

PART V

Studies in Prophylaxis

	<u>Page</u>	<u>Table</u>
Discussion of prophylaxis, general	1	
Methods of Infection	4	
Technics of prophylaxis	6	
Discussion of results		
Local application	8	V
Local application and scarification	10	VI, VII
Intracutaneous inoculation	15	VIII
Multiple pressure inoculation	18	IX, X
Summary and Conclusions	24	
Summary Table XI	26	

## STUDIES IN PROPHYLAXIS

The original purpose of the program was primarily to study the clinical effectiveness of the mapharsen-orvus prophylaxis (7) which had proven highly effective in experimental rabbit syphilis, as had several other solutions of detergents plus arsenicals. (33) To review this work it may be pointed out that the rabbit develops syphilis of the mucosa of the preputial sac and penis following application of the intact mucous membrane of an emulsion of virulent *T. pallidum*. The method used by Arnold and Mahoney (7) consisted of maintaining a cotton pledget saturated with the emulsion through repeated applications of emulsion for varying lengths of time. Following such exposure the mucosa can be treated prophylactically by the application of various local agents such as solutions, salves, etc., or systemic treatment can be given. Various authors have reported on prophylactic studies by this technic and the subject has been reviewed by Mahoney (34) while Arnold has reviewed the experience at the VDRL with a large series of compounds so tested. (35) Although the 3% calomel prophylaxis reported by Metchnikoff and Roux (36) was developed on the basis of animal experimentation on the anthropoids it has been widely used as a prophylactic in the human and general consensus based upon the experience of the military (37) has been that it is of significant value as a preventive against development of syphilis. While experimental work on the subject has been limited, it is believed that to be most effective the calomel ointment should be applied within a short time after exposure.

Attesting to the widespread acceptance of this type of agent has been the fact that in the American Army during the second world war tens of millions of tubes of prophylactic ointment were distributed. In spite of intensive efforts to educate the male to the necessity or desirability of using the agent following each potentially infective contact it has long been known that only a fraction of such exposures are followed by use of the preparation.

While many factors are involved in the failure to use the preparation only a few of the major ones need discussion here. It is instructed that the calomel ointment be applied following thorough washing of the genitalia and pubic region with soap and water. The ointment is then to be applied to the glans, shaft, pubic hair, scrotum, and if possible to the anterior end of the urethra. Many of the preparations containing, in addition to calomel, an agent protective against the gonococcus such as 15% sulfathiazole, come in a tube with a nozzle and with instructions that a part of the tubes contents should be injected into the urethra. Then the urethra and genitalia should be massaged carefully so as to coat the skin completely and to work the preparation into the hair follicles. Injection of the material into the urethra is uncomfortable, and even painful for some. Use of the preparation leaves a greasy or moist film on the genitalia which must be protected by an oiled cloth or by toilet paper and which may, even so, stain the clothing. The preparation requires careful use, is time consuming, and requires rational thought following intercourse which is not too frequently accomplished while under the influence of alcohol, so that there is a very real disinclination to take the trouble to use the preparation.

Finally, some hesitate to go to such lengths with a more or less steady paramour for fear of hurting the partners feelings.

It was felt that the use of a watery preparation of a cleansing agent which could be used immediately after contact as a simple wash might prove esthetically appealing and might meet with acceptance. For a common habit pattern is for the individual to wash the hands and genitalia with soap and water following contact, particularly if with a promiscuous partner. The orvus-mapharsen preparation which is both a cleansing agent and deodorizer, and which had been found effective in animal work was thought to present a possible answer to the search for an effective prophylactic which might satisfy some of the objections to the earlier preparations.

Following developmental studies of the preparation in vitro, then in the rabbit, and comparison with calomel ointment of 30 to 33 percent in the standard prophylactic preparations it was found that the orvus-mapharsen preparation in the rabbit offered at least the same prophylactic value as the calomel ointment, in fact, almost complete protection against experimental infection. (7) It then became necessary to evaluate the preparation in man, and for reasons mentioned earlier it was decided to do it in the manner to be described.

### Methods of Infection

Data on the rate of infection to be expected following sexual contact is meager but the experience of Alexander et al (29) and Plotke et al (30) did give some indication of the probability of infection following exposure to primary or secondary syphilis. In Alexander's group 62.1 percent of the individuals exposed to primary or secondary syphilis in the sexual partner developed an infection. In Plotke's group 25.5 percent of the patients exposed to primary or secondary syphilis became infected.

