GONORRHEA

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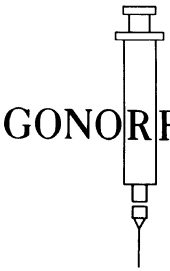

GONORRHEA

The Management of Gonorrhea in General Practice

Procedures Recommended by the American Neisserian Medical Society [1]

Gonorrhea in the United States is much too prevalent. Available data indicate that there are several million new cases every year. Although this disease occurs from three to seven times as often as syphilis, it should be controlled just as many other contagious diseases have been. If we are to succeed, each physician must (1) diagnose and treat the disease properly, (2) accept the responsibility of following up the contacts himself, or report them to the health department which will take over this duty, and (3) hold the patient under observation until cure is established. The physician should inquire regarding all recent contacts in such a manner that the confidence of the patient will be gained. After the epidemiologic information is obtained, he should see to it that all alleged contacts are examined and treated.

Sulfonamide chemotherapy is a long step in advance of the older methods of treatment. Most cases of gonorrhea can be cured rapidly and easily by its proper use. There are three types of patients, however, who need special attention:

1. Those who stop treatment before there is good reason to believe that they are cured.
2. Those who do not respond to chemotherapy.
3. Those who appear to be symptomatically cured but whose infection remains latent.

Most of the first group consist of dispensary patients, among whom a 50-percent lapse rate is common. More effort directed toward patient education and more personal interest in each patient will reduce delinquencies greatly. A good system of routine follow-up of lapsed patients will induce many more to continue treatment until they are discharged as cured. This follow-up service is frequently provided for physicians in private practice by local health departments.

PROPHYLAXIS

The value of chemical as well as mechanical prophylactic measures in the male has been demonstrated. Other than continence, mechanical prophylaxis utilizing a condom assures the greatest measure of safety for both sexes. Inspection of condoms is now the responsibility of the Food and Drug Administration, Federal Security Agency, and it insures the availability to the public of satisfactory articles.

Men who use condoms should be instructed to grasp the sheath on either side by its open end and turn it inside out as it is removed. The hands and the external genitalia should then be washed with soap and warm water. The rather common habit of using a condom only at the end of intercourse should be condemned.

Chemical prophylaxis for those who have failed to make use of a condom is best carried out by a physician. However, the proper use of some of the chemical prophylactic procedures is practical for the average man who is sober.

The steps in carrying out chemical prophylaxis should be: (1) Thorough bathing with soap and warm water of the external genitalia, the pubic region, and the inside of the upper portion of the thighs. (2) The patient then should urinate, after which not more than 6 cc. of a nonirritating protein silver solution

[1] Prepared by a Special Committee Composed of: R. A. Vonderlehr, M. D., Chairman, U. S. Public Health Service; Fred L. Adair, M. D., Chicago, Illinois; Roger W. Barnes, M. D., Los Angeles, California; Charles M. Carpenter, M. D., Rochester, New York; Oscar F. Cox, M. D., Boston, Massachusetts; and Robert M. Lewis, M. D., New Haven, Connecticut.

should be injected into the urethra and held there for 5 minutes by the clock. The chemicals most commonly used for this purpose are mild protein silver, 10 percent, or strong protein silver, 1 or 2 percent.[2] (3) When the protein silver solution has been allowed to escape from the urethra, the areas mentioned in (1) should be carefully anointed for 5 minutes with a 33⅓ percent calomel ointment as a prophylactic measure against syphilis; special care should be taken to rub the ointment well into the skin, particularly around the glans penis and the prepuce. (4) Toilet paper or other appropriate soft paper covering should be wrapped around the genitalia to protect the clothing, and the ointment allowed to remain for some hours.

The use of the condom by the man is the most efficient prophylaxis for the woman. While chemical prophylactic procedures have been recommended for women they have not been demonstrated to be effective and are so complicated that they must be carried out by a specially trained physician.

Inconclusive evidence is available to show that sulfathiazole administered orally before and after coitus may be a practical method for the prevention of gonorrhea.

DIAGNOSIS

The proper methods for the diagnosis of gonorrhea are the examination of smears by the Gram stain and the culture A positive spread, utilizing the Gram method of staining is all that is needed when the preparation is made from a frankly purulent urethral or cervical discharge. Cultures have a most important place in the study of those patients with a microscopically negative discharge or no discharge and with a history of recent gonorrhea for which a sulfonamide drug has been employed.

The technic of proper staining and culture should be that recommended by the American Neisserian Medical Society.[3] Any deviation from this method may lead to serious error in the diagnosis of gonorrhea.

Unfortunately, all physicians and dispensaries are not equipped for the laboratory diagnosis of gonorrhea. Under such circumstances, and in the presence of suggestive history and symptoms, it is probably wisest to make a provisional diagnosis of that disease, pending the time when the results of the laboratory examination are reported, and to proceed with sulfathiazole treatment as later outlined. This is necessary because too many patients with gonorrhea make only one visit, and the opportunity for cure otherwise may be lost. It is better to run the chance of treating a few persons who do not have gonorrhea than to allow those patients who have such an infection to remain untreated while the attending physician waits several days for a laboratory report.

When gonorrheal urethritis exists, frequency and "burning" on urination are often reported by men but less frequently by women. Leukorrhea is often found with gonococcal infections of the cervix. However, leukorrhea is frequently due to other causes than gonorrheal infection in women who are not promiscuous.

Gonorrhea of the cervix does not present a characteristic appearance. This infection may be present in an apparently normal cervix showing a slight discharge of mucus to one showing every evidence of violent inflammation with a profuse purulent discharge. A thick, tenacious ropy, mucopurulent cervical discharge is highly suggestive of gonorrheal infection. An everted, inflamed mucosa at the urethral orifice in the female, or tender and thickened Fallopian tubes, may give us further evidence of the character of infection in

[2] The following preparations have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association. Mild silver protein—Argyn, Cargentos, Silvol, Solargentum, strong silver protein—Protargol, Silver Protein Strong—Merck.

[3] Carpenter, C. M.: Laboratory methods for the diagnosis and determination of cure of gonorrhea. Ven. Dis. Inform., 24: 133–143, 1943.

the patient with puzzling laboratory findings.

TREATMENT

Chemotherapy.—Sulfathiazole given by mouth is the outstanding drug for the treatment of gonorrhea. It should be given to every patient as soon as the diagnosis is made, and in some cases, as noted above, before a provisional diagnosis can be confirmed.

Dosage.—One gram (two 0.5-gm. or 7½-gr. tablets) of sulfathiazole should be administered orally to ambulant patients four times daily, after each meal and at bedtime, for 5 consecutive days. All patients under this treatment should drink at least 10 glasses of fluids daily (more if the weather is unduly warm). Fluid intake above the normal is especially important for women during sulfathiazole treatment. This scheme of therapy has been found to be as efficient as schemes requiring larger doses and more efficient than those in which smaller doses are given over a longer period of time. When this plan is followed most patients show marked clinical improvement before the end of the 5 days of treatment. The determination of the blood concentration of the drug, routine blood counts and urinalyses are not necessary when the above dosage is used.

Patients should be warned to report at once to the attending physician if nausea, fever, or a rash should develop. Occasionally a patient is seen who has an idiosyncrasy to one or all sulfonamides. In these cases the drug must be stopped and large amounts of water administered; such idiosyncrasies are rarely encountered.

The great majority of patients are cured by one course of sulfathiazole when the above plan is used. It is most important, however, to keep the patient under observation for a period of 3 months after all objective symptoms have disappeared in order to make certain that there is no recurrence.

Patients whose infection persists after they have finished one course of sulfathiazole, or in whom the disease relapses, are given another similar course of the drug after a rest period of 3 or 4 days.

Carriers.—In a few patients who have been treated with sulfathiazole, an apparent cure results but the infection persists in a dormant state; carriers are thus produced. *Even in the male, freedom from symptoms and the passage of a perfectly clear urine are not necessarily proof of a true cure.* It is highly important then that the attending physician use all the laboratory methods available to determine whether the patient is cured.

Sulfonamide failures.—In some patients the sulfonamide drugs reduce the activity of the disease and prevent its extension but fail to banish completely the objective symptoms. In a small number of persons these drugs exercise no beneficial effect whatever at the time of administration. That this failure to react favorably to the drugs is sometimes a transient state is shown by the fact that many such patients are quickly rendered symptom-free and even cured by a repeated course which is given after a short rest from medication.

Those in whom sulfathiazole fails to exert any curative influence and for whom fever therapy is not available may often respond to older methods of local treatment.

Local treatment in the male.—The following method of treatment should be used in sulfonamide-resistant cases only. When the infection is confined to the anterior urethra, an anterior urethral injection once daily of not more than 6 cc. of a 5 percent solution of mild protein silver or a 0.5 percent solution of strong protein silver is advised. This solution should be retained in the anterior urethra for 5 minutes. The prolonged or too frequent use of chemicals tends to perpetuate the urethral discharge. This irritating effect may be recognized by the finding of many epithelial cells in the stained smear. All urethral injections should be administered by a physician. If this is not practical the physician should teach the patient how to self-administer properly an anterior urethral injection.

All local treatment should be stopped if acute symptoms of posterior urethritis, such as urgency, painful or marked frequency of urination, or perineal or rectal pain develops. Treatment at this time should be limited solely to hot sitz baths. When acute symptoms have subsided, anterior urethral injections should be resumed and continued until prostatic stroking (massage) is begun.

Extremely gentle prostatic stroking (massage) should be tried when the second glass of urine has been clear, and the first glass nearly so, for 2 weeks. If gentle massage is painful or causes a recrudescence of other symptoms, it should not be repeated for 1 week, or until the symptoms have subsided. If it is not painful and if no recrudescence of symptoms occurs, the gland should be gently stroked at 3- or 4-day intervals, and smears of the prostatic secretion examined every 2 weeks. *When prostatic massage is instituted too soon or applied too vigorously it often induces complications and retards cure.*

No instruments of any type should be passed into the urethra while gonococci are present.

Management of the female.—The recommended treatment with sulfathiazole is relatively so harmless that it is best to follow the maxim—"treat when in doubt." With the public health in mind it is far better to treat some women who are not infected, than to neglect to treat women whose infection is not obvious but who may serve as a source of infection to others. Any woman who has recently had intercourse with a man known to have gonorrhea should herself be given treatment regardless of clinical or laboratory findings. Women who are believed or known to practice indiscriminate sexual intercourse are usually infected and had best be treated if leukorrhea is present. Laboratory evidence in such cases is desirable but not essential for the institution of treatment by the foregoing scheme.

Ordinarily the administration of sulfathiazole gives such rapid symptomatic relief from leukorrhea and pain that no adjuvant local treatment is necessary or desirable. Vaginal douches or topical applications to the cervix are unnecessary and may be harmful. Cauterization of the cervix when gonococci are present is unwise, as an ascending tubal infection may result.

Adequate laboratory facilities are of enormous aid in the accurate determination of the presence or absence of gonococcal infection. Unfortunately, in many sections of this country such assistance is not available. Complete proof of gonococcal infection of women ordinarily depends on securing positive cultures. Culture material is obtained from the cervical canal after cleansing with a dry cotton sponge and from the clean urethral meatus after stroking the urethra outward until a drop of secretion appears. Positive cultures and positive gram stained spreads can usually be found in cases of acute gonococcal endocervicitis or urethritis. In most cases of chronic gonorrheal endocervicitis neither cultures nor spreads, even if repeatedly taken, will give positive evidence of the causative organism. Consequently one must always remember that a "negative" laboratory report, or series of such reports does not indicate that a chronic infection is not of gonococcal origin. Positive cultures are obtained more often than are positive spreads. Gram stained spreads in chronic cervical infections offer notoriously unreliable evidence of the presence or absence of gonococcal infection. Readings of identical spreads made by experienced bacteriologists disagree widely. In the case of chronic vaginitis of girls, only positive cultures should be accepted as evidence of gonococcal infection.

Patients with acute salpingitis with fever should be put to bed and given treatment with sulfathiazole exactly as described above (4 gm. each day for 5 days). Patients with pelvic abscesses should be sent to a hospital for surgical drainage through the vaginal vault. A pointing abscess of Bartholin's gland should be incised and drained; 5 days' subsequent treatment with sulfathiazole may result in cure. If a Bartholin's

gland remains chronically infected it should be removed surgically in a hospital. Pregnancy does not contraindicate treatment with sulfathiazole.

The commonest error in treating men and women with gonorrhea is the failure to find and treat the infected sexual partner, and this is often the cause of reinfection.

GONORRHEAL VAGINITIS OF IMMATURE GIRLS

In most instances, vaginitis of immature girls is not due to gonorrheal infection. An accurate diagnosis depends on securing positive cultures from discharge which is best obtained from the neighborhood of the cervix. A diagnosis which depends on an examination of spreads is not to be relied upon. Too many other Gram-negative organisms in the vaginae of children resemble gonococci. Ordinarily a gonorrheal infection is limited to the vaginal mucosa. Salpingitis occurs very rarely.

Girls with gonorrheal infections need be kept from school only while the discharge is profuse. If properly treated, this period should be a matter of only a few days. The spread of infections on toilet seats is not to be feared. The danger of institutional contacts has been grossly exaggerated. Ordinary isolation technic in well conducted hospitals is sufficient to prevent the transmission of infection to other patients. More intimate direct contacts in the family or with playmates constitute the most frequent modes of spread of the disease in immature girls.

Treatment.—Sulfathiazole given for 7 days in daily doses of ½ gr. per pound of body weight of the child, not exceeding 30 gr. a day for girls weighing less than 75 lbs. will speedily cure the great majority of these young patients. Local applications are useless or actually harmful.

UNTOWARD REACTIONS TO SULFATHIAZOLE

It should be borne constantly in mind that there are a few patients who cannot tolerate sulfathiazole. For this reason, patients not only should be warned of the possibility of toxic reactions but should be seen by the physician three times a week, if practical, while under such medication. Should severe toxic effects (fever, rash, or vomiting) occur, the drug should be withdrawn immediately and the patient's fluid intake greatly increased. The following mild reactions may occasionally be noted but they do not necessitate the withdrawal of the drug: nausea, headache, vertigo, weakness, malaise, irritability, and insomnia. Blood studies need be performed only when there is evidence of a severe reaction. The danger of renal tubular deposits of sulfathiazole crystals is remote with the recommended plan of treatment. Before the plan of treatment recommended above is started, it is important to obtain history of previous treatment with sulfonamide and the patient's reaction, if any occurred, after prior treatment.

PATIENT BEHAVIOR

Patient behavior while under treatment is an important factor in determining the rapidity of cure. The physician or an assistant should take time to instruct the patient to avoid sexual excitement and the use of alcoholic beverages, to obtain plenty of rest, and to drink at least 10 glasses of fluid daily. Emphasis must also be placed upon the need for taking the prescribed medicine regularly. In the absence of cultural studies, the patient should return for clinical observation periodically for at least 3 months to be certain that the gonorrheal infection is cured.

FEVER THERAPY

Fever therapy unfortunately is not available in many localities. It is definitely indicated in patients with severe complications and in those who are intractable to chemotherapy and local treatment.

WHEN IS THE PATIENT CURED?

A small percentage of both male and female patients harbor the gonococcus for some weeks after symptoms have disappeared. In the absence of cultural studies, all patients should be regarded as potentially infectious for a period of 3

months after all symptoms disappear. If such patients have sexual intercourse during this period, a condom should be used to protect the partner. Cultural studies are of great value in the recognition of carriers and offer the most dependable criteria of cure.

As scientific evidence of cure four consecutive negative cultures taken at intervals of 2 weeks may be accepted. In women one such culture should be taken immediately after menstruation. The first of these cultures should be taken a week after apparent clinical cure is affected. In addition to yielding negative cultures, the patient should show no clinical evidence of gonococcal infection before "cure" can be pronounced. Even after 3 months of such "established cures," recurrence may be found, but this is rare.

Practicing physicians interested in laboratory procedures for the diagnosis of gonorrhea and for the determinaton of cure should study the Report of the Referee on Gonorrhea and the Gonococcus for the Standard Methods Committee on Diagnostic Procedures and Reagents of the American Public Health Association.[4]

The practice of physicians giving certificates of freedom from gonorrhea should be condemned and avoided except when required by premarital and similar laws.

CASE-HOLDING AND CASE-FINDING

Very little attention has been given in the past to case-finding and case-holding in the control of gonorrhea. Each patient should be studied in relation to his environment. Because of the national campaign against gonorrhea and of its relationship to the war, every physician who treats gonorrhea must realize that he is just as much a protector of the public health as is the health officer. It is the physician's duty to make every effort to get all contacts in for examination and treatment if infected. It is incumbent upon attending physicians to see that every infected patient is held under observation until cure is attained. In most large and many small communities, contact-tracing and case-holding services are available from the local health department. Such services should be extended and made more readily available.

[4] See footnote 3.

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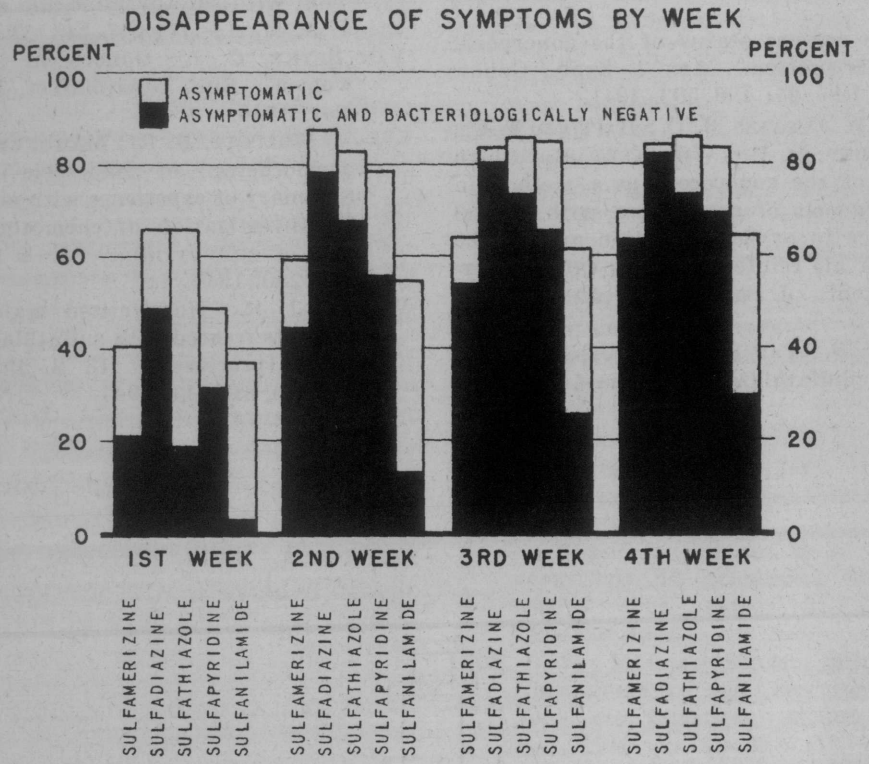
GONORRHEA

RAPID APPRAISAL OF SULFONAMIDE DRUGS IN THE TREATMENT OF GONORRHEA IN THE MALE *



*FROM AMERICAN NEISSERIAN SOCIETY AND U.S. PUBLIC HEALTH SERVICE

WAR DEPARTMENT TECHNICAL BULLETIN

TREATMENT OF GONORRHEA

WAR DEPARTMENT, WASHINGTON 25, D. C. • 21 SEPTEMBER 1944

1. DRUG OF CHOICE. Effective immediately penicillin will be the drug of choice in the treatment of gonorrhea. The use of the sulfonamides will be limited to those cases not responding to adequate penicillin therapy and those instances in which penicillin is not available through normal supply channels.

