COMMON CONTAGIOUS GENITO-URINARY DISEASES WITH REFERENCE TO THE ITO-REENSTIERNA AND FREI TESTS*†

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While serving as a medical officer in 1952 and 1953 aboard a troop transport operating between the United States, Okinawa, and Japan, I saw many patients with penile lesions which were diagnosed in these regions as chancroid. Certain clinical features led me to believe that most of these lesions more nearly fit the usual descriptions of herpes genitalis than of chancroid. Basically, most of them resembled "canker sores" or ulcerated "fever blisters". Adenitis or bubo formation was uncommon, local recurrence was frequent, artificial auto-inoculation would result only rarely in any reaction, and the lesions healed satisfactorily without scars with no treatment other than cleanliness. My interest in the use of the Ito-Reenstierna (I-R) and Frei tests began with my efforts to distinguish these commonly seen penile lesions from chancroid and lymphogranuloma venereum.

As the study progressed, it became apparent that more work was needed with the I-R and Frei tests in regard to normal values, racial differences in reaction and specificity. It also appeared that the tests would aid in diagnosing intra-urethral chancroid and lymphogranuloma venereum. The theoretic possibility also exists that there is a relationship between the common penile lesions and urethritis, particularly non-gonococcal urethritis, seen in a given region. Harkness (1945) noted that some penile lesions resembling herpes genitalis are caused by the gonococcus; syphilis, lymphogranuloma venereum, chancroid, condyloma acuminatum, tuberculosis,

herpes simplex, herpes zoster, granuloma inguinale, and actinomycosis are reported to occur intra-urethrally as well as on the external surface of the penis (Willcox, 1950; Harkness, 1950). Comparison of the reactions to the I-R and Frei tests in patients having urethritis with the reactions in those having penile lesions may aid in determining a relationship, if one exists, between these diseases.

Normal Controls

The choice of normal subjects in relationship to these tests is difficult. From a diagnostic standpoint, one is primarily interested in determining the differences in the reactions brought about by chancroid and those associated with penile lesions, urethritis, and adenitis caused by conditions not associated with the organism of chancroid. It is well known that syphilis and chancroid occur not rarely in the same patient; since identification of *Haemophilus ducreyi* is impossible in many cases of chancroid (Levin, 1941; Heyman, Beeson, and Sheldon, 1945), syphilitic patients are undesirable controls. Gonorrhoea is not infrequently associated with Gram-negative bacilli that could in some cases be *H. ducreyi*; hence, one would hesitate to accept patients having gonorrhoea as ideal controls without special studies. Lymphogranuloma venereum is probably also frequently associated with the causative organism of chancroid; therefore, patients having chancroid are poor controls for the Frei test, and patients having lymphogranuloma venereum are poor controls for the I-R test. Since the cause of most urethritides and penile lesions seen to-day is uncertain, the ideal normals from a theoretic viewpoint would be persons who had never had sexual intercourse. The minimal requirement for purposes of determining the aetiological factors should be that

* Received for publication September 4, 1957.

† This presentation is based upon studies performed by the author while on active duty in the U.S. Naval Reserve as a medical officer aboard the U.S.S. *General J. C. Breckinridge* (TAP176).

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the persons chosen should have no active or past history of venereal disease.

The control group in the present study consisted of 31 young adult white men with no apparent active infections and no history of genito-urinary disease. Of these, fifteen were given smallpox vaccinations (not primary reactions) 3 days before or 1 day after the I-R and Frei tests were made. No essential difference was noted in the results of vaccination in these groups. All 31 had reactions to the I-R test less than 6 mm. in diameter, which would be interpreted as negative reactions by accepted standards. These findings are in contrast to studies by Robinson (1940), in which 28 per cent. of the controls reacted positively to the I-R test. In his controls, 43 per cent. of syphilitic adults reacted positively, while none of eleven children did so. As just mentioned, none of my 31 normal subjects had positive reactions; for comparison with larger groups, only one of 104 patients having urethral discharges without present or past penile lesions reacted in a positive manner, and only seven of 142 patients presenting with only simple penile ulcers or vesicles without severe inguinal adenitis when seen or in the past had positive I-R reactions. None of the reactions to the Frei test in the 31 controls were more than 5 mm. in diameter and all would be considered as negative reactions by accepted standards. Contrasting experience with the Frei test by other workers will be discussed later.

Penile Lesions and the Ito-Reenstierna Test

The first study performed to check the validity of the diagnosis of chancroid was a determination of the reaction to the I-R test on 22 crew members who had been diagnosed in the past by various physicians as having chancroid. Positivity to this test is supposed to remain for life, or at least for many years (Cole and Levin, 1935); however, only two of these men had reactions that could be interpreted as even questionably positive by usual standards (Table I, Group B), and one of these had negative results in a repeat test.

Table I shows the results of the I-R test in men presenting with urethral discharges or ulcerative or vesicular penile lesions and having reactions to this test of less than 8 mm. Groups C, D, E, and G(2) represent the findings in 142 men presenting with penile lesions; of these, 79 had also had penile lesions in the past. Twelve men with urethral discharges had also experienced penile lesions in the past (Group G(1)), and 22 men without disease (Group B) had noted penile lesions in the past. Thus, the tests considered here are pertinent in the diagnosis of past lesions in 107 patients as well as in the diagnosis of the 142 presenting lesions.

A central reaction measuring 8 mm. or more in diameter was chosen as positive because this included all patients seen during this study with destructive lesions or buboes or both, and because reactions 6 or 7 mm. in diameter were frequently seen in

TABLE I

ITO-REENSTIERNA REACTIONS LESS THAN 8 MM. IN DIAMETER

Group	Condition of Patient		Number of Patients	Average Reaction (mm.)	Distribution of Reactions (per cent.)		
					No Reaction	1 to 4 mm.	4+ to 7 mm.
A	Normal controls		31	1.1	68	19	13
B	Chancroid in past; no present active disease (Table II)		22	2.6	36	50	14
C	Presenting penile lesions but not questioned about past urethritis (Table III)		43	2.3	54	12	34
D	Presenting penile lesions and no past urethritis		51	1.8	43	47	10
E	Presenting penile lesions and having had urethritis:	(1) First lesion	14	2.1	50	14	36
		(2) Second lesion	10	1.4	60	30	10
		(3) Third lesion or more	7	2.7	42	29	29
	Total Group E		31	2.0	52	23	25
F	Presenting urethral discharge without previous penile lesions (Table IV)		104	2.0	47	30	23
G	Presenting urethral discharges:	(1) Penile lesions in past	12	2.5	50	17	33
		(2) Penile lesions present	17	2.5	47	12	41
Total Groups B-G			280	2.1	47	29	24

diseases that appeared similar to those associated with absent or minimal reactions to this test. Occasionally, a central reaction less than 8 mm. in diameter was associated with a large flare, in which case it was interpreted as positive. This agrees in general with the observation of Greenblatt and Sanderson (1938) that only reactions with 7 mm. centres and surrounding erythema of 14 mm. or more in diameter are considered diagnostic.