It had been our intention at the beginning of our operations to follow a similar plan by permitting exposure of prisoner volunteers to infected prostitutes. Twelve men were exposed to two prostitutes who had been inoculated with *T. pallidum* into the cervical os and had developed asymptomatic infection. None developed clinical evidence of the disease following single exposure.

Because of the low rate of infection by this method, the small number of men available, and factors in administration of the prison which made continuation of the program along these lines scientifically impracticable, it became necessary to develop a different mode of attack on the problem. As described elsewhere a program involving inoculation was worked out. As it later developed three general methods of infection with syphilis were used for testing prophylactic technics. Because it was not possible to carry out any procedure requiring exposure of or manipulation of the female genitalia the methods of genital application were used only with male patients.

It was early found that application of the spirochetal emulsion to the intact mucous membrane could be expected to produce only a low rate of infection, while application of the same emulsion for the same length of time to the abraded mucous membrane was found to give a high-enough rate of infection to permit evaluation of prophylactic methods. In fact, such a technic provided almost certain development of the infection, and it appeared that the testing of any technic of prophylaxis against exposure by this route might be expected to provide a test method of greater severity than might be expected following usual sexual exposure. The results of this method upon a group of male patients are presented in Table 2. The rate of 91.6 percent following scarification of the penis and a one and one-half to two hour application of the spirochetal emulsion is considerably greater than that to be expected following intercourse and should therefore provide a most severe test of clinical efficacy of any prophylactic agent.

As mentioned before the number of males available was not inexhaustible and the procedure of infection of females was restricted to extra genital locations. Thus to be able to try surface-applied prophylactic agents in the female it was decided to try a method of inoculation similar to that used in smallpox vaccination--multiple pressure. With care to penetrate only the epidermis and not to draw blood it was felt that the organisms thus inoculated might be susceptible to the working of a locally applied agent. As seen in Table 5 this method of multiple pressure inoculation gave a rate of infection of 96.2 percent.

The third method that produced a high rate of infection was by intracutaneous inoculation and was used to evaluate certain types of systematic prophylaxis. This procedure produced a rate of infection of 96.8, percent ~~Table \_\_\_\_\_~~

TECHNIC OF APPLICATION OF PROPHYLAXIS

The orvus-mapharsen prophylactic was provided in several different forms. In the early experiments of the program the solution was made up for use from Dreft (Procter & Gamble Co.) which is the ordinary household form of the preparation sodium lauryl sulfate (alkyl aryl sulfate) to 1% strength in tap water. Mapharsen (Parke Davis & Co.) was then added to the orvus solution to make up a solution of 0.10% mapharsen and 1% orvus. Later the preparation was available in rubber-stoppered glass bottles, the contents of which were added to 60 ccs. of tap water to make up a solution of 1% orvus and 0.15% mapharsen. The solutions were prepared just prior to application and were used within 1 hour of preparation. At the end of the requisite exposure time following scarification of the mucous membrane of the penis the cotton pledget was removed, and, timed by a stop-watch, one of the physicians working with rubber-gloved hands carried out the prophylactic procedure. This is shown by illustrations, nos. \_\_\_\_\_ to \_\_\_\_\_. An assistant with 60 ccs. of the preparation in a beaker poured the solution onto the hands of the physician holding the penis of the subject. The glans penis, shaft, scrotum, and pubic hair were then thoroughly washed and massaged with particular attention being paid to careful cleansing of the glans penis, foreskin, and to the area of application of the pledget. The solution was allowed to dry in the air before the patient was allowed

to dress, and he was instructed not to wash any more for at least an hour.

When the calomel-ointment from the U. S. Army pro kit was used the same procedure of application was followed. Without preliminary washing of any kind the tube contents were applied to the glans, shaft, pubic hair, and scrotum just as instructed in the accompanying directions. Particular attention was paid to a careful massage of the ointment into the glans and foreskins. The patient was released from observation again with instructions not to wash. The formula of the Army Pro Kit follows: (38)

Calomel	30%
Sulfathiazole	15%
White Petrolatum	40%
Light Mineral Oil	14%
Cetyl Alcohol, Technical	1%

Use of the local prophylactic agents on the skin of the arm of the female was accomplished in essentially the same way as on the penis, with application timed, and with the solution poured by an assistant onto the skin surface and hands of the physician administering treatment. The physician used a small cotton pledget moistened with the solution with which to wash the surface.