2. OUT-PATIENT AND DISPENSARY VERSUS HOSPITAL TREATMENT. Penicillin therapy of uncomplicated gonorrhea may be carried out as a hospital, out-patient, or dispensary procedure. It is desirable, however, when satisfactory medical facilities are available, that treatment be administered without hospitalization.

3. DETAILS OF PROFESSIONAL MANAGEMENT. *a. Hospital treatment.* (1) The initial treatment schedule recommended is 20,000 units intramuscularly every 3 hours for a total dosage of 100,000 units.

(2) Patients in whom a favorable response is not evident by the third post-treatment day as determined by change in character or disappearance of the discharge and the absence of gonococci by smear or culture should be retreated, using the schedule recommended in (1) above.

(3) Those patients not responding to a second course should be given a prolonged and intensive third course of penicillin totaling not less than 300,000 units, administered in 20,000-unit intramuscular injections every 3 hours.

(4) Individuals who fail to respond to the third course of penicillin should be treated with one course of sulfadiazine or sulfathiazole, in a dosage of 4 grams initially, followed by 1 gram every 4 hours night and day for 5 days.

(5) Individuals who fail to respond to the schedules of treatment outlined above should be referred to regional hospitals for evaluation and further therapy.

b. Out-patient or dispensary treatment. (1) The schedule outlined in *a*(1) above is recommended for out-patient or dispensary treatment. However, this schedule may be compressed to be given in not less than an 8-hour period.

(2) Individuals who fail to respond to two courses of penicillin administered on an out-patient or dispensary basis will be hospitalized and treated in accordance with paragraph *a*(3) above.

c. Individuals with complications of gonorrhea, such as epididymitis, prostatic abscess, salpingitis, arthritis, ophthalmia, or septicemia, should be hospitalized immediately and treated in consultation with appropriate specialists; larger and prolonged dosage of penicillin such as that recommended in paragraph *a*(3) above is necessary.

d. Determination of cure. (1) *In the male.* Relapses following penicillin treatment are infrequent. Patients hospitalized for uncomplicated gonorrhea should be discharged to duty as soon as they are asymptomatic, usually within 2 or 3 days. The presence of urethral discharge is not considered of sufficient import to prolong

hospitalization or to continue treatment on a dispensary or out-patient status, provided the gonococcus cannot be demonstrated by smear or culture. In every case of gonorrhea, follow-up studies should include weekly physical inspection and microscopic examination of urethral discharge or urinary sediment for 3 weeks after completion of penicillin therapy. Prostatic massage or urethral instrumentation will ordinarily not be done to obtain material for bacteriologic studies. The patient may be considered cured if clinical and laboratory examination as described above are negative at the end of the 3 week follow-up period.

(2) *In the female.* Cure will be determined by:

(*a*) Absence of tender masses or points of tenderness.

(*b*) Inability to demonstrate the gonococcus by smears and cultures (when available) in material obtained from the urethra, Skene's glands, Bartholin's glands, or the cervix. Such tests will be repeated on an ambulatory basis at weekly intervals for 3 weeks after disappearance of symptoms and signs. It is recommended that the follow-up examination include smears and cultures taken during or immediately following the next menstrual period.

(*c*) To obtain material for smears and cultures, massage the urethra, Bartholin's glands, and Skene's glands, obtaining secretion with small cotton-wrapped applicator or a platinum loop. Pass bivalve vaginal speculum without lubricant, expose cervix, clean vagina and cervical canal, squeeze cervix between ends of speculum blades, and obtain expressed fluid on cotton applicators or platinum loops for smears and cultures.

4. SEROLOGIC TESTS FOR SYPHILIS. It is particularly important that patients with gonorrhea treated by penicillin be carefully followed with respect to the possible development of primary and secondary syphilis. Since penicillin in adequate dosage is therapeutically effective in early syphilis as well as in gonorrhea, it is possible that the development of primary syphilis may be retarded or masked by penicillin therapy of gonorrhea. Blood tests for syphilis should be performed at the end of the follow-up period, and careful clinical and serologic study repeated at the end of 3 months.

5. RESCISSIONS. S. G. O. Circular Letters Nos. 129, 22 July 1943, subject, "Diagnosis and treatment of gonorrhea," and 32, 1 February 1943, subject, "Duty status treatment of gonorrhea"; paragraph 8*e*, TB MED 9, Penicillin, 12 February 1944, and TB MED 16, Penicillin Treatment of Resistant Gonorrhea, 6 March 1944, are rescinded. Provisions of S. G. O. Circular Letter No. 74, 25, July 1912, subject, "Diagnosis and treatment of the venereal diseases," which are in conflict with this bulletin are rescinded.

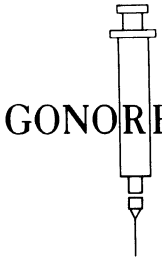
[A. G. 300.5 (14 Sep 44).]

BY ORDER OF THE SECRETARY OF WAR:

G. C. MARSHALL,
Chief of Staff.

OFFICIAL:

J. A. ULIO,
Major General,
The Adjutant General.



THE CLINICAL USE OF PENICILLIN IN GENITOURINARY INFECTIONS

CHAIRMAN'S ADDRESS

COMMANDER GERSHOM J. THOMPSON
MEDICAL CORPS, UNITED STATES NAVAL RESERVE

The Oxford investigators Abraham, Florey and their associates [1] were the first to call attention to the fact that penicillin in high dilution possesses strong antibacterial action on cultures of Neisseria gonorrhoeae. They also described a case of an infant afflicted with Staphylococcus aureus pyelonephritis in which the urine was quickly sterilized by comparatively small doses of the drug. Herrell, Cook and Thompson [2] described a series of 5 cases of gonorrhea in which response to treatment was dramatic. The extreme value of this drug in the treatment of infections of the genitourinary tract was further elaborated by Mahoney and his associates.[3]

Because of its particular value in gonococcic infections and owing to the fact that such infections are responsible for a considerable amount of disability in the armed forces, penicillin has been used in thousands of such cases during the past year or more. Through its use many service men have been quickly returned to duty. At first it was employed only in cases in which the infection resisted treatment with the sulfonamide compounds, but recently authorization for its use in all cases of gonorrhea has been granted. I report a series of cases which have been observed at a large naval hospital. In addition to cases of gonorrhea a number of cases in which treatment has been given for so-called nonspecific infection of the genitourinary tract will be discussed.

DESCRIPTION OF THE DRUG

The sodium salt of penicillin is a very fine crystalline or powdery light yellow substance. In solution it is light brown to light yellow, depending on the dilution.

Concerning the sodium salt the Floreys [4] wrote:

> This substance is extremely soluble in water but is destroyed by boiling, by acids and alkalis, by certain heavy metals, by oxidizing agents and by enzymes produced by air and other bacteria. Penicillin is bacteriostatic and not bactericidal, at least in concentrations likely to be used therapeutically, and reliance must therefore be placed on the body defenses, both humoral and cellular, to destroy the bacteria present in a lesion while penicillin prevents their multiplication.

Steady progress in the manufacture of penicillin has resulted in an increasingly pure product. The unit value varies from 50 units per milligram upward depending primarily on the purity. It is said that pure crystalline penicillin has a strength of about 1,600 units per milligram.

The drug was originally supplied packaged in glass ampules, but on request the various manufacturers now dispense it in vacuum sealed, rubber stoppered bottles containing 100,000 units each, to which isotonic solution of sodium chloride or another diluent in the proper amount can be added. Concentration of either 5,000 or 10,000 units per cubic centimeter should be used, as neither is irritating when injected intramuscularly. Further dilution can be made from this more concentrated preparation if continuous intravenous drip administration is desired. The stock solution should be stored in the icebox between injections.

The mode of action of the drug is uncertain. Studies have shown that blood and urine concentrations are highest about an hour after intramuscular injection, while after ninety to one hundred and forty minutes the methods of testing which are in use at the present time reveal its complete elimination. A constant level in the blood seems unnecessary, quite in contrast to the requirement in sulfonamide therapy. The methods of assaying the amount of penicillin in blood and urine are still rather crude, and until the substance is synthetically crystallized in commercial quantities and some colorimetric method is worked out the estimation of blood and urine levels will probably remain inexact.

Estimation of blood levels in clinical urologic practice is unnecessary for, given a penicillin sensitive organism, the important test of whether sufficient quantities of the drug have been given is whether the patient gets well. Because of the scarcity of the product a great deal of effort has been bent to finding a minimal effective dose; but when penicillin is available in unlimited quantities optimal doses considerably higher than those now in use will prevail.

CLINICAL MATERIAL

Five hundred cases in which a diagnosis was made of gonococcic infection of the urethra or its adnexa and 100 cases in which the patient suffered from various nonspecific infections of the genitourinary tract form the basis for this report. All of the patients were of the male sex.

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3. Mahoney, J. F.; Ferguson, Charles; Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea in Men, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525-528 (Sept.) 1943.
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DOSAGE AND METHODS OF ADMINISTRATION

All of these patients were given penicillin by one or more of several methods. Most of the patients received the sodium salt of penicillin. In recent weeks the calcium salt has been used in a series of cases, and it seems identical with the sodium salt in its action. A number of dosage schedules and alterations of routes of administration seemed desirable in our early experience in order to find the easiest and most efficient methods for every one concerned. It seems desirable, avoiding too much detail, to record some of these efforts so that others may evaluate and discard various ideas which arise concerning treatment with the drug.

Intravenous Administration.—It seems logical that a continuous intravenous drip would insure a steady flow of the drug throughout the body and a steady excretion through the urinary tract. At first each patient was given during each twelve hour period 1 liter of isotonic solution of sodium chloride containing 20,000 units of penicillin. The injection was continued day and night for ninety-six hours. Thus a total of 160,000 units was administered. Later the dose was reduced to a total of 80,000 units given in 1 liter of saline solution during a period of twelve hours. Even though excellent results were obtained with both these schedules it soon became apparent that patients so treated were more of a nursing problem than necessary. Needles became dislodged, and feeding and toilet problems involved more detail than did intermittent intramuscular injection. The patients themselves preferred multiple puncture rather than attachment to the end of an intravenous tube and flask for a full day. The method was therefore discarded.

Intramuscular Administration.—Injection into the gluteal or deltoid muscles of a solution containing 5,000 units of penicillin per cubic centimeter seems to be the ideal treatment method for urologic cases. The injection of 20,000 units every three hours can be continued for many doses without causing irritation. When the strength of the solution was 10,000 units per cubic centimeter a number of patients complained of pain and discomfort, although these were not severe. The patients treated by intramuscular injection are ambulatory and can take care of themselves and do cleaning details or other work around the ward. The injections have been given by nurses and by hospital corpsmen who have been properly instructed, without the slightest complication. Thus the time of a medical officer is conserved in contrast to the requirements in the case of intravenous therapy.

Injections of 20,000 units each given every three hours until a total of 100,000 units has been given will result in a high percentage of cures. All the injections are given in a twelve hour period.

An attempt was made to reduce the number of injections by giving 50,000 units in each of two injections six hours apart, or a total of 100,000 units. This scheme failed miserably.

Intraurethral Administration.—It occurred to me that perhaps intraurethral instillation might be effective. Ten patients were treated by injecting intraurethrally 3 to 4 cc. of solution containing 250 or 500 units per cubic centimeter. A Cunningham penis clamp was used to retain the solution. This was continued for twenty-four hours, penicillin being reinjected after each voiding. The urine cleared promptly and within twenty-four hours was crystal clear in all cases. However, three to four days later urethral discharge reappeared. Apparently, a few organisms lodged deep in Littré's glands and not reached by the solution provided a source of reinoculation, and after the usual incubation period urethritis again developed. Whether intraurethral injections repeated several times daily for a week or so would result in cure, I do not know. For obvious reasons this scheme of treatment was not tried. Whether penicillin solution injected locally after venereal exposure would act as a prophylactic agent is doubtful. Perhaps it would be as effective as strong protein silver (protargol). A single injection of 20,000 to 50,000 units given intramuscularly might be quite efficient. No observations along this line have been made.

Intramuscular and Intraurethral Administration.—A group of patients, in the interest of conservation of the drug, was treated by intramuscular injection of 15,000 units every three hours for four doses or a total of 60,000 units, after which 4 cc. of a dilute solution of penicillin (250 units per cubic centimeter) was injected intraurethrally and held for thirty minutes. The results by this method were not spectacular and it was therefore discontinued.

Oral Administration.—Oral administration is generally ineffective because the drug is destroyed by the gastric acid. In cases in which there is achlorhydria, effective blood and urine concentration apparently can be obtained. Rammelkamp and Helm [5] administered penicillin to 2 patients who had pernicious anemia and found satisfactory blood and urine concentration levels. Florey [1] found as little as 1,000 units given every three hours by mouth to an infant who had staphylococcic infection of the urinary tract quite effective.

I have tried oral administration in a small series of cases, supplementing the penicillin with large doses of sodium bicarbonate, but the results have been unsatisfactory. Quite likely some effective method of oral administration will be evolved later.

Intramuscular Injection of Slowly Absorbing Solutions.—After the great efficacy of penicillin in as short a time as twelve hours in cases of gonorrheal urethritis had been established, it was only natural to try to evolve a one injection method of treatment. The usual vehicles for insulin, such as protamine zinc and globin zinc, were considered. Those consulted advised against the use of protamine zinc on the ground that the large amount necessary would be irritating.

It might be thought that penicillin injected locally into the muscle might lose its potency in a few hours because of the body heat. However, Rammelkamp and Keefer [6] found that fluid aspirated from the pleural and joint cavities twenty-two and thirteen hours after injection showed appreciable amounts of penicillin remaining.

In 6 cases 100,000 units dissolved in 10 cc. of 3 per cent solution of human globin was injected. In 3 cases the result was successful and in 3 the treatment failed. Immune globulin was tried as a vehicle without success. Serum albumin was used as a diluent on the ground that the very large molecule would promote slow absorp-

5. Rammelkamp, C. H., and Helm, J. D., Jr.: Studies on the Absorption of Penicillin from the Stomach, Proc. Soc. Exper. Biol. & Med. **54**: 324-327 (Dec.) 1943.

6. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425-437 (May) 1943.

tion. In a series of 10 cases there were 4 failures. At the present time, therefore, a one shot method of treatment which would be suitable for dispensary or office practice seems only a hope.

RESULTS OF TREATMENT IN GONORRHEAL INFECTIONS

Routinely, a culture of the voided urine is obtained the morning after the administration of penicillin. This is twelve to eighteen hours after treatment is concluded. The next day, or about forty-eight hours after the first injection, a culture is obtained from the prostatic fluid. In practically all instances these post-treatment cultures were negative.

Studies of the purulent urethral secretion, the sediment from the centrifuged urine and the prostatic secretion by Gram's stain are very reliable methods of studying clinical response to treatment. In a number of cases specimens stained by Gram's method were studied hourly after the first injection. In many cases within

TABLE 1.—*Details of Treatment of Gonorrhea with Penicillin*

How Treated, Units	Doses	Total Units	Cases	Cured	Failed	Per Cent Cured
20,000 units in 1 liter of saline solution; continuous intravenous drip for 96 hours....	..	160,000	10	10	0	100
100,000 units in 2 liters of saline solution; continuous intravenous drip for 12 hours....	..	100,000	28	26	2	93
80,000 units in 1 liter of saline solution; continuous intravenous drip for 12 hours....	..	80,000	30	29	1	97
15,000 units every 3 hours intramuscularly; then intraurethral injection of 4 cc. of solution containing 250 units per cubic centimeter.....	4	61,000	20	17	3	85
50,000 units intramuscularly for 2 doses (6 hours apart)..	2	100,000	20	11	9	55
100,000 units dissolved in 10 cc. of 3% human globin injected intramuscularly	1	100,000	6	3	3	50
100,000 units dissolved in 10 cc. of 25% serum albumin injected intramuscularly	1	100,000	10	6	4	60
20,000 units every 3 hours intramuscularly	10	200,000	10	10	0	100
20,000 units every 3 hours intramuscularly	5	100,000	366	358	8	98

two hours the gonococci had disappeared from the urethral secretion. Within four to six hours no organisms could be found even by the most minute study. Before complete disappearance the gonococci gradually take on a deeper stain, so that they appear quite red and become greatly swollen and irregular. Many seem fused together instead of diplococcic in shape. Later, stains of the urethral discharge or the centrifuged urine show a profusion of pus cells and some epithelial débris but no organisms.

The dramatic cessation of the purulent urethral discharge is the most impressive point in penicillin therapy. Within a few hours after the first injection the patient will usually note a great reduction of discharge. The following morning in most instances the urethra appears dry. However, in some cases a small mucopurulent or mucous drop can be expressed from the urethra each morning for several days or even as long as a week. This should not prompt one to treat the patient again with penicillin. Study of the sediment of the first glass urine by Gram's stain or by culture will fail to reveal gonococci and in all but a small percentage of cases in which 100,000 units is used a cure will result (table 1).

In analyzing the result of treatment it must be kept in mind that the patients who were the subject of this report were followed for relatively short periods. However, it is my impression that in extremely few cases will there be an exacerbation of a latent prostatic focus. If the culture of the prostatic secretion is negative forty-eight hours after treatment it will usually remain negative.

One important point in considering results of therapy is that at present there is no great assurance that an ampule of penicillin contains the exact amount stated on the label. It is my impression that many of these patients received much more than 100,000 units. This is not the fault of the manufacturer; rather it can be attributed to the inexact methods of assay which are now available.

