

STUDIES ON THE PROPHYLACTIC EFFECT OF LOCALLY APPLIED ANTIBIOTICS IN EXPERIMENTAL SYPHILIS*. †

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At the meeting of the Subcommittee on Venereal Diseases, National Research Council, held in Washington, D. C. on May, 1952, it was the consensus that it would be advisable to test the potential value of the newer topical antibiotic preparations for their effect in preventing syphilitic infection. There was agreement that such a study could be carried out on rabbits with no great difficulty by using the technic of Arnold and Mahoney as published in the May, 1948 issue of the *Journal of Venereal Disease Information* (1). This technic is designed to produce chancres on the penis of the rabbit by inserting absorbent pledgets soaked with a suspension of live *Treponema pallidum* into the preputial sac. The prophylactic value of the newer antibiotic preparations, it was thought could be tested by first applying the treponemal suspension, and then either immediately or after a certain time interval had elapsed, by locally applying the antibiotic preparations. It was decided that these preparations should be applied in the concentrations and in the vehicles as they are commercially available. The following antibiotic ointments were considered: bacitracin, neomycin, polymyxin, thyrotricin, aureomycin, chloramphenicol, terramycin, and also hexachlorophene soap lotion.

The subcommittee entrusted the Section of Dermatology, School of Medicine, University of Chicago, to carry out this investigation.

In 1933 and 1934 Mahoney and Bryant (2, 3) reported that *Treponema pallidum* is able to penetrate the intact genital epithelium of prepuce and glans penis of the male rabbit in about three hours. They noted that the primary lesion in such cases can manifest itself in only slight and transient color changes without any characteristic features of a chancre.

It appeared that for our purposes, namely for screening of prophylactic agents, a technic producing a practically 100% yield of darkfield positive unmistakable chancres would be more suitable. This became possible by using the technic of Mahoney and Bryant with additional traumatization of the foreskin.

PROCEDURE

Healthy adult male rabbits with well developed genitalia were used. In the first experiments the technic was as follows: The penis was exposed and the edge of the foreskin was crushed with a hemostat. The tip of the hemostat grasped an area of about 3 square millimeters. This trauma caused a local hematoma.

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Later it was found that mildly stroking the inner edge of the foreskin three times with a gauze pad which was moistened with saline, constituted sufficient trauma to yield 100% typical chancres after the surface of this area was suitably infected. This milder form of traumatization did not cause any macroscopically visible injury.

The Nichols strain of *Treponema pallidum* was used to infect the prepuce and/or the penis. This strain has been carried in our laboratory since November, 1952, and kept going by intratesticular inoculations into rabbits since then.¹

Treponemal suspensions were prepared by mincing early testicular syphilomas in 10% rabbit serum broth. The suspensions were made to contain an average of five organisms per darkfield initially.

2 x 9 mm. cotton pledgets were soaked in this treponemal suspension and inserted into the preputial sac alongside the penis. The pledget was remoistened every 30-40 minutes with the suspension, and left in site for a total of three hours. During this time the preputial sac was kept closed by clamping the surrounding hair.

In the first part of this work from nine to ten animals were infected for each experiment. The animals were divided into three groups. Three animals were treated with white vaseline, three or four with the test substance and three were not treated at all. The ointments in the quantity of about one gram were richly spread all over the exposed area, with gloved fingers for one minute, with moderate pressure. Later, when in the course of this study it became evident that vaseline did not exert any prophylactic effect, the blank controls were eliminated. After application of the ointments the animals were returned to the cages. They were inspected every two to three days. The incubation period for development of a clinically visible lesion was found to range from twenty-four to sixty-three days. Darkfield preparations were made from all suspicious lesions either by the conventional technic of abrading the surface of the chancre and examining the exuding tissue fluid, or, in the case of clinically non-specific lesions, by excision and maceration of a small biopsy specimen. In this material the majority of the chancres developed on the prepuce; in some cases the chancre appeared on the glans penis.

RESULTS

Up to date experiments with terramycin, aureomycin, erythromycin, penicillin ointments, hexachlorophene soap, neomycin, bacitracin and calomel ointments have been completed. The following preparations were used:

(1) "Crystalline terramycin hydrochloride ointment" of Chas. Pfizer and Co., each gram containing 30 mg. of terramycin as the crystalline hydrochloride.