Administration of oral or intramuscular penicillin or intravenous mapharsen, or of sobisminol mass was carried out by self evident technics as indicated on accompanying tables. Local application of penicillin solution was done in the same fashion as for the orvus-mapharsen solution.

Findings of Control and Prophylactically Treated Groups

I. Very little can be said of the results produced by the method of local application. As mentioned before this method was first used because it was thought it would be a method closely approximating that of normal sexual exposure. As can be seen from the results of various experiments listed in Table 1 the rate of infection was very low. The overall infection rate by this method is 17.9 percent.

II. Orvus-mapharsen preparation used upon two groups consisting of 12 patients having an application of virulent emulsion every 15 minutes for 1-hour found none to be infected. The results of any prophylaxis, however, cannot be considered to be indicative of the effectiveness of any prophylaxis because of the very low rate of infection produced by this method in the control groups.

TABLE. I

Results of Control Groups Exposed by Method of Local Application

Experiment Number	Size of Inoculum	Variation of Application	Patients Exposed	Infected	
				Number	Percent
0103	2 to 5/field	15 minute intervals for 1 hour (4 app.)	7	0	0.0
0501	$3.69 \times 10^6$	15 minute intervals for 1 hour (4 app.)	6	0	0.0
0602	$4.61 \times 10^6$	20 minute intervals for 2 hours (6 app.)	5	1	20.0
0701	$3.36 \times 10^6$	20 minute intervals for 2 hours (6 app.)	7	4	57.1
0908	$2.85 \times 10^6$	30 minute intervals for 3 hours (6 app.)	7	1	14.3
0909	$1.52 \times 10^6$	30 minute intervals for 3 hours (6 app.)	7	1	14.3

II. In Table 2 are shown the results of control groups by the inoculation technic whereby application of the spirochetal emulsion is made upon the abraded mucous membrane of the penis. The overall infection rate of 91.6 percent is of a much greater order of magnitude than that reported following sexual exposure to a known infected individual, in which the number of separate exposures may have been multiple (29,30) and produced an infection rate of only 25 to 50 percent.

TABLE II

Results of Control Groups Exposed by  
Method of Scarification Followed by Local Application

Experiment Number	Size of Inoculum	Variation of Application	Patients Exposed	Infected	
				Number	Percent
0603	$4.61 \times 10^6$	Intervals of 20 minutes for 2 hrs.	5	5	100.0
0702	$3.36 \times 10^6$	Intervals of 20 minutes for 2 hrs.	7	7	100.0
0903	$1.47 \times 10^6$	Intervals of 30 minutes for 2 hrs.	6	6	100.0
0904	$9.8 \times 10^5$	Intervals of 30 minutes for 2 hrs.	1	1	100.0
1106	$4.48 \times 10^6$	Intervals of 20 minutes for 2 hrs.	10	10	100.0
1204	$1.56 \times 10^6$	Intervals of 30 minutes for 2 hrs.	10	5	50.0
1602	$3.18 \times 10^6$	Intervals of 20 minutes for 2 hrs.	7	7	100.0
1605	$1.98 \times 10^6$	Constant contact for $1\frac{1}{2}$ hrs.	7	6	85.7
1705	$2.01 \times 10^6$	Intervals of 30 minutes for 2 hrs.	30	29	96.7

The results of prophylaxis given to patients inoculated in this manner are given in Table 3. Following immediate application of the prophylactic treatment with orvus-mapharsen to 30 male patients only 1 or 3.3 percent became infected. In experiment 1601 further protection was demonstrated when the preparation was applied at even 4-hours following final exposure. The rate of infection following use by the Army pro kit was similarly low with only 1 of the 12 males exposed becoming infected. The efficacy of these two prophylaxes following this method of infection is readily judged. There is no statistical evidence to indicate that one is more effective than the other.

It may be noted in Table 3 that in five experiments the total length of time of exposure to emulsion was for one-hour instead of the usual two-hours. From our experience of infections produced by the two-hour application we have reason to believe that no significant difference exists between the infection rate of a one-hour and two-hour application of emulsion. Therefore we believe that any prophylaxis used following a one-hour application has had as vigorous a test as one following a two-hour application.

