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COHORT STUDY OF VENEREAL DISEASE. I: THE RISK OF GONORRHEA TRANSMISSION FROM INFECTED WOMEN TO MEN

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Reliable data on the risk of transmission of *N. gonorrhoeae* would enhance our understanding of the importance of host defenses against gonorrhea and would aid in the evaluation of prophylactic measures. This paper examines the risk of transmission of gonorrhea from infected female to male and the role that variables such as race, prophylaxis and amount of exposure play in the development of gonococcal urethritis. Volunteer crew members of a large naval vessel were followed prospectively as a cohort to study their risk of acquiring gonococcal infection during a four-day liberty period in the Far East. At the same time the prevalence of *N. gonorrhoeae* was determined in a population of females to whom the sailors were exposed. The calculated risk of transmission per exposure with an infected partner was .19 for whites and .53 for blacks. A statistically significant relationship was noted between the risk of transmission of gonorrhea and both the number of partners and the frequency of sexual intercourse. Further, the increasing infection rate with increasing numbers of exposures in men who had a single sex partner suggests that the majority of men are in fact susceptible to gonorrhea if the quantity of exposure is sufficient.

gonorrhea; military personnel; venereal disease

The risk of transmission of gonorrhea during sexual intercourse has been estimated in several ways. Pederson and Harrah (1) reported that 88.5 per cent of men named by women with gonorrhea were infected. These data would not give a valid estimate of the probability of transmission if some of the male sex partners were the source rather than the recipients of the interviewed women's infections or if the women were asymptomatic and came to medical attention only because their sex partners had recently developed gonococcal urethritis. Grouping of men who were the source of infection with men who were exposed contacts would give a falsely high estimate of the probability of transmission; similarly, interviewing women who sought treatment because their sex partner has developed urethritis will give a falsely high estimate of risk because 100 per cent of such women have at least one sex partner with gonorrhea. A large proportion of fe-

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nale VD clinic patients with gonorrhea do ome for examination because they were amed as source contacts by a male with cute gonorrhea (2). The fact that 62 of 67 97.1 per cent) of the infected male sex ontacts of infected women studied by Pedrson and Harrah had already obtained nedical treatment for gonorrhea before hey were located by the contact investigator suggests this was also true in their tudy. Because Marcussen (3) did not differentiate male and female contacts and the ources of infection were not distinguished rom secondary exposed contacts, we cannot estimate probability of transmission rom his data.

On the other hand, we can use venereal lisease clinic data to estimate the risk of ransmission of gonorrhea from men to women because most of the male patients pontaneously seek treatment for acute rethritis (not because they were named as ex contacts by infected women), and we an differentiate their female primary ource contacts from their female secondry exposed contacts. Thin et al. (4), deected gonorrhea in 92.5 per cent of unprotected women named as secondary contacts of men with acute gonorrhea. This is probably the best available estimate of the likelihood of transmission of gonorrhea from men to women, although it does not relate the risk of infection to the number of sexual exposures.

The risk of transmission from women to men was estimated in a previous US Navy study (5). Holmes et al administered a questionnaire to men aboard an aircraft carrier to determine the number who had had intercourse with prostitutes while their ship was in port and then followed them to determine the number of cases of gonorrhea occurring in the men. They estimated the proportion of prostitutes with gonorrhea by obtaining culture specimens from 702 bar girls who were undergoing routine required examinations. They used these data to estimate the risk of acquiring gonorrhea as a result of intercourse an average of 2.5 times with an infected woman. As Felton (6) discussed, Holmes' study was compromised by several factors including: the bar girls were cultured nearly a year after the men were exposed; the possibility that those who were cultured were not representative of the females contacted by the sailors; the men were not interviewed about their sexual behavior until several days after exposure occurred; and, most important, by the method of culturing the women (use of a wire loop rather than a swab). This last factor may have contributed to the marked difference observed in the rate of recovery of gonorrhea on a single examination (8.5 per cent) versus the cumulative percentage of women found to be infected by repeated weekly culturing (19.7 per cent). Use of the 8.5 per cent figure led to an estimated 50 per cent risk of transmission although use of the 19.7 per cent figure showed an estimated 22 per cent risk of transmission.

Better data on the risk of infectivity would enhance our understanding of the importance of host defenses against gonorrhea and would aid in the evaluation of prophylactic measures. In addition, it would provide needed information for mathematical models used in estimating the cost and effectiveness of control programs (7, 8). Our purpose is to re-examine the risk of transmission of gonorrhea from infected woman to man; we will correct some of the deficiencies of the earlier US Navy study (6) and determine what role variables such as race, quantity of exposure, and use of various prophylactic measures play in the risk of acquisition of gonococcal urethritis.