In a year aboard a large troopship operating in the Pacific zone, only twenty patients were seen who had positive I-R reactions and present or past histories of a destructive penile lesion or inguinal adenitis or both. As already noted, only seven (5 per cent.) of 142 tested who presented with only simple ulcers or vesicles without associated inguinal adenitis or adenitis in the past had positive reactions to the I-R test. One might postulate that this number might increase if the duration of the lesion was much longer. However, the Tables show that lesions in the past that were diagnosed as chancroid do not appreciably alter the reaction, and that the duration of these herpetiform lesions does not greatly alter the test results. On the other hand, this incidence actually may be rather high, since the incidence of false positive reactions might be greater during the early phase of an infection by an antigenically related organism.

Of the twenty patients having positive reactions to the I-R test and having destructive ulcers or adenitis or both, five had these lesions in the past. Thus, fifteen patients probably having chancroid were seen during this study, while more than 170 men had penile lesions not characteristic of chancroid. Dark-field examinations in nearly all of these, many presumptive Kahn tests, and I-R and Frei tests done on more than 140 of them suggested that nearly all these lesions were probably not syphilis, chancroid, or lymphogranuloma venereum.

These results indicate that most penile lesions seen in Okinawa, Korea, and Japan are not associated with positive I-R reactions although they are commonly diagnosed as chancroid. The problem arises, then, as to the relationship between these vesicular and ulcerative lesions and chancroid. A few patients having simple penile lesions had associated adenitis and reacted positively to the I-R test. One patient gave a history of having an herpetiform lesion that healed and was followed 1 month later by a typical bubo associated with a positive I-R reaction. Thus, one cannot tell from the clinical appearance that the herpetiform lesion is not caused in some cases by the same organisms as those producing classic chancroid associated with a positive I-R reaction. There is also the possibility that some

penile lesions might be caused by *H. ducreyi* and not be associated with an hyperimmune reaction locally or to the intradermal test.

The cases have been analysed by duration of the lesion and by past diseases in an effort to detect any existing effect of these lesions on the intradermal test. Measurements of the deeply erythematous and oedematous centre of the reaction were made 48 hours after the intradermal injection. One must admit a certain percentage of error in these measurements, but it is believed that the range of error in measurement does not invalidate certain trends to be noted in the reactions. That little of this measured reaction was due to the mechanical trauma of the injection is shown in the smallness of the reaction to the Frei test and particularly to the control injection.

Tables I(C) and II show the results of the I-R test in patients presenting with penile lesions but who were not questioned about past urethritis. There is no great change in the reactions with regard to the duration of the lesion or a history of previous lesions.

TABLE II

ITO-REENSTIERNA REACTIONS IN PATIENTS WITH PENILE LESIONS WHO WERE NOT QUESTIONED ABOUT POSSIBLE PAST URETHRITIS

Duration of Lesion (days)	Average Reaction (mm.)*			
	First Lesion	Second Lesion	Three or More Bouts of Lesions	Total
1	2.2 (5)	1.9 (8)	1.6 (4)	1.9 (17)
2	none	1.7 (6)	3.1 (6)	2.4 (12)
3-4	0 (1)	3.2 (3)	0 (1)	1.9 (5)
5 or More	3.6 (4)	4.8 (2)	1.2 (3)	3.1 (9)
Total	2.6 (10)	2.3 (19)	2.0 (14)	2.3 (43)

* Numbers in parentheses indicate number of patients.

However, there is a tendency to a slight decrease in reaction with increasing numbers of penile lesions in the past, and a slight increase in reaction with the duration of lesion. Results in patients presenting with penile lesions who had never had urethritis (Table III, opposite) show that the reaction to the I-R test increases slightly with lesions that have lasted 5 or more days. No definite difference is noted in the reaction in those with their first penile lesion and those with their second. Group E of Table I shows no definite change in the reaction which could be due to past penile lesions when the patients had also had urethritis.

These Tables indicate no pronounced increase in reaction to the I-R test as the result of a simple penile

TABLE III

ITO-REENSTIERNA REACTIONS IN PATIENTS WITH PENILE LESIONS AND NO PREVIOUS URETHRITIS

Duration of Lesion (days)	Average Reaction (mm.)*			
	First Lesion	Second Lesion	Three or More Bouts of Lesions	Total
1	1.6 (6)	1.8 (10)	0 (2)	1.5 (18)
2	0.8 (10)	2.1 (5)	0 (2)	1.1 (17)
3-4	0.6 (4)	0 (1)	None	0.5 (5)
5 or More	4.6 (8)	3.0 (2)	3.0 (1)	4.2 (11)
Total	2.0 (28)	2.0 (18)	0.6 (5)	1.8 (51)

* Numbers in parentheses indicate number of patients.

lesion in the past. There is also no striking increase in reaction with increasing duration of this disease. On the other hand, evidence that these penile lesions influence the I-R test is found by comparing the average size of the reactions associated with the diseases with that of those in normal persons. The average reaction in persons with past or present penile lesions was 2.0 mm. in diameter, while the average in normal persons was 1.1 mm. This may be within the range of accuracy of the test; however, if one looks at the various Tables with the process of sensitization and desensitization in mind, it can be seen that they show trends suggesting this process. That is, the intradermal reaction tends to increase slightly with duration of the disease, but the maximal reaction is not great enough to be called positive, and there is some suggestion of decrease in reaction with succeeding bouts of disease. Also, specificity tests suggested that such slight differences in average reactions may be real. Then, too, repeated tests in the presence of urethral discharges (Table IV) and penile lesions indicated that these slight changes, when considered as a group, may be significant for theoretic purposes.

TABLE IV

ITO-REENSTIERNA REACTIONS IN PATIENTS WITH URETHRAL DISCHARGE AND NO PREVIOUS PENILE LESIONS

Duration of Urethritis (days)	Average Reaction (mm)*			
	First Urethritis	Second Urethritis	Three or More Episodes of Urethritis	Total
1	1.4 (20)	2.1 (17)	2.3 (15)	1.9 (52)
2	2.1 (9)	2.6 (8)	2.1 (5)	2.3 (22)
3-4	1.6 (6)	3.2 (3)	1.8 (6)	2.0 (15)
5 or More	2.5 (9)	0 (2)	2.1 (4)	2.1 (15)
Total	1.8 (44)	2.2 (30)	2.1 (30)	2.0 (104)

* Numbers in parentheses indicate number of patients.