In experiments 1503 and 1506 the preparation was administered in a single dose of 0.27 gm. sobisminol mass equivalent to 0.15 gm. bismuth. Protection afforded by the dose immediately after final application of virulent emulsion was slight, but at 11 hours after inoculation complete protection of the group was found. It is possible that the differences in effectiveness may be related to the pattern of absorption and excretion of the bismuth.

The use of bismuth compounds by injection as a prophylaxis against syphilitic infection in prostitutes has been reported by numerous European workers as meeting with success, but the necessity for injection is a drawback. (45) With the development of sobisminol mass by Hanzlik and his studies in rabbits the potential value of the preparation in prophylaxis as well as in treatment was indicated. (46) To the best of our knowledge clinical reports of this type of prophylaxis use have not been made.

Oral penicillin in a dose of 1,500,000 units immediately after final application appeared to give complete protection. This is also found to be true of 500,000 units of aqueous penicillin used as a wash also given immediately after final application of emulsion. However, a similar amount of aqueous penicillin administered as a wash one-half hour after final application did not prove to be as effective, as the immediate wash. The 600,000 units of POB given intramuscularly 11 hours after final application afforded considerable protection but not complete.

TABLE III

Results of Prophylaxis Administered After Inoculation By  
Technic of Scarification Followed By Local Application

Experiment Number	Size of Inoculum	Variation of Application	Type of Prophylaxis	Patients Exposed	Infected	
					Number	Percent
0905	$1.47 \times 10^6$	Intervals of 30 minutes for 2 hours	Orvus-Mapharsen (60cc) for 2 minutes	6	0	0.0
1104	$4.48 \times 10^6$	Intervals of 20 minutes for 2 hours	Orvus-Mapharsen (30cc) for 2 minutes	12	0	0.0
1205	$1.56 \times 10^6$	Intervals of 30 minutes for 2 hours	Orvus-Mapharsen (30cc) for 2 minutes	12	1	8.3
1601	$3.18 \times 10^6$	Intervals of 20 minutes for 2 hours	Orvus-Mapharsen (15cc) for 2 minutes 4 hours after application completed	9	3	33.3
1206	$1.56 \times 10^6$	Intervals of 30 minutes for 2 hours	U. S. Army Pro for 2 min.	12	1	8.3
1503	$1.43 \times 10^6$	Intervals of 20 minutes for 1 hour	4 pulvules Sobisminol, mass 11 hrs. after final application	9	0	0.0
1504	$1.69 \times 10^6$	Intervals of 20 minutes for 1 hour	600,000 u. POB intramuscularly 11 hours after final application	8	1	12.5
1505	$1.69 \times 10^6$	Intervals of 20 minutes for 1 hour	1.5 m.u. oral penicillin	8	0	0.0
1506	$1.69 \times 10^6$	Intervals of 20 minutes for 1 hour	4 pulvules Sobisminol after exposure	8	5	62.5
1501	$1.69 \times 10^6$	Intervals of 20 minutes for 1 hour	500,000 u. aqueous penicillin wash 1/2 hour after application	5	3	60.0
1603	$3.18 \times 10^6$	Intervals of 20 minutes for 2 hours	500,000 u. aqueous penicillin for 2 minutes	6	0	0.0

III. Results of individual control experiments following intracutaneous inoculation have been combined. However, only those patients who were inoculated into only one site and that being into the skin, and who were negative or false positive prior to inoculation have been considered. Patients in experiments 1207, 1302, 1303, and 1304 have also been omitted for obvious reasons. Of a total of 155 patients considered, 150 or 96.8 percent became infected. Like the last method of infection discussed this method also affords a rigid test for any prophylaxis.

As noted in Table 4 highly inconstant and variable results were obtained with the use of penicillin G in oil and beeswax which cannot be easily explained. Various lots of this preparation were used during the course of the study, some of which were highly fluid, others of which were almost solid at room temperature. Previous experience with this type of preparation at the VDRL at Staten Island had revealed a very high degree of variability in both height of and duration of blood levels obtained with groups of individuals receiving the same lot of preparation as well as with different and probably related to the physical characteristics of the mixture.

From our experience it is our belief that POB as a prophylactic does give an appreciable degree of protection but for several reasons is not too satisfactory for use.

The variability of the preparation can best be summarized by the experience of Kirby et al. (43) with 54 patients given 300,000 units of the preparation intramuscularly. The assayable level varied from 4 to 24 hours. In one patient penicillin could be demonstrated only once, at 16 hours after injection. Of the group 69% maintained an assayable level no longer than 12 hours.

