin levels. In a patient with ascites secondary to carcinomatosis receiving 0.125 Gm. every three hours intramuscularly, the peritoneal fluid level was 23 units per cc. and the blood level 15 units per cc. at the end of 24 hours. Similar results for diffusion into pleural fluid were noted in two patients receiving the same dosage. After 24 hours the pleural fluid concentrations were 18 and 7 micrograms per cc. and the corresponding blood levels were 15 and 20 respectively. Adcock and Hettig[14] found that following a single dose of 0.5 Gm. intramuscularly, the levels in pleural and ascitic fluids rose as the serum level fell.

Large amounts of streptomycin are excreted in the bile. Zintel collected 3500 micrograms in 24 hours in the bile of a patient receiving 0.125 Gm. every three hours by intramuscular injection and found a concentration of 10 micrograms per cc. of bile at the end of 24 hours. Heilman[12] reports that two hours after the injection of 0.1 Gm. of streptomycin subcutaneously, the bile contained 12.5 micrograms per cc. and the blood serum 6 micrograms per cc. Zaslow[15] studied 23 patients in whom 0.1 Gm. was administered after insertion of a "T"-tube into the common duct. Those patients with normal livers excreted large amounts of streptomycin in the hepatic bile. On the other hand, where obstructive jaundice was present, excretion of streptomycin was poor. Streptomycin might be of most value in treating biliary infections, therefore, when obstruction is absent.

As much as 89% of a single dose of streptomycin can be recovered in the urine.[10] The average, however, is between 65% and 70%. About 2% more can be accounted for in the feces. A fairly large amount, therefore, is undoubtedly retained or destroyed in the body. Urinary excretion is slower for streptomycin than for penicillin so that blood levels are maintained more readily. Adcock and Hettig[14] measured streptomycin clearance by the kidney and found that the plasma clearance value with streptomycin was 38 to 67 cc. per minute and with penicillin 750 to 1120 cc. per minute. It has also been shown that with severe kidney damage, streptomycin accumulates in the serum even with small doses.[13]

Therapeutic levels of streptomycin in the cerebrospinal fluid following parenteral injection occurs only if meningitis is present. Blood levels of 17, 27 and 13 micrograms per cc. were associated with spinal fluid levels of 1, 1, and 5 respectively after parenteral administration to patients with no evidence of cerebrospinal disease.[10] On the other hand, an infant with H. influenzae meningitis had a spinal fluid level of 25 micrograms per cc. after receiving 1 Gm. in 24 hours.[10] These observations have been confirmed by others. Buggs[13] found spinal fluid levels as high as 41.6 mg. six hours after intramuscular administration of 0.75 Gm. to a boy with tuberculous meningitis.[8] Another patient with tuberculous meningitis was treated by Reiman[16] with 4 Gm. daily by continuous intravenous drip. Spinal fluid levels in this case ranged from 16 - 20 mg./cc. Heilman[12] states that spinal fluid concentrations approximate 1/5 that in the blood serum. Therapeutic concentrations of streptomycin can also be found in the spinal fluid 24 hours after intrathecal doses of .02 Gm.

Except for very slight amounts that may appear in the blood or urine, streptomycin when given orally is excreted entirely in the feces. That it is not inactivated by gastric juice was shown by Anderson and Jewell.[17] Large concentrations appear in the feces with striking reduction of E. coli and other organisms generally present there. Thus

Reiman, Price and Elias[16] were able to eliminate E. coli from the stools of several patients with carcinoma of the colon after administering 2 - 5 Gm. per day orally for one to five days.

## Toxic Effects

Toxic effects from streptomycin have been studied in both animals and humans. An extensive study in animals was conducted by Molitor and his associates at Merck Institute.[18] Animals could be killed by large doses parenterally with acute symptoms of restlessness, respiratory difficulty, coma and death with no histologic evidence of acute toxicity.

Non-fatal acute effects were produced which were identical to those resulting from histamine, a sudden drop in arterial blood pressure with peripheral vasodilatation. Different species varied in their susceptibility to chronic toxicity. Administration of 25 mg./Kg. to monkeys for five days resulted in reversible fatty changes in the liver and kidneys. Similar findings were noted in dogs. Mice, rats and guinea pigs, on the other hand, were free of such signs.

Human toxicity appears to be due to impurities in the products as well as to streptomycin itself. Both acute and chronic manifestations of toxicity occur. Those that are probably due to impurities are pain at the site of injection, generalized muscular aches, joint pains, chills, fever, and histamine-like effects consisting of flushing of the skin, headache, dizziness, fall in blood pressure and nausea. These histamine-like effects have been reduced by purification of the product. Pain at the site of injection can be partially controlled by the addition of 1% procaine. McDermott[9] has found that use of a highly purified form of crystalline streptomycin is accompanied by minimal discomfort.

It appears likely that the skin eruptions which occur are the result of sensitization to the streptomycin itself. They can be produced in sensitive persons by reinjection of small amounts of streptomycin many days after the drug has been discontinued. Benadryl has been found to be effective in relieving some of the drug eruptions.

Studies of renal function and liver function following large doses have been made and no disturbances have been noted.[12]

Signs of renal irritation with casts, albuminuria and microscopic hematuria have been produced with repeated large doses.

A serious toxic effect appears to be involvement of the eighth nerve and vestibular apparatus. Vertigo is a fairly common complaint, especially in ambulatory patients and is present in those receiving brief as well as prolonged courses of treatment. Hinshaw has found that almost every patient receiving large doses for long periods of time suffers some impairment of vestibular function. Whether or not vertigo is present, disturbances can usually be demonstrated by caloric tests. He believes that this impairment will prove to be permanent, although vertigo may disappear when use of other sensory systems is substituted to restore the sense of balance. Both vertigo and tinnitus are indications for reduction in dosage.[9]

## Experimental Infections

Table 3 lists the organisms which are said to be controlled by streptomycin in experimental animal infections.

Brucella abortus: Jones, Metzger, Schatz and Waksman protected chick embryos with streptomycin from B. abortus infection.[20] Hall, in our own laboratories, has confirmed these observations in part. However he found that streptomycin did not always sterilize the embryo and its fluids.

Live, Sperling and Stubbs produced a bacteriostatic effect in guinea pigs with 5000 units of streptomycin daily.[21] 45% of animals in which treatment was begun on the day of infection were free of organisms. Use of 20,000 units daily appeared to eliminate the infection from all animals.

Table 3

Control of Experimental Infections with Streptomycin

| Degree of Protection | Animal | Organism | Investigators |
|---|---|---|---|
| Complete | Guinea Pig | B. abortus | Live, Sperling and Stubbs |
| Complete | Chick Embryo | B. abortus | Jones, Metzher, Schatz and and Waksman |
| Partial | Chick Embryo | B. abortus | W. H. Hall |
| Complete | Chick Embryo | Shigella gallinarium | Jones, Metzher, Schatz and Waksman |
| Complete | Mice | Pasteurella tularense | Heilman |
| Partial | Mice | Murine Pertussis | Bradford and Day |
| Partial | Mice | Borrelia novyi | Heilman |
| Complete | Hamsters | Leptospira icterohaemorrhagiae | Heilman |
| Complete | Rabbits | T. pallidum | Dunham and Rake |
| Partial | Guinea Pig | Pasteurella pestis | Wayson and McMahon |
| Partial | Mice | Klebsiella pneumoniae | Heilman |
| None | Chick | Influenza Virus | Florman, Weiss and Corriel |
| Nearly complete | Guinea Pig | Mycobacterium tuberculosis | Feldman, Hinshaw and Mann |
| Partial | Guinea Pig | " " " | Smith and McCloskey |
| Partial | Mice | " " " | Youmans and McCarter |

Pasteurella tularense: Heilman showed conclusively that adequate dosage protected mice against heavy inoculation with a very virulent strain.[22]

Pasteurella pestis: The promising results with streptomycin in controlling Pasteurella tularense infections suggests that it might also be of value in the treatment of plague. Wayson and McMahon used streptomycin in guinea pigs infected either by artificial inoculation or flea bite and found complete cure or arrest in nearly all of the animals.[23] Its value appeared to be as great as that of sulfadiazine and greater than sulfapyrazine, both of which have been recommended for clinical use. A few animals were treated with a combination of streptomycin and sulfadiazine but the results were no better than streptomycin alone. The fact that therapy was withheld until clearcut signs of plague developed, adds to the significance of these experiments.

Salmonella: In the same report referred to previously, Jones, et al protected mice from Salmonella Schottmüllerei with 190 mg. of streptomycin in four divided doses.