During a voyage to the Western Pacific, volunteer crew members of a large naval vessel were examined and cultured for asymptomatic gonorrhea, interviewed about their past sexual behavior and history of venereal disease, and followed prospectively as a cohort to study their risk of acquiring gonococcal infection. Cohort members who had intercourse during the ship's four-day liberty period in the Far

East answered questions about their sexual exposures and participated in a double-blind study of the antibiotic prophylaxis of gonorrhea, as described elsewhere (9). We are reporting on the risk of acquiring gonorrhea by the men who received the placebo.

MATERIALS AND METHODS

Study design

Eighteen hundred ninety-six volunteers on a large naval vessel were examined for the presence of a foreskin, for evidence of urethral discharge, and were cultured for gonorrhea during the ship's voyage to a port in the Western Pacific. Six had gonorrhea and were treated. During the subsequent four days in port, a proportion of the cohort had sexual intercourse with hostesses in local bars. As soon as sexually exposed members of the cohort returned to the ship they were offered either a long-acting tetracycline or a placebo on a double blind basis and were interviewed about their sexual behavior and use of prophylaxis. On two mornings the ship was in port, registered hostesses in the nearby town were cultured for *Neisseria gonorrhoeae* and interviewed. During the subsequent 10-day at-sea period a shipboard venereal disease clinic was conducted in order to monitor the number of cases of gonorrhea.

Study population

Men. The male study population consisted of 537 sexually exposed men who received a placebo upon returning from liberty. Of these men, 74 per cent were under 22 years of age; 78 per cent were white, 19 per cent black and 3 per cent belonged to other races. More than 70 per cent were single.

Women. The men were exposed to some of the approximately 8000 hostesses employed in bars in the neighboring town. Five hundred and eleven of the 8000 previously scheduled hostesses reported to the city's Social Hygiene Clinic for their required bi-monthly examination on each of two mornings during the four-day in-port period. The hostesses were scheduled for examination on the basis of the bar at which they were registered. The average age of the sampled hostess population was 25.3. They were from 35 of the 200 local registered bars.

Questionnaire

Men. Upon returning from liberty and prior to the administration of the placebo, the men were interviewed by one of nine interviewers to determine: (a) the number of sexual partners and the number of episodes of sexual intercourse with each partner; (b) the source of the contact (e.g., bar hostess, street pick-up, other); (c) the protective method used with respect to each exposure (i.e., use of a condom, interval from time of intercourse until voiding and until washing of the penis); (d) the name of the club visited.

Women. Before being cultured, each woman was asked her age, the date of the first day of the last menstrual period, the number of months she had worked as a registered hostess and the name of the club where she worked.

Diagnostic methods

Men. During the cruise, all men who reported to the sick bay with symptoms of dysuria, urethral discharge, or penile lesions had intraurethral specimens obtained with calcium alginate nasopharyngeal swabs (Inolex Corp., Chicago, IL) for gram stain and culture. A case of gonorrhea was regarded as confirmed when typical gram negative diplococci that were oxidase positive were isolated on Thayer-Martin medium. Also included in the analysis were three individuals who had gram-negative intracellular diplococci on smear only.

Women. From all 511 women an endocervical specimen was obtained with a calcium alginate urogenital swab and inoculated on Thayer-Martin medium. We also cultured the anal canal of 50 per cent

process was diagnosed as having gonorrhea when culture positive gram negative diplococci grew on Thayer-Martin medium.

Statistical methods

We used a Chi square (χ^2) analysis to test for differences in infection rates in different groups (3d) and a regression Chi square (11) test for a linear relationship between number of partners and infection rates and between number of exposures and infection rates. Two assumptions must be made to calculate the risk of transmission of gonorrhea from infected women to men. The two assumptions are: (a) that the infection rate in the hostesses to whom the men were exposed was the same as in the cultured hostesses; (b) that the pairing was random.

