

# Gonorrhea Today

## Problems of Diagnosis, Management, Treatment

R. C. REZNICHEK, M.D., W. H. SMARTT, M.D., M.P.H., AND  
S. A. BROSMAN, M.D., *Torrance*

GONORRHEA HAS RISEN to epidemic proportion in the United States. The number of reported cases increased sharply from 246,697 in 1960<sup>1</sup> to 494,227 in 1969.<sup>2</sup> Most cases, however, are not reported. The total number is now estimated to be over 1.5 million yearly.<sup>3</sup>

Confusion in diagnosis and therapy have increased along with the incidence of gonorrhea. When the antibiotic era began, physicians assumed that the disease would soon be eradicated. Gonorrhea has escaped control, let alone eradication, for several reasons. Most women who have gonorrhea are asymptomatic. The Gram-stained smear will be negative in many patients, particularly women, who have gonorrhea. Relative resistance of gonorrhea to penicillin has developed and is increasing. Prophylaxis has lapsed with the advent of female oral contraceptives.

### Diagnostic Problems

The Gram-stained smear is a reliable method of laboratory diagnosis in the male with a thick yellow urethral discharge.<sup>4</sup> Laboratory diagnosis is more difficult when a gray watery discharge is present. Females with gonorrhea seldom have a purulent discharge. Approximately 80 percent of them are asymptomatic and only have a mild endocervicitis. Cervical and urethral smears are negative or inconclusive in at least half the cases. In a comparison of slide and culture techniques,

diagnostic accuracy doubled when cultures were obtained in asymptomatic female contacts. Pariser and Farmer<sup>5</sup> showed that 44 percent of asymptomatic female patients with known contacts did not have a positive culture while 71 percent did not have a positive smear. There is no way of predicting which of these patients will turn up positive and which negative.

Culture methods first employed were unsatisfactory because specimens were contaminated by bacteria which outgrew the more slowly developing gonococcus. Early attempts to reduce contaminating organisms were not helpful since many gonococcal strains were killed by inhibiting agents. The Thayer-Martin culture medium was introduced in 1964.<sup>6</sup> This culture medium currently uses vancomycin to inhibit Gram-positive contaminants, sodium colistimethate for gram-negative flora, and nystatin to inhibit yeast.<sup>7</sup> The Thayer-Martin culture technique is the best means of laboratory diagnosis of gonorrhea at the present time, but false negative reports still occur in significant numbers.

Since the gonococcus is an intracellular organism, no further improvements in culture techniques by *in vitro* methods are anticipated. Laboratory diagnosis cannot be fully relied upon in this disease. Treatment of suspected females is mandatory to keep them from becoming a chronic reservoir of the disease, a reservoir which Willcox<sup>8</sup> aptly termed "the promiscuous female pool."

The male patient presents other diagnostic problems. The physician may not be able to obtain urethral exudate for examination. In the absence of discharge, smear and culture of urinary sedi-

From the Departments of Surgery and Urology, Harbor General Hospital, Torrance, and the University of California, Los Angeles, School of Medicine; and the Los Angeles County Health Department, Division of Venereal Disease Control.

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Reprint requests to: Department of Urology, Harbor General Hospital, 1000 West Carson Street, Torrance, Ca. 90509 (Dr. S. A. Brosmán).

ment has been rewarding in some cases.<sup>9</sup> The male patient may be seen with a history of exposure but before symptoms begin. Pariser et al<sup>10</sup> found laboratory evidence of gonococcus following prostatic massage in 26 of 98 asymptomatic male contacts seen six days following exposure. For both male and female patients, it is clear that treatment should be based on history. The laboratory should be consulted for confirmatory diagnosis or evaluation of treatment which has already been initiated on the patient's first visit.

