

15012

Repository Injection of Penicillin in Water-in-Oil Emulsion. I. Effect on Gonorrhea.*

A. COHN, B. A. KÖRNB�ITH, I. GRUNSTEIN, K. J. THOMSON, AND JULES FREUND.

From Venereal Disease Research Unit, Department of Health, City of New York, and the Public Health Research Institute of the City of New York, Inc.

There have been numerous efforts to improve the administration of penicillin by either prolonging its absorption¹ or delaying its excretion.² Most recently methods of administering penicillin by mouth have been reported.³

This study was undertaken to determine if penicillin injected intramuscularly is more effective in a water-in-oil emulsion than in aqueous solution. It was hoped that the absorption of penicillin might be prolonged by incorporating it in a water-in-oil emulsion so that the number of injections and perhaps the amount of penicillin could be reduced. Patients with gonococcal infections were chosen for testing the method because clinical manifestations are usually clear-cut and cure can be established readily by bacteriological methods.

Water-in-oil emulsions were prepared by combining an aqueous solution of sodium penicillin with a lanolin-like substance† and peanut oil (other vegetable oils may be used). They contain microscopic droplets of aqueous

solution of penicillin in a menstruum of oil and "Falba."[†] (Fig. 1.) Such preparations can be made conveniently in a clinical laboratory as follows: One part of autoclaved and melted "Falba" is placed in a mortar and 1.3 parts of a penicillin solution are added to the "Falba" drop by drop while mixing with a pestle. Then 1.8 parts of autoclaved peanut oil are mixed slowly with the penicillin-"Falba" mixture. Solutions containing up to 200,000 units of sodium penicillin per ml can thus be incorporated; it has been found convenient, however, to use solutions containing 100,000 units per 1.4 ml of normal saline. A somewhat simpler procedure, particularly useful in preparing larger amounts of emulsion, is to mix the "Falba" with peanut oil and add the aqueous solution of penicillin slowly to the oil-Falba mixture while it is being agitated by an electric stirrer.

A single dose can be prepared without laboratory facilities in the following way: One and four-tenths ml of sterile 0.85% salt solution are drawn into a sterile syringe and ejected into a vial containing 100,000 Oxford units of dry penicillin. To this penicillin

* The laboratory work was aided by a grant from the U. S. Public Health Service.

¹ (a) Romansky, M. J., and Rittman, G. E., *Science*, 1944, **100**, 107; (b) Trumper, M., and Hutter, A. M., *Science*, 1944, **100**, 432; (c) Fisk, R. T., Foord, A. G., and Alles, G., *Science*, 1945, **101**, 124.

² (a) Rammelkamp, C. H., and Bradley, S. E., *Proc. Soc. Exp. Biol. and Med.*, 1943, **53**, 30; (b) Beyer, K. H., Woodward, R., Peters, L., Vermey, W. F., and Mattis, P. A., *Science*, 1944, **100**, 107.

³ (a) Libby, R. L., *Science*, 1945, **101**, 178; (b) McDermott, W., Bunn, P. A., Benoit, M., Du Bois, R., and Haynes, W., *Science*, 1945, **101**, 228.

† The lanolin-like substance used in this study is sold under the trade name of "Falba," manufactured by Pfaltz and Bauer, Inc., New York City.

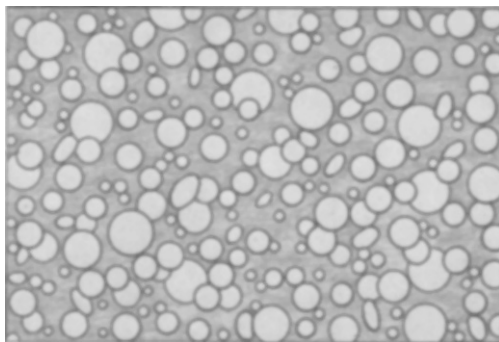


FIG. 1.

Schematic drawing of a water-in-oil emulsion of aqueous penicillin solution in peanut oil. The penicillin is contained in the water droplets.

TABLE I.
Serum Penicillin Concentration in Patients Given a Single Intramuscular Injection of 150,000 Oxford Units of Penicillin.

Patient	Penicillin, Oxford units		Hours after injection							
	Aqueous solution, $\times 1,000$	Water-in-oil emulsion, $\times 1,000$								
			$\frac{1}{2}$	1	2	4	5	6	7	8
W	150		1.25	.31	.16	0	—	0	—	0
L	150		2.5	2.5	.31	0	0	0	0	—
F		150	.62	.16	.04	0	—	0	—	0
R		150	1.25	.31	.16	.04	—	0	—	0
Q		150	1.25	1.25	.62	.06	0	0	0	—
P	50	100	.31	.31	.78	.02	—	0	—	0
C	50	100	1.25	1.25	.31	.06	.008	0	.008	0
D	50	100	2.5	1.25	.62	.31	.062	.008	.008	—

0 = No penicillin demonstrable.