Of the several methods of estimating the risk of transmission we used the "minimum chi-square" (12). The minimum χ^2 is the quantity resulting from computing the observed frequencies with the expected frequencies according to certain theories and assumptions. In this case:

$$\chi^2 = \sum_{ij} \frac{(O_{ij} - E_{ij})^2}{E_{ij}} + \sum_{ij} \frac{(O'_{ij} - E'_{ij})^2}{E'_{ij}}$$

where $E_{ij} = N_{ij}q_{ij}$ is the expected number of uninfected men for those who had i partners and j exposures; $E'_{ij} = N_{ij}p_{ij}$ is the expected number of infected men among those with i partners and j exposures; O_{ij} is the observed number of uninfected men for those with i partners and j exposures; O'_{ij} is the observed number of infected men with i partners and j exposures, N_{ij} equals the total number of men with i partners and j exposures; $q_{ij} = (1 - rs)^j$, where s = probability of infection in the hostess, r = probability of transmission per exposure from female to male, and $p_{ij} + q_{ij} = 1$. For example, an individual who had one exposure would have a probability of $1 - rs$ of not being infected. The probability of not being infected in two exposures is $(1 - rs)^2$. We would assume that the prevalence rates in female partners differed for the men with one, two, or more partners. However, we have only one estimate of s i.e., the percentage of women infected, and we have no basis for believing that the prevalence rates are different in the group of women visited by men with one partner, the group of men with two partners, etc.

We also used a second model to calculate the expected values. This formula for calculating the probability that an individual with i partners and j exposures is not infected is: $q_{ij} = (1 - s)^i + s(1 - r)^{ij}$ where i = the number of partners, j = the number of exposures, and s and r are defined as before. The value of r giving the minimum χ^2 in this model was similar to the value in the first model.

Results

Infection rates in men

During the four-day liberty period the 487 men reported a total of 1,068 exposures to 314 partners. The average was 1.6 partners, 0.7 casual exposures, and 2.4 exposures per partner. Fifty-four of the 387 men developed gonorrhea during the next 10 days for an overall infection rate of 10 per cent.

Table 1 shows infection rates with respect to the number of exposures and partners for the 480 men who did not use condoms on any exposure. As the number of exposures increased, the proportion of exposed men acquiring infection also increased, although not consistently ($\chi^2 = 14.3$, $p < .01$). Even if we considered only those men who had one partner, the relationship to exposure was still evident: the infection rate rose from 3.7 per cent with one exposure to 17.1 per cent with four exposures.

The infection rate for men with one partner was 5.4 per cent. This increased to 11.7 per cent for those with two partners and to 17.2 per cent for those with three or more partners (Table 1). Using a regression χ^2, we found this increase to be significant at the .05 level.

The difference in infection rates between blacks and whites is examined in table 2. Only 8.2 per cent of whites developed infection as compared to 19.1 per cent of blacks ($\chi^2 = 8.65$; $p < .01$). This relationship held true for almost all levels of exposure and number of partners. Apparently the infection rate in blacks was significantly higher than in whites even when the number of exposures or partners was controlled.

However, the blacks were less likely to establish contact in clubs than whites. Although 89.4 per cent of the whites established contact in clubs, only 81.3 per cent of the blacks did so ($\chi^2 = 7.6$, $p < .01$). Also the blacks were less likely to visit the clubs in which the screened hostess population worked. Only 7.3 per cent of blacks named clubs where the examined hostesses worked, although 28.5 per cent of whites did so ($\chi^2 = 25$, $p < .001$).

The proportion of sailors using protective methods during or following their sexual exposure is detailed in table 3. The condom was used sometimes or always by only 5.5 per cent of the 527 individuals in whom the condom usage pattern was known. On the other hand, 35 per cent washed within one hour of exposure and nearly 37 per cent urinated within 30 minutes. The attack rates of gonorrhea in users and non-users of each protective method are shown in the bottom rows. Although no infection occurred in condom users, the difference in infection rate between users and non-users was not significant. Infection rates were unrelated to urination within 30 minutes after exposure. Although the infection rates per 100 men were lower for men who washed within an hour, this difference was not significant ($\chi^2 = 1.0$, $p > .25$), and was accentuated by a lower number of expo-

TABLE 1

Acquisition rates of gonorrhea among non condom users with respect to number of sexual partners and exposures*

No. of exposures	1 partner			2 partners			≥3 partners			Combined		
	No. of men	No. infected	% infected	No. of men	No. infected	% infected	No. of men	No. infected	% infected	No. of men	No. infected	% infected
1	103	9	8.7							103	9	8.7
2	74	2	2.7	19	2	10.5				93	4	4.3
3	63	5	7.9	30	2	6.7	5	0	0.0	98	7	7.1
4	35	6	17.1	26	5	19.2	9	4	44.4	70	15	21.4
≥5	34	4	11.8	62	7	11.3	38	5	13.2	134	16	11.9
Total	309	26	8.4	137	16	11.7	52	9	17.3	498	51	10.2

* Excludes 29 condom users and 10 whose use was unknown.

