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EFFECT OF THE INJECTION OF NONSPECIFIC FOREIGN SUBSTANCES ON THE COURSE OF EXPERIMENTAL RABIES *

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Investigations on the treatment of infectious diseases have recently received additional stimuli as a result of many favorable reports on the effect of nonspecific biochemic therapy in some of these diseases. Principal among the latter are rheumatic arthritis, gonorrhoeal arthritis, and typhoid fever. Experimentally, it has long been known that the resistance of animals to some infections could occasionally be raised by the injection of heterogeneous nonspecific substances. Thus Pfeiffer¹ found that by injecting broth intraperitoneally the resistance of guinea-pigs to cholera infection was materially raised. Thus, also Babes,² Fermi,³ and Repetto⁴ claimed to have produced immunity to rabies by subsequent treatments with normal brain tissue. Fermi⁵ claims, furthermore, to have rendered animals immune to experimental rabies by injections of fresh egg-yolk, mixtures of cholesterol and lecithin, and other lipoidal substances. The work of Babes, Fermi and Repetto have, however, not met with universal confirmation by other investigators. The objection most frequently raised to this work has been that the rabies inoculations were made subcutaneously. Their protocols present recoveries in 50-66% in relatively large series of animals. According to Koch,⁶ however, inoculations subcutaneously of rabies virus result in positive takes in only about 50% of the animals inoculated, whereas subdural or intracerebral inoculations are positive in 100%. Repetto contends, however, that the percentage of positive infections in the subcutaneous inoculation of the virus in rats is greater than this, and that the results not in accord with his were obtained by others who did not repeat all the conditions of his experiments. The control series of

* Received for publication January 23, 1917.

¹ Hyg. Rundschau, 1900, 10, p. 357.

² Cited in Kolle and Wassermann, Handb. d. path. Mikroorg., 1913, 8, 902.

³ Centralbl. f. Bakteriol., I, O, 1907, 44, 475.

⁴ Ibid., 1909, 51, 581.

⁵ Ibid., 1908, 48, 357.

⁶ Cited in Kolle and Wassermann, Handb. d. path. Mikroorg., 1913, 8, 821.

Fermi's experiments show a high mortality. He frequently worked with an equal number of animals in the control series, and the death rate from rabies invariably was 100%. His findings, that nonspecific therapy in his street virus experiments resulted in a greater number of cures than did specific treatment administered according to the routine method of Pasteur, are almost paradoxical. If legitimate criticism is to be avoided in future experimental therapeutic investigations of rabies, all animals should receive their virus inoculations subdurally or intracerebrally. True, such inoculations are most radical and do not at all

TABLE I
RESULTS OF INOCULATION OF RABBITS WITH FRESH, FIXED VIRUS

Treatment	Day						
	1	2	3	4	5	6	7
Control.....
Control.....
Control.....
Control.....
Horse Serum.....	1.5 c.c.	1.5 c.c.
Horse Serum.....	1.5 c.c.	1.5 c.c.
Horse Serum.....	1.5 c.c.	1.5 c.c.
Egg-White.....	1 c.c.	1.5 c.c.	2 c.c.
Egg-White.....	1 c.c.	1.5 c.c.	2 c.c.
Egg-White.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....
Egg-Yolk.....

R. In. = rabies inoculation; ER = early symptoms of rabies; R = well developed paralytic rabies; AS = anaphylactic shock; X = death; Fat Emb. = fat embolism.

resemble the manner in which man or animals usually become infected. However, unless a therapeutic measure can be discovered which will withstand the most rigid conditions, it would scarcely seem advisable to substitute it clinically for the practically universal Pasteur method of treatment.