It will be noted (table 1) that failure was reduced to 2 per cent when the recommended schedule of 20,000 units every three hours for five doses was employed. Further it should be emphasized that, in the cases in which the result was classed as a failure, cure was subsequently obtained by a course of injections of penicillin. In no case did the infecting organism prove penicillin resistant and necessitate other methods of treatment. If enough of the drug was given, a cure was obtained in all cases.

REINFECTIONS

Sixteen patients in this series were readmitted to the hospital several months after initial penicillin therapy because of another gonorrheal infection. They freely admitted that infection developed again only after further exposure. After critical analysis it seemed that these were bona fide cases of reinfection rather than recurrence of the old infection.

COMPLICATED CASES

Acute gonorrheal epididymitis, prostatitis or seminal vesiculitis was observed in only 10 cases in this series. In 5 of these it seemed prudent to give an additional amount of penicillin; hence a second ampule of 100,000 units was injected according to the original schedule of 20,000 units per injection. Rapid cessation of perineal or testicular pain and prompt reduction of swelling and other signs of inflammation were noted in all cases. Rectal examination disclosed rapid diminution of the size of the prostate gland, so that within three or four days the gland was practically normal in size. Cultures of the secretion at this time were reported negative, although pus cells persisted. Examination a week later showed the prostate secretion normal.

Inflammation in the joints, so-called gonorrheal arthritis, was observed in 6 cases. In 1 case the swollen knee joint was aspirated and a dilute solution of penicillin injected into the joint space. No striking benefit was noted as a result. Nor did continued injections of penicillin seem to aid in the other cases in which there was joint involvement. In all of them, however, the gonorrheal infection in the urethra and prostate quickly subsided and repeated cultures remained negative. The fluid aspirated from the joint cavities was never positive at any stage of the disease.

RESULTS IN NONSPECIFIC INFECTIONS

In 100 cases of infections in the genitourinary tract in which one or more strains of bacteria other than gonococci were isolated by culture or identified by Gram's stain, treatment has been given during the past

six months with penicillin and the results noted. It has not been possible in many cases to study the results of therapy for as long an interval as might be desirable. However, definite opinion as to the worth of the drug has been formulated. In the majority of these cases a mixture of organisms has been noted, some of which are sensitive to the action of penicillin while some of them are not. Study by Gram's stain of the urethral or prostatic secretions will reveal the disappearance of gram-positive organisms while gram-negative organisms persist.

In table 2 the cases are listed according to diagnosis and the effect of treatment. The series of cases is not as comprehensive as might be desired but, nevertheless, some idea of the worth of penicillin in such cases can be obtained.

Acute Nonspecific Prostatitis.—In the 4 cases observed the response to treatment did not seem as rapid as it was in the cases of acute gonorrheal prostatitis.

Cultures of prostatic secretion in 3 cases were reported to be Staphylococcus albus and in the fourth case nonhemolytic Streptococcus. In the latter case the acute inflammatory process was confined to the right lobe of the gland; the region was quite indurated

TABLE 2.—*Nonspecific Infections Treated with Penicillin*

Diagnosis	Cases	Improved	Unimproved
Acute prostatitis	4	4	0
Chronic prostatitis	30	24	6
Urethritis	36	33	3
Acute epididymitis	8	7	1
Balanitis	6	6	0
Infected wound	3	3	0
Cystitis, interstitial	3	0	3
Pyelonephritis	10	8	2

and extremely tender, suggesting abscess, but there was no fluctuation. This patient also had keratitis. He was given fifteen injections of 15,000 units each. Almost immediate improvement of the ocular condition was noted and within a week the region in the prostate gland had changed to normal consistency and the expressed secretion contained much less pus than before and no organisms.

Chronic Prostatitis.—An excellent response was noted in 24 of the 30 cases in which a diagnosis of chronic prostatitis was made. The best indication of chronic infection in the prostate gland is the presence of pus cells and the finding of bacteria in stained smears of the expressed secretion. Cultures were made in the majority of the cases. Among the organisms reported found were Staphylococcus albus, Streptococcus (hemolytic), Streptococcus (green producing), Bacillus subtilis, Micrococcus, diphtheroids and Alcaligenes fecalis. In my experience more knowledge and a better idea of the severity of the prostatic infection can be obtained by noting the polymicrobial character and relative number of organisms in a smear stained by Gram's method than by cultures. I believe that many urologists will concur in this opinion.

Frequently gram-positive cocci are found in a smear when a culture of the same material is reported negative. For this reason in my opinion cultures provide corroborative data, but conclusions should not be based on cultures alone.

Of greatest importance is a correlation of all the symptoms and signs, including size of the gland and presence of induration. In 80 per cent of the cases in which penicillin was used there was improvement—in the majority, pronounced; in only a few, moderate. How many cures were obtained is conjectural, since past experience shows that chronic prostatitis does not often remain cured, and few of the cases in this series have been followed for more than a few months. The results to date, however, are very encouraging. A reduction of the pus cell count of the expressed secretion from 150 or more cells to the high dry field down to 8 or 10 per field is the rule rather than the exception. Such results may be seen a few days to a week after a course of five injections of 20,000 units each. In some cases a second course of 100,000 units two or three weeks after the first was necessary to obtain a really striking effect.

Nonspecific Urethritis.—In 36 cases in which the diagnosis of nonspecific or nonvenereal urethritis was made, treatment with penicillin was given. Purulent urethral discharge presenting as a morning drop was the chief complaint. These patients usually had noted the infection for months prior to admission. Gonorrheal infection was first ruled out. Routine examination of the prostate and the passage of urethral sounds to detect strictures of small or large caliber were done. Urethroscopy was done in most cases. A marrow meatus was found in some instances and meatotomy was performed. In the majority, however, there was no sign of urethral abnormality other than the infection. Response to penicillin therapy in this group is not as good or as dramatic as it is in the case of gonorrheal infections. However, in the uncomplicated cases a high percentage of patients noted improvement as evidenced by reduction or cessation of discharge. Shreds disappeared from the urine in some cases in which they had formerly persisted for months in spite of all other treatment.

It should be emphasized that in any case of chronic nonspecific urethritis thorough examination should be made to detect stricture and so forth before institution of treatment.

Nonspecific Acute Epididymitis.—In 7 of 8 cases there was notable response to a course of ten injections of 20,000 units each. In the 1 case in which there was no appreciable benefit the infection developed within a few days after transurethral prostatic resection. Acute inflammation in the epididymis usually is accompanied by an infection in the corresponding seminal vesicle, and sometimes the adjacent testicle is also involved. Often an acute hydrocele forms. These patients suffer great pain and discomfort and are quite disabled. The prompt relief of pain and the rapid reduction of the tenderness and swelling were most convincing of the efficacy of penicillin. In no case was epididymotomy or other incision required.

Balanitis and Wound Infections.—In 6 cases in which there was considerable infection of a redundant, unretractable prepuce treatment was by local instillation of a solution containing 250 units of penicillin per cubic centimeter. Improvement was so remarkable that circumcision was possible within forty-eight to seventy-two hours. Dorsal slit was avoided in all cases. In 2 cases wound infection following nephrectomy was quickly cleared up by instillations of 5 to 10 cc. of the

dilute solution. Apparently the antibacterial action of these solutions, when they are instilled into wounds, lasts for many hours. It has not been necessary to instil the solution oftener than twice daily. In 1 case of purulent inguinal adenitis which required incision and drainage the infection healed with remarkable rapidity as a result of instillation of penicillin solution. There was practically no drainage after the first instillation. Instillations of a few cubic centimeters once daily were continued until healing was practically completed.

Interstitial Cystitis.—In 3 cases interstitial cystitis was treated by intramuscular injection of 10,000 units every three hours for fifty doses. In addition in 2 cases intravesical instillation twice daily of 30 to 45 cc. of a solution containing 250 units per cubic centimeter was done. The patients were able to hold the solution in the bladder for an hour or two. No irritation was noted. Cultures of the urine were reported Staphylococcus albus in 2 cases and diphtheroids and Staphylococcus in the other. In none of the cases was there any benefit which could be attributed to penicillin. Subsequently intravenous injections of neoarsphenamine and irrigations of silver nitrate were given. All were benefited by this treatment.

Pyelonephritis.—As far as I have been able to determine, penicillin is equally effective in alkaline or acid urine. In several cases infection of the upper part of the urinary tract in which there was a mixture of organisms I have employed another drug such as ammonium mandelate or sulfanilamide in addition to penicillin, hoping that the combined effect would result in sterilization of the urine. Abraham and Chain [7] have shown that gram-negative rods, including Escherichia coli, actually secrete an enzyme, penicillinase, which destroys penicillin. Results of combined therapy in some cases therefore might well be superior to the use of penicillin alone.

In practically all of the cases of pyelonephritis which I have seen the disease has been acute, and it is well known that a large percentage of these will recover spontaneously. It is therefore extremely difficult to evaluate the particular virtue of penicillin. In 2 cases of chronic renal infection complicated by the presence of multiple calculi not sufficiently large to warrant operation the condition was treated with penicillin. In these there was a mixture of organisms, both gram-positive cocci and gram-negative bacilli. The cocci disappeared from the urine after penicillin therapy, but the bacilli persisted. Cultures following treatment revealed Proteus vulgaris in 1 case and Escherichia coli in the other. In the case in which there was Proteus infection a catheter was introduced into the renal pelvis and lavage with solution G and solution M [8] was performed. This resulted in a remarkable reduction of the number of organisms which could be found in stained smears, but two days after lavage was discontinued the bacilli reappeared in great number. No effect on the stones was observed.

I believe that penicillin will be of great value in the treatment of renal infections due to a susceptible organism when the patient is unable to tolerate sulfonamide compounds. For infants and small children suffering from acute renal infection it should have particular value, because the risk of toxic reactions from sulfonamide compounds is greater for them than for adults.

It is possible in any case to make tests in vitro to determine the penicillin sensitivity or resistance of the particular organism. However, because of the fact that renal infections are often of mixed type a clinical trial would seem more practical than a test in vitro.

TOXIC REACTIONS

No serious toxic reactions were noted in any of the 600 cases. One patient had an elevation of temperature to 101.5 F., but this was attributed to some contaminant rather than to the penicillin. Several days after treatment 2 patients had a mild macular eruption which faded quickly. Three patients had an id reaction on the palms which very definitely was precipitated by injections of penicillin in my opinion.

Attention should be directed to the lack of local reaction, the ease of administration and the lack of any systemic symptoms even after large doses. In a number of cases in which treatment was given for conditions other than urologic disease, doses of 500,000 units during a period of twenty-four hours have been employed without toxic manifestations. Therefore in urologic cases one need not be hesitant about using much larger doses of the drug than have been suggested in this paper.

It is unnecessary to alter the diet in any way in my opinion. In cases of septicemia, chronic osteomyelitis or severe systemic infections, changes of diet might be important while the drug is being administered, but in urologic practice any change of diet is unnecessary and superfluous.

CONCLUSIONS

1. Penicillin is a particularly valuable drug for the treatment of gonorrhea. The most practical method of administration is the intramuscular injection of a solution containing 5,000 or 10,000 units per cubic centimeter. Doses of 20,000 units injected every three hours until 100,000 units has been given will result in cure in fully 98 per cent of the cases.

2. Penicillin is unstable in solution and at room temperature will rapidly lose its antibacterial power. Solutions should be freshly prepared and kept in the icebox between injections.

3. Penicillin is an extremely useful drug in the treatment of various nonspecific infections of the genitourinary tract. If the infection is caused by penicillin sensitive organisms the result of treatment is excellent. In most cases, however, the infection is of mixed type and the result of therapy is not dramatic. Nevertheless it is worth while. Penicillin combined with other urinary antiseptics in these cases might well be superior to other methods of treatment.

4. The results of treatment in urologic cases can be determined well by making repeated Gram's stains of the urethral or prostatic secretions or of the sediment of the centrifuged urine.

5. Treatment with penicillin is so devoid of toxic reaction that there is no reason to outline difficult schedules or to use complicated methods. The physician need not be fearful of using too much of the drug and should follow the dictum that the dose of any medicine is "enough."

7. Abraham, E. P., and Chain, E.: An Enzyme from Bacteria Able to Destroy Penicillin, Nature, London **146**: 837 (Dec. 28) 1940.

8. Suby, H. I., and Albright, Fuller: Dissolution of Phosphatic Urinary Calculi by the Retrograde Introduction of a Citrate Solution Containing Magnesium, New England J. Med. **228**: 81-91 (Jan. 21) 1943.

STUDIES ON THE ACTION OF PENICILLIN

I. THE RAPIDITY OF ITS THERAPEUTIC EFFECT ON GONOCOCCIC URETHRITIS

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Although reports of the efficacy of penicillin in the treatment of gonorrhea [1] began to appear soon after the drug became available for clinical trial, not one of them has sufficiently emphasized the rapidity of its curative action. This point is brought out in the present study, which was undertaken as a part of an investigation into the mode of action of penicillin. Since infections of the male urethra lend themselves readily to bacteriologic and cytologic observations, gonococcic urethritis in the male is peculiarly suited to the study of the mode of action of a chemotherapeutic agent.

METHODS

The first 7 patients were hospitalized for treatment. Smears and cultures of urethral exudate were made on admission and before the first injection of penicillin.[2] Smears and cultures were made in duplicate. One of the smears was stained by Gram's method and examined at once, the other saved for later examination by special staining methods.

After the first 7 cases had demonstrated the rapidity of its action, we began to administer penicillin to ambulatory patients in the outpatient clinic, where they were kept under supervision during the period of treatment and observation. This practice proved to be equally successful in all particulars.

All patients, whether treated as inpatients or as outpatients, were examined by smear and culture at frequent intervals—every hour or two in most instances. Follow-up examinations were begun the following morning.

CULTURES

After the urethral orifice had been cleansed with 1:1,000 mercury bichloride and dried with sterile gauze, a drop of pus was accumulated by stripping the urethra and was taken up with a sterile cotton swab, small and tightly wound to prevent too much absorption. The swab was streaked at once across the middle of two agar plates which had been brought to the bedside or examining table. The inoculum on the second plate was spread out at once with the same swab, but the first plate was carried to the laboratory and spread with a sterile platinum loop. This precaution was taken in the interest of adequate separation of colonies and minimal contamination and was justified by occasional differences between the two cultures.

The medium employed was a meat-digest agar containing phosphate buffer and 1 per cent glucose. Defibrinated rabbit's blood was added at the time the plates were poured.

The plates were incubated in an atmosphere of carbon dioxide provided by a lighted candle in one of the metal cylinders customarily used for the sterilization and storage of Petri dishes.

After incubation overnight, colonies of gonococci were usually plainly visible, but the plates were returned to the incubator for another day and examined again. The bacteriologic diagnosis was based on morphology, staining reaction and sugar fermentation.

CLINICAL DATA

Twenty-one patients were treated in this study.[3] They varied in age from 21 to 49 years, with an average age of 30.3 years. Eight of the patients had had earlier infections. As they were selected to include early untreated initial attacks and chronic stubborn infections, the duration of the present disease varied from five days to four months; in 4 cases it was three months or longer. Three of the patients had received no treatment. Their infections were 5, 7 and 8 days old, respectively. All the other patients had been treated with one or another of the sulfonamide drugs, mostly sulfathiazole. Some of the obstinate cases had received a variety of sulfonamide preparations. Additional therapy in some cases included local instillations of silver preparations or potassium permanganate and artificially induced fever. Neither the duration of the infection nor the kind and duration of previous treatment seemed to make any difference in the response to penicillin.

Complications included acute prostatitis (case 5) and 2 cases of acute prostatitis and epididymitis (one of them, case 1) and 1 case of mild acute arthritis.

METHOD OF TREATMENT

Penicillin was administered by injection of 1 or 2 cc. quantities of aqueous solution into the gluteal muscles. The water used for its solution was sterile, pyrogen free water obtained from the operating room. The total dosage varied from 50,000 to 100,000 Oxford units. The size and spacing of the individual injections varied considerably. Table 1 gives some examples of this variation.

No symptoms or signs of toxic reactions were manifested in any of the patients.

RESULTS

With one exception, every infection was brought to an abrupt termination by the intramuscular administration of penicillin. Within two or three hours after the initiation of treatment and before the course of injections was complete, the urethral exudate underwent a striking change in character and quantity. It became paler, less viscous in consistency and much reduced in quantity. By the 5th or 6th hour it had practically disappeared. Stripping the urethra produced a small drop of clear watery secretion. The following morning no discharge was apparent, and none could be produced by stripping the urethra.

Coincident with the reduction and disappearance of these signs of infection came relief from any subjective symptoms such as local tenderness and pain on urina-

From the Departments of Medicine and Surgery and the A. B. Kuppenheimer Foundation of the University of Chicago.

1. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289-292 (May 29) 1943. Turner, F. B., and Sternberg, F. G.: Management of the Venereal Disease in the Army, ibid. **124**: 133-137 (Jan. 15) 1944. Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin: Observations in One Hundred Cases, ibid. **124**: 611-622 (March 4) 1944. Herrell, W. E.: The Clinical Use of Penicillin: An Antibacterial Agent of Biologic Origin, ibid. **124**: 622-627 (March 4) 1944. Bloomfield, A. L.; Rantz, L. A., and Kirby, M. M.: The Clinical Use of Penicillin, ibid. **124**: 627-633 (March 4) 1944. Mahoney, J. F.; Ferguson, C.; Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea in Men: A Preliminary Report, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525-528 (Sept.) 1943.

2. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

3. Drs. Russell D. Herrold, Frank M. Phifer and Harry C. Rolnick cooperated by referring some of these patients to the authors.

tion. In the 2 cases complicated by epididymitis, the pain and local tenderness disappeared within twenty-four hours, and the swelling subsided considerably in that time and disappeared altogether within one week.

The single exception noted was an especially severe acute hemorrhagic urethritis, which was scheduled to receive a larger course of treatment but in which by error only two doses of penicillin, a total of 60,000 units, was administered. The urethral discharge lessened in amount but never completely disappeared and increased again the next day. It responded, however, to a second course of penicillin (100,000 units) exactly like the other cases.

Cultures.—The time of disappearance of gonococci from the smears and cultures is shown in table 1, which contains illustrative examples of different doses and

TABLE 1.—*Rate of Disappearance of Gonococci from the Anterior Urethra During Treatment with Penicillin Administered by Intramuscular Injection*

	Patients Allowed to Void Urine at Will											
Time in Hours	Case 1			Case 2			Case 3			Case 4		
	Units	Smear	Culture	Units	Smear	Culture	Units	Smear	Culture	Units	Smear	Culture
0	15,000	++++	+++	10,000	++++	++++	10,000	++++	++++	25,000	++++	++++
1	.....	—	+	10,000	++++	++++	10,000	+++	+++	25,000	+	++++
2	15,000	—	—	10,000	+++	+++	10,000	++	+	.....	+	+++
3	.....	—	—	.....	..	..	10,000	—	—	.....	±	—
4	15,000	—	—	.....	..	..	10,000	—	—	.....	—	—
5	.....	—	—	10,000	—	—	.....	..	..	.....	—	—
6	15,000	—	—	.....	..	..	.....	..	..	.....	—	—
7	.....	—	—	10,000	—	—	.....	..	..	.....	—	—
8	15,000	—	—	.....	..	..	.....	—	—	.....	—	—
Next day	.....	—	—	.....	—	—	.....	..	..	.....	..	..