Many penile lesions are diagnosed as chancroid by noting the presence of typical Gram-negative bacilli in smears from the lesions. Table V shows the results of the I-R tests in patients with simple penile lesions from which smears showed Gram-negative bacilli of various sizes, many being morphologically similar to *H. ducreyi*. Clinically, these lesions appeared to be the same initially and during an observation period, usually of approximately 1 week but varying from a few days to several months, as those unassociated with Gram-negative bacilli. The reactions to the I-R test were essentially the same in the two groups. The time required after the appearance of the ulcer for the I-R reaction to become positive probably varies considerably. I have seen positive reactions as early as the second day and some authors have stated that the reaction usually becomes positive before the end of the second week (Becker and Obermayer, 1940; Speiser, 1942; Greenwald, 1943; Tucker, 1950), but Cole and Levin (1935) stated that the average duration of the disease before positive results appeared was 5 weeks. The duration of disease in the cases in Table V was, in many instances, less than the time usually required for a positive reaction to occur; however, when considering a number of cases, particularly when one-third of the lesions was present for 6 days or more, one would expect to see some increase in reactions to the I-R test if these lesions were chancroid. Gram-negative bacilli were seen in only three of seven herpetiform lesions associated with positive I-R tests; none of these were streptobacilli or in other ways morphologically typical of *H. ducreyi* and other bacteria were present in each case. The results observed here create doubt that *H. ducreyi* is a common cause of herpetiform penile lesions even though Gram-negative bacilli may be present, and

TABLE V

ITO-REENSTIERNA REACTIONS* IN 21 PATIENTS HAVING PENILE LESIONS WITH GRAM-NEGATIVE BACILLI

By Duration			By Past History		
Days	Size (mm.)	Number of Patients	Penile Lesions (Bouts)	Size (mm.)	Number of Patients
1	1.7	8	1	1.8	9
2-3	0.6	6	2	1.6	8
6-10	2.3	5	3 or More	0	3
10+	2.2	2	Unknown	4.5	1

* The overall average reaction measured 1.6 mm. A total of 62 per cent. of these patients had no reaction; the reactions in 19 per cent. ranged from 1 to 4 mm., and in 19 per cent. they ranged from 4+ to 7 mm.

the diagnosis of chancroid should not be made solely on the basis of examinations of smears.

It has been noted that the characteristic clinical features of chancroid, including the destructive lesion, the buboes, the positive intradermal reaction, and the early reaction at the site of auto-inoculation, are manifestations of a hyperimmune host response (Tyler, 1956). Theoretically, if a patient happened to react in a hyperergic manner to an organism that usually caused an herpetiform lesion, conceivably one might see a destructive lesion or severe adenitis. Thus, the difference in the clinical features of chancroid and these non-destructive lesions might be a difference in host reaction and not a difference in the aetiological agent. In general, the total results of the tests as shown in Table I are what one might expect from the intradermal injection of any antigenic agent. As the size of the reaction increases, the number of persons with this degree of reaction decreases. This inverse proportion changes in some groups when persons with positive reactions are added (Table VI). When these positive reactors are added, there is a definite increase over the expected positivity on the basis of incidence of reactions of less intensity in patients presenting with or having had penile lesions. Part, but not all, of this increase is due to the fact that only about 75 per cent. of the patients having herpetiform lesions were tested, whereas all patients appearing clinically likely to have chancroid were tested. Particularly noteworthy is the fact that, when one compares the distribution of the sizes of negative reactions, the reactions associated with penile lesions (Group G) are essentially the same as those associated with urethritis (Group H). The addition of the positive reactors (Group F) changes this relationship. Table VI

suggests that some element other than natural distribution of hypersensitivity produces most of these positive reactions in the presence of certain penile lesions or of adenitis. This lends support to the concept that many of these lesions probably have aetiological factors different from those of the more commonly seen simple penile ulcers and vesicles.

Urethral Discharges and the Ito-Reenstierna Test

The results of I-R tests have been analysed in 133 patients with urethral discharges (Table I Groups F, G and Table IV). Of these, 73 also had had urethritis in the past. Group E of Table I summarizes the results in 31 patients with penile lesions who had had urethral discharges. Thus, the tests are pertinent to the diagnosis of possible intra-urethral chancroid in 104 patients having had urethritis in the past, as well as in the 133 presenting urethral discharges.

A comparison of corresponding groups of patients with differences only of urethral discharges (in Table I compare Group E with D, G(2) with C and D, and F with A) suggests a slight increase in reaction to the test due to past or present urethritis. In patients presenting with urethral discharges, the average maximum reaction was reached relatively early, and with succeeding bouts of the disease it was reached sooner, suggesting sensitization and later a tendency to desensitization (Table IV). Repeated tests also suggested a slight increase in the reaction with increasing duration of the disease (Table VII, opposite). The distribution of reaction sizes and their averages were similar in patients presenting either with urethral discharge or with simple penile lesions (compare Groups D and F, Table I).

TABLE VI
PERCENTAGE DISTRIBUTION OF SIZES OF ITO-REENSTIERNA REACTIONS (POSITIVE REACTIONS INCLUDED)

Group	Condition of Patient	Size of Negative Reaction (mm.)			Positive reactions (per cent.)*	Total No. of Patients
		0	1 to 4	4+ to 7		
A	Penile lesions but not questioned about past urethritis	54	12	34	0	43
B	Penile lesions and no past urethritis	35	38	8	19 (12)	63
C	Penile lesions and past urethritis	38	17	19	26 (11)	42
D	Urethritis and past penile lesions	40	13	27	20 (3)	15
E	Urethritis and penile lesions	38	10	33	19 (4)	21
F	Total Groups A-E	41	22	21	16 (30)	184
G	Total of corresponding groups from Table I (without positives)	49	26	14	Omitted	154
H	Urethritis without past or present penile lesions	46	29	22	3 (3)	107

* Numbers in parentheses indicate patients with positive reactions.