The work now reported covers several series of rabbits, 63 in all, 17 being controls. A portion of the work, that concerned with the treatment of fixed virus rabies, was undertaken not quite 2 years ago (Table 1). Because of the negative results, the work was discontinued

TABLE I—Continued
RESULTS OF INOCULATION OF RABBITS WITH FRESH; FIXED VIRUS

Day									
8	9	10	11	12	13	14	15	16	17
.....	R. In.	ER	R	X
.....	R. In.	ER	R	X
.....	R. In.	ER	R	X
.....	R. In.	ER	X	
5 e.e. AS	1 e.e.	0.5 e.e.	R. In. 1 e.e.	1 e.e.	0.5 e.e.	0.5 e.e.	X		
5 e.e. AS	1.5 e.e.	1 e.e.	R. In. 1 e.e.	0.5 e.e. AS	0.5 e.e.	0.5 e.e.	1 e.e. ER	X	
5 e.e. AS	1.5 e.e.	1 e.e.	R. In. 1 e.e.	0.6 e.e. AS	0.5 e.e.	0.5 e.e.	1 e.e. ER	X	
2 e.e. AS	2 e.e.	1 e.e.	R. In. 1 e.e.	1.5 e.e. AS	5 e.e.	X			
5 e.e. AS	2 e.e.	1 e.e. AS	R. In. 1 e.e.	1.5 e.e.	0.7 e.e.	X			
5 e.e.	2 e.e.	R. In. 2 e.e.	1.5 e.e.	1.7 e.e.	0.7 e.e.	ER 1.7 e.e.	X	
7 e.e.	2.5 e.e.	0.6 e.e. AS	R. In. 1 e.e.	1.7 e.e.	1 e.e. AS	1 e.e.	1.7 e.e. ER	X	
5 e.e.	2 e.e.	R. In. 2 e.e.	3 e.e.	1 e.e. AS	1 e.e.	1.7 e.e. ER	X	
4.5 e.e.	2 e.e.	R. In. 2 e.e.	3 e.e. AS	1 e.e.	1 e.e.	1.7 e.e. ER	X	
2 e.e.	1.5 e.e.	R. In. 2 e.e.	3 e.e. AS	1.5 e.e.	1 e.e.	1.7 e.e. ER	X	
5 e.e.	2 e.e.	R. In. 2 e.e.	3 e.e.	1.5 e.e.	1 e.e.	1.7 e.e. ER	X	
.....	R. In. 5 e.e.	4 e.e.	2 e.e.	1.5 e.e.	1.7 e.e. ER	X	
.....	R. In. 5 e.e.	4 e.e.	2 e.e.	1.5 e.e.	1.7 e.e. ER	X	
.....	R. In. 5 e.e.	4 e.e. FatEmb.	X				

TABLE II
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED STREET VIRUS (THREE MONTHS OLD)

Treatment	Day								
	1	2	3	4	5	6	7	8	9
Control.....	R. In.
Control.....	R. In.
Control.....	R. In.
Control.....	R. In.
Control.....	R. In.
Control.....	R. In.
Tetanus Antitoxin.....	R. In.	2 c.c. 300u	1.1 c.c.	1 c.c.
Tetanus Antitoxin.....	R. In.	2 c.c. 300u	2 c.c.	2 c.c.
Deutero-Proteose.....	R. In.	5 c.c.	5 c.c.	5 c.c.	5 c.c.
Deutero-Proteose.....	R. In.	5 c.c.	5 c.c.	5 c.c.
Horse Serum.....	R. In.	2 c.c.	2 c.c.	2 c.c.
Horse Serum.....	R. In.	2 c.c.	2 c.c.	2 c.c.	2 c.c.
Typhoid Vaccine.....	R. In.	1 c.c.	0.5 c.c.	1 c.c.
Typhoid Vaccine.....	R. In.	1 c.c.	0.5 c.c.	1 c.c.	0.8 c.c.
Egg-White.....	R. In.	2 c.c.	2 c.c.	3 c.c.
Egg-White.....	R. In.	2 c.c.	2 c.c.	3 c.c.	2 c.c.
Egg-Yolk.....	R. In.	2 c.c.	2 c.c.	2 c.c.
Egg-Yolk.....	R. In.	2 c.c.	2 c.c.	3 c.c.
Diphtheria Antitoxin..	R. In.	0.33 c.c. 250u	0.66 c.c. 500u	0.5 c.c. 900u
ATK.....	R. In.	1.5 mg.	2 mg.	4 mg.	5 mg.
ATK.....	R. In.	1.5 mg.	2 mg.	4 mg.
ATK.....	R. In.	1.5 mg.	2 mg.	..	4 mg.	5 mg.