### Therapeutic Problems

The treatment of gonorrhea with penicillin has become increasingly confusing. Penicillin, though still effective, can no longer be considered a wonder drug for gonorrhea. Problems were forecast in 1958 by Epstein when United States troops treated in Korea failed to give the anticipated response to penicillin.<sup>11</sup> Although he gave the recommended injections of 600,000 units of procaine penicillin G for five days, the failure rate was 20 percent. A similar rate of penicillin failure was noted in England about the same time.<sup>12</sup>

It became evident that decreases in susceptibility of some strains of *N. gonorrhoea* was occurring. None of the strains encountered before 1954 had shown resistance to 0.05 units of penicillin per milliliter of serum *in vitro*.<sup>13</sup> Subsequent studies in Germany showed a progressive change in resistance from 0.0074 units of penicillin per ml *in vitro* in 1956 to 0.0218 units per ml in 1958, to 0.164 in 1961, and then to 0.25 units per ml in 1964.<sup>14</sup> Similar *in vitro* resistance increases were found in other parts of the world including Australia<sup>15</sup> and Canada.<sup>16</sup>

In 1966 the resistance of the gonococcus to penicillin *in vitro* was assessed in various areas of the United States. On the East Coast 7.3 percent of strains were resistant to 0.30 units of penicillin per ml, with the percentage increasing westward to 33 percent in California.<sup>17</sup> Recently it has been reported that 14 percent of strains are resistant to 0.5 units of penicillin per ml of serum.<sup>18</sup> These figures do not mean that gonorrhea is no longer sensitive to penicillin but that there has been a progressive relative resistance requiring higher and higher doses of penicillin to effect good cure rates. They also demonstrate the varying susceptibility of the organism in different geographical areas.

A single dose of 2.4 million units of procaine penicillin G was recommended by the United States Public Health Service in 1965. Holmes et al<sup>19</sup> studied gonorrhea in U.S. military personnel in the Far East. They found that procaine penicillin G 2.4 million units in a single dose, resulted in a failure rate of 29 percent for shipbound sailors. When 2.4 million units of procaine penicillin G was given intramuscularly on two successive days to Air Force personnel in Viet Nam, the failure rate was 25 percent.<sup>20</sup> If 2.4 million units of benzethine penicillin G was added on the third day, the failure rate was reduced to 9 percent.

In 1965, Lucas et al<sup>21</sup> evaluated different penicillin treatment schedules for women. Procaine penicillin G in a single injection of 2,400,000 units gave a failure rate of 8.7 percent. The failure rate for 4.8 million units was 4.0 percent. A failure rate of 3.8 percent was noted by Shapiro and Lentz<sup>22</sup> using 2,400,000 units of aqueous procaine penicillin G with 2,400,000 units of procaine penicillin G in oil. At present, the United States Public Health Service recommends 2.4 million units of aqueous procaine penicillin for males and 4.8 million units for females.

These problems led to a search for suitable substitutes for penicillin in the treatment of gonorrhea—safe agents with good cure rates and minimal side effects. Most attention has been focused on the tetracyclines. Epstein<sup>11</sup> found that most of his penicillin failures in 1958 responded to oxytetracycline. Shapiro and Lentz<sup>23</sup> gave women at the Public Health Venereal Disease Clinic in Philadelphia oxytetracycline 250 mg intramuscularly and 1.0 gram orally on a single visit. Of 120 patients with a culture diagnosis of gonorrhea, 110 had three consecutive negative cultures following therapy. Ashmalla et al<sup>24</sup> found that with oxytetracycline 500 mg intramuscularly and 250 mg orally every six hours for seven days for men the failure rate was 1.8 percent. Holmes et al<sup>19</sup> had no failures in 30 men given tetracycline 1.5 gram orally, then 500 mg every six hours for four days. Maurer and Schneider,<sup>20</sup> using the same schedule for 141 men, had 7 percent failures. In these last two studies, much less post-gonorrheal urethritis was noted than in patients who were treated with penicillin.

