chiefly by a prompt but fleeting polymorphonuclear leucocytosis with occasional minor recurrent granulocytic elevations, followed by a transitory anemia. The opsonocytophagic index, antistreptolysin and precipitin titers were not significantly affected. Clinical manifestations of disease were mild but definite, and it is concluded that the cellular reaction, aided, if at all, only in slight degree by humoral factors, was the principal demonstrable defensive mechanism which these monkeys mobilized in successfully opposing the initial invasion by streptococci via the respiratory tract.

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Reactions of Monkeys to Experimental Respiratory Infections. III. Response to Mixtures of Influenza Virus and Streptococcus.*

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In earlier studies[1] employing mice, a shorter survival period and a greater proportion of deaths were observed in those animals which received mixtures of *Streptococcus hemolyticus*, Group C, and influenza-A virus, than in those receiving only one agent alone. The present report records particularly the hematological reactions in monkeys in which one infection was superimposed upon the other via the intranasal route.

Methods. The preparation of inocula, the dosages employed, and the method of administration were carried out as previously described.[2, 3] When the two agents were given simultaneously the concentrations were so adjusted that 3 cc of the mixture contained the full dosage of each agent.

Results. Clinical Characteristics. All monkeys receiving both agents, in whatever order, survived the infections and manifested only minimal clinical evidences of disease, except monkey No. 3

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1 Schwab, J. L., Blubaugh, F. C., and Woolpert, O. C., *J. Bact.*, 1941, **41**, 59.

2 Woolpert, O. C., Schwab, J. L., Saslaw, S., Merino, C., and Doan, C. A., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 558.

3 Schwab, J. L., Saslaw, S., Woolpert, O. C., Merino, C., and Doan, C. A., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 560.

(Fig. 1-D), which became acutely ill and died with an overwhelming streptococcal septicemia.

Experiment 1. *Simultaneous Inoculation with Virus and Streptococci.* The 2 monkeys receiving a mixture of virus and streptococci, each manifested within 24 hours a marked polymorphonuclear leucocytosis. The total white blood cells increased from 12,000 to 56,000 (granulocytes 4900 to 44,300) in No. 7 (Fig. 1-A), and from 13,000 to 39,000 (granulocytes 8800 to 33,000) in No. 8. Both animals, between the 11th and 15th days after inoculation, developed a definite granulocytopenic leucopenia with, in one instance, a relative, and in the other an absolute lymphocytosis, suggesting a masked and *delayed* reaction to virus. Specific neutralizing antibodies were demonstrated.

Experiment 2. *Inoculation with Streptococcus Followed by Virus.* Four monkeys (Nos. 9, 10, 12, 13) receiving a primary inoculation of hemolytic streptococci, developed the usual leucocytosis within 24

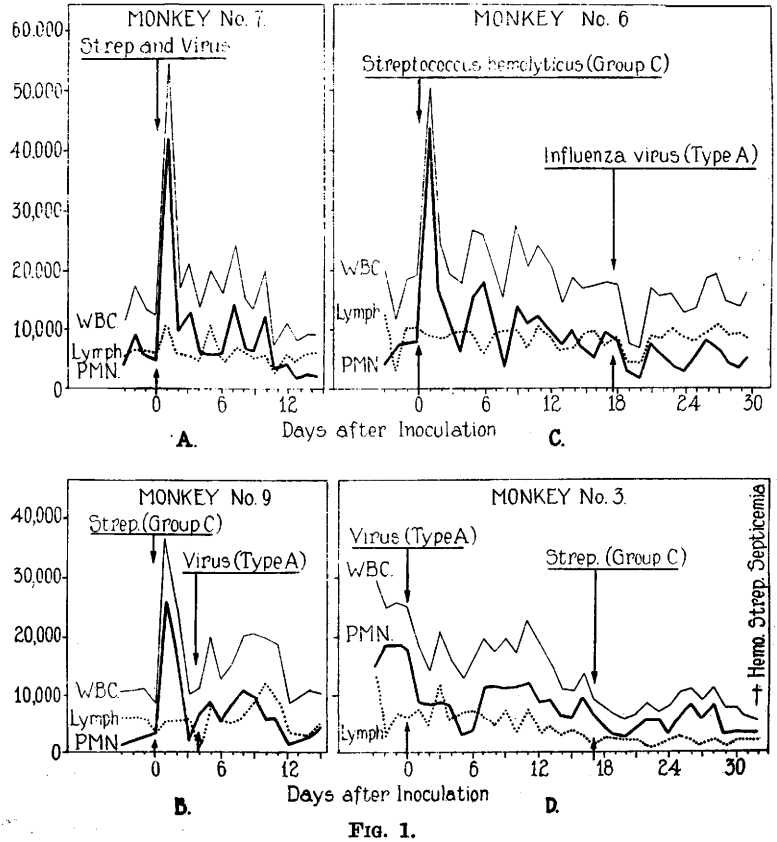

FIG. 1.

to 48 hours (Fig. 1-B) but, when inoculated 4 days later with the virus, *only one of the animals showed the typical inhibition of granulocytes which has characterized all initial, uncomplicated viral infections.*

Three monkeys (Nos. 1, 5, 6), which also responded characteristically with a marked neutrophilic leucocytosis to the primary inoculation with streptococci, when inoculated secondarily with influenza virus 15-17 days later, all developed a definite relapsing leucopenia within 1 to 3 days (Fig. 1-C), quite independently of, and apparently uninfluenced by, the original streptococcal infection.

Experiment 3. *Inoculation with Virus Followed by Streptococcus.* Four monkeys (Nos. 15, 16, 17, 18) were infected with influenza virus and 4 days later streptococci were superimposed intranasally. Two of the monkeys (Nos. 15 and 17) responded to the primary viral inoculation with a profound granulocytopenia (7800 to 1950, and 15,600 to 3230, respectively); the former, thereafter, showed an almost identical depression in neutrophils during the 48-hour period following hemolytic streptococcal inoculation (8400 to 1920), while the latter revealed a striking neutrophilic leucocytosis (8800 to 33,000), typical of primary pyogenic stimulation; no significant leucopenia developed in the other 2 monkeys prior to the superimposed streptococcal inoculation, and in one instance a moderate leucocytosis occurred (No. 16—3300 to 17,500) while in the other, both cellular and clinical reactions were negligible to virus and streptococci alike.

Three monkeys (Nos. 2, 3, 4) were inoculated with streptococci 15 to 17 days following the primary infection with influenza virus. A definite leucopenia developed in all within 3 to 4 days after the viral inoculation, as illustrated in Fig. 1-D, but *in none of the 3 did a leucocytosis, typical of initial streptococcal infection follow.* Monkey No. 3 became progressively sicker and died with hemolytic streptococcal sepsis on the 32d day following exposure to virus and the 15th day after the streptococcal complication had been introduced. Type C streptococci were recovered from all organs at postmortem.