R. In. = rabies inoculation; Lit. = litter of young born; ER = early symptoms of rabies; R = well developed paralytic rabies; AS = anaphylactic shock; X = death; F = fat embolism; ATK = old tuberculin Koch.

at that time. Since then, however, the successes of Miller and Lusk,⁷ Smith,⁸ Culver,⁹ and others, in the treatment of certain infections have caused renewed interest, and the work has been followed by the series

⁷ Jour. Am. Med. Assn., 1916, 66, 1756.

⁸ Ibid., 66, 1758.

⁹ Ibid., 1917, 68, 363.

TABLE II—Continued
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED STREET VIRUS (THREE MONTHS OLD)

Day												
10	11	12	13	14	15	16	17	18	19	20	21	22
....	ER	R	X				
....	Lit	R	R	X			
....	ER	X						
....	ER	R	R	X				
....	ER	R	X				
....	ER	R	X					
2 c.c.	3 c.c. AS	2 c.c.	2 c.c.	ER	R	R	R	X
2 c.c.	3 c.c.	2 c.c. ASX							
....	3 c.c.	2 c.c.	1.2 c.c.	R	R	R	X			
5 c.c.	5 c.c.	5 c.c. AS	R	R	X				
2 c.c.	3 c.c. AS?	2 c.c. AS	1.2 c.c. ER	R	R	R	X	
....	3 c.c.	2 c.c. AS	1.4 c.c.	ER	R	R	R	X	
1 c.c.	1 c.c.	1 c.c.	ER	R	R	R	R	X	
....	1 c.c.	1 c.c.	ER	R	R	X				
2 c.c.	2 c.c.	1.6 c.c.	1.2 c.c.	ER	ER	R	X	
....	3 c.c. AS?	2 c.c. ER	R	R	R	X				
2 c.c.	2 c.c. ASXF										
2 c.c.	2 c.c. AS?F?	2 c.c.	1.5 c.c.	ER	R	R	X
1 c.c. 1800u	1.5 c.c. 2700u	1 c.c. 1800u AS	0.8 c.c. 1400u	ER	ER	R	X
....	5 mg.	10 mg.	ER	R	R	X		
5 mg.	5 mg.	10 mg.	ER	R	R	X				
....	5 mg.	10 mg.								
Lit. on 31st day												

of experiments reported herein. Rabbits weighing from 1500 to 1800 grams were inoculated intracranially and subdurally with from 3 to 5 times the minimal lethal dose of virus. They were treated by intravenous injection of horse serum, egg-white, egg yolk, broth culture-media, globulin of horse serum (both antitetanus and antidipteria serum being used), typhoid vaccine and tuberculin. The maximum doses of these substances compatible with the physical condition of the

animal were used. Occasionally a reaction suggestive of sensitization was obtained; this was combatted by the immediate intracardiac administration of adrenin when necessary. A few of the animals succumbed in attacks resembling typical acute anaphylaxis, and grossly, the visceral changes were suggestive of this. The animals treated with egg-yolk appeared most refractory. A considerable number, not recorded in the tabulations, died at the time of the second injection with symptoms quite characteristic of anaphylaxis, the changes in these, also, being equally suggestive of anaphylaxis. Frozen section of lung, stained with sudan III, however, revealed a pulmonary vascular system filled and plugged with sudan III-stained globules of varying sizes.

The egg-white was prepared by mixing the white of hen's eggs with an equal volume of distilled water. The mixture filtered under aseptic precautions, was injected without further dilution. The egg-yolk was similarly prepared. The deuteroproteose was prepared from milk and dissolved in physiologic salt solution. It was injected as a 1% solution. The horse serum was used undiluted in doses, as indicated in the tabulations. The serum-globulins (antidiphtheria and antitetanus) were diluted with an equal amount of physiologic salt solution; the amounts of the diluted globulin injected and their value in antitoxin units are indicated in Table 1. The tuberculin was diluted with physiologic salt solution and injected in volumes of 5 c.c. The quantity of tuberculin in milligrams received in each injection is recorded in the tables. The animals treated with broth culture-media received this in dilutions equal to that of the tuberculin. They were injected and carried along as controls for the tuberculin-treated animals when it was found in a late series that some of these animals did not

TABLE III
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED FIXED VIRUS (SIX MONTHS OLD)

Treatment	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	R. In.	ER	R	R	X					
Control	R. In.	ER	R	R	X				
ATK	R. In.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg. ER	10 mg. R	X					
ATK	R. In.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg. ER	10 mg. R		X			
ATK	R. In.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
Broth	R. In.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.