TABLE VII

RESULTS OF REPEATED ITO-REENSTIERNA TESTS IN PATIENTS WITH URETHRAL DISCHARGE AND PENILE LESIONS

Disease	Size of Reaction (mm.)		Duration of Disease (days)	
	1st Test	2nd Test	1st Test	2nd Test
First urethritis	0	0	3	7
	0	0	1	26
	0	1-2	2	8
	0	3-4	2	6
Second urethritis	0	2-3	1	4
	5	2-3	3	9
Third urethritis	2-3	2-3	3	12
	0	1-2	1	7
	0	2-3	3	9
	3-4	4-5	4	8
Average with urethritis	1.1	2.1	2.3	9.6
First penile lesion	2-3	2-3	5	10
	2-3	4-5	2	7
	2-3	4-5	2	7
Second penile lesion	2-3	2-3	1	8
	0	2-3	1	6
First penile lesion with past urethritis	5	7-8	1	7
	5	7-8	1	8
Penile lesion and urethritis	0	0	9	24
Average with penile lesions	2.5	3.9	2.8	9.6
Average with urethritis or penile lesions or both ..	1.7	2.9	2.5	9.6
Total	10 with urethral discharge		3 no change 1 more negative 6 more positive	
	7 with penile lesions		2 no change 5 more positive	
	1 with urethritis and penile lesion		no change	

The results of the intradermal tests in patients with urethral discharges, stained smears of which revealed only Gram-negative cocci or diplococci, are summarized in Table VIII. These findings show that gonorrhoea and urethral discharges apparently due to

TABLE VIII

PERCENTAGE DISTRIBUTION OF SIZES OF REACTIONS IN PATIENTS WITH URETHRAL DISCHARGE CONTAINING ONLY GRAM-NEGATIVE COCCI OR DIPLOCOCCI

Reaction Size (mm.)	Ito-Reenstierna (37 patients)	Frei (26 patients)	Frei Control (15 patients)
0	49	69	87
1 to 4	27	23	13
4+ to 7	24	8	0
Average Reaction	2.0	0.9	0.3

other causes affected the tests similarly. An analysis of intradermal reactions in sixteen patients having urethral discharges containing Gram-negative bacilli yielded similar results when one patient having a positive I-R reaction was omitted. This shows the futility of diagnosing intra-urethral chancroid on the basis of the morphological appearance and staining reaction of the organisms present.

In spite of the fact that several of those tested previously had been told that they had had "internal chancroid", only one patient presenting an urethral discharge without a penile lesion at the time or in the past was found to have a positive intradermal reaction. This patient reacted positively to both the Frei and I-R tests. Many small Gram-negative bacilli were seen in stained smears. Urethroscopic examination on the day the intradermal test was done revealed three small ulcers in the anterior

TABLE IX
RESULTS OF FREI TEST

Group	Condition of Patient	No. of Patients	Average Reaction (mm.)	Control		Test Minus Control	0 mm. (per cent.)	1 to 4 mm. (per cent.)	> 4 mm.	
				No. of Patients	Average Reaction (mm.)				Patients Per cent.	No. of Patients
A	Normal controls	31	0.4	—	—	—	84	13	3	1
B	Chancroid in past, no active disease present	21	0.7	—	—	—	67	33	0	0
C	Penile lesions but not questioned about past urethritis	35	1.0	6	1.7	-0.7	69	26	6	2
D	Penile lesions and no past urethritis	45	0.4	22	0.6	-0.2	87	11	2	1
E	Penile lesions and past urethritis	22	1.0	12	0.7	0.3	77	14	9	2
F	Urethritis without past penile lesions	70	1.1	45	0.5	0.6	66	26	8	6
G	Urethritis									
	Penile lesions in past	10	1.5	5	0.8	0.7	50	40	10	1
	Penile lesions present	15	1.3	5	0.4	0.9	53	40	7	1
Total Groups B-G		218	0.9	95	0.7	0.2	71	24	6	13
Distribution of Control Test		—	—	95	0.7	0.2	76	21	3	3

urethra, but these ulcers were similar to those seen in five other patients having acute urethritis and in one of two having recurrent urethral discharges associated with negative intradermal tests who were examined urethroscopically. One patient having recurrent dysuria and one complaining of chronic morning gleet reacted positively to the I-R test; these are included in Table VI as possibly having urethritis, although an urethral discharge was not observed, and they differ in this respect from the other patients with urethritis included in that Table.

Frei Tests in Penile Lesions and Urethral Discharges

Table IX summarizes the results of Frei tests performed on 197 patients presenting with penile lesions or urethral discharges unassociated with positive I-R tests, on 21 men with no present disease who had had penile lesions in the past, and on 31 men who had no illness and no known previous genito-urinary infection. In these and a few others tested, the reaction measured more than 4 mm. in diameter in only sixteen patients (three are omitted from Table IX because of deficient histories). Control injections were made in ten of these sixteen. When the measurement of the control reaction is subtracted from the measurement of the reaction to the test, only two of these remained questionably positive, each measuring 5 to 6 mm. in diameter. The reaction sizes in the six without controls were as follows: one was 4-5 mm., three were 5 mm., one was 5-6 mm., and one was 6 mm. Probably none of these reactions should be called diagnostically

positive. This is further confirmed in Table X, which shows the lack of effect of the duration of these diseases on the test.

TABLE X
RESULTS OF FREI TEST WITH REFERENCE TO DURATION OF DISEASE*

Lesion	Duration (days)	Frei Test (mm.)	Control (mm.)	Frei minus Control (mm.)
Penile Lesions ..	1	1.0 (37)	1.3 (14)	-0.3
	2	0.4 (27)	0.4 (12)	0
	3-4	0.3 (13)	0	0.3
	4+	0.8 (24)	0.8 (13)	0
Urethritis ..	1	1.3 (35)	0.8 (19)	0.5
	2	1.2 (19)	0.3 (13)	0.9
	3-4	1.0 (14)	0.6 (9)	0.4
	4+	0.9 (14)	0.3 (8)	0.6
Penile Lesion and Urethritis ..	1	0.6 (4)	0 (1)	0.6
	2	2.4 (4)	2.0 (1)	0.4
	3-4	0 (2)	0	0
	4+	1.6 (5)	0.7 (3)	0.9
Totals	1	1.1 (76)	1.0 (34)	0.1
	2	0.9 (50)	0.4 (26)	0.5
	3-4	0.6 (29)	0.4 (12)	0.2
	1-4	0.9 (155)	0.7 (72)	0.2
Totals	4+	0.9 (43)	0.6 (24)	0.3

* Numbers in parentheses indicate number of patients.