Klebsiella Pneumoniae: Heilman found survival in 90% of streptomycin treated mice inoculated intra-abdominally with relatively huge doses of Friedlander's organisms. Similar results were obtained after intranasal inoculation.[24]

Borrelia novyi: Heilman[25] determined the effectiveness of streptomycin in reducing both the mortality rate and the relapse rate in mice infected with this organism, the causative agent of American relapsing fever. The mortality rate was found to be 8% in the treated animals and 20% in the untreated. The effect on relapse rates was much more striking. Only 11% of the treated animals compared to 85% of the untreated animals had recurrences.

Leptospira icterohemorrhagiae: Streptomycin provides complete protection in hamsters (Heilman[25]). The mortality rate was 100% by the ninth day in untreated animals whereas those receiving streptomycin remained entirely well. Penicillin appeared to be equally effective in smaller doses.

Treponema pallidum: Streptomycin is far less potent than penicillin in treating experimental syphilis. Dunham and Rake[26] found that a minimum of 375 mg./kg. of streptomycin was required to cure infected rabbits whereas .088 mg./kg. of penicillin was effective.

Mycobacterium tuberculosis: Several authors have demonstrated that streptomycin is effective in experimental tuberculosis of guinea pigs and mice. In guinea pigs receiving adequate doses of streptomycin no clinical and almost no pathological evidence of tuberculous infection was found. On the other hand, untreated animals inoculated with the same organism invariably showed widespread active lesions. Feldman, Hinshaw and Mann[27] used a method for numerically evaluating the degree of infection on the basis of lesions in the spleen, lung, liver and site of inoculation. Expressed in this fashion, the average index of infection for treated animals was less than 5 and for untreated animals was 67 to 80.

Youmans and McCarter[28] noted similar results in mice. They found tubercle bacilli in all treated animals but made the observation that active phagocytosis was occurring. This was manifested not only by the actual presence of organisms in the phagocytes but also by the increase in foamy cytoplasm in these cells. Foamy cytoplasm was regarded as an indication of bacterial digestion.

## Clinical Use of Streptomycin

The value of streptomycin in various human infections has been less than predicted by in vitro and animal experiments. Nevertheless, a number of clinical conditions formerly resistant to any specific treatment can now be cured with proper administration of streptomycin. Table 4, taken from Keefer[9], is the best available summary of results in human infections, not including tuberculosis.

Table 4

Summary of Results in 1,000 Cases[9]

| | Number of Patients | Results | | | |
|---|---|---|---|---|---|
| | | Recovered | Improved | No Effect | Died |
| Urinary tract infections | 409 | 171 | 145 | 84 | 9 |
| H. influenzae meningitis | 100 | 66 | 14 | 3 | 17 |
| Bacteremia | 91 | 49 | 12 | 4 | 26 |
| Tularemia | 67 | 63 | - | 3 | 1 |
| Pulmonary infections | 44 | 15 | 14 | 7 | 8 |
| Brucellosis | 45 | - | 30 | 15 | - |
| Typhoid | 51 | - | 51 | - | - |
| Salmonella | 26 | 10 | 2 | 6 | 8 |
| Peritonitis | 53 | 36 | 3 | 2 | 12 |
| Meningitis due to gram-negative organisms other than H. influenzae | 14 | 5 | 5 | - | 4 |
| Shigella dysenteries | 2 | 2 | - | - | - |
| Miscellaneous infections | 98 | 36 | 29 | 30 | 3 |
| Totals | 1,000 | 453 | 305 | 154 | 88 |

Tularemia is foremost among the conditions responding to streptomycin. Attempts to treat the disease with sulfonamides, specific antiserum, and vaccines have been unsuccessful. Streptomycin on the other hand results in a prompt reduction in fever and relatively rapid recovery. Herrell and Nichols[19] reported 15 cures in 15 cases treated. An analysis of 12 other cases reported is shown

in Table 5.

Table 5

Results in Treatment of 12 Cases of Tularemia

| Reported by | Type | Day Treatment Started | Duration of Fever | Complications | Dose | Total Disability |
|---|---|---|---|---|---|---|
| Foshay[46] | Ulceroglandular | 8 | 13 | -- | 0.25 Gm. q̄.3H.for 5 days | 42 da. |
| Foshay | Ulceroglandular | 23 | 32 | -- | " | 50 " |
| Foshay | Ulceroglandular | 17 | 35 | -- | " | -- |
| Foshay | Ulceroglandular | 20 | 22 | -- | " | -- |
| Foshay | Ulceroglandular | 103 | 111 | Peritonitus | 0.4Gm. q̄.3H. - 2 days<br>0.25Gm.q̄.3H. - 4 days | --<br>-- |
| Abel[47] | Ulceroglandular | 7 | 8 | Pneumonia | 1 Gm.'day - 7 days | 17 da. |
| Abel | Ulceroglandular | 8 | 9½ | -- | 1 Gm.'day - 2 days | -- |
| Abel | Ulceroglandular | 20 | 21 | Pneumonia, Pregnancy | 1 Gm./day - 8 days | 50 da. |
| Gordon[48] | Typhoidal | 10 | 11½ | Pneumonia | 1 Gm./day - 3 days<br>0.5 Gm.'day- 2 days | --<br>-- |
| Cohen & Lasser[49] | Typhoidal | 27 | 29 | Pneumonia | 7 Gm. in 10 days | 85 da. |
| Howe, et al[29] | Typhoidal | 2 | 3 | -- | 0.1 Gm. q̄. 3 H. | 35 " |
| Howe, et al | Typhoidal | 9 | 10 | Pneumonia | 0.1 Gm. q̄. 3 H. | 90 " |

The accepted dose now appears to be 1 Gm. daily; this dose usually causes disappearance of fever in 24 hours. It is interesting that three chronic cases reported by Howe[29] appeared to be uninfluenced by streptomycin. These were patients treated months after the acute stage because of continued fatigue and fever. It was suggested that the low grade fever and other symptoms were not due to residual active infection but to foci of necrosis in visceral lymph nodes.

A second organism against which streptomycin has been found very effective clinically is H. influenzae. A large number of cases of H. influenzae meningitis have been treated with streptomycin. Keefer's report[9] includes 100 cases with a mortality rate of 17% compared with 92 - 100% in untreated cases. Weinstein[30] prefers the use of streptomycin alone without concomitant sulfadiazine or Alexander's rabbit antiserum. Recently, however, Alexander[50] has suggested the combined use of streptomycin, sulfadiazine and type-specific rabbit antiserum in severe infections since streptomycin alone was often disappointing, probably because of the rapid development of bacterial resistance to the drug.

Perhaps the most important factor in successful therapy is early recognition and treatment. In chronic infections, exudates block off subarachnoid spaces which harbor the organisms and render them inaccessible to the therapeutic agent. A number of the fatal cases in Keefer's series[9] were complicated by spinal block. The recommendation by Platou[31] that heparin and air injections be used in conjunction with Alexander's specific serum, might also apply equally with use of streptomycin in these infections. Durant[32] treated three patients with H. influenzae (type B) pulmonary infections with streptomycin and the results were good.

The most extensive trial of streptomycin has been with urinary infections. Helmholz[33] measured the bactericidal power of urine from a patient receiving 2 Gm. daily in whom the urine concentration was 1330 micrograms per cc. He found that E. coli and A. aerogenes were almost completely eliminated with concentrations of 66 micrograms per cc. 75 micrograms per cc. were lethal to Proteus ammoniae and 100 micrograms per cc. to Strep. faecalis and Pseudomonas aeruginosa. It has been found that doses of 0.3 Gm. intramuscularly every three hours produce average urine levels of 70 - 100 micrograms per cc.[34] Hence it is not surprising that some observers have reported better results with Proteus ammoniae and A. aerogenes than with Pseudomonas aeruginosa. When a composite study is made of all treated cases, however, little difference in the clinical response can be found. The general recovery rate seems to be about 42%.

Management of a urinary infection requires a number of procedures and precautions in addition to the mere administration of streptomycin. The infecting organisms must be identified and their sensitivity determined so that adequate dosages and urinary concentrations may be obtained. Resistance develops very rapidly and sensitivity is readily reduced beyond the range of therapeutic possibility within a short time. Furthermore, it must be realized that streptomycin does not eliminate the need for adequate surgical management of these cases. Herrel and Nichols[19] and others suggest that better antibacterial results are obtained with an alkaline urine. Streptomycin reduces alkaline copper solutions in urinary concentrations of 1,000 micrograms per cc. This test might be used as a guide to adequate dosage in non-diabetic patients.

No clear cut alteration in the course of typhoid fever has been produced in the cases studied so far. Reimann[35] advised both oral and parenteral administration for the purpose of sterilizing both the blood and feces. But in his 85 cases, Keefer[9] reported 15 who received both oral and intra-muscular therapy with no better results than with intramuscular injection alone. The observation of Manwaring[4] that large oral doses failed to clear the feces of E. typhi has already been mentioned. Goodpasture's idea that typhoid bacilli live intracellularly in macrophages has been offered by Reimann[16] as one explanation for the disparity between *in vivo* and *in vitro* results. Their intracellular existence may protect them from streptomycin in the blood and tissues. Yet Pasteurella tularense, which also produces an intracellular infection, is readily destroyed by streptomycin.

