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Effect of Sulfapyridine on Immune Response to Pneumococcal Infection.*

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With the introduction of sulfapyridine-therapy in the pneumonias, numerous studies have appeared on the mode of action of the drug. In the hope of obtaining some evidence concerning its effect upon immune responses to the pneumococcus, we undertook the following study in patients who were treated in the hospitals of St. Louis during the year 1938-39.

To date there are in the literature very few data on this subject. Larson[1] and his associates found that mice, recovering from pneumococcal infection after treatment with sulfapyridine, developed no signs of reinfection after reinoculation with homologous type-specific (type 2) pneumococci. If the virulence of the particular strain used is great, the mice or rabbits may die before sulfapyridine inhibits the organisms.[2] A similar quantity of killed pneumococci gives the same protection against reinfection, and sulfapyridine adds nothing to this protection. This work would indicate, however, that sulfapyridine does not interfere with the usual processes of immunity.

Three groups of patients were studied to determine the occurrence of type-specific and species-specific agglutinins, heterophile antibodies, and dermal reactivity to type-specific polysaccharides. Twenty-six patients with pneumonia treated with sulfapyridine were subjected to all the tests before, during, and after their illness and 40 additional patients were tested for heterophile antibodies before and after sulfapyridine-therapy. For comparison, and in a measure as controls, data were gathered concerning 16 patients who were completely tested for agglutinins, heterophile antibodies, and dermal response before and after treatment with specific antipneumococcal serum, as well as 80

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1 Larson, W. P., Bitter, R. N., and Levine, M., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 703.

2 Long, P. H., *J. A. M. A.*, 1939, **112**, 1850.

similarly treated patients in whom heterophile antibodies only were determined. The same studies were performed on serum from 2 patients who were treated with sulfapyridine and type-specific serum.

Blood was obtained before, during (at or soon after the temperature became normal) and after treatment. In several cases specimens were obtained daily or on alternate days during hospitalization.

Agglutinations were done with suspensions of formalinized pneumococci in the usual dilutions of serum. Observations were recorded at the end of one hour and again after 24 hours at 37°C. Types 1, 2, 3, 7, and 8 pneumococci were checked for type-specificity by the Neufeld *Quellung* technic and tested for titer with homologous antipneumococcal rabbit serum. In addition to the above types, we used a rough strain of Type 2† grown on nutrient broth 8 to 12 hours and preserved with 0.2% formalin.

Skin-testing with type-specific capsular material was done as described by Francis[3] and ourselves.[4]

Heterophile antibody was titrated with defibrinated sheep-blood.

In general the titers of type-specific agglutinins following sulfapyridine-therapy did not increase either before or during defervescence, which usually occurred within 48 hours unless pneumonia was then in its sixth to eighth day, at which time an increase in type-specific agglutinins normally appears. Following intravenous type-specific serum there is, of course, an increase in type-specific agglutinins in proportion to the excess of serum given, with little or no effect on the agglutinins for the rough or species-specific pneumococcus. Sulfapyridine-treated patients, as a rule, exhibited species-specific agglutinins earlier and in a higher titer than they did type-specific agglutinins.

The skin reaction to polysaccharide was found to be a reliable guide to proper dosage of type-specific serum, being positive in the presence of an appreciable titer of type-specific agglutinins. Following sulfapyridine-therapy alone, the skin-reaction became positive again only when type-specific agglutinins were present in sufficient amount. There was no direct correlation between fall in temperature and the type-specific antibody-titer in the sulfapyridine-treated cases.

The heterophile antibody seemed to have no constant relation to the course or outcome of the pneumonia nor to the type or severity

† Obtained from Dr. Marian Morris, Department of Bacteriology, Washington University School of Medicine.

3 Francis, T., Jr., *J. Exp. Med.*, 1933, **57**, 617.

4 Edwards, J. C., Hoagland, C. L., and Thompson, L. D. Read at General Scientific Session of A.M.A. Meeting in St. Louis, May 15, 1939. Accepted for publication in *J. A. M. A.*

of any particular case, nor to the type of therapy, whether with serum or drug. Its titer did not parallel that of either the type-specific or species-specific agglutinins. Incidentally, we found, as have others,[5] no indication that the heterophile titer was directly related to or responsible for serum-sickness. There was no correlation between the heterophile titer and the positivity or negativity of the cutaneous reaction to polysaccharide. There was some increase in its titer following the administration of species-specific serum high in heterophile-antibody content.

Summary. 1. The immune responses that occur naturally in the course of an untreated pneumonia, studied by determining type-specific and species-specific agglutinins and by the dermal reactivity to type-specific polysaccharides, are apparently unaltered by treatment with sulfapyridine. 2. There seems to be no relation of the heterophile-antibody titer to the clinical course of pneumococcal pneumonia or its immune responses following sulfapyridine-therapy.

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Toxicity of the Ortho, Meta and Para Isomers of Sulfanilamide.

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While the therapeutic potency of p-sulfanilamide has been amply demonstrated, reports by a group of French investigators[1] indicate that the protective action of the ortho and meta isomers against experimental infection in mice is practically nil. The present investigation was undertaken to determine whether there is any corresponding difference in the toxicity of the 3 isomers.

The acute toxic effects for mice were determined by oral administration of the isomers in 33% suspension in 5% gum acacia to fasted animals. The manifestations of toxic action were quite different among the 3 isomers. When the para-isomer was given there usually resulted, in from 30 minutes to an hour, a preliminary stage of stimulation, with muscular incoordination and spastic paralysis of

[5] Powell, H. M., Jamieson, W. A., and Kempf, J. F., *J. Immunol.*, 1935, **29**, 267.

[1] Trefouel, J., Trefouel, J., Niti, F., and Bovet, D., *Ann. Inst. Pasteur*, 1937, **58**, 30.