In the tables, units = number of Oxford units of penicillin injected intramuscularly. Time of first injection is designated zero hour.
Smears: Number of gonococci per high power field, ++++ = more than 50, +++ = 25-50, ++ = 10-25, + = 1-10, ± = occasional, — = none found after careful search.
Cultures: ++++ = confluent growth of gonococci, +++ = more than 100 colonies, ++ = 10-100 colonies, + = less than 10 colonies, — = no colonies of gonococci.

TABLE 2.—*Rate of Disappearance of Gonococci from the Anterior Urethra During Treatment with Penicillin Administered by Intramuscular Injection*

	Urine Held During Drug Administration								
Time in Hours	Case 5			Case 6			Case 7		
	Units	Smear	Culture	Units	Smear	Culture	Units	Smear	Culture
0	30,000	++++	++++	30,000	++	++++	25,000	++	++
1	.....	++++	++++	.....	..	..	.....	+	++
2	.....	++	+++	30,000	±	++	25,000	—	+
3	.....	+	+++	.....	—	—	.....	—	—
4	30,000	—	+	.....	—	—	25,000	—	—
5	.....	—	—	.....	..	..	.....	—	—
6	.....	—	—	.....	..	..	25,000	—	—
7	.....	—	—	.....	..	..	.....	..	..
8	.....	—	—	.....	..	..	.....	..	..
Next day	.....	—	—	.....	—	—	.....	—	—

spacing of injections. The beginning of treatment is designated in each case as zero hour, and the times of subsequent procedures are given in terms of hours thereafter. The table also presents the results of the examination of smears and cultures made just before each injection of penicillin. The numbers of gonococci found in the smears and the number of gonococcus colonies developing in each culture are indicated by plus marks.

As shown by the results presented in table 2, the viable gonococci present in the urethra diminished rapidly and disappeared altogether in a very few hours. In fact, the interval between the onset of treatment and the first negative culture in all 15 cases averaged 3.7 hours, and the average length of time from the beginning of treatment to the first negative smear was 3.4 hours.

Cytologic Findings.—Examination of the smears which were made at the time of each culture confirmed the results of the latter and revealed some interesting morphologic changes in appearance of both the leukocytes and the gonococci.

During the second and third hours after the beginning of treatment many of the leukocytes appeared swollen and filled with large vacuoles and their nuclei denser and more deeply stained. A large proportion of the gonococci at this time were swollen, irregular in shape, not uniformly stained, and surrounded by clear zones. These changes can be seen in the photomicrographs. Their significance is being investigated.

SEPARATION OF THE LOCAL AND SYSTEMIC ACTION OF PENICILLIN

Our interest in the mode of action of penicillin led us to question whether its therapeutic effect resulted from the penicillin brought to the tissues by the blood stream (systemic effect) or from the local gonococcidal action of the penicillin secreted in the urine and passed over the urethral mucosa during each micturition. As the 15 patients in the first series (represented by cases 1 to 4) had been allowed to void their urine at will, it was necessary to treat two additional groups of patients differently if we were to ascertain the relative importance of the two actions of penicillin, the systemic and the local. One group consisting of 2 patients was treated solely by urethral instillations of penicillin and the second group by intramuscular injections and the retention of urine during the period of therapeutic response.

THERAPEUTIC RESULTS WITH LOCAL INSTILLATIONS ALONE

The patients were allowed to void, and 4 cc. of penicillin solution was instilled into the anterior urethra and retained for five minutes. Every two hours in 1 case and every hour in the other, smears and cultures

were made of the urethral exudate and another instillation of 4 cc. was made. One patient received 1,000 units every two hours for five injections and the other 3,000 units every hour for seven instillations.

In the first of these 2 cases the smears and cultures became negative after the first injections but were strongly positive on the following morning. In the other case neither the cultures nor the smears became negative at any time.

These 2 cases seemed sufficient to demonstrate the inability of penicillin applied locally to eradicate gonococcic infection from the anterior urethra, and no more attempts were made. Both these patients were successfully treated by intramuscular injections on the following day. The first is case 6 in table 1.

THERAPEUTIC RESULT BY SYSTEMIC ACTION ALONE

The reciprocal experiment designed to eliminate the local action of the penicillin, which washes the surface of the urethral mucosa with each urination, was carried out on 7 patients. They received intramuscular injections, as did those in the first group, but retained their urine for the period of treatment and observation. To make this possible without discomfort they had been instructed to reduce their fluid intake to a minimum the preceding day. In all cases the urethral exudate underwent the same changes in character and disappeared as rapidly as in the cases in the first series, and the smears and cultures became negative at the same rate.

The data on 3 of the 7 patients in this series are presented in table 2. In all 7 the average lengths of time from the beginning of penicillin treatment to the first negative cultures and smear were 3.8 and 3.1 hours respectively. These results are almost identical with those obtained in the first group of cases and indicate that the therapeutic action of penicillin in gonococcic urethritis is systemic rather than a local; that is, it is due to the penicillin brought to the tissues by the blood stream rather than that which passes through the urethral canal in the urine.

RESULTS OF FOLLOW-UP EXAMINATIONS

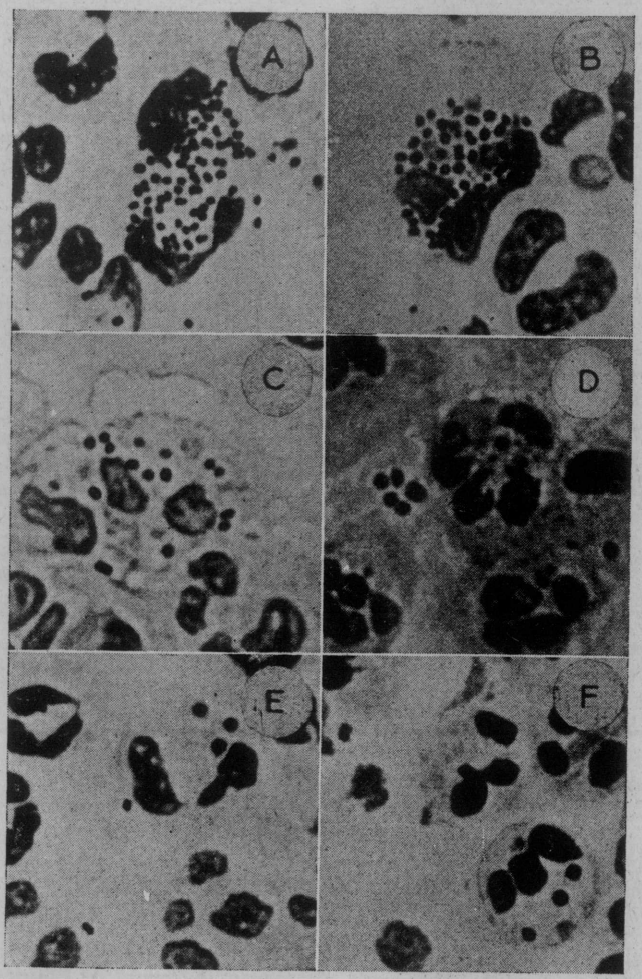
With 1 exception the patients were all followed by a systematic series of follow-up examinations, which began one week after treatment and included prostatic massage in 9 cases and provocative soundings in 2. Six patients were examined after bouts of excessive drinking. In no instance were gonococci found in cultures or smears after the examinations made during the period of treatment.

Two reinfections occurred. Both were regarded as such rather than relapses for the following reasons: One of them (case 1) occurred four months after treatment with penicillin, during which time the patient had been quite free from symptoms and had had four follow-up examinations, each including cultures, all of which were negative. He gave a definite history of exposure to account for his second infection. It was successfully treated with penicillin. Six follow-up cultures since then have all been negative.

The other occurred in case 9 a month after treatment with penicillin, during which time the patient had three follow-up examinations and cultures, all of which were negative, the last one a week before the exposure, which resulted in infection four days later. The reinfection responded promptly to penicillin.

COMMENT

Although only 21 cases were studied in this investigation, the results seem to be sufficiently striking to warrant presentation. The clinical signs and symptoms of urethritis subsided and disappeared with remarkable rapidity, in fact within two to five hours after beginning the administration of penicillin by intramuscular injection. At the same time the number of gonococci recovered by smear or culture from the urethral exudate diminished rapidly to the vanishing point. The interval between the onset of treatment and the first negative culture varied from one to six hours, with an average of 3¾ hours. The rate of disappearance was not



Microscopic appearance of smears stained by Gram's method: *A*, 0 hour (immediately before first injection of penicillin); *B*, 3d hour (after 1st injection of penicillin); *C*, 3d hour; *D*, 2d hour; *E*, 2d hour; *F*, 3d hour.

significantly slowed in those patients who retained their urine throughout the period of treatment, thereby eliminating the local action of penicillin on the urethral mucosa during urination. This finding, together with the failure of the local application of penicillin by instillation in 2 cases, indicated that penicillin is brought to the infected mucosa by the blood stream rather than from the lumen of the urethra.

The precise nature of the gonococcidal action of penicillin is not understood and lies outside the field of this investigation. The peculiar morphologic changes shown by gonococci in smears at the time their numbers were diminishing most rapidly are similar to those which can be produced in vitro by the action of penicillin

in liquid cultures. The large bizarre forms described by some authors working with other species of bacteria have been regarded as indicative of failure of cell division. Other morphologic changes observed in smears of the urethral exudate were the large clear zones surrounding the gonococci and the swollen, vacuolated appearance of the polymorphonuclear leukocytes.

Another finding worthy of note was the prompt disappearance of all evidence of inflammatory reaction which occurred almost simultaneously with the death of the infecting micro-organism and not after an appreciable lag period, as might have been expected. If this phenomenon had occurred only in chronic, sulfonamide resistant patients who had been infected for several months, an explanation might be sought in the possible activity of some humoral immune mechanism which had been brought into play. But the same thing occurred in 3 early cases of five, seven and eight days' duration respectively.

The amount of penicillin administered was 50,000 units in 3 cases, 60,000 units in 2, 75,000 in 2 and 100,000 in the remaining 14 cases. The only failure was an unusually severe infection in which, by error, only 60,000 units was administered. The size and spacing of the individual doses varied but in most cases did not extend over more than five or six hours. The treatment of ambulatory patients in the outpatient clinic was quite as satisfactory as the treatment of hospital patients.

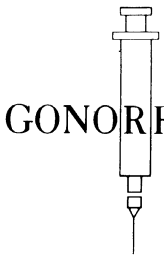
Reports of previous investigators have suggested the necessity of spreading the treatments over periods of twenty-four to forty-eight hours, and some have advised administration by continuous intravenous injection.

Our findings do not indicate that such elaborate and prolonged treatment is necessary to accomplish the desired result, either in acute or in chronic gonorrhea with or without complications.

SUMMARY

Twenty-one cases of gonococcic urethritis including early acute and chronic sulfonamide resistant infections, some with complications, were treated by intramuscular injections of penicillin. The total amount of penicillin did not exceed 100,000 units. It was given in divided doses of various sizes over periods of various lengths, mostly five hours or less.

Frequent examination by smear and culture showed that gonococci disappeared within a few hours after the first injection of penicillin.



THE TREATMENT OF SULFONAMIDE RESISTANT GONORRHEA WITH PENICILLIN SODIUM

RESULTS IN 1,686 CASES

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In May 1943, soon after preliminary evidence of the effectiveness of penicillin in the treatment of gonorrhea was obtained by Mahoney and his co-workers [1] and Herrell, Cook and Thompson,[2] studies were inaugurated by the Surgeon General's Office of the U. S. Army with a view to determining as rapidly as possible time-dosage factors in the penicillin treatment of this disease. The clinical trials were carried out in fifteen selected army hospitals. Altogether, 1,686 patients with sulfonamide resistant gonorrhea were studied.

METHOD OF STUDY

The hospitals participating in the study and the responsible investigators in each are shown in table 1. Similar requirements as to the selection of patients, methods of treatment and criteria of cure obtained in each.

Selection of Patients.—Patients admitted to the study were limited to those fulfilling the following conditions:

1. A clear history of gonorrhea acquired within the past few weeks or months.

2. Typical clinical signs and symptoms of gonorrhea at the time penicillin treatment was begun.

3. Smear and culture positive for gonococci immediately prior to penicillin therapy.

4. Sulfonamide resistant gonorrhea as determined by failure to respond to two or more courses of sulfathiazole or sulfadiazine, each course consisting of at least 20 Gm. of drug administered within a period of five days.

Plan of Treatment.—No patient was started on penicillin treatment until at least five days after the discontinuance of other medications, including sulfonamides. Solutions of penicillin in sterile saline solution or distilled water were prepared daily from the dried powder and were refrigerated at approximately 4 C. when not in use. The individual dose in all cases was either 10,000 or 20,000 Oxford units injected intramuscularly at intervals of three hours, day and night.

As originally projected this study called for the treatment of four groups of patients employing respectively a total dosage of 40,000, 80,000, 120,000 and 160,000 Oxford units, with each group further divided according to whether the individual dose was 10,000 or 20,000 units. The interval of three hours between doses remained constant for all groups.

Later, when it was apparent that favorable results were being obtained with all dosage schedules, two new groups were added, one employing a total dosage of 50,000 units and another employing 100,000. The latter dosage levels were selected largely because of convenience, arising from the fact that the drug was commonly delivered in ampules containing 100,000 units.

It should be emphasized that no other medication and no local treatment whatever were given concurrently with penicillin or during the observation period.

Criteria of Cure.—Patients included in this study were routinely retained in the hospital for at least twenty-one days following the completion of penicillin therapy. During this period the following examinations were performed:

1. Daily examination for evidence of urethral discharge.

2. Daily two glass urine examination.

3. Cultures and smears for gonococci within forty-eight hours after the completion of treatment, and on the seventh, fourteenth and twenty-first days. These bacteriologic studies were made on material obtained from the urethra as long as such material was available. If no urethral discharge was present, cultures and smears were made on prostatic secretion expressed through prostatic massage. The prostatic secretion was examined either directly or after collection in urinary sediment.

TABLE 1.—*Hospitals and Investigators Participating in Clinical Trials*

Hospital	Investigators
Camp Howze	Major G. A. Campbell, Capt. S. Bar
Barnes	Capt. L. A. Gehris, Capt. M. Giffords
Brooke	Col. J. C. Woodland, Capt. F. Geiger
Fort Dix	Major S. L. Raines, Capt. G. S. Barrett
Percy Jones	Capt. L. W. Holladay, Capt. A. W. Frisch
Fitzsimons	Lieut. Col. R. L. Smith, Major D. P. Greenlee
Fort Bragg	Major G. Campbell, Capt. M. Bolus
Lawson	Lieut. Col. E. C. Lowry, Capt. L. W. Hewit
Army and Navy	Lieut. Col. I. S. Wright, Major A. W. Pinkerton
Billings	Major E. H. Burford
Oliver	Major S. T. Flynn, Major J. M. Flood
O'Reilly	Lieut. Col. A. I. Josey, Capt. F. E. Kirshman
Walter Reed	Capt. R. J. Murphy
Lovell	Major V. S. Dick, Capt. R. A. Snyder
Fort Benning	Major C. G. Stillinger, Major R. F. Kelsey

Patients were termed "cured" and released from the hospital if they were asymptomatic and bacteriologically negative on the twenty-first day after completion of treatment. As indicated later, the vast majority of patients became clinically and bacteriologically negative within the first week. "Failure" was determined by the presence of positive smears or cultures on the seventh post-treatment day or at any time thereafter, even though the patient had no urethral discharge. Because of the wide geographic dispersal of patients on release from the hospital, no attempt was made to obtain follow-up examinations beyond the period of hospitalization.

MATERIAL STUDIED

A total of 1,686 patients with sulfonamide resistant gonorrhea were included in the study. All were men between the ages of 18 and 38 years, the mean age being 23. The average duration of infection was fifty-one days. The average amount of sulfonamide drug received prior to penicillin therapy was 58 Gm. Most of the patients included in the study had received some form of local treatment subsequent to sulfonamide therapy. In addition, 236 patients had been treated unsuccessfully with hyperpyrexia, induced either mechanically or by means of typhoid vaccine.

From the Venereal Disease Control Division, Preventive Medicine Service, Office of the Surgeon General, U. S. Army.

Read before the Section on Practice of Medicine at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

1. Mahoney, J. F.; Ferguson, C.; Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea in Men, Am. J. Syph., Gonor. & Ven. Dis. 27: 525, 1943.

2. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. 122: 289 (May 29) 1943.

RESULT OF TREATMENT

Results According to Total Dose.—In table 2 are shown the results of treatment with one course of penicillin, according to the total dose administered. It is evident that remarkably satisfactory results were obtained with all dosage schedules employed. In the first series of patients treated no important differences

TABLE 2.—*Results of Treatment According to Dose of Penicillin (One Course Only)*

Total Dose Penicillin	Number Treated	Failures	Per Cent Cured
160,000	144	3	97.9
120,000	191	9	95.3
80,000	225	10	95.6
40,000	137	12	91.2
100,000	433	15	96.5
50,000	556	77	86.2
Total	1,686	126	92.5

in the final result were noted among the groups treated with 40,000, 80,000, 120,000 and 160,000 units respectively.

When larger series were compared employing a total dose of 100,000 units for the one and 50,000 for the other, the results were significantly poorer with the smaller dose.

It should be pointed out that the dosage schedules used are only approximate, since at the time of these studies potency assays were crude and subject to as much as 25 per cent error in either direction in some instances. Furthermore, batches of the drug were shipped to the various hospitals all over the country and it is believed that in some instances, at least, conditions of shipment such as exposure to excessive heat may have resulted in a loss of potency. It was definitely noted that in certain hospitals using particular lots of penicillin the results were inferior to those of groups treated with the same dosage schedule elsewhere. This was particularly noticeable in the 50,000 unit group, since here the dosage was probably on the borderline of effectiveness and any loss of potency became evident by an appreciable increase in the percentage of failures. In two hospitals certain lots of the drug resulted in a 50 per cent failure rate at the 50,000 unit schedule of treatment. In the same hospitals using the same dosage schedule but with penicillin of different manufacture, the results were similar to those obtained elsewhere. On the other hand, the 91 per cent cure rate obtained in the 137 cases treated with 40,000 units of penicillin may have been due to the use of underassayed drug.

