

野口英世著 Journal of Experimental Medicine 所収論文

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ETIOLOGY OF YELLOW FEVER.

XIII. BEHAVIOR OF THE HEART IN THE EXPERIMENTAL INFECTION OF GUINEA PIGS AND MONKEYS WITH *LEPTOSPIRA ICTEROIDES* AND *LEPTOSPIRA ICTEROHÆMORRHAGIÆ*.

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PLATES 85 AND 86.

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It is well known that in patients suffering from yellow fever the rate of the heart has a tendency to be slow. This phenomenon was regarded by Faget,¹ who was among the first to call attention to it, and by Touatre² as pathognomonic in this disease, especially in its early stage. In the second stage, the rate falls still further. It may be as low as 30 or 40 per minute, and may continue slow during convalescence. In fatal cases in the final stage it may be either rapid or slow. In the curves of patients published by Noguchi³ and by Elliott,⁴ these relations are seen. Sarti⁵ gives, however, high rates for ten of the eleven cases he reports. It is said that death is seldom due to heart failure. At autopsy, lesions of the heart are not constantly found, except perhaps the degenerative changes and frequent

¹ Faget, J. C., *Monographie sur le type et la spécificité de la fièvre jaune établie avec l'aide de la montre et du thermomètre*, Paris, 1875.

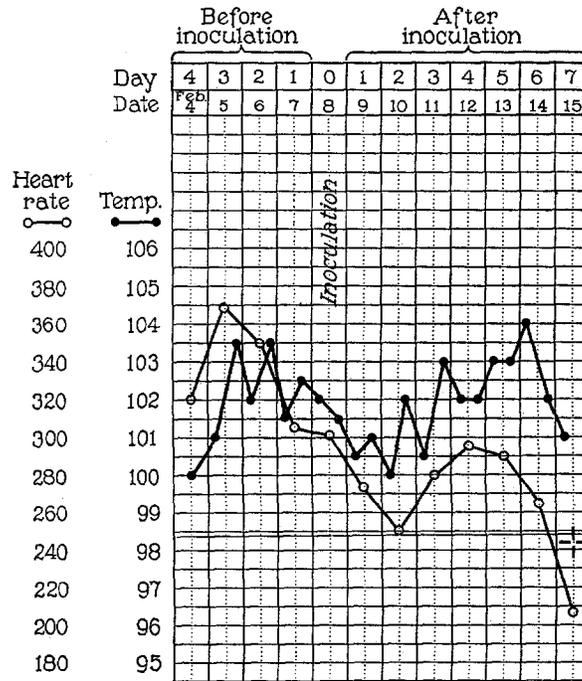
² Touatre, J., *Yellow fever; clinical notes*, translated by Chassaingnac, C., New Orleans, 1898.

³ Noguchi, H., *Etiology of yellow fever. I. Symptomatology and pathological findings of the yellow fever prevalent in Guayaquil*, *J. Exp. Med.*, 1919, **xxix**, 547.

⁴ Elliott, C. A., *A clinical study of yellow fever. Observations made in Guayaquil, Ecuador, in 1918*, *Arch. Int. Med.*, 1920, **xxv**, 174.

⁵ Sarti, J., *Contribucion al estudio de la fiebre amarilla*, Tesis, Guatemala, 1919.

endocardiac or pericardiac ecchymoses associated with fever. Recent studies on infectious jaundice⁶ indicate, however, that in that disease also the pulse rate is usually slow in proportion to the temperature; one case is reported in which the pulse fell as low as 38. This holds true even in cases without jaundice.



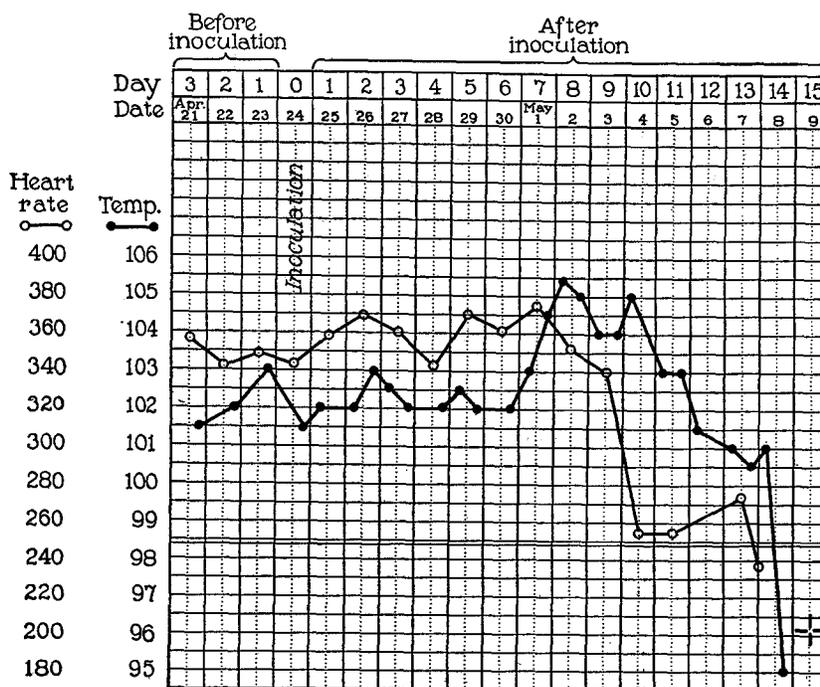
TEXT-FIG. 1. Temperature and heart rate curves of Guinea Pig 3, inoculated with *Leptospira icteroides*.

