Action of Propylene Glycol upon Experimental Tuberculosis in Guinea Pigs. (19177)

C. Bazzicalupo, A. Portella, and M. Contieri. (Introduced by A. J. Goldforb.)
From the Laboratorio di Batteriologia dell'Istituto Principi di Piemonte, Napoli (Camaldoli).

In researches on substances inhibiting growth of the tubercle bacillus, attention has been called to the glycols (propylene, dipropylene, ethylene, diethylene, triethylene, 1-3 butylene, 1-4 butylene; 2-amino-metil-1, 3-propandiol, polypropylene and other related compounds).

It has been demonstrated that 5-7% propylene glycol (PG) partially inhibits the *in vitro* growth of *Mycobacterium tbc., var. Hom.*, and that at 8-10% the inhibition is complete(2). Higher concentrations are required to inhibit the growth of bovine and avian strains; therefore PG is more active *in vitro* against the human than against bovine or avian strains. It is also less active against acid fast nonpathogenic mycobacteria. PG is equally inhibitory to streptomycin susceptible and streptomycin resistant strains(21). The activity of PG was therefore tested *in vivo*.

The toxological effects of PG are given by the following investigators: Hunt(12), Seidenfeld and Hanzlik(24), Brown(4), Braun and Cartland(3), Holck(11), Lehman and Newman(17-19), Van Winkle and Newman(27), Weatherby and Haag(28), Aiazzi-Mancini (1), Hanzlik *et al.*(9-10), Dumez(6), Latven and Molitor(14), Laug *et al.*(15), Kesten *et al.*(13), Newman *et al.*(20), Smith(25), Van Winkle(26), Bucciardi(5), Morris *et al.* (18). Launoy(16), Fabre and Rousseau(7), Randolph and Mallery(22), Whitlock *et al.* (29), Robertson *et al.*(23). Preliminary toxicological tests were made on guinea pigs and rabbits. These confirmed the data of previous workers.

In these experiments on the efficacy of PG in experimental tuberculosis, guinea pigs were treated with PG administered orally, parenterally (subcutaneously) and by aerosols. Oral administration has no antituberculous effect. Only experiments on guinea pigs in which the PG was administered subcutaneously are reported here.

Experimental. Guinea pigs were infected by subinguinal inoculation with 0.1 mg (dry weight) of an H. virulent strain (H. 49, Ist. "Principi di Piemonte"). They were divided into several groups:

Group		No. of animals
I	Guinea pigs infected and killed every 5th day	60
II	Guinea pigs infected and treated with PG. This group was subdivided into:	
	(a) those in whom treatment was begun immediately after infection	60
	(b) those in whom treatment was begun 8 days after infection	60
	(c) those in whom treatment was begun 21 days after infection	60
III	Control infected guinea pigs that died spontaneously	70
IV	Infected guinea pigs treated with PG that died spontaneously	70

Treatment. Preliminary tests were made in experimentally infected guinea pigs with various concentrations of PG (5% to 30%). We used a racemic compound, m.w. 76.09; b.p. 188.2. A 20% saline solution was found optimal, but lesser concentrations also have a therapeutic action. The guinea pigs were injected subcutaneously twice daily with 2 cc of 20% dilution of PG. This dose is well tolerated for a prolonged time, as demonstrated in another group of 30 guinea pigs, given PG only. To investigate the macroscopic tuberculous alterations in the several organs the guinea pigs of Group I were killed each 5th day. Several infected guinea pigs which died earlier were not included. The guinea pigs of Group II were infected and treated with PG at various times after infection: in subgroup (a) immediately after infection, in order to note the effect of PG upon the formation of earlier alterations; in (b) after 8 days and in (c) after 21 days. The treated guinea pigs, like the controls, were killed each 5th day and the macroscopic tuberculous alterations in the different organs

