

野口英世著 Journal of Experimental Medicine 所収論文

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ETIOLOGY OF YELLOW FEVER.

IV. THE ACQUIRED IMMUNITY OF GUINEA PIGS AGAINST LEPTOSPIRA ICTEROIDES AFTER THE INOCULATION OF BLOOD OF YELLOW FEVER PATIENTS.

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Most of the attempts to transmit yellow fever by inoculating the blood of patients into various animals have ended in failure. As stated elsewhere¹ out of 74 guinea pigs, in only eight were the results positive, and in other species of animals they were all negative. It should be emphasized that for the purpose of transmission cases were selected which were still in the early stage of the disease, previous investigators having pointed out the fact that the virus may no longer exist in the peripheral blood after the 3rd day of the illness.

In the present study the guinea pigs which failed to manifest the typical symptoms, or any symptoms at all, were kept under daily observation for many weeks. On a later date, through temporary shortage of normal guinea pigs, they were inoculated, together with several normal guinea pigs, with a virulent organ emulsion, rich in the leptospira, from a guinea pig experimentally infected with the organism, in order to prepare a large amount of organ emulsion for the purpose of immunizing two donkeys against the virus. A great many of the guinea pigs remained perfectly well, while most of the normal animals, as well as those which had been previously inoculated with the blood of malarial patients,² came down with an experimental infection.

¹ Noguchi, H., *J. Exp. Med.*, 1919, **xxix**, 565.

² In a country where æstivo-autumnal parasites infest the population many times a malarial patient is brought to the Yellow Fever Hospital on the chance that the case is one of early yellow fever. All these cases were used for the experiments on the transmission of yellow fever without the loss of time which would have been caused by waiting for a diagnosis, for which a day or two might be required.

TABLE I.
Susceptibility of Guinea Pigs to the Inoculation of Leptospira icteroides 25 Days after They Had Been Injected with the Blood of Yellow Fever Patients.

Patient.	Sex.	No. of guinea pig.	Day of disease when bled.	Amount of blood injected.	Reaction. °C.	Subsequent test for susceptibility.	Reaction. °C.	Result.
Case 27. Yellow fever. Died in 16 days.	M.	16	14th	2	None.	Virulent Arias strain after 25 days.	40.3 in 5 days.	Killed in 8 days. Typical.
		17	14th	3	"	"	39.8 " 6 "	Died in 8 days. Typical.
Case 25. Yellow fever. Mild. Recovery. Also malaria.	F.	21	6th	3	"	"	39.9 " 6 "	Died in 8 days. Typical.
		22	6th	3	39.7 in 4 days.	"	None.	Remained well.
Case 1. Malaria (Guayaquilian).	"	23		3	None.	"	40.5 in 8 days.	Killed in 11 days. Mild but typical.
		24		4	"	"	40.0 " 7 "	Killed in 9 days. Typical.
Case 27. Yellow fever. Second specimen of blood.	M.	32	15th	5	"	"	39.9 " 5 " Icterus.	Killed in 7 days. Typical.
		33	15th	5	"	"	40.0 in 6 days. Icterus.	Died in 8 days. Typical.
Case 13. Dr. Valenzuela's patient. Yellow fever. Mild. Recovery.	"	35	3rd	3	39.8 in 8 days.	"	40.2 in 4 days.	Recovered.
		36	3rd	5	39.2 " 12 "	"	39.6 " 5 "	Remained well.