In a group of thirty patients with genito-urinary infections associated with positive I-R reactions, two also reacted positively to the Frei test. One of these had a central reaction to the Frei test measuring 5 mm. in diameter; the overall reaction measured 10 by 15 mm. including the flare. A few days later, a repeat injection produced a reaction 6-7 mm. in diameter plus a small surrounding flare. The control reaction measured 2 to 3 mm. in diameter. This patient had an urethral discharge containing many Gram-negative bacilli. The other patient had a central-type reaction to the Frei test measuring 2 cm. in diameter and a smaller but positive I-R reaction. A control injection was not made. He had an urethral discharge containing Gram-negative bacilli and vesicles on his penis that, from examination of smears, apparently had no bacteria. Results of the Frei test in these thirty patients with positive I-R reactions associated with genito-urinary infections are further analysed in Table XI. The two positive reactions in this series of thirty patients represent an increase in reactivity to the Frei test in the presence of positive I-R reactions. The distribution of the negative reactions according to size was generally similar to that in the larger series of Table IX. However, there was a slight increase in the average reaction (1.3 mm. compared with 0.9 mm. in the larger series) and an increase in the reaction of the control (0.9 mm. compared with 0.7 mm.). The slight decrease in non-reactivity and the increased numbers of small reactions suggest a probable non-specific effect on the test in some of the patients with positive I-R reactions.

These results with the Frei test are considerably different from those in other reports. Willcox (1954) stated that 5 per cent. of a control group, which included those having or having had gonorrhoea, possible syphilis, and other genital lesions, had Frei reactions greater than 6 mm. in diameter. The positive reactions, three in number, were observed in patients with genital lesions. Willcox also reported that 13 per cent. of 84 patients with non-specific urethritis had Frei reactions greater than 6 mm.

Robinson (1940) found that 30 per cent. of a group of control patients reacted positively to the Frei test. His controls included some patients with syphilis and others with dermatological and gynaecological or obstetrical conditions. He noted that 43 per cent. of 85 syphilitic patients in this control group, 12 per cent. of 34 with other diseases, and none of eleven children with various diseases were Frei positive. Brandt and Torpin (1940) noted that 29 per cent. of 160 patients with definite diagnoses of chancroid or lymphogranuloma venereum reacted positively to both tests. Greenblatt (1940) stated that 25 per cent. of his patients with positive I-R reactions reacted positively to the Frei test. As already noted, in my study of Frei tests of thirty patients with genito-urinary infections associated with positive I-R reactions, only two were Frei positive. Neither of these appeared clinically to have chancroid or lymphogranuloma venereum. No reactions considered diagnostically positive were seen in the other 249 patients tested.

Racial Differences

Gelperin (1943) reported that 16 per cent. of 89 Negro control patients were Frei positive, and 19 per cent. of 89 Negro men with gonorrhoea were Frei positive. In the same study, only 1 per cent. of 149 white controls were Frei positive, while none of seventeen with gonorrhoea or penile lesions were Frei positive. The question of a possible difference in reactivity to these tests by coloured and white people has also been raised by Brandt and Torpin (1940).

In my series, the overall incidence of positive Frei reactions in Negroes with genito-urinary infections was 5 per cent. (two of 41), and the two positive reactions seen were probably non-specific. No positive reactions were observed in more than 200 white men tested. The incidence of past or present destructive penile lesions or severe inguinal adenitis or both with positive I-R reactions was 7 per cent. (four of 56) in Negroes and 7 per cent. (16 of 235) in Caucasians. On the other hand, the incidence of positive I-R reactions in Negroes who had any

TABLE XI
FREI TESTS AND CONTROLS IN PATIENTS HAVING
GENITO-URINARY INFECTIONS AND POSITIVE ITO-REENSTIERNA REACTIONS

Test	Omitting 2 Positive Reactions					Including 2 Positive Reactions		
	No. of Patients	Average Reaction (mm.)	0 mm. (per cent.)	1-4 mm. (per cent.)	4+ mm. (per cent.)	0 mm. (per cent.)	1-4 mm. (per cent.)	4+ mm. (per cent.)
Frei Test	28	1.3	64	21	14	60	20	20
Control	19	0.9	79	11	11	75	15	10
Frei minus Individual Control	28	0.7	75	21	4	70	20	10

genito-urinary infection was 14 per cent. (eight of 56); in a similar group of white men, it was 11 per cent. (25 of 235).

The reactions (negative results) in Negroes included in Tables I and IX have been treated separately in Table XII. The average I-R reaction in this group of Negroes measured 3.1 mm. compared to the overall average of 2.1 mm. The average Frei reaction measured 1.7 mm. in the Negroes compared with the overall average of 0.9 mm. The average control reaction in this group was 0.9 mm. compared with the total average of 0.7 mm. The distribution of reaction sizes indicates that mild reactions to these tests are more frequently observed and are greater in Negroes than in white men. It should be noted that the measurements of these reactions in Negroes were by necessity frequently estimated by feeling the zone of induration. Because of this, a comparison of the percentages of Negroes and white men who had no reaction to the tests is possibly of more significance than the comparison of reaction sizes. These figures for the I-R tests were 31 per cent. in the Negroes, 47 per cent. in the whites

and Negroes together; for the Frei test, they were 52 per cent. in the Negroes and 71 per cent. in the total group; for the control injection, they were 63 per cent. in the Negroes and 76 per cent. in the total group.

Thus, the relative incidence of clinical chancroid was similar in Negroes and Caucasians, but probably non-specific positive reactions to the I-R and Frei tests were proportionately more frequent in Negroes. Also, the negative reactions to these intradermal tests were on the average larger in Negroes than in Caucasians. This latter finding cannot be accounted for on the basis of differences in incidence of past disease.

Studies of Specificity

Experiments were performed that serve as tests of the specificity of the I-R and Frei tests. The first of these studies was done to determine whether or not vaccination against smallpox would affect these tests. Because the commonly seen penile lesions largely resembled descriptions of herpes genitalis, it is possible that the reported occasional effectiveness of vaccination in preventing recurrence (Andrews, 1938) might be due to some cross immunity with *H. ducreyi*. Different groups of crew members were vaccinated on various days in relationship to the time at which intradermal tests were made. The intradermal reactions were measured after 48 hours and the degree of reaction at the site of the vaccination was estimated on the basis of 0 to 4 (none were primary "takes"). This study revealed a slight but definite increase in the I-R reaction caused by the vaccination (Table XIII). There was also a slight increase in the vaccination reaction apparently due to the intradermal injections. A most interesting

TABLE XII
RESULTS OF ITO-REENSTIERNA AND FREI TESTS IN NEGROES

Test	No. of Patients	Average Reaction (mm.)	0 mm. (per cent.)	1 to 4 mm. (per cent.)	4+ to 7 mm. (per cent.)
Ito-Reenstierna Test	48	3.1	31	23	46
Frei Test	33	1.7	52	36	12
Control	19	0.9	63	37	0