An important effect on typhoid organisms has been noted in experimental animals by Welch, Price and Randall.[36] They injected various doses of streptomycin into the peritoneal cavity of white mice infected by intraperitoneal injection of E. typhi. The mortality rate of the mice receiving 0.25 to 1 microgram was seven to ten times as great as the untreated controls. With 1.5 micrograms the mortality rate was no greater than that of the controls. Hence small doses of streptomycin actually favor the propagation of the infection.

Results following the treatment of Salmonella infection with streptomycin have been no better than with typhoid fever. Slanetz[39] has had encouraging results in laboratory mice. Human infections have seldom been strikingly influenced by its use. Of 26 cases reported, only ten recovered under treatment.[9] Results in the treatment of brucellosis have been no more striking than with typhoid fever. Many cases can be classified as unequivocal failures, showing no response whatever. Those who have shown improvement while receiving the drug cannot be properly evaluated until further time has elapsed.

In nine cases reported by Nichols and Herrel[19] streptomycin seemed of value in only one. Success here was attributed to removal of the spleen in conjunction with three courses of streptomycin. In Reiman's[16] three cases only one received any benefit. Just as in typhoid, the isolated strains have been found to be markedly sensitive *in vitro*. The report by the Committee on Chemotherapeutics listed 45 cases, a third of which were

entirely unaffected. Although the others showed a reduction of fever during treatment and only two relapses in three to eight weeks, it is too early to foretell the eventual outcome of therapy.

Treatment of E. coli urinary infections has already been mentioned. Patients with meningitis, peritonitis and bacteremia due to this organism have received streptomycin with perhaps better results than in the case of the urinary infections. Herrel and Nichols studied two cases of bacteremia secondary to urinary tract infections; they found E. coli in the urine after the bacteremia had been eliminated. Similarly, Muellner and Rotenberg[37] treated a patient with severe peritonitis following surgical intervention for urolithiasis. Streptomycin was given with dramatic results. The peritonitis appeared to be completely eliminated, but persisted in the urine. Three cases of E. coli meningitis treated successfully are listed in Keefer's report.[9]

There appears to be a definite place for streptomycin in the treatment of certain varieties of subacute bacterial endocarditis according to Priest and McGee.[38] In one of their three cases a typical Strep. viridans was recovered which resisted large doses of penicillin. The lethal dose of streptomycin was found to be 0.1 microgram per cc. Although the patient died five days after streptomycin treatment was started, the fibrin deposits on the valves were sterile when examined at autopsy. In the other two cases, nonhemolytic streptococci were isolated from the blood with in vitro sensitivity of one microgram per cc. Both recovered with streptomycin therapy after penicillin failed to produce negative blood cultures.

Friedländer's bacillus (K. pneumoniae) is among the less common pathogens against which streptomycin is effective. An outstanding example of successful therapy against this organism is reported by Learner and Minnich[40] who reported an instance of Friedländer's pneumonia in which recovery promptly took place upon administration of 1.6 Gm. daily for 10 days. Eight of twelve cases in Keefer's series[9] were said to improve after streptomycin. Two cases with bacteremia were also listed, both of which recovered. Herrel and Nichols[19] mentioned five patients with ozena from which K. pneumoniae was recovered. Symptoms improved in four cases but returned in two after treatment was discontinued. In the two cases which had recurrences, increased resistance of the organisms to streptomycin was found.

Several infections of interest are included in a miscellaneous grouping as there have been too few of each treated to warrant separate classification:

Syphilis: Streptomycin in doses up to 10 Gm. was ineffective in four cases.[19]

Ulcerative colitis: A patient was given streptomycin after becoming moribund. Definiteclinical improvement resulted but unexpected death from pulmonary embolism occurred.[41]

Bronchiectasis: In treating patients with aerosol penicillin, Olson[42] found elimination of gram-positive and persistence of gram-negative organisms. Gram-negative organisms were eradicated from the sputum by streptomycin aerosol. The dose consisted of 0.5 Gm. of streptomycin in 20 cc. of physiologic saline daily. A combination of penicillin and streptomycin aerosol was advised for use in preparing patients with bronchiectasis for surgery.

Gonorrhea: Debakey reported 5 cases of gonorrhea resistant to sulfadiazine and penicillin which were cured with streptomycin.[19]

Prophylactic use: Two patients were given streptomycin to prevent peritonitis after soiling of the peritoneum during surgery. Results were good.[43]

Corneal ulcers: Instillation of two drops in the conjunctival sac every two hours resulted in shorter duration of pain and quicker healing of ulcers. It was considered a useful adjunct in the treatment of corneal ulcers.[44]

Only a brief statement can be made at

the present time concerning the treatment of tuberculosis with streptomycin. Separate reports have been submitted by Hinshaw and McDermott to the Committee on Chemotherapy[9], based on a study of 75 and 12 patients respectively. In general, it may be said that streptomycin has a definite but limited suppressive action on pulmonary and extrapulmonary lesions. In 12 cases of generalized miliary tuberculosis, for example, some had complete remissions characterized by negative chest x-rays and absence of fever. Nearly all of these cases eventually died, however. Although some died with evidence of healing, it was found that tubercles within the brain substance were not affected. As regards pulmonary tuberculosis, Hinshaw stated that chronic fibrocaseous tuberculosis is not improved by streptomycin. On the other hand, acute pulmonary tuberculosis, even if far advanced, often improves greatly.[45]

Other types of tuberculosis studied by Hinshaw include:

Osseous - five cases with encouraging results.

Draining fistulas - 15 cases with complete closure in all. Recurrence of drainage can be avoided by the continued use of streptomycin for three months.

Kidney infections - 15 cases. In nearly every case tuberculous bacilluria has recurred after treatment was discontinued.

Empyema - 7 cases. Instillation of streptomycin into empyema cavities produced no beneficial results. This may be the result of streptomycin inhibition in an acid medium.

Laryngeal - apparent complete cure has resulted from the combined use of intramuscular and aerosol streptomycin.

For the most part, Hinshaw has found that streptomycin does not eradicate infections and believes that its chief use will be as a palliative measure in conjunction with other forms of treatment.

Clinical Evaluation of Streptomycin at the University of Minnesota

In February 1946 we were given the opportunity to cooperate with the Committee on Chemotherapeutic and Other Agents of the National Research Council in the clinical evaluation of streptomycin. Since that time 22 patients have been treated with streptomycin under our direction. Prior to that time one patient had been treated with supplies obtained from Merck & Co., Inc. The present report summarizes briefly the clinical course and therapeutic result in these 23 patients. The use of the drug was confined to the treatment of infections due to gram-negative bacteria generally considered to be sensitive to the action of streptomycin. In accordance with instructions from the Committee on Chemotherapeutic and Other Agents we sought to use the drug particularly in tularemia; acute and chronic brucellosis with bacteremia; bacteremia due to Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa and Salmonella; severe resistant urinary tract infections due to gram-negative organisms and meningitis due to Hemophilus influenzae and other gram-negative bacilli. The treatment of tuberculosis was not a part of this clinical study.

The streptomycin was supplied in the form of a white crystalline powder, either as the sulfate or hydrochloride of the streptomycin base. It was packaged in sealed ampules containing 0.4 to 1.0 Gm. of the streptomycin base. The powder was dissolved in physiological saline and given by intermittent intramuscular injection every three hours. It was also given intrathecally once daily in one of the patients with meningitis. The dry powder and freshly prepared solutions were stored in a refrigerator.

In each patient treated with streptomycin repeated attempts were made to identify the organism causing the infection. Repeated blood cultures were made in tryptose broth and tryptose agar pour plates (aerobic and under 10% $CO_2$). In many instances the comparative

sensitivity of the organism to sulfadiazine, penicillin and streptomycin was tested in vitro.

A summary of the types of infections treated with streptomycin is given in Table 6.