Case 2. Malaria.	M.	30		2	None.	Virulent Arias strain after 25 days.	40.4 in 4 days. Icterus.	Died in 9 days. Typical.
" 3.	"	52		3	"	"	39.9 in 6 days. Icterus.	Died in 10 days. Typical.
" 4.	"	19		2	"	"	40.0 in 9 days. Icterus.	Killed in 12 days. Typical.
" 7. Yellow fever. Severe. Recovery.	"	20		2(?)	"	"	40.0 in 11 days. Slight icterus.	Died in 17 days. Mild but typical.
" 7. Yellow fever. Severe. Recovery.	"	37	6th	5	39.8 in 6 days.	"	None.	Remained well.
Case 12. Yellow fever. Moderate. Recovery.	F.	39	2nd	5	39.2 " 8 "	"	39.0-39.7 in 5-6 days.	"
"	"	40	2nd	3	39.2 " 8 "	"	None.	"
Case 5. Malaria.	"	41		3	39.6 " 9 "	"	40.0-40.3 in 9 days.	Died in 13 days. Typical.
"	"	42		5	39.7 " 6 "	"	Icterus.	Died in 10 days. Typical.
" 27. Yellow fever. Autopsy material 6 hrs. post mortem.	M.	48	16th	2 (kidney emulsion).	None.	"	40.0 in 8 days. Jaundice later.	Recovered (!).
"	"	49	16th	"	"	"	40.0 in 7 days. Slight jaundice later.	"
Case 21. Yellow fever. Died on 4th day.	"	54	4th	3*	39.4 in 5 days.	"	None.	Remained well.
"	"	55	4th	3	39.8 " 5 "	"	"	"

*Another guinea pig (No. 56) received the same amount at the same time and died in 7 days with suspicious lesions. From it transfers were made into two guinea pigs. Both showed mild fever in 5 days and recovered. The two also resisted the subsequent inoculations of virulent Arias strain.

TABLE I—*Concluded.*

Patient.	Sex.	No. of guinea pig.	Day of disease when bled.	Amount of blood injected.	Reaction.	Subsequent test for susceptibility.	Reaction.	Result.
Case 22. Yellow fever. Died in 10 days.	M.	198	5th(?)	3	40.0 in 4 days. Trace of icterus (?).	Virulent Arias strain after 25 days.	None.	Remained well.
		199	5th	3	40.0 in 7 days. Trace of icterus (?).	" "	"	"
Case 19. Yellow fever. Severe. Recovery.	"	200	4th(?)	3	39.6 in 4 days.	" "	"	"
		201	4th	3	40.0 " 5 " Trace of icterus.	" "	"	"
Case 20. Yellow fever. Severe. Recovery.	"	220	4th(?)	3	40.3 in 7 days. Trace of icterus (?).	" "	"	"
		221	4th	3	40.2 in 5 days. Trace of icterus (?).	" "	"	"
Case 16. Yellow fever. Severe. Recovery.	"	222	3rd(?)	3	40.1 in 7 days. Trace of icterus (?).	" "	"	"
		223	3rd	3	40.3 in 6 days. Trace of icterus (?).	" "	"	"

Case 28. Yellow fever. Died.	M.	329	(?) Brought in unconscious. Died same day.	5	None.	Virulent Arias strain after 25 days.	40.0 in 5 days. Icterus.	Died in 7 days. Typical.
Case 10. Yellow fever. Died in 7 days.	F.	338 339	2nd 2nd	4 4	" "	" "	40.1 in 6 days. Icterus. 39.5 in 7 days. Icterus.	Killed in 8 days. Typical. Killed in 10 days. Typical.
Case 24. Yellow fever. Died.	M.	340	(?) Died next day.	4	39.2 in 5 days. No icterus. Died in 8 days; hemorrhages. 40.0 in 13 days.	"		
Case 8. Yellow fever. Severe. Recovery.	"	341 342 343	" 2nd 2nd	4 4 4	No icterus. 40.0 in 12 days. No icterus. 39.6 in 6 days. Trace of icterus.	" " "	40.0 in 6 days. Icterus. 40.2 in 7 days. Icterus. None.	Died in 9 days. Typical. Died in 10 days. Typical. Remained well.
Case 18. Yellow fever. Died in 7 days.	"	407	4th	3	39.8 in 5 days. Trace of icterus.	" "	"	" "

