9355

Para-Aminobenzenesulfonamide Therapy in Experimental Type III Pneumococcal Pneumonia.

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We have reported[1] the successful treatment of experimental Type III pneumococcal pneumonias in rats by the daily oral administration of *p*-aminobenzenesulfonamide.

The present report deals with additional results obtained by treating 64 rats, suffering from Type III pneumococcal pneumonia, with *p*-aminobenzenesulfonamide.* These results are contrasted with those from a simultaneous series of 37 similarly infected, but untreated, animals.

The infection technic employed by us differs from that of Nungester and Jourdonais.[2] Under sodium amytal anesthesia the trachea was exposed by an incision 1.0 cm. long. A 16-gauge (B. & S.) trocar, 4.5 cm. long, bearing a protruding, pointed stylet, was inserted between the tracheal rings. The stylet was then withdrawn and the trocar gently inserted for a distance of 3.0 to 3.5 cm. A tuberculin-syringe containing a suspension of pneumococci in mucin was attached to the trocar and 0.07 to 0.10 cc. of the suspension injected, after which the trocar was withdrawn and the skin sutured with silk.

The suspension of organisms was prepared by diluting an 18-hour broth culture of our "420" strain of Type III pneumococcus 1000 times in broth and adding powdered gastric mucin (Armour), with constant stirring until a homogeneous, viscid mixture was obtained. No attempt was made to sterilize the mucin or to standardize the viscosity, since each different suspension had its own series of control animals. In 4 groups of rats the culture was diluted 10,000 times.

The animals were divided into 10 groups, which were treated as described under Fig. 1. Treatment consisted of the oral administration of 125 mg. of *p*-aminobenzenesulfonamide (as a 25% suspension in 15% aqueous gum acacia) daily for 14 consecutive days. All survivors in each group were killed with ether on the fifteenth

1 Gross, P., and Cooper, F. B., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 225.

* Kindly supplied by the Winthrop Chemical Co. and Burroughs Wellcome & Co.

2 Nungester, W. J., and Jourdonais, L. F., *J. Bact.*, 1935, **29**, 34.

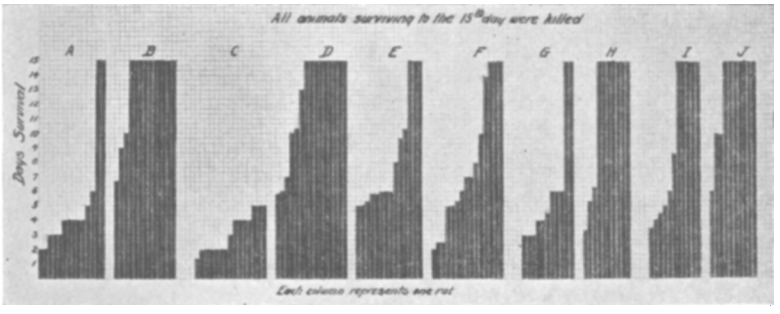

FIG. 1.

A. Fourteen rats, infected with 0.07 cc. of a 1:1000 dilution of an 18-hour broth culture. Untreated controls. (From previous report.[1])

B—Thirteen rats, same infecting dose as Group A, treated immediately after infection. (From previous report.[1])

C. Fifteen rats, infected with 0.1 cc. of a 1:1000 dilution of an 18-hour culture. Untreated controls.

D. Fifteen rats, same infecting dose as Group C, treated after 6 hours.

E. Fourteen rats, same infecting dose as Group C, treated after 30 hours.

F. Fifteen rats, infected in same manner as Group C (except that inoculum had stood for 4 hours in a warm room), treated after 18 hours.

G. Eleven rats, infected with 0.07 cc. of a 1:10,000 dilution of an 18-hour culture. Untreated controls.

H. Ten rats, same infecting dose as Group G, treated after 48 hours.

I. Eleven rats, infected with 0.07 cc. of a 1:10,000 dilution of an 18-hour culture. Untreated controls.

J. Ten rats, same infecting dose as Group I, treated after 24 hours.

day. All animals were necropsied. Smears were made of pleural exudate, peritoneum, and blood from the femoral vein. Sections were made of all lobes of both lungs, of the heart, liver, spleen, and left kidney.