From our experience it is our belief that FOB as a prophylaxis does give an appreciable degree of protection but for several reasons is not too satisfactory for use.

Intravenous mapharsen administered 2 hours after inoculation proved to be an effective prophylaxis. In connection with this particular prophylaxis it had been the recommendation that laboratory workers subjected to laboratory accidents involving material contaminated with *T. pallidum* be given an immediate prophylactic injection of an arsenical. Experimental work with rabbits had suggested the value of such a procedure, but human clinical confirmation was lacking. In our experience as indicated in Table 4 the procedure is highly effective when given 2 hours after inoculation. This again proves the value of abortive therapy which was dismissed by Stokes in the third edition of his book (39) with the statement that it was unreliable and that under such circumstances if treatment were once begun a full course should be given.

When procaine penicillin G in oil (Duracillin) was administered in a dose of 300,000 units 11 days after inoculation this dosage had a high rate of cure. By the time of prophylaxis administration patients showed darkfield positive lesions but were seronegative.

TABLE IV

Results of Prophylaxis Following Intracutaneous Inoculation

Experiment Number	Size of Inoculum	Variation of Application	Type of Prophylaxis	Patients Exposed	Infected	
					Number	Percent
0801	$2.24 \times 10^6$	Right & left forearm	300,000 U. Wyeth POB after 24 hrs.	7	6	85.7
0802	$2.24 \times 10^6$	Right & left forearm	600,000 U. Wyeth POB after 48 hrs.	7	2	28.6
0806	$2.80 \times 10^6$	Right & left forearm	600,000 U. Wyeth POB after 24 hrs.	6	4	66.7
0807	$2.80 \times 10^6$	Right & left forearm	1,200,000 U. Wyeth POB after 48 hrs.	5	3	60.0
1305	$1.04 \times 10^6$	Left forearm only	600,000 U. Wyeth POB after 12 hrs.	6	0	0.0
1306	$1.04 \times 10^6$	Left forearm only	1,200,000 U. Wyeth POB after 24 hrs.	5	0	0.0
1609	$7.95 \times 10^5$	Left forearm only	Intravenous Mapharsen after 2 hrs.	6	0	10.0
1610	$7.95 \times 10^5$	Left forearm only	300,000 U. Cryst. Pen.G. Pot. oil and wax after 11 days	8	1	12.5

IV. Table 5 is a presentation of results of control groups following inoculation by the multiple pressure technic. This method of inoculation carries spirochetes through the epidermis, breaking the integument, so that a high rate of infection is almost certain. In the six experiments which comprise the control groups the overall infection rate is 96.2 percent.

TABLE V

Results of Control Groups Exposed by Method of Multiple Pressure

Experiment Number	Size of Inoculum	Variation of Vaccination	Patients Exposed	Infected	
				Number	Percent
0605	$2.7 \times 10^5$	Left upper arm. $1\frac{1}{2}$ hrs. contact	6	5	83.3
0706	$1.5 \times 10^5$	Left upper arm. $1\frac{1}{4}$ hrs. contact	7	7	100.0
0906	$1.7 \times 10^5$	Left upper arm and on penis above coronal sulcus	3	3	100.0
1210	$1.15 \times 10^4$	Right upper arm. Contact for $11\frac{1}{3}$ hrs.	8	8	100.0
1604	$3.18 \times 10^6$	Left upper arm. Contact during vaccination only	1	1	100.0
1701	$2.24 \times 10^5$	Left upper arm. Contact during vaccination only	1	1	100.0

In Table 6 in which the results of prophylactically treated patients are given a wide range of effectiveness of the orvus-mapharsen preparation is noted. Consideration of the technic may explain this. Inoculation was done by anyone of three physicians, and an attempt was made to carry out a technic involving penetration of only the epidermis by the needle, so that the emulsion would not be carried deeply into the epidermis but only into the stratum corneum. With the patients frequently restless and not always cooperative it was sometimes noted that the needle was deeply inserted, at times even so as to draw blood. Thus material could be carried so deep as to be protected from the local action of the agent, thus giving a clinical picture found when inoculation was performed in a manner not contaminating the epidermal layers.