Since the successful transmission of yellow fever to animals, observations have been made of the rate and of the behavior of the heart in animals experimentally infected with *Leptospira icteroides* from yellow fever cases. Records were taken electrocardiographically.

⁶Stokes, A., Ryle, J. A., and Tytler, W. H., Weil's disease (spirochætosis ictero-hæmorrhagica) in the British Army in Flanders, *Lancet*, 1917, i, 142. Ryle, J. A., Spirochætosis icterohæmorrhagica (formerly known as Weil's disease). A clinical analysis of fifty-five cases, *Quart. J. Med.*, 1921, xiv, 139.

By this method the rate can be accurately counted and the mechanism of slowing, if it occurs, can be analyzed. For comparison with the animals inoculated with *Leptospira icteroides* (yellow fever) a certain number of others infected with *Leptospira icterohæmorrhagiae* (infectious jaundice) were included in the study.

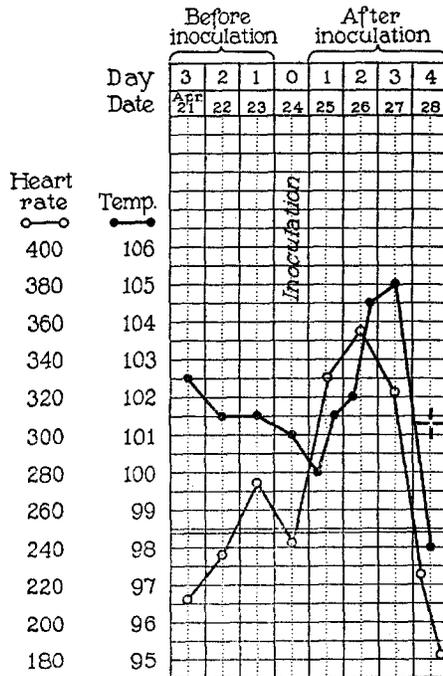
Electrocardiograms were taken either for 1, 3, or 4 days before the day of inoculation. Exception to this procedure occurred in Guinea



TEXT-FIG. 2. Temperature and heart rate curves of Guinea Pig 12, inoculated with *Leptospira icterohæmorrhagiae*.

Figs 4 and 6 and Monkey 3. The cardiac rate before inoculation of the guinea pigs was below 300 per minute three times in Guinea Pig 1, twice in Guinea Pig 2, and once in Guinea Pig 10. In the other nine guinea pigs it was always above 300, the range being from 302 to 371. In the monkeys the rate was above 400, except once in Monkey 2, and once in Monkey 5. The rate otherwise was above 400, the range being from 401 to 442.

In eleven animals there occurred a fairly consistent fall in rate either immediately after inoculation (Guinea Pigs 3, 7, and 9 and Monkey 2) (Text-fig. 1) or after a delay (Guinea Pigs 2, 4, 5, 8, and 12 and Monkeys 3 and 4) (Text-fig. 2). In several instances (Guinea Pigs 2, 4, 7, and 9) a rise occurred in the course of the disease. In each instance, however, there was a striking fall on the day of death, or during the days immediately preceding death. Guinea Pig 2