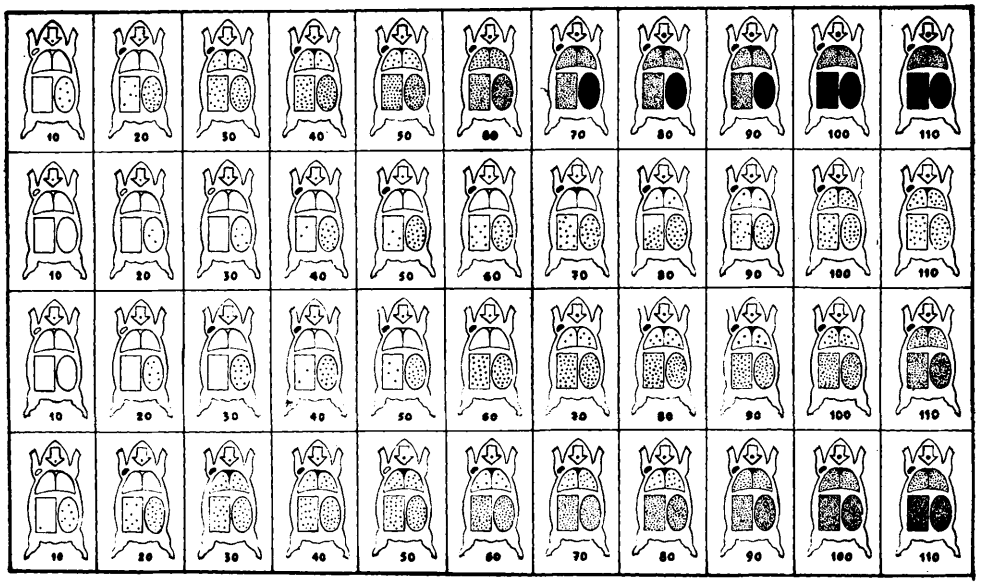

FIG. 1. Schematic representation of amount of tuberculosis observed at necropsy in untreated guinea pigs (first line), and in treated animals, in which the daily treatment is started immediately after infection (second line); 8 days after infection (third line), and 21 days after infection (fourth line).

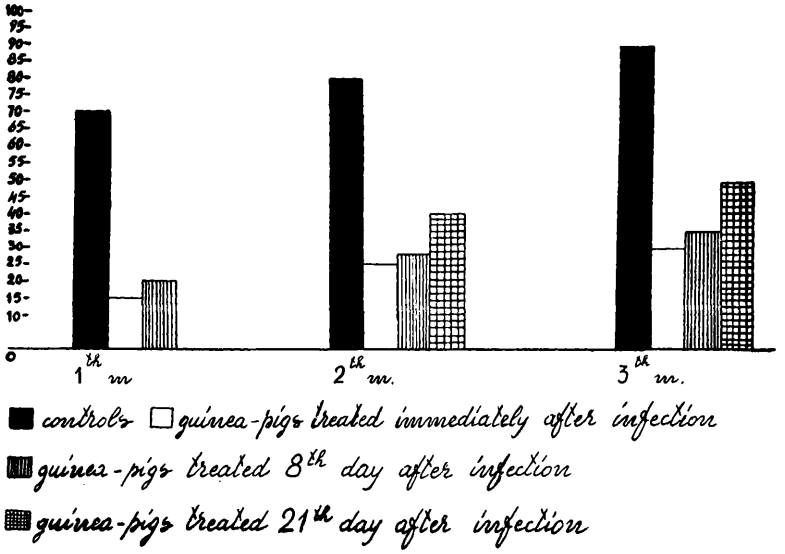

FIG. 2. Index of tuberculization at end of each month.

noted. These experiments were continued until the 110th day after inoculation. Guinea pigs of Groups III and IV were infected with the same bacillary suspensions. Group III served as untreated controls, Group IV was treated daily with the optimal dose of PG, beginning with the 10th day after infection.

Results. The degree of tuberculosis, observed macroscopically, at necropsy, every 10th day, in treated and untreated guinea pigs is shown in Fig. 1. Changes are indicated according to the scheme of Feldman and Hinshaw(8). Comparison of the macroscopic changes in controls and in treated guinea pigs shows that the treatment had a favorable effect upon the intensity and extent of the

