Problems in the Diagnosis and Treatment of Gonorrhea

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THE LIMITATIONS and special usefulness of clinical and laboratory techniques in the diagnosis of gonorrhea are not well understood by the average practitioner today. Many physicians and clinics, because of complacency or lack of ancillary aid in diagnosis, employ measures for the treatment, management, and control of this disease which appear poorly justified in the light of newer research findings.

Diagnosis in the female is a major factor in both the clinical and control aspects of gonorrhea. It is generally assumed that the best procedures for the diagnosis in women is by smears and cultures taken from appropriate sites and correlated with clinical data. Studies by the Public Health Service utilizing the very best clinical and laboratory groups indicate, however, that clinical information plus smears and cultures result at best in the diagnosis of only 50 to 75 percent of those females having gonorrhea (*1*, *2*).

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This indicates that the most sensitive, practical indicator of gonorrhea in the female is the anterior urethra of a susceptible male. Such information should clearly point out the limitations in current techniques for diagnosis and place in proper perspective the importance of the epidemiological diagnosis of this disease. Certainly our control efforts cannot succeed if one out of every two to four women who have gonorrhea cannot be detected by current laboratory procedures and are available in the community as a focus for continued transmission of the disease.

Penicillin Susceptibility

There is a rather commonly held concept that the organisms causing gonorrhea and syphilis are similarly highly susceptible to the action of penicillin. While this is true concerning *Treponema pallidum*, it is not, and never has been, true for *Neisseria gonorrhoeae*. It has always taken more penicillin per organism to achieve a minimal inhibitory concentration (MIC) for the gonococcus than for the treponeme. Furthermore, the gonococcus has been observed to have a wide range of susceptibility to the action of penicillin, depending upon the strain of the organism tested.

During the period 1945–47 several investigators tested more than 200 strains of *N. gonorrhoeae* and found that all were inhibited by 0.05 unit or less of penicillin per milliliter. In 1955, however, Thayer and asssociates of the Public Health Service Venereal Disease Experimental Laboratory found that of 31 strains tested, only 78 percent were inhibited in this

lower range, while 22 percent required 0.1 unit or more per milliliter. Subsequent studies by Thayer and associates (1957), Curtis and Wilkinson (1957), and others have shown that from 20–30 percent of the more than 500 strains tested were inhibited only by the higher levels of penicillin (see table). Thus, over the past decade natural isolates of the gonococcus have indicated a definite and continuing proportional decrease in sensitivity to penicillin (*3*). In the United States, strains of the gonococcus inhibited by a minimal concentration of penicillin as high as 0.333 unit per milliliter have been observed; and, in the past few years particularly, more and more natural strains inhibited by minimal concentrations above 0.1 and 0.2 unit per milliliter. These higher MIC's exceed levels obtainable by usual doses of the type of penicillin given in the recent past in clinics throughout this country (*4*). Under these circumstances we would, of course, expect to see treatment failures on the basis of dose of drug alone, and, indeed, this is exactly what has been observed in a number of clinics where studies have been carried out to determine this and other factors in the treatment of gonorrhea (*5–9*). While the time-dose relationship is not so apparent in gonorrhea as it is in syphilis for successful treatment, it is an important factor in approaching the logical and effective use of penicillin. Observations by Thayer and associates have shown that the bacteriocidal effect of penicillin on the usual strain of the gonococcus is detectable between the fourth and fifth hour of contact. From a practical standpoint such killing is usually complete by the 12th hour. Although a few strains tested on semisolid media were found to contain viable organisms through 24 hours of contact with penicillin, no strain has ever survived under these circumstances to 48 hours of exposure (*10*).