TABLE XIII
EFFECT OF VACCINATIONS FOR SMALLPOX ON ITO-REENSTIERNA AND FREI REACTIONS*

Group	Vaccination and Tests	No. of Patients	Vaccination Reaction (graded 1-4)	Frei Reaction (mm.)	Ito-Reenstierna Reaction (mm.)		
					With Past or Present Genito-urinary Disease	Without Past or Present Genito-urinary Disease	Total
A	Ito, Frei, and Vaccination same day	15	1.6	1.0	1.7 (9)	2.8 (6)	2.1 (15)
B	Vaccinated; Ito and Frei 1 day later	20	1.3	0.7	1.8 (6)	2.3 (14)	2.1 (20)
C	Vaccinated; Ito and Frei 2 days Later	12	1.0	0.8	1.1 (4)	3.5 (8)	2.7 (12)
D	Vaccinated; Ito and Frei 3 days Later	13	1.4	0.6	0.7 (6)	1.5 (7)	1.1 (13)
E	Ito and Frei; Vaccinated 1 day Later	12	1.4	0.4	1.0 (4)	0.5 (8)	0.7 (12)
Total		72	—	0.7	1.3 (29)	2.1 (43)	1.8 (72)

* Numbers in parentheses indicate number of patients.

observation is that the influence of the vaccination on the I-R test was less in the men who had had previous, and in a few men who had present, genito-urinary infections, indicating actual cross-immunity and not just the influence of injury. However, this series is probably too small to make this important conclusion. Overall, the influence of vaccination on the tests was rather definite and is, until otherwise proved, non-specific in nature.

Because findings in stained smears from some penile lesions have suggested the presence of organisms smaller than ordinary bacteria, many intradermal injections of 0.1 ml. typhus vaccine were made concomitantly with I-R tests. The reactions at the two sites were frequently similar, and one patient having a destructive penile lesion had positive reactions to both. A group of sixteen men inoculated for the second time (approximately 1 week after first injections) for immunization against cholera and typhus, were also given I-R and Frei tests. Positive I-R reactions were observed in two, neither of whom had ever had any genito-urinary diseases, and one of whom denied ever having had sexual intercourse. The average size of the reaction in the fourteen with negative reactions was 3.1 mm. A second group, consisting of nine men having typhus and cholera inoculations, had no positive reactions, and the average reaction measured 1.6 mm.

A third group of men, with final inoculations for immunization against typhus and cholera, were given intradermal injections of 0.1 ml. typhus vaccine, cholera vaccine, Ducrey's vaccine, and smallpox vaccine that had been heated to 60°C. for 2 hours in a water bath. Of these men, seven had intradermal tests only, six had intradermal tests and 0.5 ml. typhus vaccine given intramuscularly, nine had intradermal tests and 0.5 ml. cholera vaccine, and five had intradermal tests and 0.5 ml. typhus vaccine and 0.5 ml. cholera vaccine given intramuscularly. The average measurements of the I-R reactions in these four subgroups were 0.3, 1.7, 1.3, and 2.0 mm., respectively. One positive I-R reaction was observed in these twenty men receiving typhus or cholera vaccine or both with the tests. As already noted, two positive reactions occurred in the first group of sixteen men having typhus and cholera inoculations and none in the second group of nine. Thus, the overall incidence of positive reactions in the three groups was 7 per cent. (three of 45), and the average size of the negative reactions was 1.8 mm.

The non-specificity of the I-R test in these studies varied from 1 per cent. in the presence of urethral discharges to 7 per cent. in association with certain inoculations. These values are nearer the formerly accepted value of 1 per cent. for non-specific re-

actions (Venturi, 1928) than the values in the more recent report of Robinson, (1940). One-third of the positive reactions observed in patients with present or past penile lesions were associated with diseases resembling herpes. Certain possible influences on the tests have not been fully evaluated and should be considered in comparing the results of different studies. In the presence of hyperergic conditions or in patients who are especially prone to allergic manifestations, one might expect the non-specific reactions to be greater in number. These might also be increased in the presence of nervousness or pain; Lewis (1937) showed that the nervous system plays a role in determining the type and extent of reaction to intradermal injections. In this regard, it is impossible to evaluate the role cystoscopy played in producing the one positive I-R test seen associated with an urethral discharge, since the patient was chosen for urethroscopic examination quite fortuitously. The possible effect of temperature and humidity on intradermal reactions also should be considered. The name "climatic bubo" was applied in 1867 to a disease observed in Japan that resembled lymphogranuloma venereum or chancroid (Cole, 1933; Scheube, 1899). It has been my impression that chancroid with its hyperimmune phenomena is more likely to occur when the weather is uncomfortably hot. Theoretically, too, one might well expect vascular response to intradermal injury to be different in hot and cold weather. The possibility should also be kept in mind that workers in various parts of the world may be dealing with different diseases. For instance, the non-gonococcal urethritis seen in England may be different from that seen in the Far East. Hellerström (1929), by seasonal incidence and other clinical similarities, assumed that the buboes that he observed (which were those of lymphogranuloma venereum) were the same as those seen by Scheube in Japan in 1867 (Cole, 1933; Scheube, 1899). However, the latter could have been chanroid, particularly since this disease seems much more prevalent than lymphogranuloma venereum at present in this region. Similarly, the buboes seen in the United States, particularly those associated with positive reactions to both the I-R and Frei tests (Robinson, 1940), may represent different diseases from those observed in this study.

Comment

It has been shown that ulcerative and vesicular lesions of the penis unassociated with great local destruction of tissue or inguinal adenitis which are commonly seen in the Pacific zone are not associated with positive I-R or Frei reactions. Results of these tests in a large number of patients having such

lesions, particularly when analysed according to past disease and duration of illness, show that some such lesions probably increase the reaction to the I-R test to a slight degree. When the relatively few, grossly positive reactions are omitted, the results of these tests for diseases whose primary lesions are usually on the penis are similar in patients in the given geographical zone presenting with penile lesions or with urethral discharges. This could be evidence that the two conditions are similar; it could of course, be only a similarity in a non-specific effect on the reactions. It has been shown that immunization procedures for smallpox, typhus, and cholera can probably affect the results of the tests, indicating the possibility of non-specific influences on the reactions. The incidence of positive reactions associated with the inoculations was similar in magnitude to the number seen with urethral discharge or simple penile lesions.