Table 6

Types of Infections Treated with Streptomycin

| Disease | No. of Patients |
|---|---|
| 1. Urinary tract infections due to gram-negative, non-sporeforming bacilli | 7 |
| 2. Bacteremia due to gram-negative bacilli: | |
| Escherichia coli | 3 |
| Esch. coli and Aerobacter aerogenes | 1 |
| 3. Salmonella infections | |
| Gastroenteritis | 1 |
| Septicemia | 2 |
| 4. Chronic brucellosis | |
| with bacteremia | 4 |
| with bacteremia and bacterial endocarditis | 1 |
| 5. Tularemia | 2 |
| 6. Pneumonia due to Friedländer's bacillus | 1 |
| 7. Meningitis due to an unidentified gram-negative bacillus | 1 |
| Total | 23 |

Urinary Tract Infections due to Gram-negative Non-sporeforming Bacilli

In Table 7 the most important features in the treatment of seven patients are given. A brief abstract of each case follows:

Patient 1. - 69, male, had a total gastrectomy for carcinoma 4/5/46. He was catheterized frequently thereafter because of urinary retention. Frequency, dysuria and fever became marked. Thrombophlebitis of the right lower leg veins developed on 4/20/46. Benign prostatic hypertrophy and pyuria were present. Urine cultures yielded E. coli and non-hemolytic streptococci. He was given penicillin and sodium sulfadiazine in moderate doses with benefit. With streptomycin therapy his temperature declined and urinary symptoms became less marked. However the pyuria and bacilluria continued.

Patient 2. - 28, female, was operated upon 1/22/46 because of recurrent intestinal obstruction. A portion of the bowel was resected and an ileocolostomy performed. Urinary frequency, urgency and dysuria appeared in December 1945 and persisted following the operation. Her temperature ranged up to 102° F. Urine cultures revealed E. coli and non-hemolytic streptococci. A diagnosis of cystitis was made. There was no improvement with sulfathiazole and penicillin. With streptomycin her urine became sterile and she had no urinary symptoms for three weeks. However, she then had a recurrence of urinary frequency and dysuria,

Patient 3. - 20, female, had diabetes mellitus for nine years and had been pregnant 18 weeks. For two weeks she had fever, right flank pain and albuminuria. Sulfonamides caused nausea. Her fever was septic and her diabetes difficult to control. Urine cultures revealed Aerobacter aerogenes. Mandelic acid and an acid-ash diet were given without benefit. With streptomycin she became afebrile and her back pain disappeared. The urine became sterile temporarily, but four days after the streptomycin was discontinued the bacilluria recurred.

Patient 4. - 28, female, had recurrent left flank pain and diabetes mellitus for many years. On 8/6/46 gross hematuria, pyuria, fever and left flank pain set in. Cystoscopy revealed that the left renal pelvis was dilated and filled with pus containing E. coli. Her symptoms continued in spite of sulfadia-

Table 7

Streptomycin Therapy in Urinary Tract Infections

| Patient | Complications | Duration of Illness and previous Treatment | Urine Culture | Streptomycin dose in Gm. | Results |
|---|---|---|---|---|---|
| 1. 69 M. | Thrombophlebitis. Recent Gastrectomy | 8 days. Penicillin 160,000 U./da. x 14. Na Sulfadiazine 4 Gm./da. x 8. | E. Coli. Non-hem. Streptococci | 19 Gm. in 14 days | Improved |
| 2 28 F. | Recent bowel obstruction & ileocolostomy | 3 months. Sulfathiazole 1 Gm./da. x 14. Penicillin 160,000 U./da x 12. | E. Coli. Non-hem. Streptococci | 6 Gm. in 6 days | Temporary Improvement |
| 3. 20 F. | Pregnancy; diabetes | 2 weeks. Mandelic acid and acid-ash diet | Aerobacter aerogenes | 22 Gm. in 6 days | Improved |
| 4. 28 F. | Renal cortical abscess; pynoephrosis; diabetes | 20 years. Sulfadiazine 20 Gm. in 8 da. Penicillin. Surgery | E. Coli. A. aerogenes. Staph. (coag. +). | 31.75 Gm. in 6 days | No Benefit |
| 5. 52 M. | Benign prostatic hypertrophy | 6 months. Transurethral resection, sulfadiazine and penicillin | A. aerogenes. Proteus vulgaris | 10 Gm. in 5 days | Good |
| 6. 68 M. | Prostatitis. Purulent deltoid bursitis | 1 month. Penicillin 320,000 U./da. x 35. | Proteus vulgaris (also from buras). | 23 Gm. in 12 days | No Benefit |
| 7. 36 F. | Ureteral obstruction; renal calculus; renal insufficiency | 6 years. Bilat. nephrostomy Penicillin. Sulfadiazine | P. vulgaris. A. aerogenes. Strep. viridans Hem. & Non-hem strep., staph. (coag. + ). | 24 Gm. in 12 days | No Benefit |

zine therapy. On 8/18/46 a large cortical abscess was resected from the mid-portion of the left kidney. The defect was closed and an aberrant vein obstructing the left ureteropelvic junction was ligated and divided. A plastic procedure was then carried out to relieve the obstruction. Urine cultures revealed E. coli, A. aerogenes and Staphylococci (coag. +). Following the operation her urine output was good but she was febrile and considerable green pus containing Ps. pyocyaneus and staphylococci (coag. +) welled from the wound about the nephrostomy tube. Despite the concurrent use of streptomycin, penicillin, sulfadiazine and alkaline salts she co tinued to have fever, pyuria and bacilluria. The wound infection subsided slowly after the streptomycin was discontinued.

Patient 5. F.K. - 52, male, was operated upon in October 1945 for benign prostatic hypertrophy. His post-operative time course was complicated by a urinary tract infection due to A. aerogenes and staphylococci (coag. +). He was treated with penicillin and sulfadiazine, but urinary frequency and dysuria persisted. A urine culture taken just before the streptomycin therapy yielded A. aero-

genes and Proteuc vulgaris. With streptomycin therapy his urinary symptoms disappeared and the urine became sterile. However, shortly after the drug was discontinued the urine contained non-hemolytic streptococci, diphtheroids and staphylococci (coag. -).

Patient 6. - 68, male, had a transurethral resection of the prostate for benign prostatic hypertrophy on 4/3/46. This was immediately followed by chills and a septic fever not influenced by a prolonged course of penicillin and sulfadiazine. On April 18th pain and swelling over the right deltoid bursa appeared. Cultures of the urine and of a cloudy fluid aspirated from the bursa revealed Proteus vulgaris. Streptomycin was given from May 2nd to May 7th when it was discontinued because of the appearance of severe urticaria. The skin eruption faded and on May 10th streptomycin therapy was reinstituted with another brand. There was no recurrence of the urticaria. On May 9th the bursa was aspirated and 0.125 Gm. of streptomycin was injected into the cavity. The streptomycin did not appear to have any beneficial clinical nor bacteriological effect. On May 17th the bursa was drained surgically and a large amount of sero-purulent material and necrotic synovial tissue removed. His fever declined by lysis and his shoulder pain gradually subsided following this procedure.

Patient 7. - 36, female, developed hematuria, chills, fever and bilateral flank pain in 1940. Each attack subsided with bed rest but recurred several times during the next six years. She was admitted to this hospital in January 1946. At that time urine cultures yielded A. aerogenes, Proteus vulgaris and staphylococci (coag. +). The P.S.P. test indicated marked reduction in renal function. An intravenous pyelogram indicated the presence of hydronephrosis on the left and a "staghorn" calculus in the right renal pelvis. A left nephrostomy was performed. Two months later no improvement in the renal function could be demonstrated. Despite penicillin and sulfadiazine treatment the urine cultures continued to show a mixture of bacteria: A. aerogenes, Proteus vulgaris, Strep. viridans, hemolytic and non-hemolytic streptococci and staphylococci (coag. +). On 2/28/46 a right nephrolithotomy was performed and a nephrostomy tube inserted. Following this she was febrile and her blood urea nitrogen rose from 20 to 57 mg.%. She was then given streptomycin, but there was no clinical or bacteriological improvement even with concurrent penicillin therapy.

Comment: In this group of seven patients, gram-negative bacilli predominated in the urine cultures. Clinical improvement coincided with the streptomycin therapy in four patients. However, in one of these patients urinary symptoms recurred shortly after the drug was discontinued and in the others the bacilluria recurred. In three patients there was no clinical nor bacteriological improvement whatsoever. The complete failures might be attributed in part to the presence of obstruction, calculi or necrotic tissue. In only one instance was a concerted effort made to keep the urine alkaline. The number of cases is too small to attempt any correlation of the clinical result with the type of organism in the urine. No attempt was made to measure the in vitro sensitivity of the organisms to streptomycin. One patient with a metastatic infection of a bursa due to Proteus vulgaris failed to respond to the injection of streptomycin intramuscularly and locally but recovered promptly after surgical drainage of the bursa. Proper surgical management must accompany the use of streptomycin to obtain desirable results.

