

ANTIBIOTIC QUARANTINE OF GONORRHOEA*

I. EFFECT IN FEMALES

BY

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The penicillin era has seen a striking reduction in the incidence of syphilis in the United States (Moore, 1956; Schamberg, 1956a), Great Britain (Chief Medical Officer's Annual Report, 1957), France (Durel, 1956), Norway (Eliot, 1955; Gjessing, 1956), Sweden (Eliot, 1955; Tottie, 1956), Denmark (Eliot, 1955),* the Soviet Union (Kozhwenikov, 1956), Poland (Towpik, 1957a, b), Canada (Lossing and Allen, 1956), Chile (Coutts, Prats, Vargas-Salazar, and Infante-Varas, 1956), Australia (Booth, 1956), and Hong Kong (Thomson, 1956). Gonorrhoea has not followed suit. With the exception of the reports from Norway and Australia, all of the papers cited above which mention gonorrhoea indicate either a relatively slight reduction in incidence or none at all. Nørgaard (1956) states that gonorrhoea has increased in Denmark, and Härö and Pättälä (1957) report no decline in Finland since 1951. In the United States Navy gonorrhoea comprised 90 per cent. of the venereal diseases seen among naval personnel (Provisional Medical Statistics, 1956). Towpik (1957b) finds that in Poland the incidence of early syphilis declined by 98 per cent. from 1947 to 1955, and gonorrhoea by only 39 per cent. One of us (I.L.S.) has attempted to explore the reasons for this curious difference in the behaviour of syphilis and gonorrhoea in a previous paper (Schamberg, 1956b).

Concerned about the failure of our control efforts to reduce appreciably the incidence of gonorrhoea, the Venereal Disease Control Section of the Philadelphia Department of Public Health instituted in 1956 a programme designed to effect an antibiotic quarantine in patients with gonorrhoea. From May 1, 1956, to July 15, 1957, each male presenting himself to a venereal disease clinic with urethritis considered to be gonorrhoeal in origin was given an intramuscular injection of 2.4 million units

of benzathine penicillin G. All named female gonorrhoea contacts, and all females coming voluntarily to the clinic because of symptoms considered to be gonorrhoeal in origin, were treated in an identical manner, and in addition were asked to return at 8-week intervals for the same treatment for at least a 12-month period. In most but not all female contacts and patients urethral and cervical cultures were taken, and cervical smears were examined in the remainder. A culture was taken before treatment and the patient asked to return in one week, when the culture was repeated if the pre-treatment culture had been positive. At each treatment visit (at 8-week intervals) cultures were repeated, but only those patients who had had a previous positive culture were asked to return in one week. If a culture-positive patient failed to return in one week, letters, telegrams, and field visits by an epidemiologic worker were utilized to bring her back to the clinic.

Benzathine penicillin G was selected because of the prolonged penicillin blood level which follows its administration (Putnam and Roberts (1954); Elias, Price, and Merrion (1951); O'Brien and Smith (1952)). On the basis of duration of prevention of streptococcal pharyngitis during an epidemic in an army camp, Morris and Rammelkamp (1957) concluded that a single injection of 1.2 million units benzathine penicillin G protects for from 6 to 7 weeks. Hookings and Graves (1956) found that, after treatment with 600,000 units procaine penicillin in oil with 2 per cent. aluminium monostearate (PAM) 15 per cent. of female contacts of gonorrhoea cases were named again within 60 days by men with gonorrhoea. When the treatment scheme was changed to 600,000 units PAM plus 1.2 million units benzathine penicillin G, the rate was reduced to 6.7 per cent. In contrast to our programme, these women were treated only

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once. It was felt that benzathine penicillin G would establish a quarantine, based not on prevention of contact with other persons but on prevention of transmission of the gonococcus regardless of the patient's sexual activities. We believed we would not only cure the current Neisserian infection, but might also render the patient unable to contract and unable to transmit gonorrhoea for a period of approximately 8 weeks. Thus an impediment would be placed in the way of rapid and frequent passage of the gonococcus from one person to another.