From these results, it appears most probable that the penile lesions commonly seen in the region encompassed by this study are not caused by *H. ducreyi* or the virus of lymphogranuloma venereum. The diagnosis in such cases should probably be different from that for the disease characterized by destructive ulcers, buboes, and positive auto-inoculation and I-R reactions. In some cases, the diseases may be the same but the evidence presented in this paper would indicate that the clinical differences in the diseases are in most cases not simply due to the distribution of allergic persons. The difference in host reaction in the two conditions could, in many cases, be caused by a difference in causative organisms.

Since the commonly seen ulcerative and vesicular penile lesions observed during this study do not represent syphilis, chancroid, or lymphogranuloma venereum, the usual diagnosis for them by exclusion would be herpes genitalis. It appears that the main reason such lesions are considered to be caused by herpes is that they frequently resemble cold sores, fever blisters, and canker sores. There is actually no basis for considering these penile lesions to be specific for herpes simplex. Lymphogranuloma venereum, syphilis, ulcer vulvae acutum, gonorrhoea, and chancroid may appear similar to these lesions. Similar-appearing lesions of the oral region may be caused by herpes simplex, herpes zoster, varicella (Pfaundler and Schlossmann, 1935), variola (Pfundler and Schlossmann, 1935; Smadel, 1952), a virus immunologically related to but not that of herpes simplex (Prinz and Greenbaum, 1939), a virus capable of causing diarrhoea or being asymptomatic in carriers (Buddingh and Dodd, 1944), the virus of foot-and-mouth disease (Warren, 1952), Coxsackie group C viruses (Melnick and Curnen, 1952), measles

(Koplik, 1918), rubella (Koplik, 1918), staphylococci, various types of diplococci, and streptococci (Prinz and Greenbaum, 1939; Koplik, 1918), and possible fungi (Andrews, 1938). The lesions of syphilis, lymphogranuloma venereum, and chancroid are reported to occur in the oral region at times; when they do so, their appearance is similar to that seen on the genitalia (Becker and Obermayer, 1940; Tucker, 1950; Meyer, 1952; Stokes, Beerman, and Ingraham, 1944).

I studied more than fifty patients for the epithelial changes described by Blank, Burgoon, Baldrige, McCarthy, and Urbach, (1951) as being common in herpes simplex, herpes zoster, and varicella; only four had penile lesions with these changes. I have not seen the acidophilic intranuclear inclusions described as being sometimes associated with the lesions of herpes simplex (Andrews, 1938; Van Rooyen and Rhodes, 1948). On the other hand, bacteria of various sizes and shapes, with various staining reactions, and non-syphilitic spirochaetes may be seen at times, and forms smaller than regular bacteria are frequently noted. I have seen large acidophilic cytoplasmic inclusion bodies in epithelial cells and polymorphonuclear leucocytes from an herpetiform lesion. Such inclusions, to my knowledge, have not been reported as due to herpes simplex. Thus, microscopic study of smears from these lesions supplies little positive evidence that most of them are caused by herpes simplex; on the contrary, it suggests a multiplicity of causes.

It will perhaps be valuable in understanding the basic nature of non-specific urethritis and herpetiform lesions to consider the possibility that they are caused at times by similar organisms. As pointed out, syphilis, gonorrhoea, lymphogranuloma venereum, herpes simplex, herpes zoster, granuloma inguinale, tuberculosis, actinomycosis, and condyloma acuminatum are reported to be capable of occurring in both sites. I have compared the apparent incubation periods of 145 herpetiform penile lesions and the lesions in 202 cases of urethritis (Table XIV, opposite). The results are almost exactly the same in each series and nearly identical with the incubation periods in 1,000 cases of non-gonococcal urethritis in the United States reported by Parrino (1954). When the few grossly hyperimmune reactions are omitted, both diseases affect the I-R and Frei tests similarly. Small intraurethral ulcers similar in appearance to external penile lesions were seen in seven of eight patients with urethral discharges who were examined urethroscopically; others have also reported intra-urethral ulcers in acute gonorrhoea (Young and Davis, 1926), and herpetiform vesicles and ulcers in non-gonococcal

TABLE XIV
APPARENT INCUBATION PERIODS OF
HERPETIFORM PENILE LESIONS AND URETHRITIS

Incubation Period (days)	Herpetiform Penile Lesions (per cent.)	Urethritis (per cent.)	Parrino's (1954) series of Non-gonococcal Urethritis
1-2	8	5	—
3-5	16	23	
1-5	24	28	24
6-10	27	22	26
11-20	19	24	20
21-31	13	12	12
32+	17	14	18
Total cases	145	202	1,000

urethritis (Klotz, 1886). Both non-gonococcal urethritis and herpetiform penile lesions tend to recur at times in spite of rigorous antibiotic therapy, and similar possible causes for recurrence, including spices, alcohol, nervous tension, trauma, and intercourse, have been suggested. In a study to determine the influence of continuous prolonged drinking of ethyl alcohol on urethritis, I observed the recurrence of a herpetiform penile lesion as well as exacerbations of urethritis after withdrawal of its use (Tyler, 1957). Further evidence of possible similarity in the aetiological factors in herpetiform penile lesions and urethritis is their rather frequent co-existence. A total of thirteen of 67 successive patients (19 per cent.) seen by me, who had penile lesions acquired in the orient, had noted the onset of urethral discharge within a few days before or after the appearance of the lesions. Also, both urethritis and balanitis have been associated with Reiter's syndrome (Harkness, 1949).

It should be emphasized that nearly all of these diseases must result from sexual intercourse. In examining men with a relatively low incidence of sexual exposure at the U.S. Navy Recruiting Station in Salt Lake City, Utah, I saw extremely few penile lesions or urethral discharges, and these were all apparently secondary to intercourse. The incidence of acute and chronic upper respiratory infections is high in this region, so it appears unlikely that an appreciable number of penile lesions and urethral discharges in young adult men are secondary to these diseases. The incidence of penile lesions and urethritis in men going overseas is much less than the incidence in men returning from the orient. Again, in my experience, these diseases were apparently secondary to intercourse. Only one man having an urethral discharge and none with ulcera-

tive or vesicular penile lesions denied having had intercourse. The incidence of denial of intercourse probably would be no less than this (one in more than 350 instances) in the presence of syphilis or gonorrhoea. The venereal nature of herpes genitalis has been noted by others (Willcox, 1950); in Parrino's (1954) series, 94 per cent. of men with non-gonococcal urethritis had had sexual contact within 3 months and more than 99 per cent. had had contact within one year.

