

EXPERIMENTAL STUDIES TO DEVELOP LOCAL PROPHYLACTIC AGENTS AGAINST SYPHILIS*

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In this report a résumé is given of a series of experimental studies carried out in rabbits to develop effective local prophylactic agents against syphilis transmitted by application of a spirochaetal emulsion to the penile mucous membrane (Table). These studies were made at the Venereal Disease Research Laboratory of the United States Public Health Service between 1941 and 1946.

The development and composition of the most effective agent, Mapharsen (0.2 per cent.) in a 1 per cent. aqueous solution of alkyl aryl sulphate, has already been reported (Arnold and Mahoney, 1948). However, a large number of compounds were screened during the search, and no formal report has yet been made of the findings.

The widespread use of prophylactic agents might be found desirable and necessary in the event of some future widespread mobilization. Also, in areas of high prevalence of chancroid, the armed services still might find desirable a local prophylactic agent effective against syphilis, gonorrhoea, and chancroid. Since the search for an effective agent against all three diseases should logically be based upon attempts to incorporate an effective anti-chancroid agent into a preparation which has already been found effective against syphilis and gonorrhoea both *in vivo* and *in vitro* (Arnold and Mahoney, 1948; Funes and Aguilar, 1952), it was thought desirable to give in some detail the results of the various studies which determined the efficacy of this preparation.

In the course of these experimental studies, it was kept in mind that the desirable prophylactic preparation was one which would be simple to use, aesthetically acceptable, and not painful to the

individual (in contrast to the calomel-sulphathiazole ointment widely used as a prophylactic agent). It was thought that the preparation should preferably be an aqueous solution which could be prepared from an easily transported powder immediately after the potentially infective contact, and which would be made part of the routine of washing for cleansing purposes after contact. Thus, the agent should be cleansing, preferably lathering, deodorant, therapeutically effective against syphilis, gonorrhoea, and chancroid if possible, and not likely to produce contact dermatitis.

The details of testing the various preparations in rabbits have been described in earlier publications (Arnold and Mahoney, 1948; Mahoney, 1936). They may be summarized by stating that an emulsion of *Treponema pallidum* (Nichols strain) prepared from testes of rabbits with syphilitic orchitis, was applied for periods of 1 or 2 hrs to the intact mucosa of the penis and preputial sac of adult male rabbits. In these experiments, healthy rabbits of the chinchilla breed were used. The emulsion was applied to a small cotton pledget which was placed in the preputial sac and moistened with the emulsion every 15 to 20 min. Following exposure, a control group of rabbits was segregated. The remaining animals were treated prophylactically either by application to the mucosa of the agent to be tested or by systemic administration. The animals were examined at regular intervals to record the development of a penile chancre, the specificity of which was determined by dark-field examination. Proof of lack of development of infection or of asymptomatic infection was determined by lymph-node transfer of all animals showing no clinical evidence of infection within 140 days