TABLE 2

*Acquisition rates of gonorrhea, by race in relation to number of sexual partners and exposures (condom users excluded)**

No. of partners and exposures	Race	No. of men		Infected/100 men
		Infected	Exposed	
Single partner/single exposure	White	4	78	5.1
	Black	3	13	23.1
Single partner/multiple exposure	White	10	155	6.5
	Black	6	32	18.8
Multiple partners/multiple exposures	White	15	134	11.2
	Black	9	37	24.3

* χ^2 for differences between races: 8.65, $p < .01$.

TABLE 3

*Exposure and gonorrhea infection rate in men using various protective measures**

	Condom		Mean exposure to washing interval: 1 hour		Maximum exposure to urination interval: 30 minutes	
	Users	Non-users	Users	Non-users	Users	Non-users
No. of men	29	498	85	158	110	185
No. of exposures	66	1832	238	495	258	628
No. infected	0	51	5	17	9	20
Infected/100 exposures	0.0	2.8	2.1	3.4	3.5	3.2
Exposures/100 men	228	368	280	313	235	339
Infected/100 men	0.0	10.2	5.8	10.8	8.2	10.8

* Excludes: 10 men with unknown condom usage, 294 men with unknown washing interval after one or more exposures, and 242 men with unknown urination interval after one or more exposures.

sures by men who used this method of prophylaxis. The data were also examined for various other intervals from exposure until washing or voiding but no significant results were obtained.

The effect of circumcision on infection rate was examined. For whites only, uncircumcised men had a greater infection rate than circumcised men ($\chi^2 = 2.8$, $p < .1$) although exposure rates per man were similar.

Infection rates in hostesses

Of the 511 examined hostesses, 90 were infected for an infection rate of 17.6 per cent. Rectal cultures were obtained on 254 (49.6 per cent), of which 45 were positive; 44 of these 45 women were positive on cervical cultures also. That only one additional infection was detected by rectal culture suggests the cervical culture alone was sensitive in detecting existing infections among these women.

Table 4 shows the relation between age, months worked, and the presence of gonococcal infection. Infection rates among the screened hostess population declined rapidly with age ($\chi^2 = 21.34$, $p < .001$). Also, the longer a hostess had worked the less likely she was to be infected ($\chi^2 = 10.16$, $p < .01$).

The infection rate of the hostesses at the different clubs in relation to the predominant racial composition of the group of sailors visiting each club was also examined. The infection rate in the hostesses at the club visited predominantly by blacks was 10.5 per cent and in those clubs visited predominantly by whites it was 12.4 per cent. In clubs catering to a racially mixed clientele the infection rate was 29.4 per cent ($\chi^2 = 2.8$, 2 df, $p < .25$).

Risk of transmission

Using the minimum Chi-square method and the first formula, $(1 - rs)^s$, for estimating the risk of transmission per exposure for white males, we obtain a value of $r = .19$ for $s = .18$. That is, the risk of transmission by an infected woman to a white man per exposure is .19 per exposure. If a man has two exposures with an infected woman the probability of his being infected, assuming $s = 1$, is $1 - (1 - rs)^2 = .35$; on three exposures .47; and on four exposures .57.

We did a similar analysis for blacks. If the infection rate in the hostesses is .18, $r = .53$. However, the blacks did not frequent the same clubs as the whites, and a higher proportion of the whites established contact in clubs than did blacks. These facts raise the possibility that hostesses having sexual relations with blacks may have a higher prevalence of infection with *N. gonorrhoeae*. Therefore, if we assume that the risk of transmission per exposure for blacks was the same as for whites, $r = .19$, and solve for the prevalence rate in the female

TABLE 4

*Age, months of work as a registered hostess, and prevalence of gonorrhea**

Months of work	Age				
	<20	20–24	25–29	>29	Total
0–11.9					
No. examined	27	122	42	10	201
No. infected	9	27	7	1	44
% infected	33.3	22.1	16.7	10.0	21.9
12–23.9					
No. examined	19	43	27	8	97
No. infected	7	10	4	1	22
% infected	36.8	23.2	14.8	12.5	22.7
≥24					
No. examined	4	60	73	76	213
No. infected	2	9	8	5	24
% infected	50.0	15.0	11.0	6.6	11.3
Total					
No. examined	50	225	142	94	511
No. infected	18	46	19	7	90
% infected	36.0	20.4	13.4	7.4	17.6

* χ^2 for age on 3 df = 19.7, $p < .001$. χ^2 for length of work on 2 df = 12.79, $p < .01$.

partners of blacks, then $s = .50$, i.e., the prevalence rate in the female partners of the black men is .50, which is almost three times the measured prevalence for the sampled females.