## Bacteremia due to Gram-negative Bacilli

Four patients with bacteremia due to gram-negative bacilli will be discussed separately although in three instances the portal of entry appeared to be the urinary tract. The outstanding features in this series of cases are given in Table 8. A brief abstract of the course of each is also given:

Patient 8. - 72, male, was operated upon 8/14/46 for repair of a ventral hernia. 48 cm. of small intestine attached to the hernial sac was resected. On 8/20/46 his temperature

Table 8

Streptomycin Therapy in Patients with Bacteremia Due to Gram-negative Bacilli

| Patient | Complications | Duration of Illness and Previous Treatment | Bacteriology | Streptomycin dose in Gm. | Results |
|---|---|---|---|---|---|
| 8. 72 M. | Herniorrhaphy; resection of intestine. Pylephlebitis of portal vein | 5 days. Penicillin for 4 days | Blood culture: E. coli communior | 12.5 Gm. in 5 days | Good |
| 9. 74 M. | Transurethral prostatic resection | 2 days. Penicillin for 2 days | Blood culture: E. coli communior | 16.5 Gm. in 5 days | Good |
| 10. 57 M. | Bilateral chronic pyelonephritis | 1 month? Known bacteremia 5 days. Penicillin and sulfathiazole | Blood and urine cultures: E. coli communior | 4.25 Gm.in 2 days | Died |
| 11. 74 M. | Carcinoma of blaadder; bilateral uretero-colostomy; uremia | 4 days. Penicillin and sulfadiazine | Blood and urine cultures: E. coli and Aerobacter aerogenes | 5.2 Gm. in 5 days | Died |

rose to 102.2° F. and on each of the next four days he had chills. On 8/21/46 he became jaundiced and his liver was palpable and tender. Blood cultures yielded E. coli communior. There was no response to penicillin, but with streptomycin his fever promptly receded and his blood stream was sterilized. His jaundice faded and his liver became smaller and non-tender. By 9/25/46 he appeared to be completely well. The jaundice and hepatomegaly were attributed to portal pylephlebitis.

Patient 9. - 74, male, entered the hospital because of urinary retention due to benign prostatic hypertrophy. On 4/24/46 a transurethral resection of the prostate was performed. On April 27th had a chill and fever. A blood culture contained E. coli communis. His fever and bacteremia continued in spite of penicillin therapy. With streptomycin 0.25 Gm. I.M. q. 2 h. his blood cultures became sterile but the chills and fever persisted. When the dose was increased to 0.5 Gm. I.M. q.2h. his temperature promptly returned to normal, and he recovered uneventfully.

Patient 10. - 57, male, was admitted to the hospital in a semi-sturpoous condition. He had been in poor health for several months and had complained of urinary frequency, flank pain and urinary incontinence for one month. He had been treated unsuccessfully with sulfadiazine. His urine contained pus. Cultures of his urine and blood contained E. coli communior. He had a high fever which continued in spite of penicillin and sulfathiazole. Streptomycin was started five days after the bacteremia was disclosed. His fever continued and he died 34 hours after the first dose of streptomycin was given. No autopsy was performed.

Patient 11. - 74, male, had a right extraperitoneal uretero-sigmoidostomy on 7/19/46 for carcinoma of the bladder. On 8/9/46 a similar procedure

was carried out on the left. Following the second operation he developed chills, fever, oliguria and stupor. His blood urea nitrogen rose to 158 mg.%. Cultures of his urine and blood revealed E. coli and A. aerogenes. There was no improvement with sulfadiazine or penicillin. Streptomycin therapy was started 24 hours after the presence of a bacteremia was established. His fever declined somewhat but the bacteremia continued. He became icteric and a hemorrhagic, papular reuption appeared over the chest. He died eight days after the second operation. On the day of death blood cultures contained 180 colonies/cc. A. aerogenes but no E. coli. Autopsy revealed carcinoma of the bladder, left hydronephrosis, cardiac dilatation and pulmonary edema.

Comment: It seems apparent that at least in some instances bacteremia due to Escherichia coli will respond to streptomycin therapy. The failure in patient 10 may be attributed in part to the fact that he was moribund when the streptomycin was started. In patient 11 the E. coli bacteremia appeared to be controlled but the number of Aerobacter aerogenes in his blood stream was unaffected. The response in patient 8 suggests that portal vein pylephlebitis may be favorably influenced by streptomycin.

Salmonella Gastroenteritis and Septicemia

Three patients with Salmonella infections were treated with streptomycin. Although this is only a small group it is of particular interest since neither penicillin nor the sulfonamides are effective in diseases due to Salmonella. The essential data regarding these patients are given in Table 9.

A brief resume of their clinical course follows:

Patient 12. . - 17, female, devebped severe abdominal cramps, nausea, vomiting and diarrhea shortly after eating food of questionable purity. She had a septic fever and marked abdominal tenderness, both direct and rebound in type. She appeared to have a marked toxemia. The stools were foul and watery and on culture yielded Salmonella. Blood cultures were sterile. She was given parenteral glucose, amino acids and penicillin but remained very ill. After six days illness she was given 0.25 Gm. streptomycin orally four times daily for four days. Her temperature promptly returned to normal, and the Salmonella disappeared from her stools. The toxemia, abdominal tenderness and diarrhea subsided coincident with the use of streptomycin.

Patient 13. - 46, male, a creamtester, developed lumbar back pain and a septic fever on 4/6/46. Chest x-rays on 4/15/46 revealed a pneumonia on the

Table 9

Salmonella Gastroenteritis and Septicemia

| Patient | Complications | Duration of Illness - Previous Treatment | Bacteriology | Streptomycin Dose in Gm. | Results |
|---|---|---|---|---|---|
| 12. ... 17 F. | Gastroenteritis | 6 days Penicillin | Feces - S. give. Blood - Sterile. | 4 Gm. orally in 4 days | Good |
| 13. 46 M. | Pneumonia, septicemia and spondylitis | 5 months Penicillin and sulfadiazine | Blood - S. oranienberg. Feces & urine - no pathogens | 43.4 Gm. I.M. in 13 days | Good |
| 14. | Carcinoma of lung. Septicemia. Pleuritis. Aspiration pneumonia | 3 months. Penicillin | Blood, urine, feces. S.enteriditis | 24 Gm. I.M. in 9 days. | Died |

right upper and middle lobes with slight involvement of the left upper lobe of an unusual type suggestive of septicemia (Dr. Leo Rigler). He had chills, delirium and persistent high fever but no gastro-intestinal symptoms. He was given sulfadiazine and penicillin with no effect. When admitted to this hospital on 9/9/46 he appeared acutely ill. His lungs were clear, but his lumbar spine was stiff and tender. Feces and urine cultures revealed no pathogens, but blood cultures yielded Salmonella oranienberg. This organism was inhibited in vitro by 75 γg. streptomycin per cc. X-rays of the chest indicated clearing of the pneumonia but x-rays of the spine revealed narrowing the disc between the third and fourth lumbar vertebrae. The margins of these vertebrae were sclerotic and ragged. The patient was given 43.4 Gm. of streptomycin intramuscularly over a period of 13 days. His blood cultures became sterile as early as the third day of treatment and remained so. After eight days of treatment his temperature returned to normal. His spine became less painful and tender although x-rays revealed no change.

Patient 14. - 77, male, recluse, developed diarrhea, bilateral subcostal pain, anorexia and weakness in July 1946. He was hospitalized on 8/8/46 after an episode of syncope. A diagnosis of auricular fibrillation and pneumonia was made and after digitalization he was transferred to the University Hospitals on 8/13/46. During the several weeks of hospitalization he had an intermittent fever ranging up to 103°F. Chest x-rays revealed bilateral pleural effusion and nodular pulmonary densities resembling metastatic carcinoma. A blood culture on 8/31/46 was sterile. His fever was not effected by large doses of penicillin. His appetite was very poor, resulting in a marked weight loss and anemia. No primary source of a carcinoma was elicited after extensive study. On 10/8/46 a blood culture yielded Salmonella enteriditis. This organism was also isolated from his urine and feces. It was inhibited in vitro by 5 γg. streptomycin per cc. On 10/22/46 streptomycin (0.5 Gm. intramuscularly every four hours) was started. On 10/28/46 a blood culture was sterile. Because of his refusal of food he was given a liquid diet through a nasal tube by slow drip. He was also given several blood transfusions. He became less febrile and his general condition improved, but on 10/29/46 he aspirated some of the liquid feedings into his lungs. Following this his condition became much worse and he died on 10/30/46. Autopsy revealed bilateral pulmonary nodules and a fibrinous pleuritis on the left. The microscopic sections of the nodules resembled on "oat-cell" carcinoma. Cultures from the left pleural cavity yielded Salmonella but cultures of the heart, blood, lungs, and spleen yielded no pathogens.