R. In. = rabies inoculation; ER = early symptoms of rabies; R = well developed paralytic rabies; X = death; ATK = old tuberculin Koch.

succumb to rabies. Old tuberculin Koch, as is well known, contains not a little of culture-media and its meat extracts.

Eighteen rabbits, 4 of which were controls, constituted the first series, and were inoculated with fixed virus. These were treated as indicated in Table I, with horse serum, egg-white, and egg-yolk. The 3 rabbits treated with horse serum received 5 injections of serum prior to their inoculation with rabies virus, and following this were injected daily with smaller amounts of the serum. The rabbits lost weight rapidly. The earliest symptoms of rabies occurred on the 4th instead of the 5th day, and death occurred on the same or the following day, whereas, the controls lived 1 or 2 days after the onset of the symptoms. Two of the rabbits, treated with egg-white, received 6 intravenous injections during 11 days preceding their inoculation, and daily injections thereafter. Both of these died on the 4th day following their inoculation and within a few hours following the onset of their paralysis. One rabbit treated with egg-white, and 5 treated with egg-yolk received 2 and 3 injections, respectively, of egg-white and egg-yolk, during the 3 days prior to their inoculation with virus, and daily injections following this. In all of these, the earliest symptoms developed on the 5th day, and death occurred after a short period of paralysis, on the following day. Three additional rabbits were inoculated with virus without having received previous injections of egg-yolk, and following this, received daily injections of the yolk. One rabbit died on the 3rd day of fat embolism; the remaining 2 developed paralysis on the 5th day and were dead on the 6th day. The controls, with one exception, lived until the 7th day, dying on the 3rd day following the onset of their symptoms. It was now apparent that the results obtained by Fermi and Repetto with street virus could not be duplicated in rabbits experimentally infected with fixed virus. In all instances, the results were unfavorable; paralysis occurred earlier and the disease, after its onset, was of shorter duration and was always fatal. It was therefore decided when this work was again resumed to carry on the experiments with a somewhat attenuated

TABLE III—Continued
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED FIXED VIRUS (SIX MONTHS OLD)

Day																
15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
...	R. In.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg. ER	10 mg. R	10 mg. R	X
...	R. In.	5 c.c. ER	5 c.c. RX						

TABLE IV
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED STREET VIRUS (FOUR MONTHS OLD)

Treat- ment	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	R. In.	ER
Control	R. In.													
ATK	R. In. 10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
ATK	R. In. 10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
ATK	R. In. 10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
ATK	R. In. 10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
ATK	R. In.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
ATK	R. In.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.
Broth	R. In.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.

R. In. = rabies inoculation; ER = early symptoms of rabies; R = well developed paralytic rabies; X = death; ATK = old tuberculin Koch.

virus. Extended exposure to light, air, and gradual desiccation have a marked attenuating action on rabies virus. At 33 $\frac{1}{3}$ % neutral glycerin mixture at 4 C., protected from light rays, is the most favorable agent for preserving it. Fixed virus kept in this way has in some instances retained its virulence to a somewhat lessened degree after a period of from 3 to 3 $\frac{1}{2}$ years. Street virus is said to retain an undiminished virulence when preserved for from 80 to 90 days under these conditions. Negri bodies are still recognizable in smears made at this time, according to Mazzei.¹⁰ After preservation for longer periods, the virus diminishes in virulence gradually, slowly, but progressively. It was, therefore, decided to resume investigation with street and fixed virus that had slowly become attenuated by age, while preserved under otherwise favorable conditions. Accordingly, a street virus in which Negri bodies were present in abundance and which had never failed to infect when inoculated subdurally, was preserved in 33% neutral glycerin, in the dark, at 4 C., for 3 months. In inoculations with this virus in its fresh state, positive symptoms were observed usually as early as the 16th day, and death usually occurred on the 20th or 21st day, as illustrated by the protocols of the first 2 rabbits (Table II).

