

THE RELATION BETWEEN FATIGUE AND THE SUSCEPTIBILITY OF GUINEA PIGS TO INFECTIONS OF TYPE I PNEUMOCOCCUS.*

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PRELIMINARY.

Fatigue is quite generally believed to increase the susceptibility of individuals to disease. In a recent paper Cowles ('18) has reported that at the Groton School "in several instances boys had been discharged from the infirmary after respiratory infections and returned soon after with pneumonia" (p. 556). In a single case: "A boy who had been in the infirmary with fever, coryza and a cough went out convalescent, took a long cross-country run, came in tired and quickly developed pneumonia." A study of the infirmary records showed twenty cases of pneumonia between 1906 and 1909 "confined to boys given to athletic tasks and sports." Cowles states specifically that "the kind of fatigue, observed as a cause of pneumonia at Groton, is an acute fatigue, due to violent exercise like rowing or running, competitive sports, and not mere weariness from everyday activities."

H. M. Vernon ('21) has advanced statistical evidence showing fatigue arising directly from industrial work to be "one of the most important contributory causes of sickness" (p. 143). Men who worked excessively long hours whether at heavy or light labor showed a higher percentage of sub-normal health than their fellow workers who kept shorter hours.

After reviewing the evidence Vernon admits that but little of it indicates the influence of fatigue on sickness. Such a relation is certainly suggested but far from proven. The interpretation of industrial statistics is notoriously difficult. Sickness is frequently given as a facile excuse for lost time. When working hours are reduced "sickness" drops off also, but this fact scarcely warrants the

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conclusion that the physical fatigue of the long hours is a cause of sickness. In this connection Vernon states (l. c., p. 7) "the men at a government ordnance factory lost 7.0 per cent. of their time from sickness, when they were working 63 and a half hours per week, but only 4.0 per cent., when the hours were reduced to 54 a week. The women at the same factory lost 4.3 per cent. of their time from sickness when they were on a 54-hour week, but only 2.8 per cent. of it, when on a 44 and a quarter hour week. Hence there appeared to be a direct relationship between the amount of sickness and the duration of working hours."

Health of munition workers in relation to weekly hours of work.
(Vernon, l. c., p. 169.)

	Weekly hours of work.	Very heavy or heavy labor.		Medium or light labor.	
		Number of workers in group.	Percentage with subnormal health.	Number of workers in group.	Percentage with subnormal health.
Men aged 41 or more.....	Under 70	190	21	203	23
Ditto.....	Over 70	147	31	82	33
Boys aged 18 or less.....	Under 60	165	5	162	8
Ditto.....	Over 60	62	11	1,010	10

The experimental evidence of the relation between acute fatigue (physical exhaustion) and susceptibility to infections has been surprisingly meager. In a recent paper Miss Oppenheimer and one of us (R. A. S., '22) have reviewed this experimental evidence, and have furthermore shown that fatigue, artificially induced in white and hooded rats by forcing them to run in motor-driven drums, definitely increases the resistance of the rats to intraperitoneal injections of lethal doses of Type I pneumococcus. These results are so at variance with the generally accepted view that it seemed possible, either (1) that they might be peculiar to rats, or (2) that they might involve some obscure technical error. We have therefore carried out a similar series of experiments with guinea pigs. Our results have corroborated the previous findings in rats. Guinea pigs may be definitely protected against lethal infections of Type I pneumococcus by forcing them to run in motor-driven drums. Physical exhaustion therefore decreases susceptibility to Type I pneumococcus, both in white and hooded rats and in guinea pigs.

EXPERIMENTAL MATERIAL

Our guinea pigs were obtained from dealers. Previous to experimentation they were kept under observation for ten days or two weeks, or until they showed by their weight curves a satisfactory adaptation to their new environment. They were kept in cages of the U. S. Hygienic Laboratory type, and were fed a mixed diet of hay, oats, fresh greens, milk and water. We used pigs weighing from 150 to 300 grams. These weights correspond approximately to an age of one to two months on Minot's ('91) growth curve.

APPARATUS.