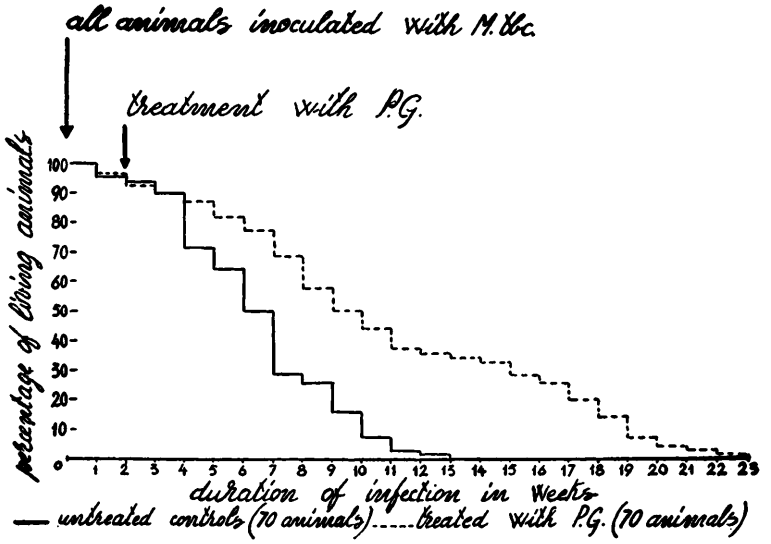

FIG. 3. Comparative survival times of guinea pigs treated with propylene glycol and in untreated controls.

alterations in the various organs. Histological studies confirmed the macroscopic observations. From the extent and character of the macroscopic tuberculous alterations in several organs of guinea pigs of Group I and of various subgroups of Group II, the index of tuberculization was calculated at the end of each month (Fig. 2).

The reduction of the tuberculization index occurred in the first and second subgroups (a and b), *i.e.* in animals that had been exposed to treatment immediately or 8 days after inoculation. In the first month the index is 15-20% against the 70% for the controls; at the end of the second month the indices are: 25%, 28%, and 40%, respectively, for each subgroup against 80% for the controls. At the end of the third month the index is 30%, 35%, 50%, respectively, for each subgroup against 90% for the controls. After a longer time (this experiment was continued to the 110th day) these differences were reduced, but still remain large. Fig. 3 shows the comparative survival times in weeks, of treated and untreated tuberculous guinea pigs (Group III and IV), which died spontaneously. While all controls died by the 13th week, several treated guinea pigs were alive and the last one died in the 23rd week.

Conclusions. In experimentally infected guinea pigs, subcutaneous treatment with PG inhibits extensive tuberculous alterations and prolongs the survival time. Therefore, propylene glycol exerts a favorable action *in vivo*. Its *in vivo* suppression of tuberculosis is equal to that of other substances with *in vitro* bacteriostatic properties. The antituberculous power of propylene glycol *in vivo* is greater when the treatment begins immediately after infection.

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Detection of Antibodies by Polyvinylpyrrolidone* II. Comparison of Sensitivity of Antihuman Globulin and PVP. (19178)

CRICHTON MCNEIL AND ELMER F. TRENTELMAN.
From the Laboratories of Holy Cross Hospital,† Salt Lake City, Utah.

This work, comparing the sensitivity of the Coomb's test and PVP titration to detect anti Rh antibody, is a natural outgrowth of our original publication concerning polyvinylpyrrolidone as a suitable antiserum diluent(1). Most serologists now concede that the Coomb's test excels other methods of incomplete antibody detection both in sharpness of reaction and sensitivity(2-6). Therefore, if PVP technics compare favorably with that of employing anti-human globulin for detection of antibodies, further expansion of the uses of PVP might be justified.

Materials. (1) Antisera—anti Rho' (CD) serum was used throughout the titrations. All of this reagent came from the same lot and has an albumin titer of approximately 1:128. The saline agglutinin titer was almost nil. (2) Red blood cell suspensions were obtained from a single donor whose type was O Rho' (CDe). The cells were drawn less than 5 days prior to use. 20% bovine albumin (Armour & Co.) in 0.9% saline was used as a diluent. (3) 10% Polyvinylpyrrolidone (PVP) was prepared as previously described (1) buffered to pH 6.9-7.0. (4) Anti-human globulin was obtained from a commercial source (Ortho) having passed the requirement for U. S. license. (5) Albumin 20% was prepared from 30% bovine albumin fraction II (Armour & Co.).

Methods. Titrations were carried out, using the serial dilution tube (size 75 x 10 mm) technic. In each titration, 0.2 ml of anti Rho' blocking serum was mixed with an equal quantity of diluent, as indicated in Table I, and 0.2 ml was transferred to the succeeding tube, which also contained an equal amount of diluent. The double dilution of serum was followed by the addition of 0.2 ml of a 4% fresh washed suspension of Rho' (CDe) red blood cells in saline or 20% albumin as indicated by the table. Mixing and incubation of tubes at 37°C water bath for one hour was

* Polyvinylpyrrolidone kindly furnished by General Aniline & Film Corp., Easton, Pa.

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