Twenty-two rabbits constituted the second series (Table II). Six were controls, the remainder, following their inoculation, were treated with serum globulin (antitetanus and antidiphtheria), deuteroproteose, horse serum, typhoid vaccine (1,000,000,000 per c.c.), egg-white, egg-yolk, and tuberculin. Three rabbits were treated with serum globulin, 2 receiving it in an antitetanus form

¹⁰ Cited in Kolle and Wassermann, Handb. d. path. Mikroorg., 1913, 8, 866.

TABLE IV—Continued
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED STREET VIRUS (FOUR MONTHS OLD)

Day																
15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
R	R	R	R	R	X											
...	10 mg.	10 mg.	...	10 mg.	...	10 mg.	...	10 mg.	10 mg.	...	10 mg.	...	10 mg.	...	10 mg.	10 mg.
...	10 mg.	10 mg.	...	10 mg.	...	10 mg.	ER	X								
...	10 mg.	10 mg.	...	10 mg. ER	X											
...	10 mg.	10 mg.	...	10 mg.	...	10 mg.	...	10 mg.	10 mg.	...	10 mg.	...	10 mg.	...	10 mg.	10 mg.
10 mg.	...	10 mg. ER	10 mg. R	10 mg. R	X											
10 mg.	...	10 mg.	10 mg.	10 mg.	...	10 mg. ER	R X									
5 c.c.	...	5 c.c. ER	5 c.c. ER	R	R	X										

and 1, antidiphtheria. They received from 6 to 7 intravenous injections during the first 15 to 17 days following inoculation. One succumbed on the 15th day with symptoms resembling anaphylaxis, and necropsy findings were typical. Of the remaining 2, the earliest symptoms of rabies appeared on the 18th day, and in the other, on the 19th day. Both died on the 22nd day after a typical course of paralytic rabies. Two rabbits received from 5 to 6 injections of a 1% solution of deuteroproteose during the first 15 days following their inoculation. Both developed symptoms of paralytic rabies on the 16th day; one died on the 18th day, the other on the 19th day. Two rabbits treated with horse serum received 7 intravenous injections during the 17 days following their inoculation with virus. Both developed initial paralysis on the 17th day, and after a typical course of the disease, death occurred, in both instances, on the 21st day. Two other rabbits received 6 injections of typhoid bacterin during the 15 days following their inoculation with virus. Both developed typical paralytic rabies, one on the 15th day, the other on the 16th day. The former died on the 18th day, the latter on the 21st day after the inoculation. Two additional rabbits received 6 intravenous doses of egg-white, during 15 days following their inoculation. In 1, early symptoms of rabies appeared on the 14th day, and death, on the 18th day. In the second, the earliest manifestations of rabies were present on the 18th day, whereas death occurred on the 21st. Another pair of rabbits received egg-yolk intravenously; 1 died of fat embolism on the 12th day, at the time of the 5th injection, and before symptoms of rabies had developed. The other received 7 injections during 17 days after inoculation. Typical paralytic rabies developed on the 19th day and death occurred on the 22nd day. Three rabbits received 6 intravenous injections of tuberculin during 14 days. In 1, rabies developed on the 15th day, and death occurred on the 18th day. The second

rabbit manifested its earliest symptoms on the 17th day, death occurring on the 20th day. The third rabbit, however, developed no symptoms. She appeared normal for a period of ten weeks after inoculation. During this time, she gave birth to a litter of 4 normal young. Following this, she was inoculated a second time with the same virus used in the first inoculation. She received 2 injections of tuberculin on the 2 following days, during which time she appeared perfectly normal. She was found dead on the morning of the third day. Death appeared to have been due to a localized, acute, encephalitis at the site of the second inoculation. She had, however, unquestionably withstood the first inoculation made ten weeks before. I do not believe that her pregnancy occurring during this period was a factor in her survival. It has been my experience and the literature in general indicates that pregnancy has no effect on the course of experimental rabies. This was the only rabbit of series II to survive. The course of the rabies in the other animals was not materially altered following treatment with the various substances administered. The controls all ran a typical course of the disease and died well within the 21-day limit of this particular virus strain.