With the second formula, i.e., $q_{ij} = (1 - s) + s(1 - r)^{j/i})^i$, the value of r for whites when $s = .18$ is $r = .25$. That is, the risk of transmission per exposure is .25. Using this formula we can calculate the probability of not being infected after the second exposure with one partner as .921, after the third exposure with one partner as .896, after the fourth exposure with one partner as .877. If, however, an individual had four exposures with two partners the probability of not being infected is .849, slightly lower than if he had one partner and four exposures.

For blacks if we assume the risk of transmission, $r = .25$, then the prevalence rate in the female partners, $s = .46$.

DISCUSSION

By making two assumptions we have calculated the risk of transmission of gonorrhea from infected women to men. The two assumptions are: 1) that the infection rate in the hostesses to whom the men were exposed was the same as that in the cultured hostesses; 2) that the men picked hostesses at random. This assumption may not be true. Men with only one exposure may have gone to bars having higher infection rates in their hostesses, e.g., those nearer to the ship.

An important consideration in our analysis is the accuracy with which the Thayer-Martin endocervical culture method identifies those women who are actually infected. Although this technique is undoubtedly more sensitive than the technique used in the earlier US Navy study (6), it has been reported that the sensitivity of the Thayer-Martin culture may be as low as 70–80 per cent (13). If the true prevalence of infection in the screened hostess population was higher than .18, then the estimated risk of acquisition of infection by the men would be proportionately lower.

Unlike previously cited studies of the risk of transmission of gonorrhea, this particular investigation examined risk of transmission in relation to number of exposures and was conducted in a prospective manner. Additionally, a good deal of information was available on the female contacts, the cul-

ire techniques used were considered optiıal, and the male population was more iosely defined and examined than in past :udies. Nonetheless, the present study sufers from uncertainty regarding the validity f the assumption that the prevalence of onorrhea in the women we tested was epresentative of the prevalence of gonorhea in women with whom members of the ohort had intercourse. On the other hand, his study does demonstrate a statistically ignificant relationship between the risk of ransmission of gonorrhea and both the ıumber of partners and the frequency of ntercourse. Furthermore, the increasing inection rate with increasing numbers of exɔosures in men who had one sex partner ıuggests that the majority of men are in 'act susceptible to gonorrhea if the quantity ɔf exposure is sufficient. For example, ımong men who had four or more expoɜures to a single partner, 10 (14.4 per cent) ɔf 69 acquired gonorrhea. If only 18 per :ent of their sex partners had gonorrhea, then 14.4/18.0 or 81 per cent of those exposed to an infected woman four or more times acquired infection. Also, the results indicate that, in this setting, whites have a significantly lower gonorrhea infection rate than blacks, even when the number of exposures is controlled. Although the data for men who became infected after receiving tetracycline prophylaxis have not been presented, the same trend toward increasing infection rates with increasing number of exposures for men who had a single partner and for lower infection rates in whites than in blacks was noted.

This investigation raises a number of questions. First, why is there a relationship between the risk of infection and the frequency or number of episodes of intercourse? This relationship may result from many different factors, including variables in the infectivity and virulence of the organism and the infecting inoculum; variability in host resistance to organisms of uniform infectivity; environmental factors such as duration of intercourse and time from ejaculation to withdrawal; the use of prophylactic measures; and the cyclic variation in the quantity of organisms. Second, why is the racial variation in risk of infection observed? One explanation is that pairing is not random and that the infection rate in the hostesses to whom the blacks were exposed was greater than the infection rate in the hostesses to whom the whites were exposed. Alternatively, the reliability of the information obtained from blacks and whites on number of contacts may have been different; i.e., blacks may have underreported or whites may have over-reported the number of contacts or partners; or racial differences in susceptibility to gonorrhea may actually exist. The declining prevalence of gonorrhea among hostesses with increasing age or increasing duration of work as a hostess is intriguing. Perhaps younger hostesses or new hostesses are more frequently exposed to gonorrhea or perhaps more experienced hostesses employ better protective measures or have acquired immunity to gonorrhea. Different study designs would be required to further answer questions raised in this study. For example, a prospective study, involving random assignment to prophylaxis would be necessary to definitely study the efficacy of condom use, or of washing or voiding after intercourse. The risk of infection may differ in other population groups in which the dynamics of sexual exposures are different, e.g., a nonprostitute population; women with acute infection may be more infectious than those with chronic or predominantly asymptomatic infection; and the infectivity of gonococcal strains may vary in different geographic regions. Finally, an attempt should be made to measure the risk of transmission of gonorrhea from men to women.

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