Approximately 2,400 males and 1,700 females were treated in this manner from May 1, 1956, to July 15, 1957; 274 female patients were admitted to the programme in the first 3 months of its operation, and after 11 months had elapsed only 2 per cent. had failed to return for at least one re-treatment; 55 per cent. had received one re-treatment, 22 per cent. two, 13 per cent. three, and 8 per cent. four. While co-operation was not complete, the period of antibiotic quarantine was prolonged well beyond 8 weeks in a significant number of our female contacts.

We immediately set ourselves the task of attempting to determine whether gonorrhoea in the female is cured by such treatment. 126 named female contacts of males suffering from urethral discharge were asked to return to the clinic weekly for tests of cure for 8 weeks after treatment. (85 per cent. of male patients applying to our clinics because of urethral discharge show gonococci on smear examination, so that the great majority of our contacts had in fact been exposed to gonococcal infection.) Cervical and urethral swab cultures, and curette cultures from the cervix (Kalodner) were utilized routinely in this group. In 79 patients with negative pre-treatment cultures, 231 cultures 1 to 8 weeks after treatment were all negative. 116 cultures were performed 1 to 8 weeks after treatment in 46 women who had had a positive pre-treatment culture; of these all but five were negative, and these five occurred repeatedly in a single patient (Case 1).

Table I shows the laboratory findings and treatment in this patient. Gynaecological examination revealed only a mucoid cervical discharge and bilateral non-tender adnexal thickening which was considered to be the result of chronic pelvic inflammatory disease. Both she and her husband denied extramarital relations within the past 18 months and stated that they indulged in unprotected sexual intercourse approximately three times a week. A cervical culture from this patient was studied by Dr. James D. Thayer, Bacteriologist

TABLE I
RESULTS IN CASE 1 (FEMALE NEGRO AGED 19)

Date	Gonococcus Culture		Treatment		
	Positive	Negative	Benzathine Penicillin G		PAM*
			2·4 m.u.	4·8 m.u.	
July 17	+		X		
July 24	+				
July 31	+				
August 7	+				
August 21	+			X	
August 28		-			
1956 Sept. 5	+				
Sept. 11		-			
Sept. 18	+				
Sept. 25	+				
Oct. 2	+			X	
Oct. 10		-			
Oct. 17		-			
Oct. 24		-			
Nov. 14	+				
Nov. 28	+				
Dec. 4	+		X		
Dec. 26	+				
1957 Jan. 9	+				X
Jan. 18	+				X
Jan. 29		-			X†
Feb. 5		-			
Feb. 19		-			
March 5		-	X		X
March 19		-			
April 15		-			
May 21		-	X		
July 2		-	X		
Aug. 26		-	X‡		
Oct. 21		-	X‡		

*Procaine penicillin in oil with 2 per cent. aluminium monostearate
 †2·4 million units.
 ‡Benzathine penicillin G 1·2 million units plus aqueous procaine penicillin 600,000 units.

at the Venereal Disease Experimental Laboratory in Chapel Hill, North Carolina, who reported as follows:

"Colonies were typical for the morphology and oxidation reaction of the gonococcus, and microscopic examination revealed typical Gram-negative diplococci. Subcultures to unenriched broth and agar media failed to

grow. Sugar fermentations in dextrose, lactose, levulose, maltose, mannitol, and sucrose showed acid only in dextrose. The culture is a typical gonococcus."

In two other laboratories sugar fermentation studies were also typical for the gonococcus. Tube dilution penicillin sensitivity tests in three laboratories reported resistance of these organisms to penicillin G (growth) in amounts ranging from 0.15 to 0.2 u./ml., with inhibition of the organisms (no growth) in amounts ranging from 0.2 to 0.32 u./ml. These levels are considered to be at or near the upper level of resistance of the gonococcus as determined by Love and Finland (1955). In one laboratory the organism was resistant to 0.45 u./ml., inhibited by 0.50 u./ml. of penicillin V. Antibiotic sensitivity studies carried out by the disk method in two laboratories showed the usual spectrum of sensitivity to the other common antibiotics. Penicillin blood levels after injection of 2.4 million units PAM were reported as follows:

Before treatment, 0; post-treatment one day, 1.225 units/ml.; 3 days, 0.365 units/ml.; 7 days, 0.043 units/ml.