These investigators have also shown that cellular components can protect at least some of the gonococci from the action of penicillin. Using tissue culture techniques, it was observed that both HeLa cells and rabbit fibroblasts were capable of engulfing a certain proportion of the gonococci to which they were exposed. Further, it was demonstrated that penicillin, when applied to the medium, would kill extracellular gonococci but would not affect intracellular organisms. The presence of penicillin up to as long as 96 hours had no effect against the intracellular organisms, while at the appropriate MIC most extracellular daughter cells were killed within 5 to 12 hours. Inactivation of penicillin by penicillinase and changing either the osmotic relationships of the medium or disrupting tissue cells with engulfed organisms allowed for the recovery of the gonococci in a viable form on culture media up to as long as 240 hours thereafter. These recovered gonococci had the same MIC as the killed extracellular organisms. That the gonococcus is inevitably protected against all agents tested to

Reported studies on susceptibility of Neisseria gonorrhoeae to penicillin

Author	Survey dates	Number of strains	Percent inhibited by (units per milliliter)		Range
			0.06 or less	0.10 or more	
Lankford	1945	100	100	0	0. 005 –0. 025
Love and Finland	1945	24	100	0	. 002 – . 008
Romansky and Robin	1947	53	100	0	. 002 – . 060
Love and Finland	1947	104	100	0	. 002 – . 033
Love and Finland	1949	52	96	4	. 005 – . 333
Marcuse and Hussels	1950–52	232	99. 6	0. 4	. 008 – . 125
Schümmer and Hubbes	1951	100	98	2	. 004 – . 125
Love and Finland	1954	106	100	0	. 002 – . 033
Thayer and associates	1955–56	31	78	22	. 005 – . 200
Thayer and associates	1957	46	70	30	. 005 – . 200
Cradock-Watson	1957	200	81	19	. 008 – . 512
Curtis and Wilkinson	1957	302	80	20	. 004 – . 500
Thayer and associates	1958	40	92	8	. 0025– . 120

date under these circumstances has been shown by extension of this work to include not only penicillin but also a wide variety of antibiotic and chemotherapeutic agents (*11*).

Proposals

On the basis of these findings, Garson in 1956–57 proposed a working hypothesis for the treatment and management of gonorrhea which may be summarized briefly as follows (*4*).

- Sufficient penicillin must be given the patient so that the units per milliliter of serum will exceed the highest known MIC associated with any strain of the gonococcus in this country. Roughly, at this time, this would mean a serum level of 0.35 unit per milliliter.
- Such a level must be maintained in contact with the gonococcus for a period of at least 24 hours and preferably 48 hours. Based upon the laboratory in vitro work previously described, such time contact would allow for a complete bacteriocidal effect against any known gonococcus.
- Provisions should be made for treatment with very long-acting penicillin. This is necessary for two reasons: although 48 hours of exposure will kill all gonococci in vitro, we do not know when such exposure is liable to occur in vivo, particularly in the female. In other words, we could not treat a patient, obtain a 48-hour continuous penicillin blood level, and assume that the gonococcus in various foci in the female genitourinary tract had had an equal 48 hours of exposure. The second point is even more important. After being cured of gonorrhea, the individual may return to a milieu of venereal disease as a susceptible person and become reinfected in short order. It is possible with benzathine penicillin to obtain blood levels beyond 45 days in the human patient. While we do not know the exact minimum concentration of continuous penicillin that will protect an individual exposed to gonorrhea, it is known empirically that this system when applied does reduce the repeater load in venereal disease clinics.

This treatment is termed "antibiotic quarantine" by Dr. Ira Schamberg of the venereal disease clinics in Philadelphia, where he, as well as others, have demonstrated the effectiveness of this approach in reducing repeaters in attendance (*8, 9, 12, 13*).

There is yet another factor to be considered in relation to the use of a long-acting penicillin. If it is true that, particularly in the female, certain tissue cells of the genitourinary tract are capable of taking viable gonococci within them and protecting such organisms from the effects of penicillin as has been demonstrated in tissue cultures, then with the dissolution of the host cell, viable gonococci are available for the autoinfection of the host. As such viable gonococci could be released some weeks after the initiation of therapy, it is obvious that the presence of long-acting penicillin in such a patient would be a deterrent to autoinfection. I must stress here that this is a hypothesis and has not yet been confirmed by clinical research. Nonetheless, until we know more about the disease in this regard, it behooves us to take such action as would prevent the likelihood of its occurrence.