This theory is strengthened by the fact that 4 of the 5 failures of protection in the group of patients in experiment 0707 were asymptomatic infections. It was further found that in a group of inoculations by intravenous technics, which were designed to test this hypothesis, that when the emulsion could be introduced in a manner not contaminating the epidermis asymptomatic infection would result. Furthermore in patients inoculated in two sites with orvus-mapharsen prophylaxis used on one site it was noted that the untreated location would usually develop a lesion while the prophylactically treated site would show no evidence of a cutaneous lesion.

In this type of experiment there was also evidence of the lack of systemic action of the locally-applied preparation. The only effect was noted at the place of application with no effect on the development of the lesion at points of inoculation elsewhere on the body. It is thought, then, that failure of prophylaxis in some instances and the extreme variability in rates of protection reflect differences in the depth to which the emulsion was carried during the inoculating procedure, with failure probably being more likely in individuals in which the organism was carried out of reach of a locally acting agent. As a result there was prevention of development of local lesions even though systemic dissemination from the site of application gave rise to asymptomatic infection such as seen by intravenous inoculation.

As discussed elsewhere it was realized that a method of inoculation such as this could not be carefully controlled as to depth of deposition of inoculum as a consequence of the limitations in the technic. But it was felt that it would give a means of utilizing the female subjects in a method which theoretically would provide a very severe test of the efficacy of the prophylactic technic. Reference to Table 5 reveals that the technic affords a high rate of infection, of the same magnitude as intra-cutaneous injection, and that even under these conditions local wash with orvus-mapharsen solution provided a high degree of protection.

As in experiment 1505 where 1,500,000 units of oral penicillin was administered after exposure to virulent emulsion by scarification, 300,000 units of oral penicillin also offered complete protection.

TABLE VI

Results of Prophylaxis Following Multiple  
Pressure Inoculation

Experiment Number	Size of Inoculum	Time of Application of Prophylaxis	Type of Prophylaxis	Patients <u>Infected</u>		
				Exposed	Number	Perce
0606	$2.7 \times 10^5$	$1\frac{1}{2}$ hrs after inoculation	Orvus-mapharsen (15cc) for 2 minutes	7	0	0.0
0607	$2.7 \times 10^5$	$2\frac{1}{4}$ hrs after inoculation	Orvus-mapharsen (15cc) for 2 minutes	7	0	0.0
0707	$1.5 \times 10^5$	$1\frac{1}{4}$ hrs after inoculation	Orvus-mapharsen (15cc) for 2 minutes	7	5	71.4
1211	$1.15 \times 10^5$	$11/3$ hrs after inoculation	Orvus-mapharsen (10cc) for 2 minutes	10	1	10.0
1608	$1.59 \times 10^5$	2 hrs after inoculation	300,000 u. oral penicillin	13	0	0.0

### Discussion

From the foregoing findings of experiments it is evident that every one of the agents used prophylactically, or as abortive therapy, has had a rigid test of its therapeutic effect and has shown value. Thus choice of any agent used must be based upon considerations such as acceptance of patient, ease of use, freedom from undesirable side or after effects, etc.

Oral penicillin in doses of 300,000 units 2 hours after inoculation or 1,500,000 units immediately after inoculation appeared to give complete protection. When compared with the results of FOB administration at a later time and with local application of aqueous penicillin it is suggested that oral administration may give a rapidly attained blood level which may effectively prevent establishment of infection within the body. For in the experimental work of Eagle (40) there is evidence to suggest that the treponema is particularly vulnerable to anti-spirochetal substances at the time of invasion of the host. The sooner administered following inoculation the smaller the dose required for abortive therapy.

This finding strongly suggests that the use of an oral penicillin prophylaxis against gonorrhea of 300,000 units should offer a high degree of protection against concurrently acquired syphilis if it is taken immediately following contact. In light of the use of oral penicillin as a gonorrheal prophylaxis in the Armed Services following Eagles field demonstration (41) this finding answers one of the questions which has tended to slow the adoption of the method. As little as 300,000 units of oral penicillin given 2 hours after inoculation offers complete protection under circumstances of risk of infection, which are not approximated in usual sexual exposure.

The preparation of orvus-mapharsen when applied after scarification and multiple pressure inoculation had an overall rate of protection of 90.2 percent. However, if experiment 0707 were omitted because of suspected reasons of inoculation error then the protection rate would be raised to 98.1 percent.. The value of this prophylaxis has been unequivocally demonstrated and because of its other favorable properties of cleansing and deodorizing it can be suggested for general use as a preparation for immediate post coital use.