Much of the difficulty in recognizing this relationship of sexual intercourse to the diseases under consideration probably results from what appears to be an outmoded concept of "venereal disease". Venereal disease, according to present usage, is defined as a disease usually acquired through sexual intercourse (Taylor, 1953). Since the cause and possible relationships of many commonly seen diseases of various mucous membranes, including the common cold, canker sores, chronic and recurrent ulcerations of the gastro-intestinal tract, and non-gonococcal urethritis and penile lesions, are unknown, it appears less subject to error and more realistic to apply the term "venereal disease", if it is to be used, to the contagious nature of a genito-urinary infection rather than to its specific cause. If a disease is acquired from sexual intercourse, it is reasonable to think that it can be again transmitted in a similar manner and should be considered a "venereal disease" regardless of the responsible organism. An infection or infectious disease of the genitalia and lower part of the urinary tract, regardless of the mode of acquisition, would best be considered a "potential venereal disease", inasmuch as the consort might acquire it. Since the term "venereal disease" has many unfortunate connotations and is intimately associated with moral values by both the laity and medical profession, it would perhaps aid in understanding these diseases unemotionally to delete this term from medical literature and to consider and classify all transmissible genito-urinary diseases as "contagious genito-urinary diseases" of known or unknown specific cause.

In observing these genito-urinary infections, I am impressed with the likelihood of their being the primary lesions of systemic diseases. It is difficult to comprehend the idea of an infection being consistently of a local nature only, particularly since nearly all known viruses and pathogenic bacteria have been associated with lesions distant from the site of the primary lesion. Diseases such as syphilis, gonorrhoea, lymphogranuloma venereum, and herpes simplex are recognized as systemic conditions. As it becomes possible to recognize readily the presence of various

causative organisms and their products, it may become possible to prove their existence in secondary lesions. Probably one of the reasons why the penile lesions and urethritides of undetermined cause have not more frequently been associated clinically with systemic diseases is that they have been considered as a few entities, and the possible variation of secondary lesions, even to the degree seen in syphilis, is not usually considered. The apparent great incidence of these diseases and their probable similarity to diseases of other systems, such as cankers and upper respiratory infections, add considerable difficulty in establishing relationships between primary and secondary lesions. Also, the more commonly seen contagious genito-urinary diseases frequently have prolonged incubation periods, and the interval between the appearance of primary and secondary lesions is often so long that their relationship is not suspected. Also, it is possible that the diseases may be transmitted at times with unrecognizable or extremely transient asymptomatic primary lesions.

I have observed many dermatoses of various types, joint lesions, ocular lesions, and behaviour suggestive of involvement of the nervous system following within a reasonable period the onset of penile lesions or urethritis apparently from causes other than syphilis, lymphogranuloma venereum, chancroid, or gonorrhoea. The primary lesions in most of these cases have not been chronic. Many of the secondary manifestations of these diseases are probably not recognized as such because most physicians must see evidence of chronic balanitis or urethritis to associate with it another condition such as arthritis. Also, some must see several sites of involvement, as described in Reiter's syndrome, to make the association. This is as illogical as requiring a chronic chancre in order to make the diagnosis of chronic syphilitic aortitis, or the requirement of parotitis, orchitis, and pancreatitis occurring simultaneously to make the diagnosis of mumps meningoencephalitis. One may see many patients having conjunctivitis or other ocular diseases, many having arthritis, and many having dermatoses apparently secondary to genito-urinary infections, sometimes in combination; however, to see all these conditions together with a chronic primary lesion seems to be relatively rare.

It is most unfortunate that more basic research concerning the contagious genito-urinary diseases has not been done. Theoretically, the aetiology and epidemiology of these diseases should be much easier to determine than those of diseases of other systems, such as the upper respiratory tract. Treatment of these diseases is not satisfactory; recurrence

of the primary lesions is not uncommon in spite of rigorous treatment, and the natural disappearance of the primary lesion is often mistaken as a cure of the disease, a fallacy formerly common in syphilis. The possibilities of immunization against venereal diseases also have been grossly neglected. For instance, the use of Ducrey's vaccine, while it would probably not greatly influence the overall incidence of penile lesions, might possibly decrease the incidence and severity of buboes and certain penile lesions. The probable contagious nature of many genito-urinary diseases seen in civilian practice is inadequately recognized, and consequently the pathogenesis of these diseases is poorly understood. Because of lack of basic understanding of venereal diseases and the bigotry of the laity and medical profession in general, research in this field has been grossly neglected.

Summary and Conclusions

Of approximately 200 patients with penile lesions seen aboard a troopship in the Pacific zone, only fifteen had lesions or buboes characteristic of chancroid and positive reactions to the Ito-Reenstierna (I-R) test. Of 142 men presenting only penile lesions that did not appear to be chancroid, seven had positive reactions to the test. Only five of more than 100 men who had had penile lesions in the past (nearly all diagnosed as chancroid) had positive reactions apparently due to previous chancroid. From these findings, it appears that the incidence of chancroid with that of other penile lesions in this region is probably less than 15 per cent. Only one positive Frei reaction was observed in the patients with penile lesions. Only a few patients were seen with primary syphilitic lesions.

Most of the non-syphilitic penile lesions associated with negative Frei and I-R reactions were diagnosed by other physicians in these regions as chancroid. The same situation probably exists in other parts of the world. Analysis of the results of intradermal tests shows that most of these lesions are probably not caused by *Haemophilus ducreyi* or the virus of lymphogranuloma venereum. Most of them more nearly resembled herpes genitalis than chancroid. However, herpetiform lesions are apparently not specific for herpes simplex, and studies of smears from many of these lesions suggested the possibility of other aetiological factors.

The commonly seen simple penile lesions and the urethritides affect the I-R test similarly, namely a slight effect similar in degree to the non-specific effects produced by immunization procedures against smallpox, cholera, and typhus. Other similarities in these two diseases are the incubation

periods, appearance of the ulcers, recurrent nature, purported causes of recurrence, not uncommon coexistence, and association of chronic external penile lesions as well as chronic urethritis with Reiter's syndrome.

Herpetiform penile lesions and urethral discharges in young male adults are apparently caused by organisms transmitted by sexual intercourse. Because the aetiological agents of so few apparently infectious lesions of the mucous membranes have been determined or can readily be isolated, a new concept of "venereal disease" is proposed based on the contagious nature of genito-urinary infections rather than on whether or not intercourse is the usual mode of transmission of a particular organism. Because the term "venereal disease" is emotionally associated with moral values, it is suggested that knowledge of these diseases will be facilitated by deleting the term "venereal disease" from the medical literature. As a substitute, it is proposed that all transmissible genito-urinary diseases be considered as "contagious genito-urinary diseases", whether or not the specific cause is known.

The probable systemic nature of these diseases is noted.

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