We used the apparatus of Oppenheimer and Spaeth (l. c.). In order to prevent the pigs' catching their long hind toes in the wire mesh, the drums were partly wound with tire tape. As in the case of rats, some pigs learned to run very quickly, while others floundered and slid about in a bewildered and helpless fashion. We had little difficulty, however, in exhausting the pigs, even though they failed to solve the problem of running. As in the rat experiments, the animals were considered exhausted, when they lay down in the drums and failed to respond to ordinary exciting stimuli, such as pounding on the table, tapping on the drums and gentle handling. Exhaustion is not a function of the number of drum revolutions. It varies with individual pigs and with the extent of their mastery of the running problem.

The pigs were always weighed immediately before and after having been run. They always lost weight, but unlike the rats they did not regain this weight-loss on the following day. Each animal was subjected to three running periods, and the injections of pneumococci were given either before or after running.

VARIATIONS IN THE SUSCEPTIBILITY OF PIGMENTED AND ALBINO GUINEA PIGS TO TYPE I PNEUMOCOCCUS.

At the outset of our experiments we attempted to determine a minimal lethal dose for our culture of pneumococci. We tried to establish a dosage, independent of the weights of the animals. This procedure, which had been successful with rats, proved quite hopeless in the case of guinea pigs. At least two variables complicated the results. After a long series of preliminary experiments, in which we were working in the dark, we found that constant results could

be obtained by giving a definite dose per gram weight. At once it became evident that albino guinea pigs were more susceptible to our culture than were the pigmented pigs. This difference in susceptibility was of the order of 300 per cent. It is clearly shown in Fig.

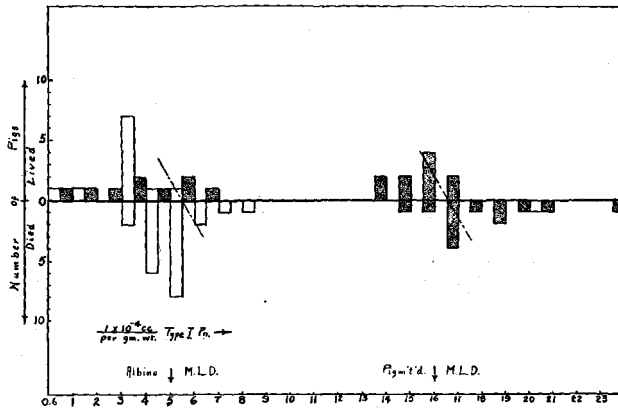


FIG. 1. The difference of susceptibility to Type I pneumococcus in albino and pigmented guinea pigs is shown in this chart. The heavy abscissa represents dosage increase from left to right. Ordinates above 0 are pigs that lived; below 0 are pigs that died. Albinos are shown as white rectangles; pigmented pigs as stippled rectangles. A dosage of 0.0005 c.c. per gm. wt. is fatal to albinos, but in this region all pigmented pigs live. Not until the dosage becomes 0.0016 c.c. per gm. wt. do all pigmented animals die. Albino guinea pigs are therefore about three times as susceptible to Type I pneumococcus as are pigmented pigs. Sixty-three animals are represented in the chart. The virulence of the pneumococcus culture was constant throughout the experiments.

1 where all the unfatigued control pigs that were used in our subsequent experiments have been charted. A dose of 0.0005 c.c. of culture, per gram weight, was lethal for albino pigs, while 0.0016 c.c. was necessary to kill pigmented pigs.

The maintenance of a constant virulence in Type I pneumococcus is not a simple matter. From our previous experience with this organism we concluded that for our experiments a culture of minimal virulence was preferable. We therefore selected a culture (2) that had never, to our knowledge, been through a guinea pig. The viru-

lence of this culture was apparently at base-level. We had no difficulty in maintaining it constant by transplanting to fresh blood-broth medium according to the scheme of Table I.

TABLE I.

<i>No. of Transplants</i>	<i>Original Culture</i>	
1)	↓ 24 hours incub. ↓ 3-4 days on ice. ↓	
2)	↓ 24 hours incub.	
3)	↓ 18 hours incub. →	to pigs
	↓ →3-4 days on ice. ↓	
3a)	↓ 24 hours culture	
4)	↓ 18 hours culture →	to pigs
etc.	↓ →3-4 days on ice.	

METHODS OF CONTROL.

In the experiments of Oppenheimer and Spaeth (l. c.) on rats, none of the experimental animal stock died of extraneous infections. Nevertheless autopsies were not systematically made, nor was the pneumococcus organism recovered in the dead animals. In our experiments with guinea pigs we therefore made systematic autopsies and smears of the heart's blood, pleural and peritoneal exudates. In all doubtful cases, or where secondary infections were indicated, the heart's blood was grown on blood agar. Only deaths that were unequivocally attributable to pneumococcal infections are included in our tabulated results.