Comment: The Salmonella oranienberg septicemia with spondylitis appeared to respond well to streptomycin therapy. Since the mortality rate in this type of infection runs as high as 80% this was quite encouraging. However, it must be said that the clinical improvement was delayed until the 9th day of treatment, and in vitro the organism was quite resistant to streptomycin. Patient 14 apparently had a chronic septicemia and gastroenteritis due to S. enteriditis. The organism was sensitive to streptomycin in vitro, and with streptomycin therapy his condition improved and the bacteremia was eliminated. However, he died as a result of aspiration of some liquid food. At autopsy cultures revealed persistent infection only in a localized fibrinous process in the left pleural cavity. Patient 12 with acute gastroenteritis due to Salmonella given improved dramatically during streptomycin therapy but as in the patients with septicemia it cannot be definitely stated that streptomycin altered the natural course of the disease. In cases of gastroenteritis without septicemia or other complications the administration of the drug by mouth seems more logical than parenteral injection. In patients with septicemia or tissue invasion the drug should be given parenterally as well. As in so many other serious infections it is important to know the in vitro sensitivity of the causative organism to the drug so that rational doses may be given.

Acute and Chronic Brucellosis with Bacteremia

Five patients with brucellosis with bacteremia have been treated with streptomycin. One of these patients had outspoken signs of bacterial endocarditis, and his treatment has not been completed. The outstanding features of each case are given in Table 10; the details of each are as follows:

Table 10

Chronic Brucellosis with Bacteremia

| Patient | Complications | Duration of Illness Previous Treatment | Bacteriology | Streptomycin Dose in Gm. | Results |
|---|---|---|---|---|---|
| 15. ... 11 F. | Splenomegaly & hepatomegaly | 6 months. None | Br.abortus isolated x 4 from blood | 19 Gm. in 9 days | No benefit |
| 16. 47 M. | Hepatomegaly Alcoholism | 5 weeks Penicillin | Blood - Br. abortus x 1. | 27.6 Gm. in 9 days | Doubtful |
| 17. 33 M. | Bacterial endocarditis of aortic valve; splenomegaly | 52 months. Sulfonamides and penicillin | Blood - 9 to 104 col. Br. abortus per cc. Urine - Br. abortus. Bone marrow- Br. abortus | 118 Gm. in 31 days | Improved |
| 18. ... 46 M. | Spondylitis and thoracic radiculitis | 18 months Salicylates | Blood - Br. abortus x 4. | 23.5 Gm. in 8 days | Improved |
| 19. ... 24 M. | Splenomegaly | 2 months. Sulfonamides and penicillin | Blood - Br. abortus x 4. | 28 Gm. in 7 days | Improved |

Patient 15. - 11, female, complained of headache, malaise, weakness and fever beginning about 1/1/46. In March her serum agglutinin titer for Brucella was 1:640. A blood culture for Brucella in April was sterile. In August 1945 she had visited a farm where she drank raw milk from cows not known to have Bang's disease. When admitted to this hospital on 6/6/46 she was thin and febrile. Cervical lymph nodes, spleen and liver were enlarged. Skin tests with Brucella protein and carbohydrate antigens were positive. Brucella abortus was isolated from her blood on four occasions. She was given 19 Gm. of streptomycin intramuscularly over a period of nine days. During this period she became more febrile, her temperature rising as high as 106° F. A few hours before the drug was discontinued a maculo-papular rash appeared over her arms and chest. Her fever declined and the rash faded. Four days after the streptomycin was discontinued a fine, erythematous rash appeared on her back, abdomen and to a lesser extent on her extremities. Her temperature had risen to over 104° F. This reaction was attributed to phenobarbital, and when this drug was discontinued the rash and fever disappeared. There was no symptomatic improvement and Br cella abortus was isolated from the blood during and seven days after the completion of the streptomycin therapy. In vitro all the cultures of Brucella isolated from her blood were inhibited by 2 µg. of streptomycin per cc. Two weeks later she was afebrile and felt well. Blood cultures have been consistently sterile and she has remained asymptomatic to this date.

Patient 16. . - 47, male, storekeeper, had fever, sweats, anorexia, headaches, weight loss of 17 lb. and weak-

ness of one month's duration. Penicillin therapy did not alleviate these symptoms. He had drunk raw milk from a herd of cattle known to have Bang's disease. He had also used alcoholic beverages excessively for 20 years. Upon admission to this hospital his temperature was 101.8° F., pulse 118. The liver was palpable 3 - 4 cm. below the right costal margin and slightly tender. There was a coarse tremor of the hands. Brucella agglutinins were present in a titer of 1:5120. Brucella skin tests were positive. Brucella abortus was isolated from a blood culture on 6/24/46. This organism was inhibited by 2 µg. of streptomycin per cc. in vitro. Liver function tests indicated moderate impairment. A liver biopsy obtained by Dr. F. W. Hoffbauer revealed fatty infiltration of the parenchyma as well as small granulomatous nodules similar to those found in other cases of brucellosis. The patient was given 27.6 Gm. of streptomycin intramuscularly in nine days. During this period his blood cultures became sterile but his fever did not abate. On the last day of treatment a macular, copper-colored rash appeared on his back, chest, abdomen and extensor surface of his arms and legs. On the lower legs a fine purpuric eruption was present. The cuff test was positive, but the platelet count was 200,000. After the streptomycin was discontinued his fever declined, the rash faded and he felt much improved. Although his blood cultures were sterile he was given a course of sulfadiazine, 87 Gm. in 15 days, because it was felt that he still had active brucellosis. He has felt well since that time, but tires easily upon exertion. The growth of the organism in vitro was inhibited by 15 mg.% sulfadiazine.

Patient 17. - 33, male, farmer, noted weakness, weight loss and sweats in June 1944. His Brucella agglutinin titer was 1:1280, but a blood culture yielded no Brucella. He drank raw milk, but the cows showed no evidence of Bang's disease. He was given sulfonamides for six weeks and by October 1944 he felt well. However, in June 1946 he developed fever up to 104° F., sweats, weakness and anorexia. Tender red spots appeared on his fingers and toes. He was given penicillin and sulfonamides without benefit. At the age of 12 he had rheumatic fever. When hospitalized on 9/25/46 his temperature was 101.8° F. Petechiae were noted in both conjunctivae and scattered over both lower legs. The left ventricle of the heart appeared enlarged. The cardiac rhythm was regular. There were systolic and diastolic murmurs in the aortic area and a systolic murmur at the apex. B.P. - 108/38. The spleen was palpable 5 cm. below the costal margin. Duroziez/ sign was present. His Brucella agglutinin titer was 1:2560. Skin tests with Brucella vaccine and protein fractions were negative, but Brucella carbohydrate sensitivity was present. Cultures of the blood, urine and bone marrow revealed Brucella abortus. The blood colony counts varied from 9 to 104 col/cc. In vitro the organism isolated from his blood was killed by 2 µ g. of streptomycin per cc. On 10/9/46 streptomycin therapy was begun with doses of 0.625 Gm. intramuscularly every three hours for 13 days; the dose was then reduced to 0.5 Gm. every four hours. Treatment was continued to 11/8/46. His temperature gradually returned to normal. However after being afebrile 4 days, he began to have a low-grade fever. Four blood cultures during streptomycin therapy were sterile. Conjunctival petechiae continued to appear during treatment. Beginning on 10/21/46 he complained of vertigo without tinnitus nor apparent hearing loss; the vertigo disappeared when the streptomycin dose was reduced. Brucella protein and vaccine skin tests have remained negative to date. His spleen can no longer be palpated.

Patient 18. - 46, male, farmer, complained of weakness, bilateral chest and flank pain of 18 months duration. He had lost 25 lbs. in weight. He drank raw milk from a herd of cattle not known to have Bang's disease. He also butchered his own hogs. When hospitalized on 4/15/46 physical examination revealed no fever or tachycardia. Cervical and axillary lymph nodes were palpable. On 4/16/46 a blood culture for Brucella was sterile. Also a skin test with a purified Brucella protein derivative was negative, and his serum contained no Brucella agglutinins. X-rays revealed moderate compression of the eighth and ninth thoracic vertebrae with some hyper-

trophic spur formation. On 5/1/46 he developed a low grade fever rising to 101° F. It was not affected by salicylates. On 5/21/46 his Brucella agglutinin titer was 1:320, and on 5/31/46 Brucella abortus was isolated from his blood. On 6/7/46 his Brucella protein skin test was positive. At this time it was found that one of his cows had recently aborted, and several of his cows were found to have Bang's disease. He was given 0.5 Gm. of streptomycin intramuscularly q. 4 h. from 6/14 to 6/15 and from 6/19 to 6/24/46. A total of 23.5 Gm. was given. Serum streptomycin levels ranged from 33 to 50 μg./cc. During the streptomycin therapy his temperature rose to a peak of 104.4° F., and on 6/22/46 he developed an erythematous macular rash on his trunk and extremities. The macules became confluent and on 6/24 petechiae appeared on his chest and thighs. The drug was then discontinued because of his apparent sensitivity. His temperature promptly returned to normal, and the rash faded. Subsequent blood cultures were sterile and he remained afebrile. His symptoms had also receded although he continued to have mild aching pain along the costal margins.