The effect of the treatment on the survival-time of the infected rats is shown graphically in Fig. 1. Group B, treated immediately after infection, showed a 77% survival contrasted with a 14% survival in Group A. Group D, treated 6 hours after infection, had a 60% survival, whereas no animals survived in Group C. Furthermore, the shortest survival-time in the treated group was greater than the longest in the control group. Even in Group E, where treatment was delayed 30 hours after infection, 21% of the rats survived, while all controls (Group C) died within 5 days. Group F, representing an earlier treatment (18-hour interval following infection), but a larger infecting dose, showed practically the same survival-rate, 20%, as Group E. Group H, representing a smaller infecting dose with treatment delayed 48 hours after infection, showed 80% survivals against 18% in Group G. Group J, infected with a dose that allowed a 45% survival-rate in Control Group I, showed a 70% survival when treatment was delayed 24 hours after infection.

The pneumonic consolidation was lobar in distribution, usually involved more than one lobe, sometimes an entire lung, and occasionally both lungs. The animals that succumbed, treated or untreated, showed no consistent difference in the degree of pulmonary involvement. Similarly, no qualitative or quantitative differences could be detected microscopically in the cellular reaction of the treated animals that would distinguish them from the controls.

All smears and sections from both treated and untreated rats revealed a marked infrequency of phagocytic activity; also, they gave no indication that this activity was greater in the treated animals than in the controls.

Empyema, often sufficiently severe to cause the compression of non-pneumonic lobes, was observed in all of the control rats, and 87% of the treated rats that died. Of the fatalities, 26% of the controls showed pneumococci in blood smears, whereas the blood smears of all treated rats were negative. Peritonitis, based on the presence of polymorphonuclear leukocytes and pneumococci in peritoneal smears, was present in 29% of the control fatalities, compared with 8% of the fatalities among the treated animals.

The average survival-time of the rats that succumbed was 3.9 days for the combined control groups, and 6.9 days for the treated groups. Pneumococci were never found in smears of the blood, peritoneum, or pleura, in animals that survived to the fifteenth day. Of all the control rats that survived 15 days, 56% (5 out of 9) showed no grossly demonstrable pneumonia. A similar percentage (56%, 22 out of 39) was found in the treated survivors. Some animals in both series showed pleural adhesions, and all gave microscopic evidence of pneumonitis. The histologic changes in the lungs of the survivors were similar to those described by Gunn and Nungester.[3] Changes in the heart, liver, spleen, and kidney of rats that succumbed were no different in the treated than in the untreated animals.

Treatment resulted in a marked reduction of the mortality-rate of rats infected intrabronchially with virulent Type III pneumococci. This reduction was related to both the interval between infection and initial treatment and the size of the infecting dose.

Of the rats that succumbed to the infection, the average life of those treated was greater than that of the untreated controls. Similarly, there were fewer cases of bacteremia and peritonitis in the treated rats. (This should be qualified to a certain extent since the criterion used to determine the presence or absence of bacteremia

[3] Gunn, F. D., and Nungester, W. J., *Arch. Path.*, 1936, **21**, 813.

is, at best, a very rough one.) Empyema was only slightly less common in the treated animals.

The treatment had no apparent effect upon the type or extent of the pulmonary involvement, which, due to the longer survival-time, was frequently greater in the treated animals than in the controls. The percentage of pneumonias that subsided with a minimum of residue was practically the same in treated and control animals.

Rosenthal[4] found that *p*-aminobenzenesulfonamide was bactericidal for pneumococci of Types I, II, and III *in vitro*. However, since the course and the extent of the pneumonia was not lessened by the therapy, it seems that such bactericidal action was relatively unimportant. Nevertheless, this treatment enabled the host, in many cases, to survive an otherwise fatal toxemia.

Because of these encouraging results, similar therapy was used on human Type III pneumococcal pneumonia. Heintzelman, Hadley, and Mellon[5] report the survival of 7 out of 9 patients treated with *p*-aminobenzenesulfonamide; of 10 cases not treated with this drug only 2 recovered.

Conclusions. *P*-aminobenzenesulfonamide given orally to rats suffering from experimental Type III ("420" strain) pneumococcal pneumonia reduced the mortality and increased the survival-period. The effectiveness of this treatment varied inversely with the interval between infection and initial treatment, and with the magnitude of the infecting dose. The treated rats which succumbed showed less bacteremia and a lower incidence of peritonitis than the untreated ones which succumbed. The course and extent of the pneumonia was not appreciably affected. Treatment apparently enables many of the animals to survive the associated toxemia which is commonly fatal to similarly infected, but untreated, rats.

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[4] Rosenthal, S. M., *Public Health Reports*, 1937, **52**, 192.

[5] Heintzelman, J. H. L., Hadley, P., and Mellon, R. R., *Am. J. Med. Sc.*, 1937, **193**, 759.