Attention recently has turned to doxycycline, a new semi-synthetic tetracycline which chemically is  $\alpha$ -6-deoxy-oxytetracycline. This drug is distinguished from other members of the tetracycline

family by a more efficient gastrointestinal absorption which is not significantly affected by food or milk, and also achieves high blood levels earlier and has a longer serum half-life. Single doses of 300 mg of doxycycline have been used in Montreal with a failure rate just over 5 percent.<sup>25</sup> However, the length of time before re-examination was not specified in the report. With single doses of 250 mg given to 169 males by Domesik et al<sup>26</sup> the failure rate was just under 5 percent. In this study patients returned for re-examination in 96 hours. One of us (w.h.s.) used a single dose of 300 mg of doxycycline briefly but met with a failure rate of 62 percent with re-examination in seven days.<sup>17</sup> Unless therapy is continued to include three life cycles of the gonococcus, suppression without cure apparently can take place.

### The Physician's Legal Responsibilities

The physician's obligation under the law must be considered in cases of gonorrhoea. Statutes describing the physician's responsibility vary from state to state. In California, Title 17, Section 2500 of the Administrative Code states that it is the duty of the physician in a case of suspected venereal disease to notify the local health authority immediately. In addition, Section 2536h states that the attending physician must endeavor to find the source of the infection, including any intimate contacts made while the patient's disease was communicable. He must make an effort to bring the contacts in for examination and, if necessary, treatment. If such contacts are not under care of a physician within ten days, they must be reported to the health officer. The statutes indicate that all information given to the local health authority will be kept confidential.

Section 3198 of the California Health and Safety Code states that any person who refuses to give information or reports having to do with venereal disease is guilty of a misdemeanor. (A legal consultant on this point thought it reasonable to conclude that a physician who does not report a suspected case of gonorrhoea to the local health office could be convicted of a misdemeanor for failing to do so.)

In 1969, there were 36,641 cases of gonorrhoea reported in the County of Los Angeles.<sup>27</sup> Public health investigators interviewed all male patients for their contacts. The contacts were in turn referred to a public health office or private physi-

cian. Patients or contacts who refused to cooperate were served with an order to appear at a public health office. Each year in Los Angeles County it is necessary to serve such an order on about 35 persons. The eight or so who still refuse to be examined are taken to court for not complying with the law. They are usually ordered to go to a public health office and are given a one-year summary probation.

The State of California supplies physicians and institutions with confidential morbidity report forms. They should be used for reporting all communicable diseases including gonorrhoea to the local health officer.

### Management of Patients with Gonorrhoea

The district health centers of the County of Los Angeles have established a protocol for the management of gonorrhoea which is sensible and expedient.

Past and present venereal history is obtained from each patient. Men are considered symptomatic if they complain of a urethral discharge. Women are considered symptomatic if they have lower abdominal pain, dysuria or a vaginal discharge. A specimen of blood for Venereal Disease Research Laboratory (VDRL) test is drawn. The genitalia are examined for lesions. In males a smear of the urethral discharge, if present, is made with a cotton applicator onto a glass slide. A charcoal-impregnated applicator is used to obtain urethral discharge for culture. If no discharge is present, urine is obtained for smear and culture of the spun sediment. In females, smears of the urethral meatus and cervical os are obtained for Gram-staining. Cultures are collected by swabbing the same areas. All culture swabs are placed in Stuart's transport medium.<sup>28\*</sup>

Specimens are sent to the central Los Angeles County Public Health Laboratory. Smears are read as positive, negative or inconclusive for Gram-negative intra-cellular diplococci. Cultures are obtained by plating the swabs onto Thayer-Martin medium and incubating the plates anaerobically at  $35^{\circ} \pm 0.5^{\circ}\text{C}$ . At 48 hours oxidase reagent is placed on the plates. Colonies which turn dark (oxidase positive) are smeared for Gram-staining. A positive Gram-stain is read as a positive culture.

Therapy is instituted on the first clinic visit for

\*Holding Transport Medium available from Hyland Laboratories, Costa Mesa, California.

symptomatic patients and patients with a history of known sexual exposure regardless of symptoms or findings.