Apparently some of the guinea pigs previously inoculated with the blood from yellow fever cases were refractory to the subsequent inoculation with a known virulent organ emulsion. As shown in Table I, those which resisted the infection were found to have had a febrile reaction of varying degree and duration on about the 5th day after the injection of the blood. This seemingly unimportant fever reaction must have been the result of a very mild abortive infection totally unsuspected on account of the absence of the main symptom, the jaundice. This fact is proved, in my opinion, by the acquired resistance of an animal which, when a sufficient quantity of a passage strain of *Leptospira icteroides* is introduced, is so susceptible. There is reason to believe that the strains of *Leptospira icteroides* as they occur in man are on the whole less virulent to the guinea pig and are incapable of producing a fatal infection from the beginning except in rare instances. It may be recalled here that with one strain (Case 2) the organism did not become thoroughly adapted to the guinea pig until it had been passed through three generations in this animal.¹

A complete, or nearly complete refractoriness or resistance to *Leptospira icteroides* was demonstrated in sixteen guinea pigs previously inoculated with the blood of yellow fever patients, representing nine out of fourteen cases of yellow fever. Four out of six guinea pigs injected with the blood of two other yellow fever patients died, and two survived. In this group the protection was present in some of the guinea pigs only. In a doubtful case one of the two guinea pigs resisted a subsequent infection. On the other hand, of six guinea pigs, which received the blood of three patients, all died with the typical symptoms and lesions when tested later with a virulent passage strain of *Leptospira icteroides*. Of ten, which received injections of blood from four malarial patients, all proved to be susceptible to a later inoculation with the same strain of *Leptospira icteroides* that was used in the foregoing experiments.

Of the guinea pigs representing the yellow fever group, those which had had a febrile reaction several days after the injection of the blood are the ones which acquired the immunity against the inoculation of *Leptospira icteroides*. There seems to exist some relation between the febrile reaction and the acquired immunity. In several instances, moreover, these guinea pigs showed a suspicious trace of

jaundice in the scleras some time after the height of fever had passed, but the disease had failed to advance further. If the animals had been killed at the proper time and transfers made to normal guinea pigs the virulence of the causative organism might have been gradually increased to reproduce the disease more completely in later passages. As a matter of fact it was possible to accomplish this in one instance (Case 2).

The injection of blood from some cases of typical yellow fever into guinea pigs caused a rise of temperature in about 5 days similar to that of other cases, and there was even a suspicion of a trace of icterus in the scleras, yet no protection against a later infection with a passage strain of *Leptospira icteroides* (Case 1) could be demonstrated. Perhaps this lack of protection may be explained by assuming the strain variations among different strains of the leptospira.

Another point of interest brought out in this series is that the injection of organ emulsions obtained from fresh postmortem material (Case 27) conferred upon guinea pigs sufficient protection against a subsequent infection to prevent its being fatal, although these animals showed fever and jaundice. It is possible that the emulsion contained a certain amount of the antigen and produced a mild immunity, or a limited amount of the immune bodies.

SUMMARY.

The majority of guinea pigs inoculated with the blood of yellow fever patients escaped a fatal infection.

There were a number of instances in which the inoculation of yellow fever blood induced in these animals a temporary febrile reaction on the 4th or 5th day, followed in some cases by slight jaundice, but with a rapid return to normal. Most of these guinea pigs when later inoculated with an organ emulsion of a passage strain of *Leptospira icteroides* resisted the infection. On the other hand, the animals which had previously been inoculated with the blood of malaria patients or normal guinea pigs died of the typical experimental infection after being inoculated with the infectious organ emulsion.

It appears from the results just described that a number of non-fatal, mild, or abortive infections follow the inoculation of blood of yellow fever patients into guinea pigs. The fact that such animals manifested refractoriness to a subsequent attempt to infect with a highly virulent passage strain of *Leptospira icteroides* is an indication, judging from the reciprocal immunity reaction, that they actually passed through an infection with the same organism, or a strain closely related to it, as that which was used for the second infection experiment