Procaine penicillin G in oil (Duracillin administered in a dose of 300,000 units 11 days after inoculation was seen to have a high rate of cure even though by this time the patients had shown darkfield positive lesions. Only one patient of this group necessitated further treatment. It is realized that in this group the infection was full blown by the time treatment was given, although still in the seronegative stage. Thus it might be better called abortive rather than prophylactic, but results substantiate fully the findings of Schoch et al and Alexander et al (29,30) and coupled with findings relative to POB presented here, demonstrate that the procedure is sound.

This rate of cure may be compared with the observation of the Division of Venereal Disease (52) in which the rate of cure of seronegative darkfield positive syphilis is about 90 percent regardless of dose ranging from 300,000 to 12,000,000 units of penicillin.

The superiority of this preparation over POB can probably be explained by the fact that the blood levels with this preparation are much more constant and are maintained from 24 to 36 hours or even longer in some individuals which is sufficient to arrest the reproduction cycle of *T. Pallidum*.

### Summary

Three different technics for experimental production of syphilis against which a thorough test of prophylaxis can be made are discussed.

In general the types of prophylaxis used can be classified as follows:

1. Locally applied agents
  - a. 30 percent calomel ointment (Army pro kit).
  - b. 1 percent sodium lauryl sulfate - 0.15 percent mapharsen in aqueous solution.
  - c. Aqueous penicillin solution.
2. Parenterally administered preparations
  - a. Penicillin in oil and beeswax.
  - b. Procaine penicillin in oil.
  - c. Intravenous mapharsen solution.
3. Orally administered preparations
  - a. Penicillin tablets for oral use.
  - b. Penicillin in solution.

Each type of preparation and type of application revealed some degree of effectiveness as either prophylaxis or abortive therapy. However, it was found that the highest degree of effectiveness was obtained with either orvus-mapharsen solution applied locally, 30 percent calomel ointment applied locally, oral penicillin, or intravenous mapharsen given immediately after inoculation. Under these conditions no one preparation revealed superiority over the others.

The effectiveness of parental penicillin or of oral bismuth as prophylaxis or abortive therapy is related to the size of the dose, the maintenance of an effective blood level for the requisite time, and the length of time after inoculation at which administered.

While locally applied penicillin solution demonstrated spirochetal and prophylactic properties the lack of cleansing and deodorant properties diminishes the practical value as compared with the orvus mapharsen preparation.

Summary Table

Results of Patients Subjected to Various Methods of Infection  
and Prophylactic Treatment for Syphilis

Method of Infection	Type of Treatment	Patients Exposed	Infected	
			Number	Percent
Local application	Control	39	7	17.9
	Orvus - mapharsen after exposure	12	0	0.0
Scarification followed by local application	Control	83	76	91.6
	Orvus - mapharsen after exposure	30	1	3.3
	Orvus - mapharsen after 4 hours	9	3	33.3
	Sobisminol Mass after exposure	8	5	62.5
		9	0	0.0
	500,000 aqueous penicillin wash after exposure	6	0	0.0
		5	3	60.0
	1.5 m.u. oral penicillin after exposure	8	0	0.0
	600,000 u. POB intramuscularly after 11 hours	8	1	12.5
	U. S. Army prophylaxis after exposure	12	1	8.3
Multiple pressure	Control	26	25	96.2
	Orvus - mapharsen after exposure	24	1	4.2
	Orvus - mapharsen after exposure (exp. 0707)	7	5	71.4
	300,000 u. oral penicillin	13	0	0.0

Method of Infection	Type of Treatment	Patients Exposed	Infected		
			Number	Percent	
Intracutaneous inoculation	Control (arm only)	155	150	96.8	
	Intravenous - mapharsen after 2 hours	6	0	0.0	
	300,000 u. cryst. pen. G. pot. oil and wax after 11 days	8	1	12.5	
	300,000 u. Wyeth POB after 24 hours	7	6	85.7	
	600,000 u. Wyeth POB	after 12 hours	6	0	0.0
		after 24 hours	6	4	66.7
		after 48 hours	7	2	28.6
	1,200,000 u. Wyeth POB	after 24 hours	5	0	0.0
after 48 hours		5	3	60.0	
Scarification and intra- cutaneous inoculation of penis	Control	10	10	100.0	
Ingestion	Control	6	2	33.3	
Cisternal	Control	6	6	100.0	
Intravenous	Control	13	13	100.0	