Preston and Dunsworth in 1957 found that of 135 female patients treated with 600,000 units of penicillin aluminum monostearate (PAM), 24.4 percent yielded positive cultures 7 or 14, or both, days after treatment (*7*). In a second series of 65 such patients, the dosage of PAM was increased to 1.8 million units and the followup time was shortened to 3 and 7 days after treatment. In this series, only 4.6 percent yielded positive cultures. Two additional groups were tested to verify the finding that the dosage of 600,000 units of PAM was inadequate for a high percentage of cure. Of 77 women treated with 600,000 units, 16.8 percent yielded positive cultures during followup. Of 106 women treated with 1.8 million units, only 3.8 percent yielded positive cultures. If the number of probable reinfections is deducted, these authors estimate that the true failure rate with 600,000 units of PAM is 13 percent. They conclude that 1.8 million units of PAM is necessary for an acceptable rate of cure in females.

Hookings has used a treatment regimen consisting of a mixture of 600,000 units of PAM plus 1.2 million units of benzathine penicillin G. (*5, 6, 13*). His treatment schedule, applied in a rapid casefinding gonorrhea program, includes not only diagnosed early gonorrhea in women but also the prophylactic treatment of

all other women brought to observation; in addition, he has submitted men to this treatment schedule.

The results may be described briefly as follows: Using the attendance of diagnosed male cases as the criterion of success, the number of such cases was reduced by 18 percent at the end of 9 months and further reductions have occurred in subsequent experience. There was a decline also in the number of women who, having been named as contacts, were again named within 60 days. This decline was from 15 percent with the treatment previously employed (that is, 600,000 units PAM alone) to approximately 1.7 percent with the 1.8-million-unit dosage of mixed treatment.

In the light of today's knowledge, we must raise our sights in the treatment of gonorrhea to higher levels of penicillin extending over a much longer time period than has been used in the past (*14*). I believe it is obvious that the control of gonorrhea can be enhanced by the application of this knowledge in treatment. The epidemiologist can feel more secure that his patient will not be reinfected before he has the opportunity of finding source and spread cases, and he will have a longer effective period during which investigations may be conducted to bring contacts to epidemiological or specific treatment. Of greater importance, the tendency of the gonococcus to develop further resistance to penicillin can be blocked.

The problem of uncomplicated gonorrhea in the male is of course considerably less difficult in relation to diagnosis and treatment. In these days of the rediscovery of nongonococcal urethritis (NGU), it would be wise to take routinely at least smears on male patients to aid in the differentiation between gonorrhea and NGU. When occasional treatment failures of gonorrhea occur and NGU has been excluded, cultures should be obtained and the susceptibility of the gonococcus to penicillin determined to aid as a guide in therapy. It is perhaps worth while, too, to remind the epidemiologists that British, Danish, and American investigators have reported what appears to be cases of asymptomatic gonorrhea in the male (*15–19*).

For many years, it has been rather widely accepted that the endotoxin of *N. gonorrhoeae*, responsible for the basic cellular pathology of the disease, was a protein. Recently, however, Tauber and Garson have obtained a protein material from the gonococcus which is consistent with all past criteria referable to the endotoxin of the gonococcus (*20*). In an attempt to increase the toxicity and lethality of this endotoxin to animals and to purify the endotoxin for chemical characterization, they found that most of the toxicity could be related to nucleoprotein (*21*). By applying techniques unavailable to workers of the past, they were able to separate a previously unknown lipopolysaccharide phosphate from the protein endotoxin. The bulk of the toxicity was to be found in this phosphate rather than the nucleoprotein (*22*). If these new studies are confirmed, it would appear that the endotoxin of the gonococcus is not a protein, but rather a lipopolysaccharide.

This observation would be of extreme importance in relation to development of specific antigens for serologic testing for gonorrhea, as well as to the possible development of a relatively specific skin test for the disease. Further, as saccharide antigens are usually more closely related to protective immunity than are protein antigens, such studies may lead to a means of developing hyperimmunity in the host sufficient to protect against naturally acquired gonorrhea.

It appears we are once again upon the threshold of a renaissance in new knowledge about the gonococcus and gonorrhea. One of the many areas of findings being pursued is the exciting research concerning the adaptation of the fluorescent antibody techniques to the gonococcus, which could allow for the specific detection of gonococci in a stained smear within 30 minutes or the utilization of this technique for a serologic test for the disease (*23*). If this research is successful, it may be reflected in our clinical and public health practice in the not too distant future.