All patients with a presumptive diagnosis of gonorrhea are treated with doxycycline. Two 100 mg tablets are given in the clinic. In addition, the men are given envelopes with instructions to take doxycycline 100 mg tablets twice a day for three days. Women are given 100 mg tablets to take twice a day for five days. Patients are told to abstain from sexual intercourse to prevent reinfection while under treatment. Reports of the VDRL and bacteriologic studies are reviewed with the patient in one week. All are requested to return in three months for a second VDRL test.

Criteria for cure of gonorrhea have been established. Men who are asymptomatic on return in one week are considered cured. For women two negative smears and cultures a week apart are considered necessary for cure. If any initial report is positive, follow-up visits are scheduled until two consecutive weekly reports are entirely negative. Retreatment is instituted when necessary.

Each positive case is reported to the Los Angeles County Public Health Department as a communicable venereal disease. Case finding is then carried out by public health investigators.

Records of 490 patients attending the Torrance District Health Center Venereal Disease clinics from April to November 1969 were reviewed. Only patients with symptoms of gonorrhea or a history of exposure to gonorrhea were included in the study. Patients whose treatment had already been begun were excluded. Patients seen primarily for the diagnosis or therapy of syphilis were excluded.

A total of 226 patients received doxycycline for a presumptive diagnosis of gonorrhea and returned for follow-up in one week. These patients were the material of our study. One-hundred twenty-nine patients were males and 97 were females. Ninety-one percent were between 15 and 29 years of age. A previous history of gonorrhea was elicited from 51 males and females (27 percent of patients in the study). Only two males were asymptomatic. Seventy-five (77 percent) of the female patients were asymptomatic. None of the 226 patients had a positive VDRL test report.

The initial laboratory results of all patients in the study were compared (Table 1). All inconclusive reports were considered negative. The large number of symptomatic males with negative re-

**TABLE 1.—Initial Laboratory Results in 226 Patients with a Presumptive Diagnosis of Gonorrhea**

	Females	Males
<i>Symptomatic Patients</i>		
Positive for GC by smear, culture or both	11	64
Negative for GC by smear, and culture	11	63
<i>Asymptomatic Patients</i>		
Positive for GC by smear, culture or both	34	1
Negative for GC by smear, and culture	41	1
	97	129

**TABLE 2.—Comparison of Smears and Cultures in Symptomatic Patients with Laboratory Evidence of Gonorrhea**

	Females	Males
Smear positive } Culture positive	5 (45%)	54 (84%)
Smear positive } Culture negative	0	3 (5%)
Smear negative } Culture positive	6 (55%)	7 (11%)
	11	64

**TABLE 3.—Comparison of Smears and Cultures in Asymptomatic Females with Laboratory Evidence of Gonorrhea**

Smear positive } Culture positive	10 (30%)
Smear positive } Culture negative	6 (18%)
Smear negative } Culture positive	18 (52%)
	34

ports reflects the prevalence of non-specific urethritis seen in our area. A total of 110 patients had laboratory evidence of gonorrhea. A laboratory diagnosis by smear could be made for 89 percent of the men but only for 45 percent of the women in patients who were symptomatic (Table 2).

A laboratory diagnosis of gonorrhea in asymptomatic females could be made by smear in only 48 percent of cases (Table 3). The diagnosis doubled when the culture was also included. These findings were accentuated when smears and cultures in females with laboratory evidence of gonorrhea were compared (Table 4). More than

**TABLE 4.—Comparison of Smears and Cultures in All Female Patients with Laboratory Evidence of Gonorrhea**

	Symptomatic	Asymptomatic	Total
Smear negative } Culture positive }	5	10	15 (33%)
Smear positive } Culture negative }	0	6	6 (14%)
Smear negative } Culture positive }	6	18	24 (53%)
			45

**TABLE 5.—Results with Doxycycline in Patients with Laboratory Diagnosis of Gonorrhea**

	Cures	Failures	% Cure
Males .....	60	5	92
Females .....	43	2	96
	103	7	94

half of these women, whether symptomatic or not, could only be diagnosed by culture. The tables also show that in a few males (5 percent) and some females (14 percent) diagnosis can be made only by smear. Both smear and culture techniques are necessary to obtain confirming laboratory evidence of gonorrhea.