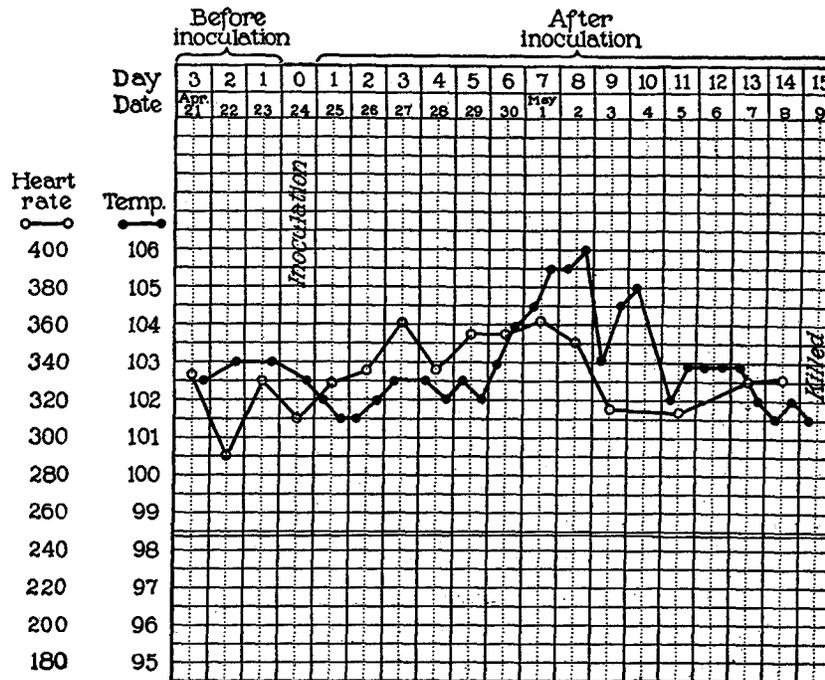
TEXT-FIG. 3. Temperature and heart rate curves of Guinea Pig 1, inoculated with *Leptospira icteroides* but with negative results.

appears to be an exception, but this is one of the animals in which low initial rates were recorded. The animals inoculated with *Leptospira icteroides* reacted, then, with a fall in rate. Those inoculated with *Leptospira icterohæmorrhagiæ* behaved in a similar manner (Table I).

In Guinea Pigs 1 (Text-fig. 3) and 6 the rates before inoculation were low, rose abruptly to high levels after inoculation, and then

fell. Guinea Pig 1 was inoculated with *Leptospira icteroides*, but died of a complicating peritonitis. Guinea Pig 6 ran an atypical course and died perhaps of a secondary infection.

This account leaves for consideration four animals, Monkeys 1 and 5 and Guinea Pigs 10 (Text-fig. 4) and 11. The monkeys did not develop disease of a nature that could be regarded as characteristic and are therefore offered as controls. They showed no striking



TEXT-FIG. 4. Temperature and heart rate curves of Guinea Pig 10, inoculated with *Leptospira icterohæmorrhagiæ* but with negative results.

change in rate. Like observations are afforded by Guinea Pigs 10 and 11. They were killed after 14 days. The course of the disease in them was mild and the lesions were atypical. They are, therefore, also to be regarded as controls.

Mechanism of the Heart Beat.—During the control period preceding inoculation in the *icterohæmorrhagiæ* group, a single animal, Guinea Pig 12, showed an irregularity of the cardiac mechanism on one

TABLE I—*Concluded.*

Animal No.	Rate.																				Fall in rate.	Irregularity.	Result.				
	Days before inoculation.				Day of inoculation.	Days after inoculation.																					
	4	3	2	1		Average.	1	2	3	4	5	6	7	8	9	10	11	12	13	14				15			
G. P. 10	333	289	332	318	309	327	334	363	335	357	355	362	352	313	314	330	331								+13	-	Killed in 14 days. Probably negative or very mild: <i>L. icterohæmorrhagie</i> (French). Fever 7th to 10th days; no jaundice; no hemorrhage; no lesions (Text-fig. 4). Killed in 14 days. Mild: <i>L. icterohæmorrhagie</i> (French). Fever 7th to 14th days; intercurrent infection; no jaundice; no hemorrhage; no lesions. Died in 14 days. Atypical: <i>L. icterohæmorrhagie</i> (French). Fever 7th to 10th days; incubation 6½ days (Text-fig. 2). Died in 4 days. Negative: <i>L. icterohæmorrhagie</i> (French). Doubtful; irregular fever; slight hemorrhage in lungs; no jaundice.
" " 11	360	340	360	353	361	360	376	363	350	371	367	362	342	306	320	327	328								-25	-	
" " 12	358	343	347	349	345	360	370	363	344	370	363	374	356	340	254	276	238	D.							-111	+	
M. 5	436	436	372	415	432	415	431	392	370	D.															-45	-	

occasion. During the 14 days following, with two exceptions, curves were taken daily. A recurrence of the arrhythmia was not seen. During the course of the disease nothing remarkable in the behavior of the heart was recorded, although curves of the animals in this group which died were taken on the day of death (Guinea Pig 12 and Monkey 5) and on the day preceding (Monkey 4).