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Quarantine Data

★ The number of people detained in ports of entry for medical observation in fiscal year 1959 increased nearly 400 percent, from 124 in fiscal year 1958 to 607 in 1959. This sharp increase was due largely to the outbreak of smallpox in Heidelberg, Germany, in December 1958.

★ The number of incoming travelers who were allowed to continue to their destinations in the United States but were required to be under medical surveillance for a time because of possible exposure to a quarantinable disease, increased more than 100 percent, from 58,083 in fiscal year 1958 to 117,310 in 1959. Most of these persons came from areas where there were occurrences of smallpox and yellow fever. In cases where the danger of exposure was serious, the Foreign Quarantine Service notified local health officials at the destination of the traveler.

★ In fiscal year 1959, 5,264,354 persons subject to quarantine inspection arrived in the United States, both aliens and returning citizens. This was an increase of more than 2 million over 1949.

★ In fiscal year 1959, there were 70,607 inspections of airplanes for quarantine or immigration-medical purposes, an increase of 50 percent over 1949. There were 33,271 inspections of ships, an increase of 37 percent over 1949.

★ The Public Health Service has increased its vigilance against yellow fever in two ways: control measures in the United States and cooperation with other countries.

To reduce the number of *Aedes aegypti*, the yellow fever mosquito, the Public Health Service has recently carried out a survey and control program at more than 100 international airports and dock areas in the southern States, Hawaii, Puerto Rico, and the Virgin Islands, and at Mexican border crossing points. Highest "population index" was nearly 10 percent in Key West, Fla.; that is, mosquito larvae were found in 10 percent of the premises surveyed there. By an all-out campaign against the mosquito, the Key West health department reduced the index to less than 3 percent.

In Miami, the index at the international airport was 4 percent in July 1957. The Foreign Quarantine Service and the local health department set out to reduce this index and was so successful that during a 6-month period in 1959, when the weather was most favorable to insect breeding, no yellow fever mosquitoes were found at the airport.

★ At the Mexican border, local crossings subject to quarantine inspection totaled an estimated 90,000,000; crossings from the interior of Mexico, 1,500,000; migratory labor examinations, 440,000. The staff numbered 124.

★ The 1959 Foreign Quarantine Service budget for activities at United States ports was $3,950,869.

Statistics of the Foreign Quarantine Service, Public Health Service, fiscal year 1958–59.

Stations	Number of inspections		Number of inspections of passengers and crew		Number of inspection personnel [1]
	Vessels	Planes	Vessels	Planes	
Mobile, Ala	986	1	41, 182	15	6
Anchorage	1	830	35	34, 775	([2])
San Diego	560	551	25, 098	2, 182	4
San Francisco	1, 051	294	104, 419	9, 960	7
Los Angeles	1, 974	2, 364	86, 956	77, 254	8
Jacksonville	676	22	12, 766	106	1
Miami	1, 998	19, 293	14, 000	248, 067	27
Tampa	1, 032	859	19, 458	5, 437	8
Honolulu	360	3, 346	55, 917	165, 030	5
Chicago	73	1, 139	1, 100	43, 620	2
New Orleans	2, 271	2, 053	81, 582	64, 440	9
Baltimore	1, 688	43	59, 581	1, 735	8
Boston	934	2, 688	40, 080	95, 480	12
Detroit	85	432	34	17, 103	1
New York City	5, 655	18, 837	901, 466	874, 269	80
Philadelphia	2, 349	92	85, 403	4, 298	9
Fort Monroe, Va	1, 897	4	70, 165	245	9
Galveston	501	2	21, 874	79	5
Seattle	524	462	58, 949	11, 041	5
San Juan, P.R	760	4, 578	50, 683	85, 507	6
Smaller stations	7, 896	12, 717	225, 012	119, 200	20
Total	33, 271	70, 607	1, 955, 760	1, 859, 843	232

[1] Includes medical officers, quarantine inspectors, and sanitation inspectors. Does not include part-time contract personnel.
[2] Coverage provided by contract personnel.