— = No sample.

TABLE II.
Duration of Urinary Excretion of Penicillin in Patients Given a Single Intramuscular Injection 150,000 Units of Penicillin

Patient	Penicillin, Oxford units		Hours after injection								
	Aqueous solution, $\times 1,000$	Water-in-oil emulsion, $\times 1,000$									
			$\frac{1}{2}$	2	4	5	6	8	10	24	28
W	150		—	—	+	—	+	+	+	0	0
L	150		—	+	+	—	+	—	—	—	—
F		150	+	+	+	—	+	+	+	+	—
R		150	—	—	+	+	—	+	+	—	—
Q		150	—	+	+	—	+	—	—	+	+
P	50	100	—	+	+	+	+	+	+	+	—
C	50	100	—	+	+	—	+	—	—	+	+
D	50	100	—	+	+	—	+	—	—	+	—

— = No sample.

+

TABLE III.
The Effect of a Single Intramuscular Injection of Penicillin on Acute Gonococcal Infection.

Group	Penicillin, Oxford units			Males			Females			Total		
	Aqueous solution, × 1,000	Water-in-oil emulsion, × 1,000	Total, × 1,000	T. C. F.			T. C. F.			T. C. F.		
				T.	C.	F.	T.	C.	F.	T.	C.	F.
1	150	0	150	13	11	2	0	0	0	13	11	2
2	300	0	300	8	7	1	0	0	0	8	7	1
3	0	150	150	43	41	2	9	9	0	52	50	2
4	50	50	100	7	6	1	2	2	0	9	8	1
5	50	75	125	10	9	1	3	3	0	13	12	1
6	50	100	150	38	38	0	11	11	0	49	49	0
7	50	150	200	8	8	0	0	0	0	8	8	0

T = Total number of patients treated.

C = Cures. Minimum criteria for cures are: in males at least 3 negative smears and cultures of urethral and prostatic secretions in 21 days; in females, at least 3 negative smears and cultures of urethral and cervical secretions in 21 days.

F = Failures.

aqueous solution as a "priming" dose was reached on the basis of the previous observation showing that 150,000 units in water-in-oil emulsion alone (Group 3) failed to cure all patients so treated. A single injection of 150,000 units in salt solution (Group 1) resulted in 2 failures among 13 cases. A single injection of 300,000 units in salt solution (Group 2) resulted in 1 failure among 8 cases.

Immediate reactions to the intramuscular injection of water-in-oil emulsions either alone (Group 3) or in combination with aqueous solution (Groups 4, 5, 6, 7) were not different from those occurring when aqueous solutions were injected. These consisted chiefly of transient pain at the site of injection radiating down the thigh, often associated with a sensation of "stiffness" of the leg. Such discomfort gradually subsided after 3 to 5 minutes. The site of injection was examined carefully during the follow-up period (up to 3 weeks) and no local infiltration or other abnormalities were found.

Water-in-oil emulsions of antigens such as diphtherial toxoid, horse serum, typhoid and Bordet-Gengou bacilli and gonococci have

been injected in animals and man.⁶ It was found that antibody formation is sustained for a remarkably long time after the injections of antigens in water-in-oil emulsions. It was also found that mice tolerate the injection of approximately one hundred lethal doses of tetanus toxin when administered in water-in-oil emulsion.⁷ These observations suggest that absorption of substances from the aqueous phase of a water-in-oil emulsion is considerably prolonged. Strauch's observation that the absorption of strychnine and morphine is very much retarded from water-in-oil emulsions⁸ supports this interpretation.

The present method used for treating gonorrhea with penicillin consists of at least 3 intramuscular injections of a total dosage of 100,000 to 150,000 Oxford units of penicillin during a 4-hour period. The method described here which requires a single injection of penicillin has obvious advantages.

The technic of administering therapeutic agents employing repository injections, affords wide clinical and investigational possibilities not only for penicillin but for other substances as well.

⁶ Freund, J., and Behan, M. A., unpublished experiments, 1941.

⁸ Strauch, C. B., *J. Am. Med. Assn.*, 1929, **92**, 1177.

⁶ (a) Freund, J., and Bonanto, M. V., *J. Immun.*, 1944, **48**, 325; (b) Freund, J., and Thomson, K. J., unpublished experiments, 1944.