Patient 19. - 24, male, packing plant employee, developed weakness and a high fever on 7/23/46. He lost weight and also noted headache, nervousness and lumbar back pain. Sulfonamides and penicillin were given for a few days without effect. He had ingested raw milk several months earlier, and during April and May 1946 he worked in a packing plant washing fresh hog fat. On 8/24/46 physical examination disclosed no fever, but his liver and spleen were palpable 1 cm. below the costal margins. Brucella skin tests with carbohydrate and protein antigens were positive. His Brucella agglutinin titer was 1:1280. Four blood cultures yielded Brucella abortus. During most of his hospitalization he felt quite well. Beginning on 9/27/46 he was given 0.5 Gm. of streptomycin intramuscularly every three hours for a total of 28 Gm. Streptomycin serum levels varied from 40 to 90 μg. per cc. On 9/29/46 his temperature rose to 102° F. but promptly returned to normal. He continued to feel well and thereafter he was afebrile. His blood cultures became more sterile after the streptomycin therapy.

Comment: In patient 15 streptomycin did not eliminate the bacteremia although the organism remained sensitive in vitro. The explanation of this phenomenon is not immediately apparent. We have not been able to show that human serum has any inhibiting effect upon the action of streptomycin against Brucella abortus in vitro. The treatment had to be discontinued in patients 15 and 16 because of drug sensitization. In patient 16 the bacteremia was apparently controlled but symptoms of active disease continued so he was given sulfadiazine when the streptomycin had to be discontinued. The treatment of the patient with Brucella endocarditis has not been completed; hence a final statement of the result cannot be made. However, during streptomycin treatment the disappearance of fever and bacteremia has been encouraging. On the other hand his failure to develop Brucella protein skin sensitivity and the recurrence of fever have been disappointing. All such cases previously reported have ended fatally. In patient 18 streptomycin apparently eliminated his bacteremia; the treatment had to be discontinued because of drug fever and rash. His symptoms appeared to be lessened by the drug. Patient 19 was treated with streptomycin because of persistent bacteremia although he was essentially asymptomatic. The bacteremia disappeared. The treatment of this group of patients has been so recent that no prediction can be made concerning the permanence of the clinical benefit.

## Treatment of Tularemia with Streptomycin

Two patients with tularemia have been treated with streptomycin under our supervision. The essential facts concerning them are given in Table 11; a brief resumé of their clinical course follows:

Patient 20. - 35, male, farmer, handled a dead jack-rabbit with his bare hands. Eight days later he noted headache, malaise, a stiff neck and chills. He was given penicillin and sulfadiazine

Table 11

Tularemia Treated with Streptomycin

| Patient | Type and Complications | Duration of illness. Previous Treatment | Streptomycin Dose in Gm. | Results |
|---|---|---|---|---|
| 20. 35 M. | Typhoidal. Pneumonia, meningoencephalitis | 22 days. Penicillin, sulfonamides and anti-tularense horse serum | 10 Gm. in 10 days. | Recovered. Delayed resolution of pneumonia. |
| 21. 39 M. | Ulceroglandular. Pneumonia and pleuritis | 2 months. Penicillin | 9.9 Gm. in 5 days. | Recovery but pneumonia slow to resolve. |

without improvement. Upon admission to this hospital he was acutely ill with a temperature of 102.4° F. His neck was rigid. His heart and lungs were normal. No local ulcer or lymphadenopathy were found. His spleen was not palpable. Kernig's sign was positive. Tendon reflexes were normal in the legs but decreased in the arms. Toe signs were positive on the right. Blood cultures without added cystine were sterile. The spinal fluid was examined on five occasions and was turbid on only one occasion. The maximum cell count was 47, one-third of which were polymorphonuclear leucocytes. The maximum protein content was 51 mg.%, and the sugar content fell below 30 mg.% on only one occasion. Smears and cultures with added cystine were sterile. Injection into fertilized chicken eggs and guinea pigs failed to reveal any organisms. Further penicillin and sulfadiazine were given without benefit. The patient became drowsy and a chest x-ray on the second day of hospitalization revealed a patchy consolidation of the lower lkbe of the left lung with a small pleural effusion. The pleural fluid was aspirated; cultures were sterile on cystine media. On the 14th day of his illness his blood serum agglutinated P. tularense in a titer of 1:160. X-rays revealed extension of the pneumonia to the right lung. On the 20th day his agglutinin titer rose to 1:1280. A diagnosis of typhoidal tularemia with pneumonia and meningoencephalitis was made. He was given 90 cc. of concentrated antitularense horse serum in divided doses intravenously without improvement. He was then given 10 Gm. of streptomycin intramuscularly over a period of 10 days. He became less febrile and more alert mentally. During this therapy a papulovesicular eruption appeared on his back and chest which subsided spontaneously. He then developed a pericardial friction rub, generalized lymphadenopathy and urticaria. This was interpreted as serum sickness due to the horse serum, but tularemic pericarditis could not be ruled out. The urticaria responded to adrenalin. Clinical and x-ray evidence of pulmonary consolidation and pleural effusion persisted for many weeks after the streptomycin was discontinued, but the signs of meningoencephalitis rapidly disappeared. Two months after the onset of his illness he appeared entirely well.

Patient 21. - 39, male, scratched his left thumb cleaning catfish and carp during the last week of July 1946. The scratch failed to heal and a small abscess also appeared on the left little finger. Painful, enlarged lymph nodes appeared in the left axilla. On 8/27/46 he noted general malaise, chills, fever and sweats. Penicillin and atabrine were given without benefit. Physical examination on 9/3/46 revealed a temperature of 100° F. and an open ulcer on the dorsal aspect of the left thumb. A crusted ulcer was present on the little finger of the same hand. Axillary nodes were palpable bilaterally. Penicillin therapy was again given without benefit. On 9/7 his P. tularence agglutinin titer was 1:80, and on 9/13 it rose to 1:1280. No Pasteurella could be isolated from cultures of the ulcer fluid nor blood on cystine media. On 9/8 a chest x-ray

revealed patchy consolidation within the left lower and right upper lobes. On 9/13 streptomycin therapy was begun with 0.3 Gm. intramuscularly every three hours. On 9/16 the dose was reduced to 0.2 Gm. q. 4 h. A total of 9.9 Gm. was given. On 9/17 his temperature reached normal and remained so. He felt well and the ulcer healed. On 9/22 however he developed fibrinous pleuritis on the left. Chest x-rays revealed persistent bilateral pneumonitis. His temperature did not rise, and by 9/30/46 he felt well although his pulmonary consolidation had not entirely cleared.

Comment: Streptomycin appears to be the most effective therapeutic agent available for the treatment of tularemia and should supplant the use of anti-tularense horse and goat serum. Patient 20 is of particular interest since there are only 12 case reports of tularemic meningitis or encepahlitis in the literature, all of which ended fatally. The clinical impression was that streptomycin probably saved his life, but the previous administration of anti-tularense horse serum clouded the issue. In both patients it was apparent that the pulmonary lesions were not dramatically affected by the drug; perhaps the doses administered should have been larger and the drug given for a longer time. Intrathecal therapy did not appear to be necessary in the treatment of the patient with meningo-encephalitis.

Pneumonia due to Friedländer's Bacillus

Only one patient in this group was treated with streptomycin. A brief resume of the clinical course is given:

Patient 22. - 56, male, was hospitalized on 7/25/46 after a two weeks' alcoholic bout. For three weeks had had right upper quadrant abdominal pain and vomiting. He was febrile and very nervous. Signs of consolidation were present over the upper lobe of the right lung. His liver was palpable, and signs of ascites were present. For the next five days he had delirium tremens. He became jaundiced and ankle edema appeared. He had a septic fever. Chest x-rays revealed a well-demarcated consolidation of the right lung extending from the hilum into the upper lobe. By 8/6/46 the consolidation had spread to the right lower lobe. Bloody sputum was raised by the patient; it contained no tubercle bacilli but smears and cultures revealed numerous Klebsiella pneumoniae. The pulmonary lesion progressed to abscess formation with cavitation in the right upper lobe. Streptomycin was given in doses of 1.5 to 2.75 Gm. daily for six days (total dose 10.25 Gm.). During this period his temperature became somewhat lower, but his general condition did not improve and Friedländer's bacillus continued to be present in his sputum. On 9/2/46 an abdominal paracentesis yielded 4000 cc. of brown fluid. Soon thereafter he became irrational and he died on 9/5/46. No autopsy was performed.

