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N'Dodecanoylsulfanilamide, and Sulfapyridine Plus Vitamin C, in Experimental Tuberculosis in Guinea Pigs.*

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The striking chemotherapeutic effects obtained recently by the use of sulfanilamide and related compounds have led many workers to study the therapeutic effects of these chemicals on experimental and clinical tuberculosis. The findings reported have been conflicting, and the search for a chemotherapeutic agent which would act efficiently in tuberculosis is still being continued.

As early as 1920, the fatty acids of chaulmoogra oil were suggested for the treatment of tuberculosis (Walker and Sweeney[1]), and clinical success in the treatment of skin tuberculosis with hydnocarpic acid has been reported by Rogers[2] and by Burgess.[3] Kolmer and his associates,[4] however, showed that chaulmoogric acid does not inhibit the course of experimental tuberculosis in guinea pigs. Recently Crossley, Northey, and Hultquist[5] synthesized N'dodecanoylsulfanilamide with the thought that a combination of a long chain fatty acid with sulfanilamide might provide a more effective chemotherapeutic agent for tuberculosis than either constituent alone. When this compound was administered to guinea pigs by stomach tube in 100 mg amounts daily for 45 days after infection with H37, Climenko and Schmidt[6] reported no sign of generalized tuberculosis, as evidenced by the absence of gross involvement of liver or spleen or of general lymphadenitis in these animals, 120 days following infection. Through the courtesy of Dr. D. A. Bryce[7] we were supplied with generous amounts of N'dodecanoylsulfanilamide for the purpose of studying its action in experi-

* This work was in part supported by a grant from the National Tuberculosis Association.

1 Walker, E. L., and Sweeney, M. A., *J. Inf. Dis.*, 1920, **26**, 238.

2 Rogers, L., *Brit. Med. J.*, 1933, **1**, 47.

3 Burgess, W., *Brit. Med. J.*, 1935, **2**, 835.

4 Kolmer, J. A., Davis, L. C., and Jager, R., *J. Inf. Dis.*, 1921, **28**, 265.

5 Crossley, M. L., Northey, E. H., and Hultquist, M. E., *J. Am. Chem. Soc.*, 1939, **61**, 2950.

6 Climenko, D. R., and Schmidt, R. L., personal communication.

7 Bryce, D. A., Medical Director, Calco Chemical Co.

mental tuberculosis. Throughout the course of this work, tuberculin-negative, male guinea pigs were used.

Experiment I. Eighteen guinea pigs were infected subcutaneously in the region of the groin with 1 mg of human type tubercle bacilli (H37) and divided into 3 groups of 6 animals each as follows:

Group I. Untreated controls.

Group II. Treated with 100 mg N'dodecanoylsulfanilamide in 2% olive oil solution, administered by stomach tube. Treatment started on the day of infection and continued daily for 45 days.

Group III. Treated with 100 mg N'dodecanoylsulfanilamide in 2% olive oil solution, administered by stomach tube. Treatment started 5 days after infection and continued daily for 40 days.

Results. Three control animals died 40 days after infection, 1 animal of Group II died 25 days after infection, and 2 animals of Group III died 40 days after infection. The remaining guinea pigs were sacrificed 60 days after infection. The macroscopic findings, averaged for severity of involvement, are presented in Table I.

TABLE I.
Extent of Tuberculosis.

Group	Lungs	Liver	Spleen	Size of spleen	Glands	Summary
I	1.6+	3.0+	2.5+	4.6 × normal	2.1+	2.3+
II	1.1+	2.1+	2.1+	3.5 × "	2.1+	2.0+
III	1.2+	2.4+	2.6+	4.8 × "	2.6+	2.2+

Although the treated animals showed somewhat less disease than the control pigs, there was no evidence of localization and the differences were very slight indeed.

The experiment was, therefore, repeated with a smaller infecting dose. For purpose of comparison, groups of animals treated with sulfapyridine and with sulfapyridine plus vitamin C were included in this series. The latter were added in view of the favorable results obtained previously with vitamin C treatment of experimental tuberculosis.[8]

Experiment II. Thirty-five guinea pigs were infected subcutaneously in the region of the groin with 0.1 mg of H37 and divided into 5 groups of 7 animals each, as follows:

Group I. Untreated controls.

Group II. As in Experiment I.

Group III. As in Experiment I.

Group IV. Treated with 100 mg sulfapyridine in 2% olive oil solution, administered by stomach tube. Treatment started on the day of infection, and continued daily for 45 days.

[8] Steinbach, M. M., and Klein, S. J., in preparation.

Group V. Treated with 100 mg sulfapyridine in 2% olive oil solution, administered by stomach tube, and 10 mg vitamin C dissolved in normal saline, administered subcutaneously. Treatment started on the day of infection and continued daily for 45 days.

Results. One control animal died 33 days, and 1 died 120 days after infection. One animal in Group III was killed accidentally the day after infection. Two animals in Group IV died 140 days after infection, and 1 guinea pig in Group V died 120 days after infection. Three of the animals in each group were sacrificed 62 days after infection. The findings at this time were the same as obtained in Experiment I. The rest of the animals were sacrificed 140 days after infection. The average autopsy scores, including all the animals of each group, are presented in Table II.

TABLE II.
Extent of Tuberculosis.

Group	Lungs	Liver	Spleen	Size of spleen	Glands	Summary
I	2.3+	3.0+	3.9+	6.3 × normal	3.5+	3.2+
II	2.3+	3.0+	2.2+	3.0 × "	2.9+	2.6+
III	3.0+	3.4+	3.4+	5.0 × "	2.6+	3.1+
IV	2.5+	3.5+	2.5+	4.7 × "	2.6+	2.7+
V	2.7+	3.4+	3.4+	5.2 × "	3.0+	3.1+

In all groups the infection had spread to every susceptible organ of the guinea pig. The differences which exist in gross appearance and size of spleen between treated and untreated animals cannot be considered significant in view of Corper's[9] report that this effect may be due to the toxic action of the drug. The general impression gathered at the autopsy table was that no group of animals showed significant differences in the extent or degree of tuberculous infection.

Conclusions. (1) Under the conditions of our experiments treatment with N'dodecanoylsulfanilamide shows no inhibitory effect on the course of experimental tuberculosis in guinea pigs infected with the human tubercle bacillus. (2) The administration of sulfapyridine, alone or in conjunction with vitamin C, is ineffective in the treatment of guinea pigs infected with the human tubercle bacillus.

[9] Corper, H. J., Cohn, M. I., and Bower, C., *Am. Rev. Tuberc.*, 1939, **40**, 452.