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N^1-Dodecanoylsulfanilamide. I. Experimental Infections with Beta Hemolytic Streptococci.

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The chemical properties of N^1-dodecanoylsulfanilamide have been described by Crossley, Northey and Hultquist[1] and the absorption, distribution, and toxicity of the drug will be discussed in another paper of this series. The present report deals with the chemotherapeutic effects of the drug in experimental infections of mice with beta hemolytic streptococci.

While 3 strains of beta hemolytic streptococci, C-203,* SH-1685,† and "Todd",‡ have been employed in this work, the results have been so consistent that the report will only deal with the effects on C-203. Virulence titrations of a 16-hour culture of this organism grown on fresh beef infusion, whole blood media give 100% mortality figures within 24 hours for concentrations down to 1×10^{-6} cc and 100% mortality figures within 72 hours for concentrations down to 1×10^{-7} cc. These virulence figures refer to young mice of the Swiss strain weighing between 10-12 g. The absorption of N^1-dodecanoylsulfanilamide from the gastrointestinal tract seems to be dependent on the absorbable lipoids present in the gut. This fact manifested itself to us in our earlier experimental work when it appeared that the drug had no protective action in streptococcal infections after it had been administered either orally or subcutaneously in acacia suspension. The following experiment illustrates this point.

Experiment 1. All animals infected by the intraperitoneal administration of 1×10^{-6} cc of a 16-hour culture of C-203.

Group A. 10 mice. Untreated controls.

Group B. 10 mice. Sulfanilamide controls. 1 cc of a 1% acacia suspension of sulfanilamide administered orally 1 hour and 24 hours after infection.

Group C. 10 mice. Experimental series. One cc of a 1% acacia suspension of N^1-dodecanoylsulfanilamide administered subcutaneously 1 hour and 24 hours after infection.

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1 Crossley, M. L., Northey, E. H., and Hultquist, M. E., *J.A.C.S.*, 1939, **61**, 2950.

* From the Johns Hopkins Hospital, Baltimore, Md.

† From the National Institute of Health, Washington, D. C.

‡ From the Lilly Laboratories, Indianapolis, Ind.

TABLE I.

Group	% Mortality at 12 hr	24 hr	48 hr	72 hr	96 hr
A	20	100	—	—	—
B	0	0	10	20	20
C	20	100	—	—	—
D	10	100	—	—	—

Group D. 10 mice. Experimental series. One cc of a 1% acacia suspension of N^1-dodecanoylsulfanilamide administered orally 1 hour and 24 hours after infection.

The evidence elicited from the study of the absorption and distribution of the drug suggested that it would be necessary to administer the drug together with fats capable of being absorbed from the gastrointestinal tract if any therapeutic effect was to be demonstrated. Accordingly all subsequent experiments involved the administration of the drug orally in olive oil or milk and oil suspensions. When administered in this manner, the drug appeared to be somewhat more effective against beta hemolytic streptococcal infections than sulfanilamide itself.

Experiment 2. All animals infected by the intraperitoneal administration of 1×10^{-6} cc of a 16-hour culture of C-203.

Group A. 100 mice. Untreated controls.

Group B. 250 mice. Sulfanilamide controls. One cc of a 1% acacia suspension administered orally 1 hour and 24 hours after infection.

Group C. 200 mice. Experimental series. One cc of a 1% olive oil solution of N^1-dodecanoylsulfanilamide administered orally 1 hour and 24 hours after infection.

Group D. 100 mice. Experimental series. One cc of a 1% suspension of N^1-dodecanoylsulfanilamide in milk and oil administered orally 1 hour and 24 hours after infection.

As is the case with sulfanilamide itself, N^1-dodecanoylsulfanilamide shows no protective action against overwhelming infections.

Discussion. An exhaustive pharmacological study of this drug is being carried out at the present time and the results will be reported in

TABLE II.

Group	% Mortality at 12 hr	24 hr	48 hr	72 hr	96 hr
A	26	100	—	—	—
B	0	2	8	10	16
C	0	0	2	4	4
D	0	1	1	1	1

the immediate future. It has been suggested[2] that the activity of the drug is dependent on its breakdown with a resultant liberation of sulfanilamide. Our present direct evidence shows that no such breakdown occurs in the gastrointestinal tract. Indirect evidence from studies on therapeutic efficacy[3] indicates that this N^1-acyl compound is more active than sulfanilamide on a molecular basis.

Results. 1. N^1-dodecanoylsulfanilamide, when administered in oil to mice, shows marked therapeutic efficacy against beta hemolytic streptococci. 2. This therapeutic effect is lost when the drug is administered in an aqueous medium.

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N^1-Dodecanoylsulfanilamide. II. Experimental Infections with *Mycobacterium tuberculosis.*

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It was pointed out[1] that N^1-dodecanoylsulfanilamide, when administered in fatty menstrua, exerted a more potent therapeutic effect against experimental beta-hemolytic streptococcal infections than sulfanilamide. This compound, whose chemical and physical properties have been described,[2] differs from sulfanilamide only in so far as a long chain fatty acid has been substituted for an H atom in the N^1 position. This gives to the compound a very high degree of fat solubility.

A new impetus has been lent to the subject of the chemotherapy of tuberculous infections by the report of Rich and Follis[3] that sulfanilamide is capable of inhibiting the development of the tuberculous process in guinea pigs after the experimental infection with human tubercle bacilli. Greey and his associates[4, 5] have repeated

2 Marshall, Jr., E. K. Personal communication.

3 Feinstone, W. H., Wolff, R. and Williams, R. D. To be published.

1 Climenko, D. R., and Schmidt, R. L., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 622.

2 Crossley, M. L., Northey, E. H., and Hultquist, M. E., *J.A.C.S.*, 1939, **61**, 2950.

3 Rich, A. R. and Follis, A. H., *Bull. Johns Hopkins Hosp.*, 1938, **62**, 77.

4 Greey, P. H., Campbell, H. H., and Colly, A. W., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 22.

5 Greey, P. H., Boddington, G. D. H., and Little, M. H., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 448.