Failure to absorb penicillin from a muscle depot can be ruled out as the cause of failure to cure.

TABLE II
RESULTS IN CASE 2, HUSBAND OF CASE 1 (NEGRO AGED 20)

Date	Test for Gonococcus		Clinical and Treatment Data
	Positive	Negative	
1956	July 9	S+	Discharge 1 day duration, 2.4 m.u. benz. penicillin G
	July 16		Discharge improved, still present.
	Oct. 2	S+	Slight discharge, 4.8 m.u. benzathine penicillin G.
	Oct. 10		Slight discharge.
	Dec. 4		Slight discharge
1957	Jan. 18		Intermittent discharge, 1.2 m.u. PAM
	July 5		Intermittent discharge for 3 weeks, 0.5 g. streptomycin

S=Smear. C=Culture.

Table II presents clinical and laboratory findings in Case 2, the husband of Case 1. No detailed urologic studies were carried out. Therefore, we can only say that the husband may have been cured and then re-infected by his wife, or may, like his

TABLE
FEMALE PATIENTS WITH POSITIVE GONOCOCCUS CULTURES WITHIN 8

Case No.	Race	Age (yrs)	Treatment							
			First		Second			Third		
			Days after Treatment		Days after Previous Treatment	Days after Treatment		Days after Previous Treatment	Days after Treatment	
			Culture Positive	Culture Negative		Culture Positive	Culture Negative		Culture Positive	Culture Negative
3	C	20	56	12	56	56	—	56	47, 60	7, 31
4(e)	C	17	58	—	58	25, 40	—	40	—	12
5	C	14	54	6	54	35(d)	15, 44	44	—	64
6(a)	C	20	56	—	56	56	7	56	—	14, 105
7	C	16	7	19, 28, 49	49	—	56	56	—	66
8	W	15	9, 27	—	27	14, 25, 31	7	31(c)	—	7
9	C	40	14	—	23	—	7, 21, 28, 70	70	—	—
10	W	35	8	15, 22	—	—	—	—	—	—

*In all patients pre-treatment culture was positive.

(a) Benzathine penicillin G 4.8 million units on initial treatment.

(b) Procaine penicillin in oil with 2 per cent. aluminium monostearate 1.2 million units plus benzathine penicillin G 2.4 million units.

wife, have failed to achieve cure. It may be noted that the wife had fifteen positive gonococcal cervical cultures over a 6-month period despite repeated injections of benzathine penicillin G. After treatment with 2.4 million units PAM, ten negative cultures were reported in the subsequent 9 months. Thus only one of 126 carefully followed female patients was found not to have been cured by benzathine penicillin G.

During the 14½ months of the programme, eight females (in addition to Case 1) and six males were discovered to be harbouring the gonococcus on at least one occasion within 8 weeks of treatment. The failures in females were detected through the routine follow-up procedures outlined above. It is probable that more failures would have been found had follow-up been more strict. Pertinent data on the eight female failures (Cases 3-10) is shown in Table III. Another paper in this series will present the findings in the male patients.

Fifty patients submitted to a single penicillin blood level determination 1 to 53 days after an injection of 4.8 million units benzathine penicillin G (twice the amount used in our control programme); the findings are shown in Fig. 1 (overleaf).

Discussion

In many studies of the venereal diseases a major obstacle in determining the failure rate lies in the difficulty or impossibility of differentiating relapse from re-infection (Schamberg, 1956b; Schamberg and Steiger, 1948). We are fortunate that this problem does not arise in the present study, since failure has been sought only during the 8-week post-treatment period when the antibiotic should prevent re-infection as well as achieve cure. Even if re-infection played a part in the course of the patients listed in Table III, it is still evidence of failure of the antibiotic quarantine.