Comment: Streptomycin therapy was ineffective in this patient. Several factors were probably operative in leading to this failure--insufficient dosage, alcoholism, hepatic insufficiency with portal hypertension, and far advanced pulmonary destruction.

Meningitis due to an Unidentified Gram-negative Bacillus

Patient 23. - 11, male, American Indian, was admitted to this hospital on 7/10/46 with a history of occipital headaches for six months. In March and April 1946 he was treated for pneumonia. Physical examination revealed impaired vision, edema of the optic discs, ataxia, positive Romberg and marked weakness. He was afebrile and his lungs were clear to percussion and auscultation. On 7/13/46 a right lateral ventriculostomy with insertion of a catheter was performed; the fluid was clear. On 7/15/46 a posterior fossa craniotomy was done; the cerebellar hemispheres bulged into the wound but no tumor or abscess was found. On 7/17/46 a left lateral ventriculostomy was made and a catheter inserted; the fluid was clear. The next day the fluid aspirated was cloudy, and he became febrile. Cultures of the spinal fluid revealed a gram-negative bacillus which was designated as "non-pathogenic." In spite of penicillin and sulfadiazine signs of meningitis persisted. Blood and spinal

fluid cultures on 7/24/46 yielded gram-negative, spore-forming bacilli. The catheter was removed from the left lateral ventricle on 7/21/46. On 7/22/46 streptomycin therapy was started. He was given 60 Gm. intramuscularly over a period of 20 days and for 12 days intrathecal injection of 0.4 Gm. once daily. Drainage of cerebro-spinal fluid from the posterior craniotomy wound persisted until 8/11/46. During the streptomycin therapy signs of meningitis disappeared, his fever decreased and his spinal fluid became clear and sterile. The ataxia and edema of the optic discs persisted.

A chest x-ray on 7/11/46 revealed consolidation of the inferior portion of the upper lobe of the right lung with widening of the mediastinum. On 7/16/46 some emphysema of the right middle lobe was seen as well. On 7/24/46 a chest x-ray revealed increased consolidation of the right upper lobe with partial atelectasis of the right lower lobe. On 9/5/46 there was evidence of resolution of the process in the right lower lobe but no improvement in the upper lobe. His Mantoux was positive (1 - 10,000). Repeated smears of the spinal fluid revealed no acid-fast bacilli.

Comment: The clinical diagnosis in this case was in doubt, but it seemed most likely that he had pulmonary tuberculosis of a pneumonic type with a cerebellar tuberculoma. The meningitis and bacteremia were presumably the result of contamination of the wound during the third operation. The organisms isolated were of a type ordinarily considered to be "non-pathogenic". The response to streptomycin was not dramatic but coincident with its use the patient recovered from the meningitis and the wound ceased to leak cerebro-spinal fluid and healed. During the streptomycin therapy there was very little improvement in the pulmonary and cerebellar lesions, but they did not spread.

## Toxic Reactions

Unfortunately streptomycin appears to be considerably more toxic than penicillin. The most serious of these reactions was development of drug fever and a toxic rash. This type of reaction developed only after the drug had been given several days and promptly subsided when the streptomycin was discontinued. There were three patients in which the diagnosis of drug fever due to streptomycin appeared certain. Each of these patients also developed a rash. In one instance the rash was maculo-papular and in the others it was macular and petechial. A fourth patient developed a hemorrhagic, papular eruption, fever, flushing of the skin, and jaundice during streptomycin therapy, but it was not certain that they were due to drug intoxication. Two patients exhibited urticaria during streptomycin therapy. In one the urticaria seemed to be a manifestation of serum sickness due to horse serum, but in the other a particular lot of streptomycin appeared to be the inciting agent. Most of the patients who were not critically ill complained of rather severe burning pain at the site of the intramuscular injections. This pain often lasted 12 - 18 hours after the injection was given. In two patients indurated, erythematous, tender nodules were apparent after each injection, and each persisted for several hours. One patient developed vertigo on the twelfth day of streptomycin therapy (5 Gm. daily). This was not accompanied by tinnitus or hearing loss, and when the dose was reduced to 3 Gm. daily the vertigo decreased.

## Summary

1. A review of the literature concerning streptomycin is given.

2. Streptomycin has been evaluated in the treatment of 23 patients at the University of Minnesota.

3. Streptomycin appears to be the drug of choice in the treatment of tularemia. Although its antibacterial activity against Brucella *in vitro* is remarkably greater than that of any other therapeutic agent the effectiveness of streptomycin in the treatment of chronic brucellosis in humans remains doubtful.

In some instances it has appeared that urinary tract infections due to E. coli, A. aerogenes and P. vulgaris responded to streptomycin therapy but the number of patients treated was too small to permit definite conclusions. Although only two of four patients with E. coli bacteremia survived the course of three patients indicated that streptomycin was effective in eliminating the bacteremia. The therapeutic result in patients with paratyphoid fever was good, but it was not certain that the course of the disease had been shortened by streptomycin therapy.

4. Streptomycin is more toxic than penicillin. The most serious toxic reactions observed were rashes and drug fever. Other toxic manifestations observed were local pain at the site of injections and vertigo.

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Primary tularemic pneumonia treated with streptomycin.
J.A.M.A., 131:1126 (Aug. 3) '46.

50. Alexander, H. E., Leidy, G., Rake, G., and Donovick, R.
Hemophilus Influenzae Meningitis treated with streptomycin.
J.A.M/A., 132:434, (Oct.26) '46.

III. GOSSIP

Thanksgiving Day 1946 should be an occasion for sincere expressions of gratitude by us. The veterans have learned that the University of Minnesota was sincere in her desire to help them in their program of self improvement. As they dreamed of this day during the long years they were away, it must seem good to be back, as little did any of us realize that we could move over and make room for as many veterans as we did. We should be grateful to the Kellogg Foundation and the Commonwealth Fund for their continued support of Postgraduate Medical Education at Minnesota. Without their assistance and backing, many of our programs could not have materialized. We should be grateful for the splendid leadership of Dean H. S. Diehl, who through the years has displayed outstanding ability in guiding Minnesota to a place as one of the top medical schools of the nation. His ability has not gone unrecognized elsewhere for his council in general university affairs, and those of government have been widely sought. His contribution to the mobilization of medical men during the war has received great praise in high places. We should be thankful as we enter our program of hospital expansion that we have at our head Raymond M. Amberg who has demonstrated his ability to work with our prima donnas in determining what their needs for the future will be, and in arranging for the same. The University of Minnesota and the state should be thankful for the wisdom of the regents in selecting James L. Morrill as our President. He has brought to this office dignity, sincerity, enthusiasm and understanding. On every occasion he has justified his selection and lived up to all the fine things which had been said of him. He was bold in stating the University's program of needs. He was courageous when he struck at intolerance, and at the meeting of the A.A.U.P. on Wednesday evening of this week, he received an ovation from a faculty whose committee just a year ago had characterized his appointment as satisfactory but not meeting their requirements as far as his manner of selection was concerned. We should be thankful in case of our major department as far as many of our people are concerned - football - we have demonstrated that able teachers could instruct the youth in the proper way in which this game should be played, if given a little time. We should be grateful that an "issue" has not developed out of the inability of the coaching staff to effect a quick change. We should be especially grateful that the time has arrived for us to honor one of our own men, Radiologist Leo G. Rigler, who has done so much for this school and hospital. When the committee which planned his lectureship canvassed the field, they decided to ask Nils Westermark of Sweden to give the lecture. This not only indicates the high regard we have for Doctor Westermark but also how much we appreciate Leo's contributions. We should be thankful for the many new men who have joined our staff and especially for the long range views of Donald Hastings, our new psychiatrist. He struck a strong note at our recent staff meeting and this is indicative of better things to come. With his courage, intelligence and vigor he will see it through or be the first to admit he was wrong. Dr. J. C. McKinley, his predecessor, who is ill in the hospital, was not forgotten by his friends. On the occasion of his 55th birthday, his friends sent him letters, the Journal Lancet dedicated its November issue to him, and J. A. Myers wrote a sincere tribute to him. It is good to remember the sick. We should be thankful for the many gifts which our institution has received and for the continued support by our people. The turning point is closer than it was a year ago and our leaders see light ahead. The guns have now been silent for more than one year and while armies of occupation must still be maintained and many of our young men are still in service, some day the peace of understanding will be ours. I have a good friend, Mrs. Bernard Druck, St. Paul, mother of a large family, good citizen, and leader in child welfare, who is behind a national movement for proper observance of Thanksgiving Day. She believes that Americans are not thankful enough for the great gifts that are ours. I believe she has a point as we take too much for granted. Let each one take time out next Thursday to recount the good things that have been given to him with no special effort on his part and I am sure it will make Thanksgiving Day 1946 a red letter day.....