RELATION BETWEEN FATIGUE AND PNEUMOCOCCAL INFECTIONS
IN GUINEA PIGS.

Our experimental results are shown in Fig. 2, *B*. In the unfatigued control group 80 per cent. of the animals died, while in the case of animals fatigued three times before injection, 80 per cent. lived. As in the case of the rat experiments of Oppenheimer and Spaeth (l. c.) fatigue after injection protected the guinea pigs less

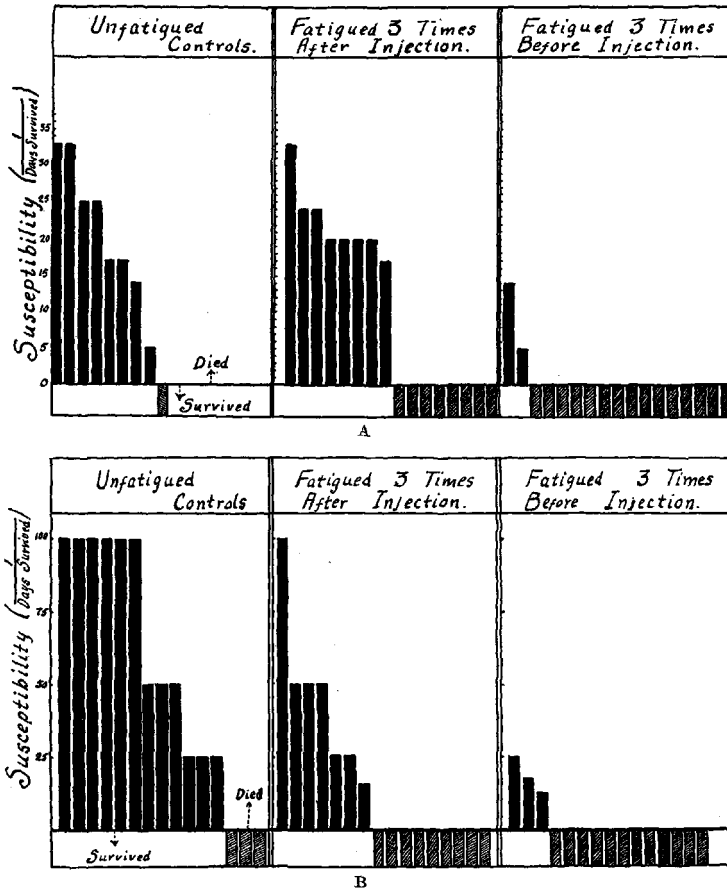


FIG. 2. The relation between fatigue and susceptibility to Type I pneumococcus is shown in these charts for rats (*A* from Oppenheimer and Spaeth (1, c.)) and guinea pigs (*B*). The similarity in the two charts is unmistakable. Fatigue before injection (three periods of physical exhaustion) definitely increases the resistance of both rats and guinea pigs to lethal doses of Type I pneumococcus. This decrease of susceptibility is indicated by the diminution of the black areas from left to right in both charts. See text for details.

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TABLE II.