Effect of Size of Individual Dose.—No significant differences in the final results were noted when a given total dose was administered in individual injections of 10,000 or 20,000 units. For example, employing a total dose of 100,000 units, of 261 patients treated with five injections of 20,000 units each, favorable results were obtained in 96.6 per cent, while of 172 patients treated with 10 doses of 10,000 each, exactly the same percentage responded favorably (table 3).

These observations are of very practical importance from a military and probably a civilian standpoint. When the total amount of drug is administered in five doses at three hour intervals treatment is accomplished within a total period of twelve hours, while with ten doses at the same interval treatment must extend without interruption through the night. In situations in which hospitals are understaffed or blackout precautions must be observed, it is advantageous to complete treatment during the daylight hours and largely during the normal working day.

Response to Treatment in General.—The response to treatment was ordinarily dramatic, with prompt disappearance of symptoms and reversal of cultures and smears to negative. The average time for the urethral discharge to disappear or change from purulent to mucoid was two days, although in the majority of cases both objective and subjective improvement was noted within a few hours after the beginning of treatment.

In patients responding to treatment, cultures were almost invariably negative within forty-eight hours, although smears taken within this period occasionally showed degenerated coccoid organisms. Smears of this type were rarely noted after forty-eight hours.

In roughly 20 per cent of the patients a slight intermittent mucoid discharge persisted from one to three weeks, gradually resolving over this period. At first it was thought that this indicated failure of therapy; however, since careful study commonly failed to reveal the presence of gonococci and this slight discharge eventually ceased spontaneously, it is now regarded as a normal finding incidental to the healing process.

Analysis of Failures.—Of the 1,686 patients treated, 126 failed to respond to one course of penicillin. Of these failures 84 became manifest by the end of the first treatment week, 31 during the second and 11 during the third. For the most part the 84 failures during the first post-treatment week were those patients receiving the lower total dosages of penicillin. In these cases the clinical response was not conspicuous. Moreover, while twenty-four to forty-eight hour cultures were usually negative, possibly because of the presence of excreted penicillin, the smears frequently remained positive and cultures became positive within a few days

TABLE 3.—*Results of Treatment (Effects of Size of Individual Dose and Length of Treatment)*

Total Dose	Size of Individual Dose	Length of Treatment, Hours	Number Treated	Number of Failures	Per Cent Cured
120,000	20,000	15	105	3	97.1
100,000	20,000	12	261	9	96.6
80,000	20,000	9	124	8	93.6
Total			490	20	95.9
120,000	10,000	33	86	6	93.0
100,000	10,000	27	172	6	96.5
80,000	10,000	21	101	2	98.0
Total			359	14	96.1

thereafter. The majority of the 31 failures which became manifest during the second post-treatment week responded temporarily to treatment and then relapsed both clinically and bacteriologically. Of the 11 failures appearing in the third post-treatment week, 6 were completely asymptomatic and were judged failures on the basis of bacteriologic evidence. Since these 6 patients were promptly and successfully retreated with penicillin, it is not known whether spontaneous bacteriologic cure would have resulted without the second course of penicillin.

Influence of Duration of Infection.—In 1,154 patients of this series the onset of gonorrhea was less than sixty days prior to the initiation of penicillin therapy, and in 532 infection had been present for longer than sixty days. A successful outcome was observed in 92 per cent of the one group and in 93 per cent of the other, indicating that duration of infection is not an influential factor in determining the response to penicillin therapy.

Influence of Previous Fever Therapy.—In addition to at least two courses of sulfonamides, 236 patients had been subjected to artificially induced hyperpyrexia for sulfonamide resistant gonorrhea. Of these 92.2 per cent responded to one course of penicillin, as compared with a response rate of 92.7 per cent for those who had not had previous fever therapy.

Influence of Race.—Of 139 Negro patients in the entire series of 1,686, 125, or 90 per cent, responded favorably to one course of penicillin, as compared with a favorable response of 92.8 per cent in the white group. This small difference in the results in the two groups is not considered significant.

Response of Patients with Complications.—In general it can be said that the complications of gonorrhea responded well to treatment with penicillin. In most instances improvement began shortly after the penicillin was administered and continued until the patient was well. Of 47 patients with acute epididymitis at the time penicillin therapy was initiated, 43 responded to one course and 4 required a second course. Of 14 patients with severe acute prostatitis 13 responded immediately, while the additional case responded to a second course of penicillin.

Included in this series of patients were 9 who had mild to moderately severe articular involvement associated with a persistent gonococcic urethritis. Presumably the joint lesions were gonococcic in origin. Of these 9 cases 3 responded to one course of penicillin and 2 to an additional course. In 4 cases there was no substantial improvement to two courses of penicillin, although the coexisting urethritis responded satisfactorily.

Not included in this series are 5 patients with sulfonamide resistant gonorrhea and severe acute arthritis, presumably gonococcic in origin, who, because of the severity of the disease, were given considerably larger doses of penicillin. The results were excellent in each case. Among the complications of gonorrhea observed was 1 case of gonococcic conjunctivitis, proved by culture, which responded to 160,000 units, and a case of keratoderma blennorrhagicum, which responded to 120,000 units.

Retreatment of Failures.—Of the total of 126 failures to one course of penicillin 85 were retreated, a total dose of 100,000 units being used in each. Of these, 78, or 91.8 per cent, were cured. In 4 of the 7 cases which failed to respond, a third course of 100,000 units of penicillin was given, with a satisfactory outcome in all. No true instance of penicillin resistance was observed.

Reactions to Treatment.—No serious reaction to penicillin treatment was observed. In 98 patients soreness at the site of injection was noted, but 42 of these patients were in a group of 50 who were treated with one lot of the drug. Other reactions listed were mild fever in 7, slight nausea in 5, headache in 4, chilliness in 4 and dizziness in 3. However, since the conditions of the study required that all untoward signs or symptoms occurring during or immediately after penicillin treatment be recorded, it is probable that in many instances the symptoms noted were coincidental and not true reactions to the drug.

COMMENT

It is evident from the foregoing results that penicillin is remarkably effective in the treatment of gonorrhea. Doses totaling more than 80,000 to 100,000 units appear to offer little advantage over these amounts, and, indeed, the results obtained with 40,000 and 50,000 units are sufficiently good to warrant the use of these total doses when supplies of the drug are limited.

It is quite possible that somewhat better results might be obtained by varying the time-dosage relationship. Perhaps a two hour interval between doses would be more effective than the three hour interval employed in these studies. Likewise, larger initial doses followed by smaller doses might offer advantages over the schemes described here, but these variations appear to be questions of detail rather than ones of major importance.

In this series of cases, penicillin was administered by the intramuscular route, which on the basis of studies by Rammelkamp and Keefer [3] appears to be superior for this purpose to intravenous administration. The practical advantages of intramuscular over intravenous administration are obvious. In order further to simplify the mechanics of treatment a practicable method of prolonging absorption and excretion of penicillin is needed. In this connection experiments are now in progress employing penicillin incorporated in oil vehicles in the hope that satisfactory results may be obtained by the administration of one or two large doses of penicillin.

While at the very onset of these studies it was evident that penicillin was greatly superior to the sulfonamides in the treatment of gonorrhea, it was nevertheless expected that a proportion of cases treated would prove to be resistant. This expectation of penicillin resistance failed to materialize, since all patients in this series subjected to three courses of treatment responded favorably. Furthermore, of the many thousands of soldiers treated for gonorrhea with penicillin during the past six months, instances of penicillin resistance have been extremely rare. The recent report of Cohn and Seijo [4] tends to confirm this observation, since in their in vitro experiments penicillin concentrations of 1 to 10,000 killed all gonococcus strains tested.

The ability of the gonococcus to develop resistance to penicillin through initial exposure to small concentrations of the drug is still undetermined. The evidence afforded by this series indicates that this happens rarely, if at all, since 92 per cent of failures to the first course of treatment responded to a second course. Furthermore, of the 77 cases which failed following initial therapy with the small first course of 50,000 units of penicillin, 57 were retreated with a 100,000 unit schedule, of which 52, or 91.2 per cent, responded favorably. Of the 5 failures to the second course, 3 were given a third course of similar dosage, with satisfactory results in all.

The possibility of penicillin treatment of gonorrhea masking or delaying the appearance of manifestations

3. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425, 1943.
4. Cohn, A., and Seijo, I. H.: The In Vitro Effect of Penicillin on Sulfonamide Resistant and Sulfonamide Susceptible Strains of Gonococci, J. A. M. A. **124**: 1125 (April 15) 1944.

of early syphilis must be borne in mind. While most of the patients in this series were beyond the incubation period of primary syphilis, several cases were observed in which it is possible that penicillin affected the development of early syphilis. The most definite instance was that of a patient with a small ulcer at the frenum, to whom 100,000 units of penicillin was administered before the lesion was studied by dark field examination. The dark field examination was negative the day following and the lesion healed rapidly. Six weeks later a typical dark field positive chancre appeared in the same location. The patient denied further sexual exposure. Because of the known effect of penicillin on Treponema pallidum, patients receiving penicillin therapy for gonorrhea should be observed clinically and serologically for evidence of syphilis for a period of at least three months.

SUMMARY AND CONCLUSIONS

Studies have been carried out in fifteen selected army hospitals with a view toward determining as rapidly as possible time-dosage factors in the treatment of sulfonamide resistant gonorrhea with penicillin. A total of 1,686 patients refractory to at least two courses of a sulfonamide and in some cases to artificially induced fever were treated with total dosages varying from 40,000 to 160,000 Oxford units per case, the individual dose being 10,000 or 20,000 units intramuscularly every three hours.

These studies showed penicillin to be a remarkably effective drug in the treatment of gonorrhea, usually causing disappearance of symptoms and reversal of bacteriologic findings within forty-eight hours. One course of treatment with a dosage of 160,000 units per case effected cures in 98 per cent, 80,000 to 120,000 units in 96 per cent and 50,000 units in 86 per cent. No significant differences in the final results were noted when a given total dose was administered in individual injections of either 10,000 or 20,000 units. Furthermore, little advantage was gained by prolonging the time of treatment schedules beyond twelve hours.

Factors such as duration of infection, previous fever therapy and race appeared to have no effect on the results of therapy.

Of the total of 126 failures to one course of penicillin, 85 were retreated, using a 100,000 unit dosage. Of these, 78, or 91.8 per cent, were cured. Thus, by retreatment of failures with a second course, 99 per cent cures were obtained. No case in the entire series proved to be penicillin resistant.

Complications of gonorrhea responded well to penicillin, although the more serious forms of complications required prolonged treatment with higher dosage.

Reactions to penicillin were inconsequential, and in no instance was it necessary to discontinue treatment for this reason.

Because of the known effects of penicillin on Treponema pallidum, the possibility of masking or delaying the development of early syphilis must be considered.

Finally, it should be recognized that the treatment of gonorrhea has been completely revolutionized in the past few years, first by the introduction of the sulfonamides and, more recently, by the development of penicillin. It is clear that the management of gonorrhea now belongs within the sphere of the chemotherapeutist, and that local treatment is rarely necessary and may do more harm than good.

ABSTRACT OF DISCUSSION

LIEUTENANT COLONEL IRVING S. WRIGHT, M. C., A. U. S.: This compilation of important data represents an encouraging example of cooperation in clinical research. This should encourage others to embark on similar studies when maximum data are needed in the shortest space of time. A few comments based on experiences at the Army and Navy General Hospital and at many hospitals later visited may prove of interest. In some patients, both male and female, the cultures became negative within four to six hours after the initial dose. Certain of these patients had had profuse discharges, with positive cultures for six months or more. The possibility that the excretion of penicillin in the discharge is a factor in inhibiting the culture growth must be considered. Two patients, both men, had had profuse discharges for months. Smears from each were positive in the usual sense of interpretation; that is, many gram negative intracellular diplococci, which could not be differentiated from gonococci, were found. Cultures failed to grow the organism. One of these patients had twenty-seven negative cultures in a laboratory that grew practically 100 per cent positive cultures in the remainder of the gonorrhea patients. These 2 patients were treated with five and eight courses of sulfonamides respectively, with hyperthermia and with two courses of penicillin of 100,000 units each. This therapy had absolutely no effect on the discharge or on the organisms seen in the smears. The findings suggest that the organism may not be a true gonococcus, but that is as far as we are able to go. I should like to ask Colonel Turner whether he knows of other examples of this group. We have tried penicillin in the treatment of rheumatoid arthritis which arose during the acute phase of gonorrhea and continued after the discharge had ceased. The etiologic classification of these cases is difficult. They differ from the so-called acute gonorrheal arthritis reported in the paper under discussion. The treatment of patients with typical rheumatoid arthritis has been disappointing in our hands. The broader implications arising from the findings of this and similar studies cannot be overestimated. Once more the scientific approach is leading the way, but the problems of its application must be carefully considered. This is easy for members of the armed forces and relatively easy for the professional prostitute. Today, however, our great source of infection is from the amateur pick-up, the girl who comes from a surprising cross section of our population. The widespread use of penicillin in this group must be the result of careful but intense educational programs. A note of caution must be raised, however, against the widespread increase of promiscuity which may arise, with its resultant serious dislocations to our social structure.

DR. JOHN F. MAHONEY, U. S. P. H. S.: It would be an error not to call attention again to the point that the use of penicillin in the treatment of gonorrhea may have the effect of masking or greatly altering the symptoms of the invasion of a concomitantly acquired syphilis. As the product becomes more generally available and more generally used, an increasing number of instances of faulty and delayed recognition of the latter disease probably will be encountered. Repeated serologic tests for syphilis for at least two months following treatment appears to offer the best safeguard, and this feature may well become an important part of follow-up work. In much of the early work with penicillin, investigators have been faced with the necessity of working with limited amounts of the product. This has called forth efforts to refine the dosage to a point where the utmost in results would be produced by each unit available. In the future, and especially if the material becomes as plentiful as now appears certain, the concept that "the dangerous dose is the small dose" will probably gain adherents. The objective will then be to use a sufficient amount of the drug to produce a clinical response as rapidly as possible. In view of the nontoxic character of the substance, the utilization of larger amounts may be accomplished without an appreciable risk of producing untoward symptoms. The questions of total dosage, the duration of treatment, the interval between injections and the number of injections cannot be considered as established at the present even in the light of the favorable results which have been recorded in the present report. Products of greater purity and the development of preparations which are absorbed and excreted less rapidly may have the effect of permitting treat-

ment schedules to be utilized which are less burdensome and as effective as those in use at the present. The impact of the therapy on incidence of gonorrhea and especially on the public health approach to the disease forms an interesting field of speculation. Should the experiences of the future confirm the impressions which are inescapable on the basis of the material at hand, then surely control of the disease through the medium of the venereal disease clinic will require reorientation. A different type of facility may be needed to implement the new therapy. That gonorrhea may cease to be of major public health importance in the none too distant future seems to be an entirely reasonable assumption.

LIEUTENANT COLONEL THOMAS H. STERNBERG, M. C., A. U. S.: The existence or development of penicillin resistant cases of gonorrhea has been a possibility of great interest and of some concern to the Army. In the data presented by Colonel Turner it is of interest that no true instance of penicillin resistant gonorrhea was encountered, provided three courses of penicillin were administered. Since the termination of these studies, many thousands of individuals with gonorrhea have been treated with penicillin in various army hospitals, and particular efforts have been made to uncover cases not responding to adequate penicillin therapy. While such cases are not infrequently reported, investigation reveals that usually they have been labeled as penicillin resistant on the basis of either inadequate penicillin treatment or persistence of a mucoid discharge, which is bacteriologically negative and later proves to be nongonococcic in origin. I have just completed an extensive trip throughout the southwestern portion of the country, visiting numerous army hospitals routinely using penicillin in the treatment of gonorrhea. During these visits the relatively few instances of so-called penicillin resistant gonorrhea were investigated. In most instances the total dosage of penicillin did not exceed 200,000 units, and in no case was it possible to isolate a strain of gonococcus which was resistant in vitro to the more concentrated dilutions of penicillin. To date the army experience indicates that the incidence of truly penicillin resistant gonorrhea is at least unusual and further suggests that the term penicillin resistant gonorrhea should be applied cautiously and only after failure to respond to comparatively large doses of penicillin as determined by adequate clinical and laboratory studies.

DR. ALFRED COHN, New York: May I report the essential findings of a study on penicillin therapy in 100 women and 20 men who suffered from sulfonamide resistant gonococcic infections. This study is still in progress in collaborations with my associates Dr. Borris A. Kornblith and Dr. Isaak Grunstein. The 100 women were hospitalized for penicillin treatment at the gynecologic service of Dr. Howard C. Taylor Jr. at Bellevue Hospital. Our studies were directed first toward evaluating the optimal total dosage and second to determine an adequate time schedule for cure. The results of administering various amounts of penicillin in the female group point to the fact that a minimum total dosage of 100,000 Oxford units intramuscularly is both necessary and sufficient for bacteriologic cure. The time schedule that was found to be most satisfactory without failure averaged between six and nine hours. The penicillin was administered either in four intramuscular injections of 25,000 units each or by an initial injection of 50,000 units followed by two injections of 25,000 units each. Twenty ambulatory men who suffered for a number of months from sulfonamide resistant gonococcic infections with chronic complications, 18 with prostatitis and 2 with epididymitis, were treated at the Central Clinic of the Department of Health, City of New York. A total dosage of 100,000 Oxford units of penicillin was administered intramuscularly to all 20 patients. Two schedules of therapy were employed: 1. An initial injection of 50,000 units was followed by two subsequent injections of 25,000 units each at three hour intervals; total time of therapy, six hours. 2. An initial injection of 40,000 units was followed by two subsequent injections of 30,000 units each at two hour intervals; total time of therapy, four hours. Thus far no failure of therapy has been encountered in any of these 20 patients who have been followed up by repeated urethral and prostatic smears and cultures over a period of between two and four weeks. Urethral cultures taken at one hour intervals after the initial injection of penicillin became negative between the third and fourth hour after treatment was initiated. Smears of urethral discharges showed involution and disintegration of the gonococci and leukocytes by the end of five hours in most cases. Our findings indicate that an adequate minimal dosage of 100,000 units of penicillin administered over a period of from four to six hours to ambulatory patients is a satisfactory routine in the treatment of sulfonamide resistant gonococcic infection.

COLONEL THOMAS B. TURNER, M. C., A. U. S.: In reply to Colonel Wright's question about observing the organisms which do not grow out on culture, we have observed a similar thing in our hospitals. We assume that it is due to the presence of penicillin and that they do not grow out.