Our findings suggest that one in approximately 190 female patients with gonorrhoea can be shown by culture to harbour the gonococcus within 8 weeks after injection of 2.4 million units benzathine penicillin G. The true failure rate cannot be determined, since tests of cure, smear, and even culture, may be negative in the presence of infection.

In a monumental study, Love and Finland (1956) have determined the susceptibility to penicillin of 286 strains of the gonococcus. 95 per cent. of the strains studied required only 0.03 units penicillin/ml. for inhibition; 3.5 per cent. required

III

WEEKS OF TREATMENT WITH 2.4 MILLION UNITS BENZATHINE PENICILLIN G*

Treatment						
Fourth			Fifth		Sixth	
Days after Previous Treatment	Days after Treatment		Days after Previous Treatment	Days after Treatment	Days after Previous Treatment	Days after Treatment
	Culture Positive	Culture Negative				
60	—	51	51	11, 18 25, 63	63	34, 41
12(b)	179	—	179(c)	13, 27, 38, 54 66	66	8
64	—	66	66	56	56	—
105	—	—	—	—	—	—
66	—	65	65	—	—	—
—	—	—	—	—	—	—
—	—	—	—	—	—	—
—	—	—	—	—	—	—

(c) Benzathine penicillin G 1.2 million units plus aqueous procaine penicillin 600,000 units.

(d) Smear positive, culture not taken. Patient presented febrile pelvic inflammatory disease at this time.

(e) Acute pelvic inflammatory disease on first visit; on fifth treatment visit purulent discharge, inflammation of cervix, and fundal and right adnexal tenderness.

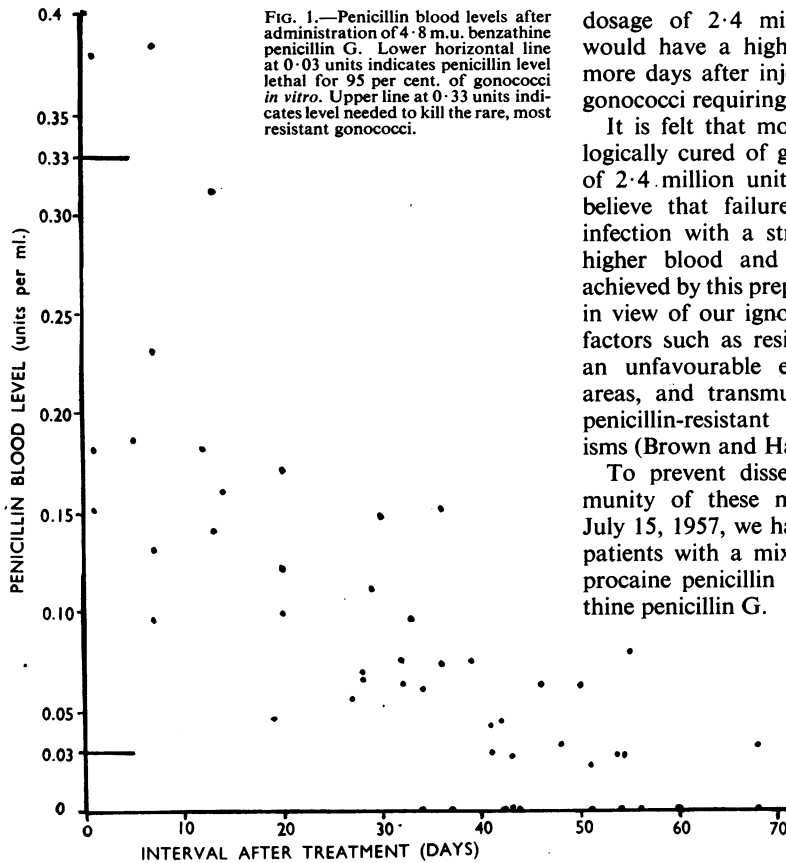


FIG. 1.—Penicillin blood levels after administration of 4.8 m.u. benzathine penicillin G. Lower horizontal line at 0.03 units indicates penicillin level lethal for 95 per cent. of gonococci *in vitro*. Upper line at 0.33 units indicates level needed to kill the rare, most resistant gonococci.