Date.	Color.		Weight of pig in grams.	Dose per gm. wt.	Dose in c.c.	Fa-tigued.		Un-fa-tigued con-trols.	Death.
	Albino.	Pig. m'ld.				Before.	After.		
Dec. 21, '21.....	*	-	257	0.0005 c.c.	0.13	*	-	-	-
	*	-	241	"	0.12	-	*	-	-
	*	-	163	"	0.08	-	*	-	4th day
	*	-	301	"	0.15	-	-	*	1st "
	*	-	191	"	0.09	-	-	*	1st "
Jan. 18, '22.....	-	*	239	0.0016 c.c.	0.38	*	-	-	-
	-	*	185	"	0.30	*	-	-	6th day
	-	*	202	"	0.32	-	*	-	2d "
	-	*	230	"	0.37	-	-	*	1st "
	-	*	192	"	0.30	-	-	*	2d "
Jan. 25, '22.....	*	-	158	0.0005 c.c.	0.08	*	-	-	-
	*	-	193	"	0.09	*	-	-	-
	*	-	158	"	0.08	-	*	-	4th day
	*	-	221	"	0.11	-	*	-	-
	*	-	154	"	0.07	-	-	*	-
	*	-	173	"	0.08	-	-	*	4th day
Feb. 1, '22.....	-	*	228	0.0016 c.c.	0.36	*	-	-	4th day
	-	*	216	"	0.34	*	-	-	-
	-	*	173	"	0.28	-	*	-	1st day
	-	*	231	"	0.31	-	*	-	6th "
	-	*	207	"	0.33	-	*	-	-
	-	*	170	"	0.27	-	-	*	-
	-	*	216	"	0.34	-	-	*	1st day
	-	*	216	"	0.34	-	-	*	1st day
Feb. 22, '22.....	*	-	224	0.0005 c.c.	0.11	*	-	-	-
	*	-	209	"	0.10	*	-	-	-
	*	-	231	"	0.11	*	-	-	-
	*	-	206	"	0.10	-	*	-	2d day
	*	-	195	"	0.09	-	*	-	-
	*	-	192	"	0.09	-	*	-	-
	*	-	166	"	0.08	-	-	*	4th day
	*	-	203	"	0.10	-	-	*	1st "
Mar. 3, '22.....	-	*	241	0.0016 c.c.	0.38	*	-	-	-
	-	*	225	"	0.36	*	-	-	-
	-	*	272	"	0.43	-	*	-	-
	-	*	288	"	0.46	-	*	-	-
	-	*	220	"	0.35	-	-	*	-
	-	*	199	"	0.32	-	-	*	4th day
	-	*	199	"	0.32	-	-	*	4th day

Experimental data of animals plotted in Fig. 2, B.

well than fatigue before injection. In this group nine of the sixteen pigs (56 per cent.) lived while seven (44 per cent.) died.

The essential corroboration of our results of the findings on rats by Oppenheimer and Spaeth (1. c.) is shown by comparing *A* and *B* in Fig. 2. The relations between pneumococcus infection and fatigue are given both for rats and guinea pigs. The most striking difference between the response of guinea pigs to pneumococci and that of rats is the much shorter incubation period in the pigs. Sixty per cent. of the control pigs died within two days after the injection, whereas, with a minimal lethal dose, no control rats died before the third day. Forty-six pigs are included in our chart. Of this number 28 were albinos and 18 were pigmented. The albinos and pigmented pigs received quite different doses of pneumococci (*vide infra*), but each group was independently controlled for its particular minimal lethal dose (see Table II).

GENERAL CONCLUSIONS.

1. There is in guinea pigs a definite correlation between pigmentation and susceptibility to Type I pneumococcus. White-coated, pink-eyed pigs, which are probably genetically pure albinos (3), were found to be approximately 300 per cent. more susceptible to a given culture of Type I pneumococcus than were pigmented pigs.

2. Fatigue, artificially induced in white or pigmented guinea pigs by forcing them to run in motor-driven drums, definitely increases the resistance of these pigs to lethal injections of Type I pneumococcus. This occurs whether fatigue precedes or follows the pneumococcal injections, but is distinctly more effective in the case of fatigue before injection.

3. The experimental results of our study corroborate the work of Oppenheimer and Spaeth (1. c.) on the relation between fatigue and susceptibility to Type I pneumococcus in white and hooded rats.

NOTES.

1. From the Physiological Laboratory of the School of Hygiene and Public Health, Johns Hopkins University.

2. We are indebted to Dr. C. G. Bull and to Miss Clara McKee of the Department of Immunology for our original pneumococcus culture, for the standardized media used throughout the experiments and for much invaluable advice.

3. It is necessary to make this reservation, since Sewall Wright ('16) has found a white-coated, pink-eyed guinea pig that does not breed true. This type of "somatic albino" may be produced by combining two other factors with dilute sepia. Whether susceptibility to pneumococcus infection is correlated with the genetic or the somatic white pig, or with both, can easily be shown experimentally. Oppenheimer and Spaeth (l. c.) found no difference in susceptibility to pneumococcus between white (albino) and hooded rats. Lewis and Wright ('21) likewise reported no difference between the susceptibility of white and pigmented guinea pigs to tuberculosis. Guinea pigs, therefore, offer a unique opportunity to test the relation between natural resistance and an inherited character-albinism. With Dr. Wright's collaboration the problem is under investigation.

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