None of the patients whose bacteriological studies were negative on the initial visit, before treatment, had positive follow-up studies. There were seven treatment failures. The cure rate was 94 percent (Table 5). One man was given a second course of doxycycline and then did not return. The other six patients were treated with penicillin in aluminum monostearate in oil (PAM) 3.0 million units intramuscularly. Three (all men) did not return. The remaining man was asymptomatic with negative studies after PAM. Neither woman had been symptomatic. One was treated with PAM a second time before she was cured. The other had to be retreated three times (PAM, PAM, and doxycycline, and finally tetracycline alone) before she had negative laboratory studies.

### Summary

Reasons for the alarming increase in the incidence of gonorrhea in the United States include problems in diagnosis and therapy. The physician who sees a patient with the possible diagnosis of gonorrhea is obligated to treat and follow the patient. In addition, he is obligated by law to report these cases to the local health authority so that

public health investigators can see that contacts receive medical attention.

The lack of symptoms in 75 percent of women known to have had contact with gonorrhea is particularly distressing. In both sexes, positive cultures with negative smears are often found. Occasionally, the opposite is true. However, even the best laboratory methods, used in complementary fashion—that is, both smears and cultures—yielded positive evidence in less than half of the patients treated for gonorrhea. Each patient who seeks medical care with a history of exposure to gonorrhea should be treated on the first visit without waiting for laboratory evidence. For both male and female patients, treatment should be based on history. Complete reliance on a laboratory diagnosis is not possible. Laboratory culture results are useful in confirming the diagnosis and evaluating a course of treatment. Antibiotic sensitivity results are not routinely obtained unless there are signs of resistance.

Treatment of gonorrhea, however, is no longer easy. The disease has shown varying susceptibility to penicillin in different geographical areas and the relative resistance of various strains has been steadily increasing, requiring higher dosage schedules for cure. Currently, the minimum dose of penicillin G injected intramuscularly is 4.8 million units in women and 2.4 million units in men. Benzathine penicillin is used in conjunction with the crystalline form. Benemid is of value in maintaining a high serum concentration.

Ampicillin, cephaloridine (Loridine®), kanamycin and carbenicillin represent other agents effective in the treatment of gonorrhea. Currently, the Los Angeles County Venereal Disease Center recommends tetracycline as the drug of choice. The patients seen in these centers are treated with the long-acting tetracycline, doxycycline. Therapy is begun with two 100 mg tablets administered under the watchful eye of a nurse. Treatment is continued with 100 mg twice a day for five days in women and three days in men.

We do not intend to imply that the therapeutic agent (doxycycline) and the dosage schedule give statistical advantage over other forms of tetracycline therapy. The suggested treatment schedule for the short-acting tetracycline is 2 grams to begin with and then 500 mg four times a day for five days in women and for three days in men. Erythromycin may be used in pregnancy or if there is allergic sensitivity to tetracycline. A course of

long-acting tetracyclines is two to three times as expensive as a course of the conventional 250 mg tetracycline capsules.

No amount of sophisticated laboratory diagnostic studies, new therapeutic measures, or increased case finding will eliminate gonorrhea. More attention must be placed on prophylaxis and on education of both the physician and the patient. Gonorrhea must be approached anew to make headway in its control.

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#### CORONARY CARE UNITS—FOR WHOM?

Should all patients with myocardial infarction be admitted to the coronary care unit—or just the seriously ill patients?

"Fifty-seven patients in a series reported by Melzer appeared to have mild myocardial infarction and were not admitted to the coronary care unit, but look what happened: 7 developed heart failure; 5 developed shock; there were 30 major arrhythmias, leading to 5 deaths. So we feel that *all* patients with myocardial infarction, even the good-risk patients, should go into a coronary care unit. There's just no doubt about it because we could save many of these patients in such a unit."

—ÉLIOT CORDAY, M.D., Los Angeles  
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