URGE SPECIAL MICROSCOPIC TESTS BEFORE TREATING GONORRHEA WITH PENICILLIN

Dr. C. J. Van Slyke of the Public Health Service Venereal Disease Research Laboratory, Staten Island, N. Y., and Dr. S. Steinberg of the U. S. Marine Hospital, New York City, recently reported the possibility of overlooking syphilis symptoms in gonorrhea patients treated with penicillin in patients who have both diseases. This can be avoided, however, if special microscopic tests are made before penicillin is used, and if blood tests are made after penicillin treatment has been completed. The masking effect of penicillin on syphilis symptoms is due to the fact that the relatively small amounts of penicillin required to cure gonorrhea are sufficient to cause disappearance of the spirochete germs of syphilis from syphilis lesions, although not sufficient actually to cure syphilis. When serum from the lesions is examined under a special microscope after penicillin has been used, the spirochetes will not be seen, and the examining doctor may be misled to conclude that the patient was not infected with syphilis. Making the microscope examination before treatment with penicillin prevents this possible error. A blood test for syphilis some time after the treatment of gonorrhea has been completed is advisable, because blood tests do not always reveal very new syphilis infections immediately after they have been acquired.

PENICILLIN FOR THE TREATMENT OF CHEMORESISTANT GONORRHEA IN THE FEMALE

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With the advent of the sulfonamides the eradication of gonorrhea from the human race seemed quite likely. The promise contained in the earlier reports for the treatment of gonorrhea with sulfonamides, however, has not been completely fulfilled. Moreover, the therapeutic results for the female have not been so good as for the male, because of vagaries in her anatomic makeup. The physiologic mucoid alkaline secretions of the cervix aid and abet the growth of the gonococcus; the anatomic arbor-like arrangement of the cervical glands conceal this micro-organism in protective depots for survival. Even against such odds the sulfonamides brought under control a very large number of women with acute and chronic gonorrhea. The exceptions were the females who harbored resistant strains or in whom, because of chronicity of long duration, the gonococcus had taken tenacious hold in the subepithelial layers of the mucosa lining Skene's ducts, Bartholin's glands, the endocervix or the fallopian tubes. Chronicity and chemoresistant strains proved a barrier that sulfonamides frequently failed to overcome.

The early reports of 85 per cent cures of gonorrhea with sulfonamides no longer hold, for the persistence of certain strains which have gradually permeated a selected stratum of the populace has reduced the effectiveness of sulfonamides to little better than 55 per cent. It is further true that improved bacteriologic technics have helped to uncover many carriers of gonococci in spite of complete absence of clinical signs and symptoms.[1] The sign on the door, namely a purulent urethral discharge, is not a worthy criterion on which to base a clinical diagnosis of gonorrheal infection. Too frequently, particularly in the old infected case, is it lacking. Too frequently, in spite of a frank urethral discharge, gonococci are not to be found and other organisms, among them the trichomonad, are common offenders.

Pelouze, the prophet of doom in the sulfonamide wilderness, was haunted by the specter of the carrier and the chemoresistant strain. He continually exhorted medical authorities to beware of the false security into which we have been lulled by sulfonamides. Shall we be lulled into a similar state of complacency with penicillin? This much is known: that penicillin is an extremely effective bacteriostatic and bactericidal agent, many times more powerful and efficient than the sulfonamides. Much had been expected of other drugs in the past. Penicillin offers much now because it is effective against sulfonamide resistant strains. Will penicillin fast strains develop? Time is of the essence.

MATERIAL

This series comprises 551 females ranging in age from 3 to 48 years, studied at the Southeastern Medical Center during a given period. Of this number 54 per cent were of the Negro race and 46 per cent were white. It is revealing and surprising that 82 per cent of the white females had bacteriologically proved gonorrhea, while a similar diagnosis could be established in only 41 per cent of the Negro women (table 1). Although, comparatively, a far greater number of Negro than white women had clinical evidence of gonorrhea, such as urethritis, induration of the broad ligaments, scarring of the cul-de-sac or pelvic inflammatory masses, nevertheless, the diagnosis was confirmed bacteriologically twice as frequently in white females. Each patient had a minimum of six cultures in an effort to establish a diagnosis of gonorrhea.

One hundred and nine patients in this series were treated with penicillin, and of these 93 per cent had had one or more courses of sulfonamides. Several gonorrheic females received penicillin without a full course of sulfonamides because of sensitivity to them. Penicillin was administered on a few occasions without a prior course or completion of a course of sulfonamides because of certain considerations, such as pelvic peritonitis or acute exacerbation of a chronic salpingitis. Penicillin was dissolved in a few cubic centimeters of distilled water or saline solution and administered intramuscularly in 10,000 to 20,000 units at three hour intervals until 60,000 to 150,000 units had been administered. One 3 year old girl received a total of 25,000 units and two 9 year old girls each received 50,000 units. One patient had concomitant granuloma inguinale and received 1 million units (table 2). There were no untoward reactions resulting from penicillin therapy.

TABLE 1.—*Analysis of Patients Treated with Penicillin*

Race	Females Studied for Venereal Diseases		Bacteriologically Proved Gonorrhea		Penicillin Treated	
	Number	Percentage	Number	Percentage	Number	Percentage
White.....	258	46.8	213	82.1	84	39.4
Negro.....	293	54.2	122	41.6	25	20.5
Total....	551	100	335	60.8	109	32.5

TABLE 2.—*Dosage and Results of Penicillin Therapy*

Dosage of Penicillin	No. of Courses	Relapses
25,000 units.....	1*	0
50,000 units.....	2†	0
60,000 units.....	31	1
75,000 units.....	3	0
100,000 units.....	1	0
120,000 units.....	2	0
150,000 units.....	70	4
250,000 units.....	2	0
300,000 units.....	1	0
1,000,000 units.....	1	0
Total.....	114‡	5

* Age 3 years.
† Two 9 year old girls.
‡ In all, 109 patients; 5 received a second course of penicillin therapy.

It is of interest that proportionately one and one-half times as many white females received penicillin as did Negro females. Following penicillin therapy four or more cultures were taken in 85 per cent of the cases. Cultures were taken daily for the first few days and then at intervals of one, two or more days. On the average 6 to 15 cultures were obtained in the greater number of instances (table 3). In 3 instances follow-up cultures were not obtained, as the patients were sent back for observation to the referring agency immediately after therapy and reports were not available at the time of writing. Five patients received a second course of penicillin because positive gonococcus cultures were obtained after a lapse of five or more days following

1. Koch, R. A.; Mathis, E. N., and Geiger, J. C.: Ven. Dis. Inform. **25**: 35, 1944.

the administration of the first course. One of these, however, was not considered as a relapse but rather as a reinfection. The second round of penicillin varied from 120,000 to 300,000 units. These patients remained bacteriologically negative during the period of observation following the second course of therapy and were dismissed after 6 to 12 cultures as bacteriologically negative for gonorrhea.

The analysis of statistical data in this series reveals two important facts that require further study:

1. A laboratory diagnosis of gonorrhea was established in twice as many white as Negro patients, although the ratio of white to Negro in this series was practically 1:1.

2. Proportionately one and one-half times as many white patients as Negroes received penicillin therapy because of chemoresistance to sulfonamides.

Several questions arise:

1. Is a bacteriologic diagnosis more readily made in white gonorrheic women?

2. Are gonorrheic Negro females more responsive to sulfonamides?

3. Is there a racial factor?

Certain facts must be considered before drawing conclusions. White women are more apt to be seen during the acute phase of gonorrhea, and bacteriologic proof is probably easily obtained during this period. Then again, chronicity of long duration in the Negro group, as evidenced by chronic pelvic inflammatory disease, makes for greater difficulty in establishing laboratory proof of gonorrhea. Failure to obtain a positive gonococcus culture in such cases does not constitute a priori evidence of absence of gonorrhea. In 3 Negro females in whom gonorrhea was suspected, positive cultures were obtained only after the thirteenth, seventeenth and twenty-fourth culture respectively.

TABLE 3.—*Cultures Following Courses of Penicillin*

	None	1-3	4-5	6-10	11-15	16-20	21-25
White.....	3	12	10	38	21	2	1
Negro.....	0	2	2	13	7	1	2
Total.....	3	14	12	51	28	3	3

Are sulfonamides more specific for gonorrhea in the Negro race? It is the opinion in military circles that this is so, and this view is shared by Pelouze.[2] This phenomenon may be more apparent than real and is worthy of further study. If such a racial factor exists it may explain the proportionately larger number of white females for whom the administration of penicillin was required because of chemoresistance to sulfonamides. We feel, however, that this discrepancy is not a real one. The study of the Negro female for a longer period of time, under more rigid tests, such as slight cauterization of the cervix, mild dilatation of the cervical os and repeated pelvic examinations, may yield a greater number of positive cultures in this group during the carrier and asymptomatic state.

ANALYSIS OF RESULTS WITH PENICILLIN THERAPY

Following penicillin therapy the cultures obtained within twelve to twenty-four hours usually were negative. In 9 instances positive cultures were obtained twenty-four hours after penicillin, in 3 after forty-eight hours, in 3 after seventy-two hours and in 4 after ninety-six hours. Patients in whom a positive smear or culture was obtained after the fifth day were considered to be therapeutic failures. In 4 patients positive cultures were obtained on the fourth and ninth days, fifth and seventh days, sixth and ninth days and the eighth day respectively. In 2 others positive smears but negative cultures were obtained, in 1 on the fourth and eighth days and in the other on the tenth day. In reality, 6 patients gave evidence that the gonococcus was not eradicated by the fifth day following penicillin. Positive cultures were obtained in 5 other patients who received penicillin therapy on being checked at various intervals by the referring agency after their dismissal from the hospital. Positive cultures were obtained on the tenth, seventeenth, twenty-first, twenty-fourth and sixtieth days respectively. In each instance it was believed that reinfection rather than a relapse occurred.

It must be said that, following penicillin, urethral discharge and symptoms of vaginitis, salpingitis and pelvic peritonitis frequently abate within twenty-four to forty-eight hours. On the other hand, purulent urethral and cervical secretions continued in many despite absence of bacteriologic proof of gonococcic infection.

CONCLUSIONS

Penicillin is an effective drug for the therapy of chemoresistant gonorrhea in the female. One hundred and nine patients received courses of penicillin; of these, 84 were white women and 25 were Negroes. Five hundred and fifty-one women (46 per cent white and 54 per cent Negroes) were studied for venereal diseases and in 61 per cent laboratory evidence to support the diagnosis of gonorrhea was obtained. Proportionately, one and one-half times as many white women received penicillin for chemoresistant gonorrhea. The impression that Negro women are more responsive to sulfonamides is more apparent than real. During the period of observation in this series, therapeutic failures were obtained in 5 women following penicillin. A favorable response was obtained after a second course of therapy.

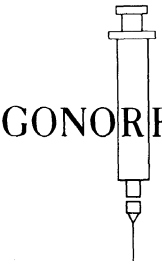
The excellent results that are being obtained now with penicillin will not engender, it is hoped, too great a degree of optimism.[3] The dosage of penicillin should not be reduced to the minimum necessary for good results. It should be maintained at a sufficiently high level so that the development of penicillin resistant strains may be thwarted.[4] To this end it is recommended that 150,000 units be used, although good results may be obtained with as little as 60,000 units. A warning note is sounded that asymptomatic carriers may develop and that penicillin resistant strains of gonococci may appear.

2. Pelouze, P. S.: Ven. Dis. Inform **25**: 76, 1944.

3. Cohn, A.; Studdiford, W. E., and Grunstein, I.: Penicillin Treatment of Sulfonamide Resistant Gonococcic Infections in Female Patients, J. A. M. A. **124**: 1124 (April 15) 1944. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, ibid. **122**: 289 (May 29) 1943. Cook, E. N.; Pool, T. L., and Herrell, W. E.: Proc. Staff Meet., Mayo Clin. **18**: 433 (Nov. 17) 1943. Mahoney, J. F.; Ferguson, C.; Buchholtz, M., and Van Slyke, C. J.: Am. J. Syph., Gonor. & Ven. Dis. **27**: 525 (Sept.) 1943. Robinson, N. J.: Brit. M. J. **2**: 635 (Nov. 20) 1943. Van Slyke, C. J.; Arnold, R. C., and Buchholtz, M.: Am. J. Pub. Health **33**: 1393 (Dec.) 1943. Penicillin in War Wounds: A Report from the Mediterranean, Lancet **2**: 743 (Dec. 11) 1943; The Treatment of War Wounds with Penicillin, Brit. M. J. **2**: 755 (Dec. 11) 1943. Strauss, H.: Am. J. Obst. & Gynec. **47**: 271 (Feb.) 1944.

4. Mahoney, J. F.: Communication to Medical Director, Venereal Disease Division, United States Public Health Service.

From the Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of Louisiana.



CURE BY PENICILLIN FOLLOWING REPEATEDLY UNSUCCESSFUL SULFONAMIDE THERAPY IN A PREGNANT WOMAN WITH GONORRHEA

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PENICILLIN therapy has already been reported in a large series of cases by various investigators. In this country, Keefer and his associates have published a notable series covering a variety of infections. Their report included 129 gonorrheal cases treated by Mahoney and his associates in the United States Public Health Service, seventy-five of which have already been reported. To date Mahoney and Van Slyke have treated 179 cases.

It is, therefore, with humility that I present this single patient but I feel justified in doing so because the case has certain unusual aspects and was most carefully checked culturally and clinically during and after treatment. The report is also unique in that there was no alternative therapy possible. We know of no similar case noted in such detail.

F. C., female, white, single, nullipara, 21 years of age, was admitted to the Kingston Avenue Hospital April 16, 1943, pregnant six and one-half months, with a cervical culture positive for the gonococcus. The cervical smear was negative. Urethral smear and culture were negative, as was the blood Wassermann.

The findings after admission, however, disclosed a profuse purulent urethral discharge with smears and cultures positive for the gonococcus. Skene's ducts were thickened. The left Bartholin's gland was the size of a cherry, while the right was normal. Condylomata accuminata about a quarter of an inch in diameter were present on the labia majora. The vaginal walls were inflamed and trichomonads were found in the discharge. The cervix was bluish with small erosions on both lips. There was a profuse mucopurulent discharge which disclosed gonococci on both smear and culture. The uterus was soft and enlarged to two fingers-breadth above the umbilicus, and the fetal parts were easily outlined. Urine analysis, blood count and sedimentation rates were normal.

On the day following admission she was started on a course of sulfathiazole. This consisted of four grams of the drug given daily for seven days. Lactic acid douches were given for her trichomonas infection. On April 26, and 28, gonococci were found in smears and cultures of the urethral and cervical discharges. Clinically, the urethritis and cervicitis showed no improvement.

On May 5, she was started on a course of four grams of sulfadiazine and sixteen grams of sodium bicarbonate daily for four days. Gonococci persisted in both the urethra and cervix and the clinical picture was unchanged.

On May 13, she was given three grams of sulfapyridine daily for ten

days. The urethritis and cervicitis persisted and gonococci were still found in cultures from each.

Having failed to effect a cure with sulfathiazole, sulfadiazine and sulfapyridine and fever therapy being contraindicated because of the pregnancy, it was decided to administer penicillin. We were fortunate to secure 88,000 Oxford units.* On June 9, administration of the drug by continuous intravenous drip was begun. Penicillin (8800 units) were dissolved in 1,000 c.c. of normal saline and repeated every six hours. The intravenous administration was continued over a period of sixty hours. The patient was kept on a soft diet and fluid intake and output were charted. Temperature, pulse and respiration remained normal. Cultures and smears were taken from the cervical and urethral discharges at 3- to 6-hour intervals during the penicillin treatment. In three hours, after 4,400 Oxford units of penicillin had been given, the first cultures were taken and found to be negative. Thereafter sixteen consecutive cultures and smears from both the urethra and cervix remained negative. Clinically, the patient improved and ten days after completion of penicillin therapy, she was sent home free of gonococcus infection. The cervical erosions were also almost completely healed.

On July 4, she was admitted to another hospital at term in active labor. Twenty-two hours later she was delivered spontaneously of a normal female infant weighing 5 pounds, 12 ounces. Puerperium was uneventful. Smears and cultures taken from the baby's eyes were negative for gonococci.

On August 11, 23, 25, and September 8, the patient returned for post-partum checkups. She showed the usual post-partum findings, with no evidence of gonorrhea. Cultures and smears from both urethra and cervix were negative at these times making a total of twenty consecutive cultures and smears.

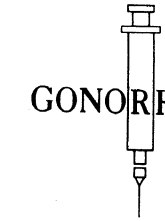
Comment

This patient was refractory to sulfathiazole, sulfadiazine and sulfapyridine. Fever therapy was considered to be contraindicated because of the risk involved. She responded dramatically to penicillin and remained culturally and clinically free of the disease despite the provocation of delivery. The child likewise showed no evidence of infection.

Although this is but a single case and one hesitates to draw conclusions, it is quite possible that further experience will disclose that smaller dosage is effective in gonorrhea. Extensive studies on the use of penicillin in sulfonamide refractory individuals has so far been limited to the male. It is well known that the more scientific study in gonorrhea resolves itself about the female who is the principal disseminating factor of the infection. Moreover, the presence of such naturally occurring provocative tests as menstruation and pregnancy enhance the value of female studies. It is hoped that the means will soon be available for such clinical evaluation.

Penicillin therapy was effective in producing a rapid laboratory and clinical cure of a sulfonamide-refractory pregnant individual, in whom fever therapy was contraindicated. The baby likewise was free from infection.

*The penicillin was furnished by Charles Pfizer & Company, Brooklyn, N. Y.



PENICILLIN IN THE TREATMENT OF OPHTHALMIA NEONATORUM

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Although the sulfonamides have been of great value in the treatment of ophthalmia neonatorum, certain problems have arisen in connection with their use which seemed to justify a study of the effects of penicillin.

For several years the Illinois Department of Public Health has provided hospitalization and treatment for patients with ophthalmia neonatorum. The plan provided for immediate hospitalization of the infant in a centrally located hospital where the services of an ophthalmologist and a pediatrician were available. The infants were treated with sulfonamides orally and with irrigations locally. Although no blindness resulted in some 35 cases so treated, it was found that many infants were either intolerant to the sulfonamides or quickly became resistant. Prolonged hospitalization usually was necessary before the infant could be discharged as clinically and bacteriologically cured.

STUDY

Through the courtesy of the Committee on Chemotherapeutics and Other Agents of the National Research Council, a limited supply of penicillin was made available to study its effect on ophthalmia neonatorum.

Of the 8 cases included in this study, 5 showed gram-negative intracellular diplococci on smear and organisms giving a positive oxidase reaction and fermentations typical of gonococci on culture.