While series II was in progress, a third series of 6 rabbits was inoculated with an old fixed virus, of the same strain as that used in series I. It was a virus-containing brain tissue which had been preserved in the dark for 6 months at 4 C. in a 75% neutral glycerin solution. Two of the inoculated rabbits were reserved as controls. Three were treated with tuberculin and 1 with broth, intravenously. Table I showed that this virus in its fresh state always produced the first symptoms of rabies on the 5th day after inoculation, and that death usually occurred on the 7th day. The controls inoculated with this same but age-attenuated virus, in series III, developed their first symptoms on the 6th and 7th days, respectively, and in each, death occurred on the 4th day of the paralysis.

TABLE V
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED STREET VIRUS (FOUR AND ONE-HALF MONTHS OLD)

Treatment	Day									
	1	2	3	4	5	6	7	8	9	10
Control.....	R. In.	Ab				
Control.....	R. In.
Control.....	R. In.
Broth.....	R. In.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.
Broth.....	R. In.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.
ATK.....	R. In.	20 mg.	20 mg.	10 mg.	10 mg.	10 mg.
ATK.....	R. In.	20 mg.	20 mg.	10 mg.	10 mg.	10 mg.
ATK.....	R. In.	20 mg.	20 mg.	10 mg.	10 mg.	10 mg.

R. In. = rabies inoculation; ER = early symptoms of rabies; R = well developed paralytic rabies; X = death; ATK = old tuberculin Koch; Ab = abscess.

One of the tuberculin-treated animals of this series developed symptoms of rabies on the 7th day, and died on the 9th day. A second tuberculin-treated animal became paralyzed on the 8th day, and died on the 11th day. The remaining 2 rabbits, one treated with broth injection, and the other with tuberculin, were given 10 and 11 injections, respectively, during 13 days following their inoculation. During this time, they appeared normal. These animals continued apparently normal more than 3 weeks. On the 31st day following their first inoculation, they were reinoculated with the same virus, now 214 days old. The rabbit formerly treated with tuberculin again received daily treatments of the same; the rabbit previously treated with broth culture-media received the same broth treatment. The broth-treated rabbit died suddenly on the second day following its reinoculation, apparently of an acute encephalitis, at the site of its second inoculation. The tuberculin-treated rabbit appeared normal for 5 days. Late on the 6th day, there was an early paralysis which progressed, but was incomplete at the end of the 7th day. On the 9th day, paralysis was complete, and death occurred on the 10th day.

The results obtained in Series II and III are too meager to justify general conclusions. It was not apparent why those animals which had apparently survived their first inoculation should have succumbed or have been more susceptible to a subsequent reinoculation. Was the treatment which they had received following their first inoculation a therapeutic factor which had raised their resistance at that time so that they survived this inoculation? If so, it had not resulted in a perma-

TABLE V—Continued
RESULTS OF INOCULATION OF RABBITS WITH TIME-ATTENUATED STREET VIRUS (FOUR AND ONE-HALF MONTHS OLD)

Day															
11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
....	ER	R	R	X	.					
....	ER	R	R	R	X					
5 c.c.	5 c.c.	5 c.c.	5 c.c.	ER	5 c.c. R	R	5 c.c. R	R	X				
5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c.	5 c.c. ER	X	
10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	X						
10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	10 mg.	ER	X
10 mg.	10 mg.	10 mg.	10 mg.	10 mg. FR	R	10 mg. R	R	10 mg. R	R	10 mg. R	X	

ment or even temporary immunity. Furthermore, this same treatment had proved totally inadequate in inhibiting or preventing infection from a subsequent reinoculation with the same infecting agent. This latter condition, however, is not incompatible with our experience in some other infectious diseases. Thus, not infrequently, reinfection with syphilis subsequent to a former initial mild luetic infection, manifests itself clinically and symptomatically as a most virulent type. Another explanation, that of faulty technic at the time of the first inoculation, does not come into question. In several hundred experimental intracerebral inoculations with nonattenuated rabies virus, I have never before failed to infect the animal with rabies.

