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.

11283 P

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

DAVID R. CLIMENKO. (Introduced by Harry Gold.)

From the Pharmacological Laboratory, The Calco Chemical Company, Cold Spring Harbor

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.

these observations, but Kolmer, Raiziss and Rule[6] and Smithburn[7] have been unable to reproduce these results. Smithburn produced an experimental tuberculous meningitis, and administered the drug intraperitoneally, while Kolmer and his associates administered the drug intramuscularly. We have always found that oral administration of sulfanilamide is the most effective method of administration.

The fatty acids of chaulmoogra oil have been suggested for the treatment of tuberculous infections for some time. Walker and Sweeney[8] made this suggestion in 1920, while Rogers[9] and Burgess[10] reported clinical successes in the treatment of the dermal manifestations of tuberculous infections with hydnocarpic acid esters. Walker and Sweeney pointed out that chaulmoogric acid was not capable of penetrating the wall of the tubercle, and Kolmer, Davis and Jager[11] demonstrated that chaulmoogric acid had no inhibiting effect on the development of experimental tuberculous infections in guinea pigs.

The combination of a long chain fatty acid with sulfanilamide, combining the fat solubility of the one with the penetrating properties of the other, might provide a more effective agent in controlling experimental tubercular infections in guinea pigs than was available in sulfanilamide itself or in any member of the fatty acid series itself. It was with this specific purpose in mind that N^1-dodecanoylsulfanilamide was synthesized.

It was first demonstrated that N^1-dodecanoylsulfanilamide was capable of inhibiting the growth of human tubercle bacilli *in vitro*. A series of flasks containing beef infusion, glycerine, dextrose broth were set up to contain N^1-dodecanoylsulfanilamide in concentrations of 10 mg/100 cc, 20 mg/100 cc, and 100 mg/100 cc. A similar preparation was made containing sulfanilamide at a concentration of 100 mg/100 cc. A series of untreated control flasks were also set up. All flasks were inoculated with the H.37 strain of human tubercle bacilli and incubated at a temperature of $37.5°C \pm 2°C$ for a period of 90 days. Concentrations of 10 mg/100 cc of N^1-dodecanoylsulfanilamide in the culture medium inhibited growth over this period, while a similar inhibition was produced by a concentration of 100 mg/100 cc of sulfanilamide. The controls grew out luxuriously.

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6 Kolmer, J. A., Raiziss, G. W., and Rule, A. M., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 581.

7 Smithburn, K. C., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 574.

8 Walker, E. L. and Sweeney, M. A., *J. Infect. Dis.*, 1920, **26**, 238.

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

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

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

The *in vivo* work was carried out on guinea pigs. A group of 80 animals, weighing between 350-400 g were infected by the subcutaneous administration of 1 mg of the H.37 strain of human tubercle bacilli, administered in the region of the groin. These animals were then divided into 4 groups of 20 as follows: Group A. Untreated controls. Group B. Sulfanilamide series. 100 mg sulfanilamide in 1% acacia suspension administered daily by stomach tube for 45 days. Treatment initiated immediately after infection. Group C. Experimental series. 100 mg N^1-dodecanoylsulfanilamide in 2% olive oil solution administered daily by stomach tube for 45 days. Treatment initiated immediately after infection. Group D. Experimental series. 100 mg N^1-dodecanoylsulfanilamide in 2% olive oil solution administered daily by stomach tube for 40 days. Treatment initiated 5 days after infection.

All animals in Group A developed the classical signs of tuberculous infection with human strain organisms. Tubercles formed at the site of inoculation, and in most instances, discharged through a secondarily infected sinus. These animals developed generalized tuberculous peritonitis and lymphadenitis with gross splenomegaly and liver involvement. Pulmonary involvement was rarely seen. With the exception of those animals sacrificed 30 days after infection for postmortem examination, all members of this group died within 65 days.

Animals of Group B developed localized tubercular lesions at the site of injection, which rarely showed secondary infections. Animals sacrificed at the end of 30 days for comparison with untreated controls show very slight generalized disease. The splenomegaly in this series was not nearly as pronounced as in the case of the controls and the glandular involvement was considerably less extensive. The results were essentially similar to those described by Rich and Follis and by Greey and his associates.

Animals of Group C showed localized tubercular lesions at the site of infection, which in some instances spread by direct contact to involve a considerable area of tissue. One animal (No. 51 in the series) developed a tuberculous orchitis, but showed no signs of generalized tuberculous lymphadenitis or peritonitis. A large proportion of these animals developed secondary infections at the site of injection, sinuses formed, and heavy purulent material was discharged. In most instances the secondary organisms were staphylococci. Animals of this group sacrificed 120 days after infection showed no gross splenomegaly as compared with the untreated controls. In no instance was there macroscopic evidence of tuberculous peritonitis or tubercles in the liver or kidneys.

Animals of Group D showed localized tubercular lesions at the site of infection and involvement of the adjacent lymphatics. Practically all of these animals developed discharging purulent infections at the injection site. They showed no gross splenomegaly, liver involvement or kidney involvement. There was no macroscopic evidence of generalized tuberculous lymphadenitis; in no instance did the disease process extend beyond the periaortic glands at the bifurcation of the aorta.

Conclusions. 1. N^1-dodecanoylsulfanilamide inhibits the growth of tubercle bacilli *in vitro* at a concentration of 10 mg/100 cc in beef infusion-dextrose-glycerine media over a period of 90 days. 2. N^1-dodecanoylsulfanilamide inhibits the development of the tuberculous process in guinea pigs infected subcutaneously with a human strain of tubercle bacilli.

11284 P

Production of Pneumonia in Rats by Intravenous Injection of Pneumococci.*

ALICE H. KEMPF AND W. J. NUNGESTER.

From the Hygienic Laboratory, University of Michigan, Ann Arbor, Mich.

Rake[1] demonstrated that pneumonia could be produced in mice when the pneumococci were introduced by the intravenous route. The important factors were the strain and dose of the organism, and the breed of mice. Twelve of 87 mice had macroscopic lesions; 6 of the 87 failed to show any microscopic lesions. The pathology of the various stages encountered was clearly described.

Prior to this work, with a few exceptions, intravenous injection of pneumococci has failed to give rise to pneumonia. Although it has long been postulated that the origin of the infection might be by way of the blood stream, there has been little evidence to support it.

Employing the Schwartzman phenomenon, Witebsky, Neter, and Ward[2] were able to localize pneumococci injected intravenously in dermal lesions of rabbits.

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1 Rake, Geoffrey, *J. Exp. Med.* 1936, **63**, 191.

2 Witebsky, Ernest and Neter, Erwin, PROC. SOC. BIOL. AND MED., 1938, **38**, 187.