Two cases showed gram-negative intracellular diplococci on smear and oxidase positive colonies of gram-negative diplococci on culture. The organisms isolated from these two cultures failed to grow on subculture.

In 1 case the etiologic agent could not be determined, although the clinical findings were typical of ophthalmia neonatorum (case 7).

Because of the lack of precedent it was necessary at the beginning of the study to outline more or less arbitrary procedures with respect to both the dosage of penicillin and the criteria of cure.

Ten thousand units of penicillin injected intramuscularly at intervals of three hours for a total of six injections was selected as the original treatment schedule. Later this was felt to be inadequate and the dosage was adjusted individually for each case (table 1).

The criteria of cure chosen were (*a*) absence of clinical activity, (*b*) three consecutive negative smears for gram-negative intracellular diplococci and (*c*) three consecutive negative cultures for gonococci.

All patients received instillations of 0.5 per cent atropine sulfate and irrigations of sterile water during the acute clinical phase of the infection.

REPORT OF CASES

CASE 1.—A Negro girl born Nov. 19, 1943, with onset November 20, admitted November 23, received a total of 39 grains (2.5 Gm.) of sulfadiazine in several courses together with 2 per cent sulfathiazole solution irrigations in both eyes between the date of admission and Jan. 8, 1944. Sulfadiazine was stopped because of persistent vomiting. Smears and cultures from both eyes were positive for gonococci on January 8, and examination revealed moderate swelling and injection of both conjunctivas with a moderate amount of purulent exudate. The corneas were normal. The patient was given 60,000 units of penicillin intramuscularly over a fifteen hour period. Definite clinical improvement was noted at the end of twenty-four hours; there was no further discharge. Both eyes were clinically normal within three days and remained so thereafter. Cultures and smears became negative on the 2d day following completion of penicillin therapy. Except for one positive culture from the right eye on the 3d day, all cultures and smears remained negative.

CASE 2.—A white boy born Dec. 10, 1943, with onset December 22, admitted Jan. 10, 1944, received no treatment prior to admission other than silver nitrate prophylaxis at birth. Examination revealed moderate redness and swelling of both eyes externally. The conjunctivas were injected, and a frankly purulent discharge was present bilaterally. The corneas were clear. The patient received 60,000 units of penicillin intramuscularly during a fifteen hour period. Because of persistent clinical and laboratory findings a second course of 90,000 units (15,000 every three hours) was given on the 5th day of hospitalization but failed to effect any improvement. A short course of sodium sulfadiazine during the 13th to 16th hospital days likewise failed to elicit any response. On the 23d and 24th days a third course of penicillin was administered, 20,000 units for six doses followed by 10,000 units for six doses. The conjunctivitis continued unabated, and smears and cultures remained positive. Recovery finally occurred after the use of sulfonamides combined with foreign protein therapy.

CASE 3.—A Negro boy born Jan. 12, 1944, with onset January 17, admitted January 18, had been given silver nitrate prophylaxis at birth and boric acid solution irrigations following the onset. Intense swelling and redness of both eyes externally and pronounced chemosis and injection of the palpebral conjunctivas with a frankly purulent exudate were noted on admission. No corneal involvement was found. Over a fifteen hour period 120,000 units of penicillin was administered intramuscularly. Considerable improvement occurred in both eyes within eight hours after the beginning of therapy. Chemosis and injection gradually subsided, so that both eyes appeared normal on the 6th day of hospitalization and remained so thereafter. Following treatment, smears failed to show any intracellular diplococci and all cultures were negative.

CASE 4.—A white girl born Jan. 12, 1944, with onset January 27, admitted January 28, had been treated with silver nitrate at birth. On admission the right eye showed moderate swelling externally, a purulent discharge and injection and chemosis of the conjunctiva. The only involvement of the left eye consisted of slight conjunctival injection. The corneas were clear bilaterally. Initial smears and cultures revealed both gonococci and Haemophilus influenzae. The patient received 180,000 units of penicillin intramuscularly over a period of thirty-four hours (6 doses of 20,000 units followed by six doses of 10,000 units). Definite improvement was noted in nine hours, and both eyes were clinically normal on the 4th hospital day and remained so. Following the initial laboratory findings

From the Illinois Department of Public Health, Roland R. Cross, M.D., Director.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

all cultures were negative for gonococci, and smears failed to show any intracellular gram-negative diplococci. Organisms resembling Haemophilus were seen in small numbers in both smears and cultures periodically throughout observation.

CASE 5.—A Negro girl born Jan. 31, 1944, with onset February 3, admitted February 4, with delivery by a midwife, received no treatment prior to admission. The left eye showed external swelling and redness with a frankly purulent discharge The left palpebral conjunctiva was injected and chemotic. There were minimal findings in the right eye. The corneas were clear bilaterally. During thirty-six hours 180,000 units of penicillin was administered intramuscularly. Improvement was noticeable after the 2d injection, and the eyes were practically normal twenty-one hours after the beginning of therapy. All cultures were negative after completion of therapy, and smears failed to show any intracellular gram-negative diplococci.

CASE 6.—A Negro boy born Jan. 23, 1944, with onset January 28, admitted February 4, had been given only silver nitrate prophylaxis at birth. External redness and swelling, chemosis and purulent discharge were all present in the left eye. Minimal findings were seen in the right eye. The corneas were clear bilaterally. Initial smears were typical for gonococci in the right eye, and a culture revealed oxidase positive colonies of gram-negative diplococci which failed to grow on transplants and could not therefore be confirmed. The patient received

TABLE 1.—*Results of Treatment of Ophthalmia Neonatorum with Penicillin*

Case No.	Duration of Infection, Days	Etiologic Agent	Total Penicillin, Units	Beginning of Improvement, Hours	Clinical Cure, Days	Laboratory Cure, Days	Final Results
1	47	N. gonorrhoeae	60,000	24	3	9	Satisfactory
2	20	N. gonorrhoeae	330,000*	..	..	..	Unsatisfactory
3	2	N. gonorrhoeae	120,000	9	6	7	Satisfactory
4	2	N. gonorrhoeae, H. influenza (?)	180,000	9	4	6	Satisfactory
5	2	N. gonorrhoeae	180,000	6	6	24	Satisfactory
6	8	N. gonorrhoeae(?)	180,000	9	5	8	Satisfactory
7	4	(?)	230,000	..	..	..	Unsatisfactory
8	25	N. gonorrhoeae(?)	240,000	9	5	7	Satisfactory

* 60,000 units 1st day, 90,000 units 4th day, 180,000 units 22d and 23d days.

180,000 units of penicillin intramuscularly during a thirty-two hour period. At the time of the 4th injection definite clinical improvement was noted and by the 5th hospital day both eyes were clinically normal. All subsequent smears and cultures were negative following completion of therapy.

CASE 7.—A white boy born Feb. 21, 1944, with onset February 28, admitted March 1, had received silver nitrate prophylaxis at birth and instillations of mild protein silver during the three days following onset. The right eye was moderately involved with external redness and swelling, inflammatory chemosis and a purulent discharge. Slight conjunctival findings were present in the left eye. No gonococci were found in the initial smears or cultures, but in the latter several colonies of diphtheroids were isolated. These proved to be avirulent in guinea pigs. There were no other findings which helped to determine the etiologic agent, and smears taken from the child's mother proved negative for gonococci. Penicillin was administered intramuscularly every three hours, 15,000 units in each of six doses followed by 10,000 units for fourteen doses (total 230,000 units). Specific therapy was prolonged in this case because of its failure to effect adequate improvement in clinical findings at the end of fifteen hours. At the completion of therapy moderate improvement was noted, but for the next thirteen days the condition remained static and complete recovery was not achieved. Following a short course of sodium sulfadiazine during the 17th to 19th hospital days, both eyes quickly returned to normal. Smears and cultures failed to reveal any significant organisms throughout the entire period of observation.

CASE 8.—A white boy born Feb. 19, 1944, with onset February 22, admitted March 17, concerning whose treatment prior to admission no information was available other than silver nitrate prophylaxis at birth, exhibited a bilateral purulent conjunctivitis at the initial examination. The conjunctival surfaces of the upper lids were granular. The corneas were not involved. Initial smears were typical for gonococci, and culture revealed oxidase positive colonies of gram-negative diplococci, which failed to grow on subcultures and could not therefore be confirmed. The patient received 20,000 units of penicillin intramuscularly every three hours for twelve doses (total 240,000 units). Definite clinical improvement was noted

TABLE 2.—*Results of Smears and Cultures During and Following Penicillin Therapy*

Hospital Day	Case 1 S	Case 1 C	Case 2 S	Case 2 C	Case 3 S	Case 3 C	Case 4 S	Case 4 C	Case 5 S	Case 5 C	Case 6 S	Case 6 C	Case 7 S	Case 7 C	Case 8 S	Case 8 C
Admission	P	P	P	P	P	P	P	P	P	P	P	P*	N	N	P	P*
9th hour	N	P	P	P	..	..	D	N	D	N	D	N	N	N	P	N
2.....	N	P	..	..	N	N	D	N	D	N	D	N	N	N	N	N
3.....	N	N	D	N	N	N	N	N	D	N	N	N	..	..	..	..
4.....	D	P	D	N	D	N	N	N	..	..	..	..	N	N	N	N
5.....	N	N	N	N	N	N	..	..	..	..	..	..	N	..	..	..
6.....	..	..	N	N	N	N	N	N	..	..	..	..	N	..	..	..
7.....	..	..	N	N	N	N	..	..	D	N	N	N	..	N	N	N
8.....	N	N	..	..	N	N	..	..	D	N	N	N	..	..	..	..
9.....	N	N	..	..	..	..	..	..	..	..	..	..	..	..	..	..
10.....	..	..	..	..	..	..	N	N	..	..	..	..	..	N	..	..
11.....	..	..	N	P	..	..	..	..	..	..	..	..	..	..	..	..
12.....	..	..	..	..	N	N	..	..	..	..	..	..	..	..	..	..
13.....	..	..	N	N	N	N	..	..	..	..	..	..	..	..	..	..
14.....	..	..	N	P	D	N	..	..	..	..	..	..	..	N	..	..
15.....	..	..	N	N	..	..	N	N	..	..	..	..	..	N	..	..
16.....	..	..	..	..	N	N	D	N	D	..	..	..	..	..	..	..
17.....	..	..	..	..	D	N	..	..	D	..	..	..	..	..	..	..
18.....	..	..	..	..	N	N	..	..	D	..	..	..	..	..	..	..
20.....	..	..	N	P	D	N	..	..	..	..	..	..	..	..	..	..
21.....	..	..	D	P	N	N	..	..	..	..	..	..	..	..	..	..
22.....	..	..	D	P	..	..	..	..	N	..	..	..	..	..	..	..
23.....	..	..	..	..	..	..	..	..	N	..	..	..	..	..	..	..
24.....	..	..	..	..	..	..	D	..	N	N	..	..	..	..	..	..
25.....	..	..	..	..	D	N	D	..	..	..	..	..	..	..	..	..
26.....	..	..	..	..	D	N	N	N	..	..	..	..	..	..	..	..
27.....	..	..	N	N	..	..	..	..	..	..	..	..	..	..	..	..
28.....	..	..	D	N	..	..	..	..	..	..	..	..	..	..	..	..
29.....	..	..	N	P	..	..	..	..	..	..	..	..	..	..	..	..
30.....	..	..	..	..	..	..	N	N	..	..	..	..	..	..	..	..
31.....	..	..	..	..	..	..	N	N	..	..	..	..	..	..	..	..
32.....	..	..	..	..	..	..	N	N	..	..	..	..	..	..	..	..
33.....	..	..	P	N	D	..	..	..	..	..	..	..	..	..	..	..
34.....	..	..	P	N	D	..	..	..	..	..	..	..	..	..	..	..
36.....	..	..	..	..	N	N	..	..	..	..	..	..	..	..	..	..
40.....	..	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..
41.....	..	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..
57.....	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..	..
59.....	..	..	D	..	..	..	..	..	..	..	..	..	..	..	..	..
60.....	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..
62.....	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..
66.....	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..	..
67.....	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..

* Cultures showed oxidase positive colonies of gram-negative diplococci which failed to grow on subculture and therefore could not be confirmed. S = smear, C = culture, P = positive, gram-negative intracellular diplococci in smears or gonococci in confirmed cultures, D = doubtful, gram-negative extracellular diplococci in smears, N = negative smear or culture, no gonococci.

at the time of the 9th injection, and both eyes were clinically normal by the 5th hospital day. Smears and cultures reverted to negative on the 2d day of therapy and remained so thereafter.

COMMENT

Clinical Response.—All except 2 of the 8 cases in this series responded to therapy within twenty-four hours, as manifested by subsidence of active inflammation. Case 2 and case 7 showed some improvement during and immediately after penicillin therapy but, instead of progressing to complete recovery as did the other 6 cases, again developed signs of active inflammation. Repeated courses of penicillin in case 2 produced the same initial response of short duration, followed by relapse.

Because of the large amount of penicillin given initially in case 7, it was not felt that a repeated course would be effective.

In the 6 cases that responded to the specific therapy, clinical recovery occurred in from three to six days, with complete absence of purulent discharge, chemosis and injection.

No corneal complications developed in any of the 8 cases.

As can be seen in cases 1, 3, 4, 5 and 6, occasional gram-negative extracellular diplococci were found on smears taken at varying intervals, even though cultures remained negative and the eyes were clinically normal. No further treatment was given and these cases were kept under observation until three consecutive negative smears and cultures were obtained.

Because of the persistence of clinical activity in case 2, treatment was continued despite the three consecutive negative smears and cultures obtained early in the period of observation, and later both smears and cultures were again found positive.

The treatment progress of each case is outlined in table 1.

Bacteriologic Response.—Smears and cultures were taken in all cases before beginning therapy, at the time of the third injection of penicillin and at intervals thereafter until the bacteriologic criteria of cure as outlined had been fulfilled.

As shown in table 2, all cases except 2 and 8 showed the absence of gram-negative intracellular diplococci in the smears taken at the time of the third injection, although smears in cases 4, 5 and 6 showed the presence of extracellular organisms. Cases 1 and 2 also gave positive cultures at this time, but cultures for all other cases were negative.

Of those cases that responded to penicillin, only 1, case 1, showed a positive culture after the 3d injection of the drug.

Reactions.—A possible reaction to penicillin was observed in case 2. Four days after the second course of penicillin a generalized papular eruption occurred and gradually subsided. Following the third injection of the third course the patient developed a generalized vesicular rash, which subsided during the following ten hours even though penicillin injections were continued. The day after completion of the 3d course a typical urticarial eruption was noted on the trunk and scalp. Although no additional penicillin was administered, the child continued to develop periodic allergic skin manifestations in the form of vesicular, urticarial and pustular lesions.

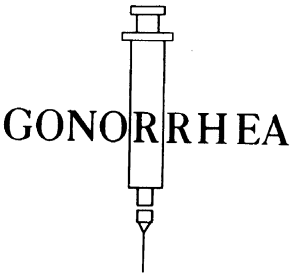
SUMMARY

1. Eight cases of ophthalmia neonatorum were treated with intramuscular injections of penicillin in total dosages varying from 60,000 to 330,000 units.

2. In 5 of the 8 cases the etiologic agent was definitely established as Neisseria gonorrhoeae by confirmatory fermentation tests; in 2 of the cases gram-negative intracellular diplococci gave positive oxidase reactions when grown on chocolate agar but could not be subcultured for confirmatory fermentation tests; in 1 case the infective agent could not be determined.

3. Six of the 8 cases responded promptly to penicillin with pronounced clinical improvement within twenty-four hours and complete recovery within three to six days.

4. The disappearance of specific organisms in smears and cultures was noted in from nine to twenty-four hours after beginning treatment with penicillin.



Penicillin

1. Prolonged Action in Beeswax-Peanut Oil Mixture
2. Single Injection Treatment of Gonorrhea

CAPTAIN MONROE J. ROMANSKY
Medical Corps, Army of the United States
and
TECHNICIAN FOURTH GRADE GEORGE E. RITTMAN
Medical Department, Army of the United States

The clinical effectiveness of penicillin has been well established. However, to date, a completely satisfactory method of administering penicillin has not been found. The present methods of administration have acted, in a sense, as a barrier in determining the optimum dose and the period of time necessary for treatment; in addition these methods involve inconvenience to the patient and to the personnel administering the penicillin.[1 2 3 4 5]

The intramuscular route, which has been used most commonly, results in high blood levels of penicillin enduring for brief periods of time and necessitates frequent injections. The intermittent intravenous method also results in transitory high levels and necessitates repeated venipunctures. The constant intravenous procedure, although maintaining a satisfactory level, is difficult on the patient and involves the possibility of thromboses. The constant subcutaneous infusion,[3] the drip infusion into bone marrow,[4] and the continuous intramuscular drip infusion,[4] all are inconvenient to the patient and require further trial.

A method of administration of penicillin which would decrease the rate of absorption and prolong the duration of an effective level in the blood, in addition to being of minimum inconvenience to the patient, would be of much importance.

From the Penicillin Section, Laboratory Service, Walter Reed General Hospital.

Sixty-five additional cases of gonococcic urethritis have been treated since this paper was written. The only failure in the entire group was the first case reported above. The data on these cases will be reported later with Captain Robert J. Murphy.

Miss Dorothy Talbot and Technician Fourth Grade Minna Levy rendered valuable technical assistance.

1. Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin; Observations in 100 Cases, J. A. M. A., 124:611-622, 4 March 1944.
2. Herrell, W. E.: The Clinical Use of Penicillin; an Antibacterial Agent of Biologic Origin, J. A. M. A., 124:622-627, 4 March 1944.
3. Bloomfield, A. L., Rantz, L. A., and Kirby, W. M. M.: The Clinical Use of Penicillin, J. A. M. A., 124:627-633, 4 March 1944.
4. Morgan, H. V., Christie, R. V., and Roxburgh, I. A.: Experiences in the Systemic Administration of Penicillin, Brit. M. J., pp. 515-516, 15 April 1944.
5. Unpublished data on observation of 250 cases treated with penicillin at Walter Reed General Hospital.

Prolonged action of histamine,[6] desoxycorticosterone acetate,[7] and heparin[8] can be obtained by placing them in a mixture containing beeswax.

In the present study the beeswax has been utilized to decrease the absorption rate of penicillin and maintain a constant effective level in the blood for a longer period of time than that obtained with penicillin in physiologic saline. Prior to the utilization of beeswax, in February 1944, we had suspended penicillin in refined peanut oil, sesame oil, cottonseed oil, corn oil, castor oil, olive oil, and protamine zinc in an attempt to produce prolonged action in rabbits after intramuscular injections. This resulted in more enduring levels than occur with penicillin in physiologic saline but it was felt that a greater prolongation was desirable.

