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Oral Administration of Pneumococcus Antigen as a Therapeutic Agent in Experimentally Infected Rats.

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The object of the experiments reported here was to determine whether or not rats inoculated with lethal doses of pneumococci could be successfully immunized by means of oral vaccination begun after the introduction of the infecting dose. Various investigators[1] have demonstrated that young rats can be immunized against many lethal doses of virulent pneumococci by means of feeding certain pneumococcus antigens. Such experiments have all been along prophylactic lines; we have seen no reports of experiments testing the therapeutic value of pneumococcus antigens. Since it is possible to render young white rats resistant, by oral means, to comparatively large intraperitoneal or subcutaneous inocula of pneumococci, and since this resistance manifests itself within 24-48 hours, these animals were considered to be suitable for investigating the therapeutic value of oral immunization.

The method consisted of intraperitoneal injection of 100 lethal doses of Type I pneumococci into young white rats (60-100 gm.), followed by various antigenic preparations in single and also multiple doses. Certain rats were fed the antigen immediately after they received the injection of living organisms, and others were fed later during the course of their infection. Measured feedings were given by means of stomach tube and syringe. The antigenic preparations fed were tested for their efficiency on control animals;

[1] Killian, H., *Z. f. Hyg. u. Inf.*, 1924, **102**, 279. Eguchi, C., *Ibid.*, 1925, **105**, 74. Kimura, R., *Ibid.*, 1927, **107**, 390. Ross, V., *J. Immunol.*, 1926, **12**, 219. Maëji, Y., *Acta Scholae med. univ. imp.*, Kioto, 1929, **12**, 295.

the minimum lethal dose was freshly determined and the lethality of the dilution actually used in the experiments was also checked on control animals. Rats dying during the course of these tests were all found to have pneumococci in the heart's blood.

As antigens in these tests, we used broth cultures which had undergone autolysis of 2 crops of pneumococci. This material was fed alone in some experiments; in others 2.0 cc. of egg-white[2] plus 3 cc. of autolysate was used. Bile was also used as an accessory substance with the autolysate in some of the experiments. This was sterile 5.0% ox bile, so that when 2 cc. was added to 3 cc. of autolysate, the resultant concentration of bile was 2.0%.

The results of single feedings are summarized in Table I.

TABLE I.

Rat	Live Pneumococci	5 cc. autolysate	Results	Remarks
1	100 M.L.D	Immediately	S	
2	" "	"	D-2	
3	" "	4 hr.	D-2	
4	" "	4 "	D-3	
5	" "	8 "	D-2	
6	" "	8 "	D-3	
7	" "	12 "	D-2	
8	" "	12 "	S	
9	" "	24 "	D-3	
10	" "	24 "	D-4	
11	" "	32 "	D-2	(Died before feeding)
12	" "	32 "	D-3	
13	" "	not fed	D-3	(Control to indicate
14	" "	" "	D-3	normal time of death)
15	1000 M.L.D. given 48 hours after feeding		S	(Control of efficiency
16	100 M.L.D. given 48 hours after feeding		S	of autolysate)

S = survived. D-2 = died second day.

A similar set-up, using 32 rats, was tested with a single dose of the egg-white and bile reinforced antigens described above. The control animals, tested 48 hours after feeding each antigen mixture, where found to be resistant to 10 times the dose used in the test animals. All of the test animals died from the second to the fourth day.

Ten rats, inoculated with 100 M.L.D. and fed 5.0 cc. of autolysate every 2 hours (5 doses over a period of 10 hours), beginning immediately after the inoculation, all died within 2-4 days.

From these experiments it seems that although the course of ex-

[2] McDaniels, H. E., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 587.

perimental pneumococcus peritonitis in rats is of 2-4 days' duration, a time which is adequate for the development of orally stimulated immunity in control rats, the infection proceeds to a fatal termination in spite of the immediate institution of this treatment. The survival of 2 rats out of the 60 animals used in these experiments is to be attributed to individual differences in the rats; this factor of variation ordinarily appears in such experiments to an even greater extent than in this case. The immune response in already infected rats apparently is inhibited so that oral immunization is ineffective as a therapeutic agent under these conditions in these animals.

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Cerebral Action Potentials.*

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The following observations, some confirmatory, based on experiments on 8 cats and 2 monkeys, were made during an exploration of the cerebral cortex and underlying structures for spontaneous and evoked activity. Anatomical relations given are only approximate; the work is being continued with the aid of a Horsley-Clark stereotaxic instrument. Action potentials picked up by an Adrian-Bronk electrode, amplified, and fed into a loud speaker and high-voltage cathode ray oscillograph, were the index of activity. Numerous controls have convinced us that extraneous pick-up did not confuse true action potentials in the phenomena described. For example, during penetrating movement of the needle of less than 1 mm. there appeared successively: nothing, strong auditory responses, nothing, strong optic responses, nothing. Clearly, responses may be highly localized, and a non-specific spread is excluded.

Auditory responses were obtained from the temporal cortical surface, projection tracts, auditory thalamus, and lower structures in the monkey, from all but cortex in the cat. With the electrodes on a large tract, responses were obtained to stimuli near the human threshold. Different sounds (*e. g.*, watch tick and voice) and pitches are recorded most strongly at different needle positions, indicating a spatial separation of impulses set up by different pitches. Similarly, a fairly sharp di-, tri- or polyphasic wave appears on the

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