0.06 units; 0.7 per cent. required 0.13 units; and 0.7 per cent. required 0.33 units. Over a period of 9 years (1945 to 1954) no increase in resistant strains was noted. Fig. 1 demonstrates that a blood level above 0.03 units/ml. (lower horizontal line), the concentration which *in vitro* kills 95 per cent. of strains of gonococci, is maintained by 4.8 million units benzathine penicillin G in all patients for a period of 30 days and in the majority for as long as 55 days. However, the level required to kill the rare resistant gonococci, 0.33 units (upper horizontal line), was reached by only two of sixteen patients tested within 20 days after treatment, and by none thereafter. Our therapeutic dose of 2.4 million units is believed to provide about 60 per cent. of the blood level achieved by 4.8 million units. In confirmation of this, Welch (1957) has reported the mean blood level after 2.5 million units benzathine penicillin G to be 0.105 units/ml. at 3 days, 0.110 at 7 days, 0.060 at 10 days, and 0.050 at 14 days. Therefore, a blood level above 0.33 units/ml. would rarely be achieved with a

dosage of 2.4 million units, but most patients would have a high enough blood level for 50 or more days after injection to kill the more sensitive gonococci requiring only 0.03 units/ml.

It is felt that most female patients are bacteriologically cured of gonorrhoea by a single injection of 2.4 million units benzathine penicillin G. We believe that failure to cure usually results from infection with a strain of gonococcus requiring a higher blood and tissue penicillin level than is achieved by this preparation. It is of course possible, in view of our ignorance of the disease, that other factors such as resistance of inactive gonococci in an unfavourable environment, loci in avascular areas, and transmutation of the gonococcus into penicillin-resistant pleuro-pneumonia-like organisms (Brown and Hayes, 1942) may also play a part.

To prevent dissemination throughout the community of these more resistant organisms, since July 15, 1957, we have been treating all gonorrhoea patients with a mixture of 600,000 units aqueous procaine penicillin G and 1.2 million units benzathine penicillin G.

Fig. 2 (opposite) presents the mean, maximum, and minimum blood levels in twenty human subjects after injection of this preparation. For the first 6 hours all sera contained over twice the concentration of penicillin required by the most resistant gonococci (upper horizontal line), but after one day

all but one had fallen below this level. Garson (1957) advises that, in the treatment of gonorrhoea, a blood level of 0.35 units should be maintained for at least 48 hours. Experience will determine whether so prolonged a high level is necessary for cure.

Summary and Conclusions

(1) The attack rate of syphilis has plummeted in the past 10 years. Gonorrhoea has not followed suit.

(2) In an effort to reduce the gonorrhoea attack rate, an antibiotic quarantine was created in about 2,400 male gonorrhoea patients and 1,700 female gonorrhoea contacts by injection of 2.4 million units benzathine penicillin G. The female contacts were asked to return for identical treatment every 8 weeks.

(3) Gonococci were demonstrated in nine females and six males within 8 weeks after treatment. Thus failure of antibiotic quarantine was discovered in about 0.5 per cent. of the women and in 0.25 per cent. of the men.

(4) In one female, infection persisted for 6 months despite repeated injections of benzathine penicillin G in dosage as high as 4.8 million units, but was apparently cured by procaine penicillin in oil with 2 per cent. aluminium monostearate.

(5) Benzathine penicillin G in a dosage of 2.4 million units provides a blood level for 50 or more days after injection sufficiently high to kill 95 per cent. of strains of gonococci. However, it rarely produces the blood level required to kill the most resistant organisms.