After preliminary trials with varying amounts of U.S.P. bleached beeswax in the different oils, the most satisfactory results in these pilot experiments were obtained with a beeswax-peanut oil mixture. Because calcium penicillin is less hydroscopic than the sodium salt and also forms better mixtures with the oils, it was used for the majority of the experiments.

The pipettes, syringes, needles, beeswax, and peanut oil were sterilized by autoclaving at 17 pounds of steam pressure for twenty minutes. Before sterilization, the beeswax had been heated to a liquid state and filtered through six layers of gauze and the peanut oil had been filtered through a Seitz filter. Under sterile conditions, 0.75 percent, 1.0 percent, 1.25 percent, 2.0 percent, 3.0 percent, 4.0 percent, 5.0 percent, and 6.0 percent mixtures of beeswax in peanut oil were prepared in the following manner: The sterile beeswax was heated until it became clear and liquid and the desired amount was added by means of a warm pipette to the sterile peanut oil which had been brought to about 37° C. This mixture was shaken well and left at room temperature. An ampule* of calcium pencillin was shaken by hand to break the penicillin into as powdery a state as possible. The contents of the ampule were then placed in a warm (37° to 40° C.), dry, sterile bottle and 2 to 3 cc. of the clear, warmed beeswax-peanut oil mixture was added with a warm pipette, the mixture being allowed to drip down the inside walls of the bottle. Three to five sterile glass beads were then placed in the bottle. The bottle was stoppered with a sterile rubber stopper and shaken by hand for ten to fifteen minutes until the particles of penicillin were well dispersed.

6. Code, C. F., and Varco, R. L.: Prolonged Action of Histamine, Am. J. Physiol., 137:225-233, Aug. 1942.

7. Code, C. F., Gregory, R. A., Lewis, R. E., and Kottke, F. J.: Prolonged Action of Desoxycorticosterone Acetate, Am. J. Physiol., 133:P240-241, June 1941.

8. Bryson, J. C., and Code, C. F.: Prolonged Anticoagulant Action of Heparin in a Beeswax Mixture, Proc. of Staff Meeting, Mayo Clinic, 19:100-108, 23 Feb. 1944.

*The ampules of calcium penicillin which were used practically throughout these studies assayed 83,000 instead of 100,000 Oxford units per ampule. If sterile stoppered bottles containing penicillin are available, the contents of several bottles may be added to one and the oils added in necessary quantities.

Following the above procedure the penicillin is distributed throughout the mixture, which is sufficiently liquid to be injected with a 20-gage needle. It can be used at once or, if stored in the refrigerator, should be brought to room temperature and reshaken before injection. Aerobic and anaerobic sterility tests have shown no evidence of contamination. The factor limiting the amount of penicillin which can be dispersed in a given volume of beeswax-peanut oil mixture is the

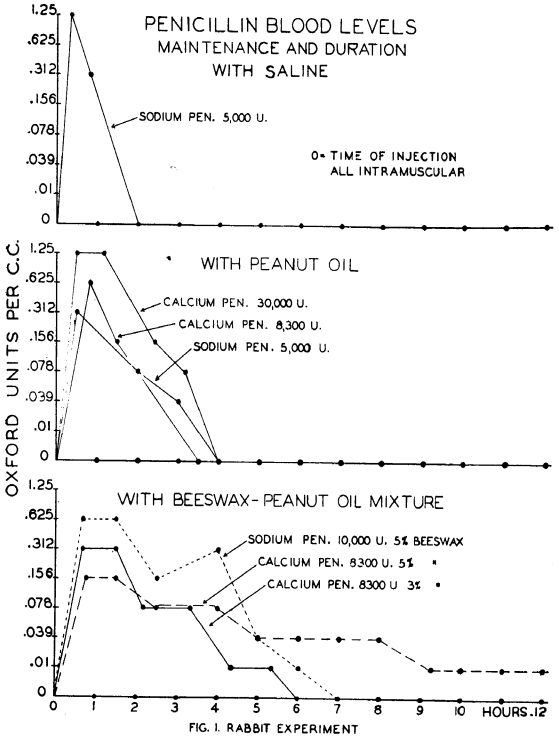


FIG. I. RABBIT EXPERIMENT

weight of the penicillin. This is demonstrated by the fact that different brands of penicillin may vary between 300 and 1,000 Oxford units per milligram. Therefore, the greater the potency of a brand of penicillin in terms of Oxford units per milligram, the greater will be the number of units that one can contain in a given volume of beeswax-peanut oil mixture.

Stability tests* on the penicillin in oil and in beeswax-peanut oil mixture show no deterioration in various batches kept at refrigerator, room, and 37° C. temperatures for thirty to sixty-two days. These stability determinations are being continued. Peanut oil and beeswax-peanut oil mixture, *per se*, show no antibacterial action when tested in the same manner as the penicillin beeswax-peanut oil mixture.

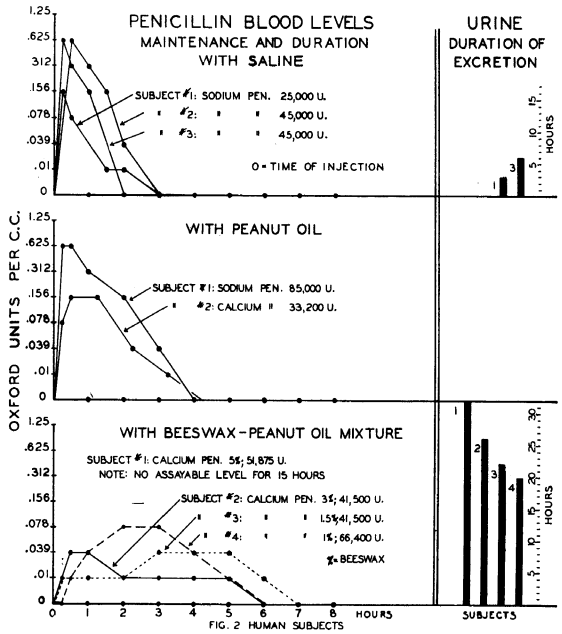


FIG. 2 HUMAN SUBJECTS

As pilot experiments, rabbits weighing from 2.5 to 3.5 kg. were injected intramuscularly with 5,000 to 10,000 Oxford units of penicillin contained in 1 cc. of beeswax-peanut oil mixture and blood assays[9] were made to determine the duration and maintenance of effective levels. Figure 1, which is typical of results obtained in a series of rabbit exper-

*Assays were made by the methods of Rammelkamp9 and Rake.10 Penicillin assays of the urine were also done by these methods.

9. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exp. Biol., N. Y., 51:95-97, Oct. 1942.

10. Rake, G., and Jones, H.: A Rapid Method for Estimation of Penicillin, Proc. Soc. Exp. Biol., N. Y., 54.189, Nov. 1943.

iments, compares the levels produced by penicillin in physiologic saline, in peanut oil, and in the various percentages of beeswax-peanut oil mixture.

Human subjects were then given single injections of 41,500 to 66,400 Oxford units of penicillin intramuscularly in the upper outer quadrant of the buttock. These doses were contained in 2 to 2.4 cc. of beeswax-peanut oil mixtures. Bloods were collected for penicillin assay at intervals indicated in figure 2. Figure 2, which is typical of the results

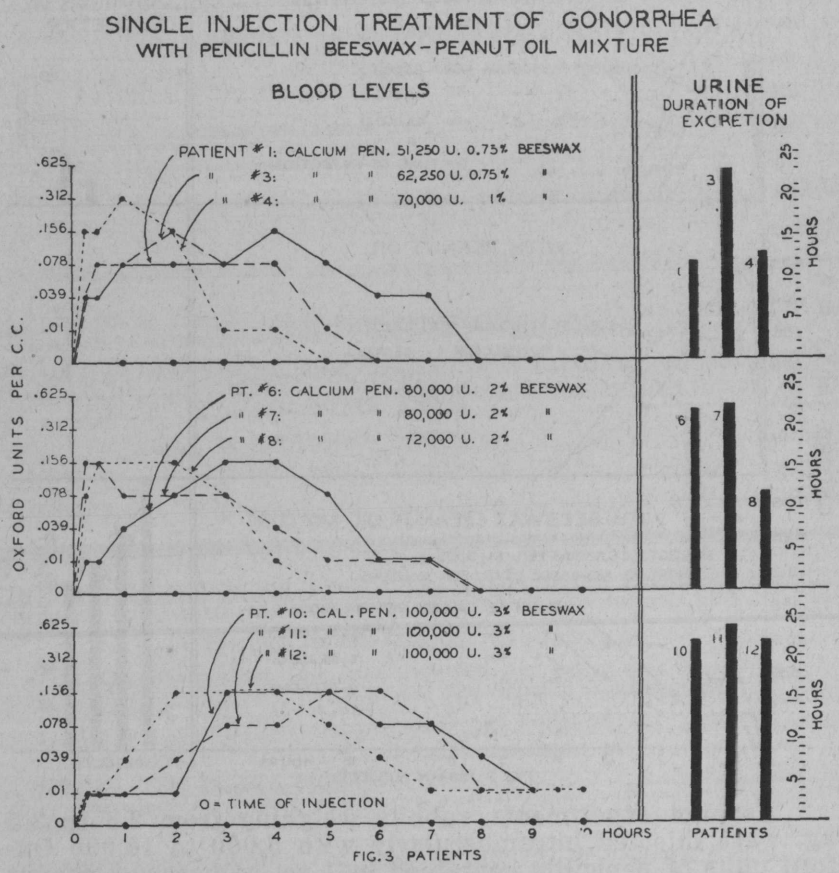


FIG. 3 PATIENTS

obtained with human subjects, shows the maintenance and duration of penicillin levels in the blood obtained by the use of penicillin in saline, peanut oil, and the various percentages of beeswax-peanut oil mixtures. Figure 2 also compares the duration of excretion of penicillin in the urine after the injection of penicillin in saline and in beeswax-peanut oil mixture.

The beeswax-peanut oil mixture delayed penicillin absorption and maintained a level in the blood for six to seven hours. In addition, the presence of penicillin in the urine for

twenty to thirty-two hours indicated a persisting level in the blood for that period of time, though not assayable by present methods.

CLINICAL TRIAL

The results obtained in the preceding experiments warranted a clinical trial of the penicillin beeswax-peanut oil mixture. Twelve patients* with gonococcic urethritis, three without previous treatment, and nine sulfonamide resistant have been treated with single injections of penicillin beeswax-peanut oil mixture. The doses varied between 51,250 and 100,000 Oxford units contained in 2 to 3 cc. of the beeswax-peanut oil mixture. The 100,000 unit doses were contained in 2 cc. of the mixture, since penicillin in smaller bulk was available at that time. Figure 3 shows the doses given, the levels produced, and the duration of penicillin excretion in the urine in nine of the twelve patients treated. The patients who received 100,000 Oxford units as indicated in figure 3 had no blood assays done beyond the tenth hour.

Of the twelve patients, eleven were cured as evidenced by freedom from clinical symptoms and negative smears and cultures at the end of two, five, and seven days after treatment. Hourly smears and cultures, which were taken, indicate that this preliminary group became negative at the fifth to seventh hour after the single injection of penicillin beeswax-peanut oil mixture.

The only failure was the first patient,† previously untreated, who had received the smallest dose of penicillin, 51,250 Oxford units. The size of the dose does not entirely explain the failure, since the levels obtained in the blood compare favorably (figure 3, patient No. 1) with the levels of patients who were cured and received somewhat larger doses of penicillin. It is likely that the gonococcus in this case was more resistant to the action of penicillin.

None of the patients complained of local pain or irritation in the region where the penicillin beeswax-peanut oil mixture had been injected. The subjects who had received both the penicillin in saline and penicillin in beeswax-peanut oil mixture had a decided preference for the latter. Nothing suggestive of an allergic reaction occurred in any of the patients.

Intramuscular injections of 500 to 1,000 Oxford units of penicillin, contained in 0.05 to 0.10 cc. of 3 percent beeswax-peanut oil mixture, have been given to ten hamsters twice a day for five days. These animals are now being sacrificed at the rate of one per week for the purpose of examining the tissue from the site of injection.‡ The stains used in the

*The cooperation of Captain Robert J. Murphy of the venereal disease ward is appreciated.

†This patient was not re-treated with penicillin in oil but was cured with a total of 100,000 units of penicillin in saline given in five divided injections.

‡Capt. W. S. Randall, pathologist at Walter Reed General Hospital, examined the sections.

histologic studies were sudan, and hematoxylin and eosin preparations. To date, the gross findings have been minimal, consisting of oil cysts 1 to 2 mm. in diameter identified after the seventh day. The tissues at the end of twenty-four hours presented collections of polymorphonuclears between the muscle fibers at the site of injection. No muscle necrosis was associated with this reaction, the fibers being merely separated. The microscopic picture at the end of 10 days was that of a sterile, foreign body reaction with scattered disintegrating leukocytes. Some of the giant cells surrounded particles of beeswax. At the 17th day there was a diminution in the amount of remaining beeswax, which had completely disappeared by the 30th day. The few leukocytes on the 17th and 24th days were of the mononuclear type. Minute cysts having thin fibrous walls with scattered giant cells were seen in sections taken at 24 days. By the 30th day the cyst walls were less cellular and some were partially collapsed.

It is hoped that this method of producing an effective enduring blood level of penicillin will aid not only in determining the optimum amount of penicillin necessary in various diseases but will decrease the number of injections and shorten the time required for treatment. Studies along these lines are now in progress.

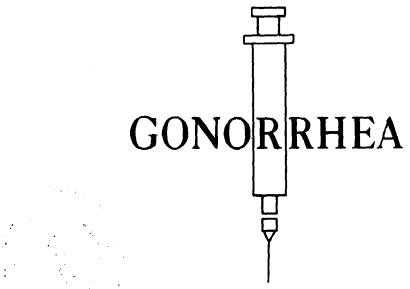
SUMMARY

1. Single injections of penicillin in beeswax-peanut oil mixture will produce and maintain levels of penicillin in the blood for seven to ten hours.

2. These mixtures have maintained their potency at room, incubator, and refrigerator temperatures for thirty to sixty-two days and show no signs of deterioration to date.

3. No abnormal reactions, locally or constitutionally, have been produced by this mixture.

4. Eleven of twelve patients with gonorrhea have been cured by a single injection of penicillin in beeswax-peanut oil mixture.



PENICILLIN X

SUCCESSFUL TREATMENT OF GONORRHEA WITH A SINGLE INTRAMUSCULAR INJECTION

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In a recent issue of *Science*[1] it was reported that gonorrhea had been successfully treated with single injections of 100,000 units of commercial penicillin incorporated in a beeswax-peanut oil base. For the past several months we have had an opportunity to investigate the properties of so-called penicillin X,[2] sometimes referred to as factor X, or allopenicillin. This material was furnished to us by three manufacturers.[3] A small amount of crystalline penicillin X[4] was also made available to us.

When assayed by the cup-plate method[5] the potency of crystalline penicillin X is approximately 900 units per milligram, while crystalline penicillin[6] has a potency of 1,650 units per milligram. In addition, in vitro studies (serial dilution) show that penicillin X is more effective than commercial penicillin against a strain of Klebsiella pneumoniae type A and a strain of Bacillus cereus. No difference in effect could be shown between penicillin X and commercial penicillin on four strains of Staphylococcus aureus. However, preliminary studies indicate that penicillin X is three to five times more effective in protecting mice against 10,000 lethal doses of pneumococcus type I than commercial penicillin.

On the basis of the increased activity of this new preparation against certain organisms in comparison with commercial penicillin, it appeared desirable to determine the effect of penicillin X on the gonococcus. Accordingly, 68 patients with gonorrhea,[7] most of whom were sulfonamide resistant, were treated with a single intramuscular injection of 25,000 units of penicillin X. The group consisted of 35 males and 33 females. Our criterion of cure was three negative cultures obtained one, three and five days after treatment had been completed, although in some cases, because of menses or other factors, cultures were taken at greater intervals and over a longer period of time. Sixty-four patients, or approximately 94 per cent of those treated, were cured. For comparative purposes a group of 58 patients with gonorrhea (31 males and 27 females) were treated with a single intramuscular injection of 25,000 units of commercial penicillin. Using the same criterion, 37 patients, or approximately 64 per cent of those treated, were cured. It is of interest that 3 of the patients in whom we failed to obtain a cure with commercial penicillin were cured by a subsequent treatment with a single injection of 25,000 units of penicillin X.

Studies of the blood concentration were made on 7 patients treated with penicillin X and on 8 patients treated with commercial penicillin. These concentrations were determined with the serial dilution technic using Bacillus subtilis as the test organism, one-half hour, one hour and two hours following intramuscular injection. During the first two hours after treatment a consistently higher concentration of penicillin X was maintained in the blood. Urinary excretion studies were made over a period of eight hours on 9 patients, 4 treated with penicillin X and 5 with commercial penicillin. During the first two hour period 59 per cent of the penicillin X injected was excreted, as compared with 68 per cent of the commercial penicillin. After eight hours the total excretion of penicillin X was 71 per cent as compared with 80 per cent of commercial penicillin. Further studies are in progress using larger doses of penicillin X in a single intramuscular injection to determine its efficacy and rate of excretion at higher levels.

Although the number of cases reported here is small, if further work substantiates the fact that a large proportion of cases of gonorrhea can be cured with a single intramuscular injection of penicillin X, the public health control of this disease, which has been materially affected by the use of commercial penicillin, will be further facilitated.

1. Since this report was submitted for publication, 5 additional pneumonectomies have been performed in accordance with the procedure outlined in this study. All 5 patients received the prophylactic course of penicillin. Four of them were resected for bronchiogenic carcinoma and 1 for a bronchial adenoma. None of these patients became infected and all of them survived.

From the Food and Drug Administration, Federal Security Agency.

1. Romansky, M. J., and Rittman, G. E.: A Method of Prolonging the Action of Penicillin, Science **100**: 196, 1944.

2. Commercial penicillin and penicillin X in this article refer to the sodium salts of these substances.

3. Obtained through the courtesy of the Upjohn Company, Cutter Laboratories and Cheplin Biological Laboratories.

4. Robert D. Coghill of the Northern Regional Research Laboratory supplied the crystalline penicillin X.

5. Mimeograph: "Methods Used by the Food and Drug Administration for the Assay of Penicillin, January 1944."

6. Crystalline penicillin G prepared from commercial penicillin.

7. The clinical work in this study was done at the Rapid Treatment Center, Gallinger Municipal Hospital, Washington, D. C. Drs. Sidney Olansky, A. M. Gamboa and M. J. Cannon aided in these studies.