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TABLE

Duration of Exposure (hrs)	Type of Treatment	Number of Animals Exposed	Number of Animals Infected	Number of Animals Protected
1	Controls	28)	261	28
	Arsenicals, alone or in combination with Soaps, Synthetic Detergents, or Wetting Agents			
1	Two liberal applications of 3-amino-4-hydroxyphenylarsineoxide hydrochloride (Mapharsen) powder	5	4	1
1	0.025 per cent. solution of Mapharsen	13	5	8
1	0.1 per cent. aqueous solution of Mapharsen	21	1	20
1	Aqueous solution 1 per cent. 3-amino-4-hydroxyphenyldichlorarsine hydrochloride (Phenarsen)	4	0	4
2	Aqueous solution 1 per cent. Mapharsen and 2 per cent. Orvus	9	0	9
1	Aqueous solution 1 per cent. Mapharsen and 2 per cent. sodium salt of technical lauryl sulphate (Orvus)	20	0	20
1	Aqueous solution 0.1 per cent. Mapharsen and 1 per cent. Orvus ME	14	2	12
1	Aqueous solution 0.1 per cent. Mapharsen and 1 per cent. Orvus ME (2-yr-old preparation)	15	8	7
2	Aqueous solution 0.1 per cent. Mapharsen and 1 per cent. Orvus ME	9	0	9
1	Aqueous solution 0.2 per cent. Mapharsen and 0.1 per cent. Orvus	3	0	3
1	Aqueous solution 0.2 per cent. Mapharsen and 1 per cent. Orvus	39	1	38
1	0.2 per cent. Mapharsen in 2 per cent. aqueous solution of quaternary ammonium compound No. 238	6	0	6
1	0.2 per cent. Mapharsen and 2 per cent. Duponol C solution	5	0	5
1	0.2 per cent. Mapharsen and 2 per cent. sodium alkyl sulphate	14	5	9
1	2 per cent. dichlorophenarsin hydrochloride, sodium citrate, and sodium carbonate (Chloarsen) and 0.1 per cent. Orvus	4	1	3
1	2 per cent. Intracol S and 1 per cent. arsphenamine	5	0	5
	Sulphonamides, alone or in combination			
1	Two liberal applications of sodium sulphapyridine powder	4	4	0
1	Two liberal applications of sulphathiazole powder	4	1	3
1	Two liberal applications of acetyl sulphathiazoline	3	3	0
1	Two liberal applications of nicotiny sulphaniilamide	4	4	0
1	30 per cent. Calomel and 15 per cent. sulphathiazole for 5 min. inunction	9	0	9
1	30 per cent. Calomel and 15 per cent. sulphathiazole ointment	8	2	6
	Penicillin			
1	One injection aqueous solution amorphous penicillin, 500 units per pound body weight	5	5	0
1	One injection aqueous solution amorphous penicillin, 2,000 units per pound body weight	5	4	1
1	One injection aqueous solution amorphous penicillin, 5,000 units per pound body weight	4	3	1
1	One injection procaine penicillin G in oil, 4,600 units per pound body weight	5	0	5
1	20,000 units calcium penicillin with 1 per cent. Orvus in 1 ml. glycerine, local application	4	2	2
	Antiseptics, alone or in combination			
1	Benzalkonium chloride (Zephiran) aqueous solution 1 : 1,000	5	5	0
1	Aqueous solution of cetylpyridinium chloride (Ceprynychloride) 1 : 100	3	3	0
1	Solution of 5 per cent. sodium ethyl mercuri thiosalicylate (Merthiolate), 5 per cent. glycerine, 2 per cent. TEA (triethanolamine)	3	2	1
1	Solution of 5 per cent. Merthiolate	3	2	1
1	Benzethonium chloride (Phemeral) 1 : 100 aqueous solution	3	3	0
1	0.5 per cent. phenothiazine in salad oil, and 1 per cent. Aerosol MA	4	4	0
1	1 per cent. phenylmercuric nitrate in 0.5 per cent. TEA	4	1	3
1	2 per cent. phloroglucin	3	3	0
1	0.1 per cent. fumerane in aqueous solution	30	3	27
1	1 per cent. fumerane in glycerine	33	1	32
1	0.5 per cent. 1-12-diamidoxine dodecane in 1 per cent. Aerosol MA	9	9	0
1	1 per cent. lauryl-thiocyanate in salad oil and 1 per cent. Aerosol	4	4	0
1	1 per cent. tetra-ethyl thiuram in salad oil and 1 per cent. Aerosol	4	4	0
1	1 per cent. alpha-naphthalenic acetic acid in aqueous solution	4	4	0
1	0.1 per cent. alpha-naphthalenic acetic acid in 1 per cent. Aerosol	4	4	0
1	0.5 per cent. alpha-naphthalen acetic acid in 0.05 NaOH+1 per cent. Aerosol MA	5	0	5
1	1 per cent. amino 2 naphthol 4 sulphonic acid in sodium sulphite solution	4	4	0
	Soaps, Synthetic Detergents, or Wetting Agents			
1	Wash with white soap solution and rinse with water	15	13	2
1	10 per cent. white soap solution	8	7	1
1	10 per cent. aqueous solution of alkyl arylsodium sulphate (Santomerse No. 3)	3	2	1
1	10 per cent. aqueous solution of decyl benzene sodium sulphate (Santomerse D)	3	2	1
1	10 per cent. aqueous solution of a wetting powder (Intracol 5Z)	3	2	1
1	10 per cent. aqueous solution of dihexyl ester of sodium sulphosuccinic acid (Aerosol AV)	4	3	1
1	2 per cent. aqueous solution of sodium alkyl sulphate	3	3	0
1	10 per cent. aqueous solution of sodium salt of alkylated aryl polyether sulphate (Triton W-30)	3	3	0
1	Aqueous solution of 10 per cent. sodium lauryl sulphate (Duponol C)	3	2	1
1	Glee Pac soap cloth	5	2	3
	Miscellaneous Agents			
1	GAW (glycerine 10 ml., alcohol 10 ml., water 20 ml.)	5	5	0
1	Ethylene glycol 30 per cent.	3	2	1
1	10 per cent. glycerophosphate	4	4	0
1	1 per cent. cadmium chloride—pH 6.6	4	4	0
1	Glee Pac, silver picrate jelly 0.25 per cent. Schabelitz	5	5	0
1	Bismuth sodium tartrate	3	3	0
1	1 per cent. aqueous solution of subtenolin	5	5	0

after exposure. Observations lasted an additional 100 days in cases of gland transfer.

It should be added that there were no diagnostic or evaluation problems introduced in this study by *T. cuniculi*. This organism, a normal inhabitant of the rabbit preputial mucous membrane, produces, if any, a lesion which is different from that of syphilis (McLeod and Turner, 1946), in fact, it can only be made to produce a lesion with any degree of certainty under special experimental conditions.

Summary

Experimental studies of the effectiveness of various agents in local or systemic prophylaxis against syphilis are reported. No attempt has been made to

determine the relative effectiveness of the prophylactic preparations tested but the high degree of effectiveness of locally applied solutions of Orvus-Mapharsen and of solutions of Fumerane, or of parenteral penicillin, is indicated.

The Table, which lists the prophylactic agents, including combinations of preparations, shows the number of animals protected in relation to those exposed for various intervals of exposure.

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