Because of the inconclusive results so far obtained, a fourth series of 9 rabbits was inoculated with the same street virus used in the series tabulated in Table II. This virus, preserved under the same conditions was now 122 days old. The results in this series are recorded in Table IV. Two of the rabbits of this series were reserved as controls; 1 was treated with broth, the remaining 6 received tuberculin. The rabbits received 4 intravenous injections of broth or tuberculin per week, as indicated in the table. The broth-treated rabbit developed early symptoms of paralytic rabies on the 17th day and succumbed on the 21st day. Four of the tuberculin-treated rabbits died of rabies. Death occurred in 3 of these, after a period of illness of only 24 hours' duration. The remaining 2 continued to receive tuberculin 4 times per week for 31 days, when it was discontinued. These rabbits remained apparently normal, and at this date, 75 days after their inoculation, are alive and apparently normal. One of the control animals developed symptoms of early paralysis on the 14th day and succumbed on the 20th day, after 5 days of complete paralysis. The remaining control animal went into convulsions immediately following the trephining and intracerebral inoculation. During the course of these convulsions it severely traumatized its right cheek by violent contact with the walls of its cage. On the 3rd day, an extensive cellulitis involving all of the soft parts of the right half of the head developed. This finally localized in a large submaxillary abscess which, when opened and curetted, was found to have its focus in a suppurative osteitis of the lower jaw. This was repeatedly opened and curetted and drained through several fistulas until January 23, at which time healing was almost complete. During this time the animal failed to manifest any symptoms of rabies and it can be said that it is well beyond any possibility of developing it. The survival of this control animal vitiated any conclusions which may have been drawn from the recoveries among the treated animals. It might have been argued that recovery of this control could have been due to the severe suppurative contemporary infection, existing during the period of incubation, following the inoculation with rabies virus. However, it raised the just doubt that we were now dealing with a virus so attenuated that it was no longer sufficiently potent to produce disease in 100% of inoculations in untreated animals.

Because of this new complication, a final series of 8 rabbits was inoculated with the same street virus, which at this time was 137 days old. Three of these animals were reserved as controls, 2 were treated with broth, and 3 received tuberculin. The results obtained in this series are recorded in Table V. The periods of paralysis of the rabbits that died were of varying durations. In one

instance, a tuberculin-treated rabbit, which at no time presented symptoms of rabies, was found dead on the morning of the 20th day. Necropsy revealed an extensive subcutaneous, pulmonary and splenic tuberculosis. Other treated rabbits succumbed within 24 hours of their first paralytic symptoms, whereas one of the tuberculin-treated animals lived a week after the earliest symptoms developed. All of the treated animals died, 1 on the 21st day, 1 on the 22nd day, 2 on the 25th day, and 1 on the 26th day. One of the controls died on the 25th day after typical paralytic rabies. The other control animal still lives, and is now apparently normal, and well beyond the possible development of rabies from the former inoculation. I had hoped, after my experience in the first few series of these experiments, that tuberculin might prove to have a beneficial effect in encephalitis due to rabies, as has some time been claimed for it for syphilis by von Yaregg¹¹ and others who have used it in extremely large doses in the treatment of the chronic encephalitis of general paresis. The scope of these experiments, extended as they are, are not extensive enough to warrant any favorable conclusions. In a desperate case of rabies in man, in which death appeared certain, and the possibility of activating a latent tuberculosis was negligible because of this apparent certainty of death from rabies, it might be justifiable to administer tuberculin in superdoses as a measure of last resort.

CONCLUSIONS

The injection of certain nonspecific substances (horse serum, serum globulin, egg-white, egg-yolk, broth, typhoid vaccine, or tuberculin) does not inhibit the course of experimental rabies in rabbits produced by nonattenuated virus. The seemingly beneficial effect of tuberculin in the early series of the experiments must be disregarded because of the survival of some control animals inoculated at a later date with the same virus.

The results of Fermi and Repetto cannot be obtained with egg-yolk injections when potent rabies virus is inoculated subdurally or intracerebrally in rabbits.

Rabbits surviving an intracerebral inoculation of attenuated rabies virus (fixed or street virus), may become hypersensitive to a reinoculation of the same virus made in the same way.

¹¹ Wien. med. Wchnschr., 1909, 49, p. 21.