(6) In order to prevent dissemination of these more resistant organisms, a preparation providing a higher initial blood level is advisable. Therefore, a mixture of 600,000 units aqueous procaine penicillin and 1.2 million units benzathine penicillin G is now being used in our control programme.

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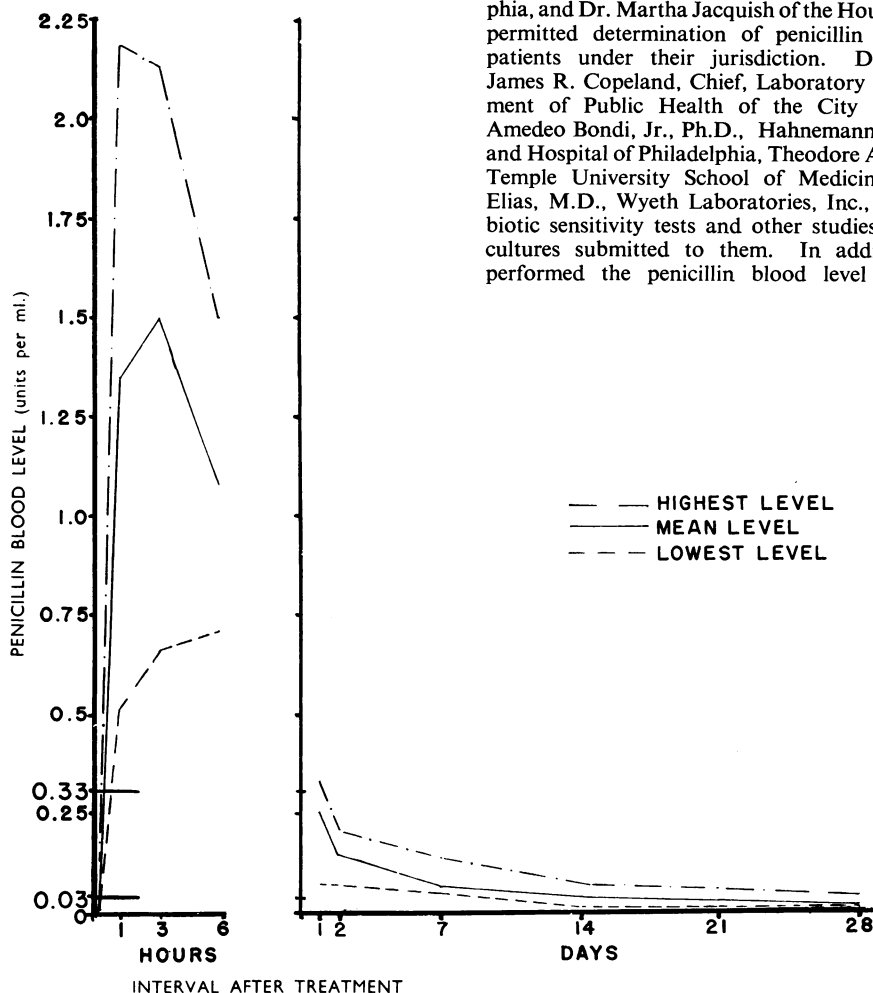


FIG. 2.—Penicillin blood levels in twenty human subjects after injection of 1.2 m.u. benzathine penicillin G plus 600,000 u. aqueous procaine penicillin. Lower horizontal line at 0.03 units indicates penicillin level lethal for 95 per cent. of gonococci *in vitro*. Upper line at 0.33 units indicates level needed to kill the rare, most resistant gonococci (Welch, 1957).

Mr. John Powe, Chief, Epidemiologic Unit, Venereal Disease Control Section, Philadelphia Department of Public Health, carried out statistical analyses. Mr. Sam Glenner, Health Program Representative assigned to the Section of Venereal Disease Control, assisted in procuring the penicillin blood level determinations. Wyeth Laboratories, Inc. generously donated a portion of the benzathine penicillin G (Bicillin) used in this programme.

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