with Dr. A. S. Wiener to run parallel to the anti-Rh of Landsteiner and Wiener.[3] cf[4]

These antibodies were designated as warm-agglutinins[2] in order to differentiate them from atypical agglutinins that act at 20° C but not at 37° C, and from those which act equally well at both temperatures.

As to the origin of the warm-isoagglutinins in the pregnant women, it is assumed that they are one of several varieties of antibodies resulting from isoimmunization of the mother by the products of conception.[5] As originally stated by Levine and Stetson, it is believed that the fetus inherits certain dominant agglutinable substances from the father which if lacking in the mother may stimulate her to produce isoantibodies.

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Action of Sulfapyridine upon Pulmonary Lesion of Experimental Pneumococcal Pneumonia.

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The action of type specific antiserum upon the pulmonary lesion of lobar pneumonia has been described in a previous paper.[1] Pneumonia was produced experimentally in white rats by intrabronchial inoculation of type I pneumococci suspended in mucin. The disease was uniformly fatal in untreated animals, and pneumococci were found to spread through the lung by way of edema fluid at the advancing margin of the lesion. Type specific antiserum penetrated the pneumonic lesion and apparently stopped its spread by agglutinating and immobilizing the invading organisms in the outer edema zone. The fixed pneumococci were then overtaken and were rapidly phagocytized by leucocytes.

Although sulfapyridine has proven beyond any doubt to be effec-

[3] Landsteiner, K., and Wiener, A. S., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 223.

[4] Wiener, A. S., and Peters, H. R., *Ann. Int. Med.*, 1940, **13**, 2306.

[5] Levine, P., and Stetson, R. E., *J. Am. Med. Assn.*, 1939, **113**, 126.

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[1] Wood, W. B., Jr., *Science*, 1940, **92**, 2375, p. 15.

tive in the treatment of lobar pneumonia, the mechanism by which recovery is induced is not yet understood. Fully encapsulated living pneumococci are resistant to phagocytosis unless opsonized by specific antibody,[2, 3] and phagocytosis is the only known method by which the host can destroy these organisms.[4] Since chemotherapy often causes a crisis long before antibodies appear in the blood,[5] and sulfapyridine in the usual dosage is mainly bacteriostatic rather than bactericidal,[6] it is not at all clear how the drug brings about the final destruction of pneumococci in the lung.

Thirty-eight albino rats were treated with sulfapyridine 6 hours after inoculation. The drug was suspended in 10% gum acacia and introduced into the stomach through a blunt cannula. Two hundred and fifty milligrams of sulfapyridine suspended in 4 cc of gum acacia mixture were given as an initial dose, and half of this amount in 2 cc of acacia was administered thereafter every 12 hours. In uninfected rats no toxic effects were noted after 1 week of treatment.

The protective action of sulfapyridine was tested on a group of 20 rats. Sixteen survived, and when sacrificed at the end of one week, showed sharply demarcated localized lesions obviously arrested by the action of the drug. Eleven of the surviving rats developed bacteriemia 12 to 36 hours after the start of treatment. The bacteriemia in each case was transient and cleared in less than 4 days. The 4 rats that died developed bacteriemia early and succumbed within 3 days, the drug having failed to arrest the spread of the pneumonic process. All untreated animals died.

The manner in which sulfapyridine acted upon the lesion was studied in rats sacrificed in groups of 3 at 6, 18, 42, 66, 96, and 168 hours after the start of treatment. During the first 18 hours the drug had little effect upon the advancing pneumonia. The border of the lesion remained irregular and hemorrhagic, and the many pneumococci in the edema-filled alveoli at the margin indicated that the infection was still spreading rapidly.

At the end of 18 hours there was evidence that the sulfapyridine was beginning to exert its effect. Examination of the pneumococci in the edema zone showed a striking change in their morphology; many were swollen, pleomorphic, and irregularly stained, and a few

2 Ward, H. K., and Enders, J. F., *J. Exp. Med.*, 1933, **57**, 527.

3 Robertson, O. H., and Van Sant, H., *J. Immunol.*, 1939, **37**, 571.

4 Heffron, R., *Pneumonia with Special Reference to Pneumococcus Lobar Pneumonia*, The Commonwealth Fund, 1939, p. 151.

5 Wood, W. B., Jr., and Long, P. H., *Ann. Int. Med.*, 1939, **13**, 612.

6 Finland, M., Spring, W. C., and Lowell, F. C., *J. Clin. Invest.*, 1940, **19**, 163.

had grown in short chains. Forty-two hours after the start of treatment the edema zone had disappeared completely, the pneumococci at the margin having been overtaken by leucocytes. Most of the organisms were already within phagocytes. The phagocytic reaction was pronounced but resembled that seen deep in the pneumonic lesion in untreated animals[7] rather than that observed in rats treated with antiserum.[8] † Organisms could still be seen within phagocytic cells after 66 hours of treatment but by this time macrophages were numerous in the alveolar exudate and appeared to be taking an active part in destroying the bacteria. On the fourth day no pneumococci could be found in the stained sections, and after one week there was extensive resolution with only macrophages remaining in the rapidly clearing alveoli.

It is significant that phagocytosis occurred in the lungs of animals with bacteriemia and was, therefore, apparently independent of circulating type specific opsonins.[9, 10] The same phenomenon has been observed in untreated animals with bacteriemia.[7] Although phagocytosis in the absence of type specific antibody may be explained by injury to the pneumococcus capsule, the exact mechanism of the process in untreated animals and in those receiving sulfapyridine is not known. Since the natural defense of the lung against pneumococcal infections appears to depend largely upon this type of phagocytic reaction; an attempt is being made to study it further.

Conclusions. Whereas antipneumococcal serum acts immediately and stops the spread of the pneumonic lesion by immobilizing the invading organisms through agglutination, sulfapyridine exerts the same effect more slowly through bacteriostasis. In both cases the final destruction of the pneumococci depends upon phagocytosis, but in animals treated with sulfapyridine the phagocytic reaction may apparently occur in the absence of circulating type specific antibodies.

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7 Wood, W. B., Jr., *J. Exp. Med.*, in press.

8 Wood, W. B., Jr., *J. Exp. Med.*, in press.

† Following serum therapy the reaction was more striking with many more pneumococci in each leucocyte.

9 Robertson, O. H., Graeser, J. B., Coggeshall, L. T., and Harrison, M., *J. Clin. Invest.*, 1934, **13**, 621.

10 Terrell, E. E., *J. Exp. Med.*, 1930, **51**, 425.