(2) "Aureomycin hydrochloride crystalline ointment 3%" of the Lederle Laboratories containing aureomycin HCl 30 mg. per gm., methylparaben 2.4%, propylparaben 0.6%.

¹ The author is indebted to Dr. T. B. Turner, Johns Hopkins University for providing this material.

(3) "Erythromycin 1% ointment" of Abbott Laboratories containing 1% erythromycin in a bland hypoallergenic petrolatum.

(4) "Procaine Penicillin G ointment" each gram contains 1,000 U. of crystalline penicillin G of the Lederle Laboratories.

(5) "Septisol with Hexachlorophene 0.75%" an antiseptic liquid soap of the Vestal Laboratories.

(6) "Ointment Myciguent (Neomycin sulfate 5 mg. per gram)" of the Upjohn Co.

(7) "Ointment Baciguent, 500 units per gram (Bacitracin ointment)" of the Upjohn Co.

(8) "White Vaseline", U.S.P.

(9) "Calomel Ointment", U.S.P.

The results are given in Tables I to VI.

TABLE I
Experiment with Terramycin ointment

Treatment	No. of Animals	No. of Chancres
Terramycin ointment.....	4	2
Vaseline controls.....	3	3
Blank controls.....	3	3

TABLE II
Experiment with Aureomycin ointment

Treatment	No. of Animals	No. of Chancres
Aureomycin ointment.....	3*	1
Vaseline controls.....	3	2
Blank controls.....	3	3

* One rabbit died 14 days after infection.

TABLE III
Experiment with Erythromycin ointment

Treatment	No. of Animals	No. of Chancres
Erythromycin ointment.....	3	1
Vaseline controls.....	3	3
Blank controls.....	3	3

TABLE IV
Experiment with Penicillin ointment

Treatment	No. of Animals	No. of Chancres
Penicillin ointment.....	4	0
Vaseline controls.....	4	4

TABLE V

Experiment with Hexachlorophene soap, Neomycin ointment, Bacitracin ointment

Treatment	No. of Animals	No. of Chancres
Hexachlorophene soap	2	2
Neomycin ointment.....	2	1
Bacitracin ointment.....	2	2
Vaseline controls.....	2*	1

* One rabbit died 17 days after infection.

TABLE VI

Experiment with Calomel ointment USP

Treatment	No. of Animals	No. of Chancres
Calomel ointment.....	2	1
Vaseline controls.....	2	2

DISCUSSION

From the data presented, it appears that in the experimental arrangement as described, none of the antibiotic ointments, except penicillin, had a satisfactory prophylactic effect. It should be emphasized that the test conditions have been rather severe. It is obvious that a local prophylactic agent which protects in only 66 % or less of the cases must be considered as unsatisfactory. However, for an orientation study it seemed to be more appropriate to use such severe condition. With this method the control groups yielded clinically typical chancres in 96 % of the cases. It was thought advisable to use severe conditions for the test because the human natural infection frequently is associated with minor abrasions.

The apparently satisfactory results with penicillin ointment require comment. The absence of a clinically visible lesion, of course, does not exclude the possible occurrence of a silent infection. This possibility was not pursued further by the lymph node transfer method for two reasons: Firstly, from the practical point of view, local prophylaxis with penicillin ointment seems inadvisable because of the potential danger of eczematous sensitization of the skin with locally applied penicillin. Secondly, from the experimental point of view, it would be extremely difficult, if not impossible, to separate local prophylactic action from the systemic effect of penicillin which may be absorbed into the general circulation from the site of application. A similar situation has been considered to prevail in local prophylaxis with calomel ointments (1).¹

No attempt was made to demonstrate general infection by lymph node transfer in the above experiments because the newer antibiotics were found to be failing even in suppressing the development of chancres.

¹Of course, the number of our experiments with penicillin is far too small as to conclude that penicillin ointment does protect against syphilitic infection in 100% of the cases under the given experimental conditions.

SUMMARY

Ointments containing terramycin, aureomycin, erythromycin, penicillin, neomycin, bacitracin and hexachlorophene soap were tested locally in an experimental screening arrangement for their potential prophylactic value in experimental syphilis.

With the exception of penicillin ointment, no satisfactory protecting effect was evident with the tested preparations.

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