Of the yellow fever group, no irregularity was seen in any animal in the period preceding inoculation. A single guinea pig, No. 7, on the 2nd day afterward, showed an arrhythmia (premature ventricular contractions). It died 5 days later but the irregularity did not recur. In four other animals, irregularities took place (Guinea Pigs 3 and 4 and Monkeys 2 and 3), but in two of them (Guinea Pigs 3 and 4) they occurred on the day of death, indeed during the terminal period. At this period Guinea Pig 3 showed heart block (Fig. 1). Monkey 2 (Fig. 2) began to show changes in the electrocardiogram on the day before death. The alterations are not different from those which have been described in connection with the death of the heart in other diseases. There was slowing of the auricles and the whole heart, and increase in the length of the auriculoventricular interval in Guinea Pig 3 and Monkey 2 (Fig. 2) and lengthened conduction time leading to block in Guinea Pig 3. In only two of the animals, Monkeys 2 and 3 (Fig. 3), did changes occur before the day of death. In both the change was detectable 2 days before death. Both showed slowing of the rate and alteration in the form of the ventricular complex in the electrocardiogram. An S wave not previously present appeared, and the T wave increased in size (Fig. 2).

It may be said, then, that the mechanism of slowing in all cases until the day of death was of a simple variety—a slowing of the whole heart, depending on the sinus, the pacemaker of the heart. On the day of death, although increased length of the auriculoventricular interval occurred, it led to heart block only once. Changes in the form of the electrocardiogram were seen twice (Monkeys 2 and 3, Fig. 3) in the course of the disease 2 days before death. In curves that were obtained during death of the heart changes were seen which resemble those usually found at this time.

CONCLUSIONS.

1. Slowing of the heart occurred in monkeys and guinea pigs during the febrile period of the experimental infection due to *Leptospira icteroides*. A similar reaction took place in animals inoculated with *Leptospira icterohæmorrhagiæ*.

2. The mechanism of slowing was usually due to slowing of the whole heart.

3. Once incomplete heart block was seen. Changes in the ventricular complex occurred four times.

EXPLANATION OF PLATES.

In the curves divisions of the abscissæ equal 0.04 second, divisions of the ordinates 0.1 millivolt. The electrodes were placed on the right fore and the left hind legs.

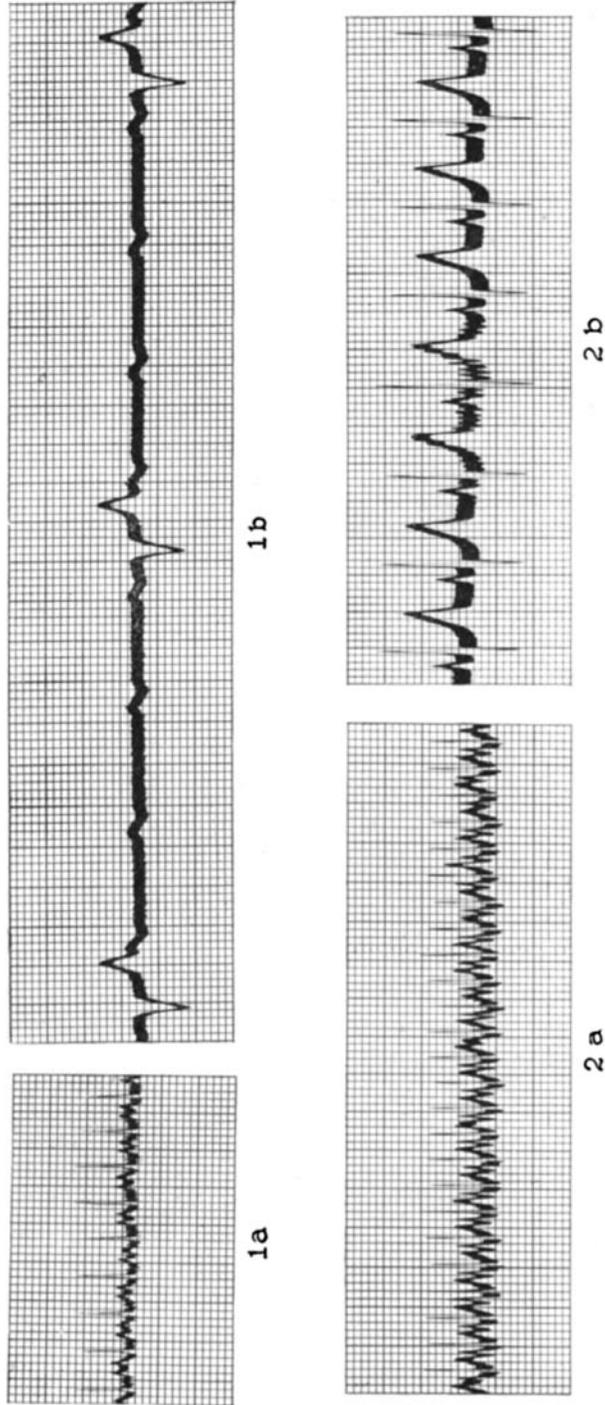
PLATE 85.

FIG. 1, *a* and *b*. Guinea Pig 3. (*a*) February 4, 1919. Control curve. (*b*) February 15. Auriculoventricular dissociation and a marked change in the ventricular complex are seen.

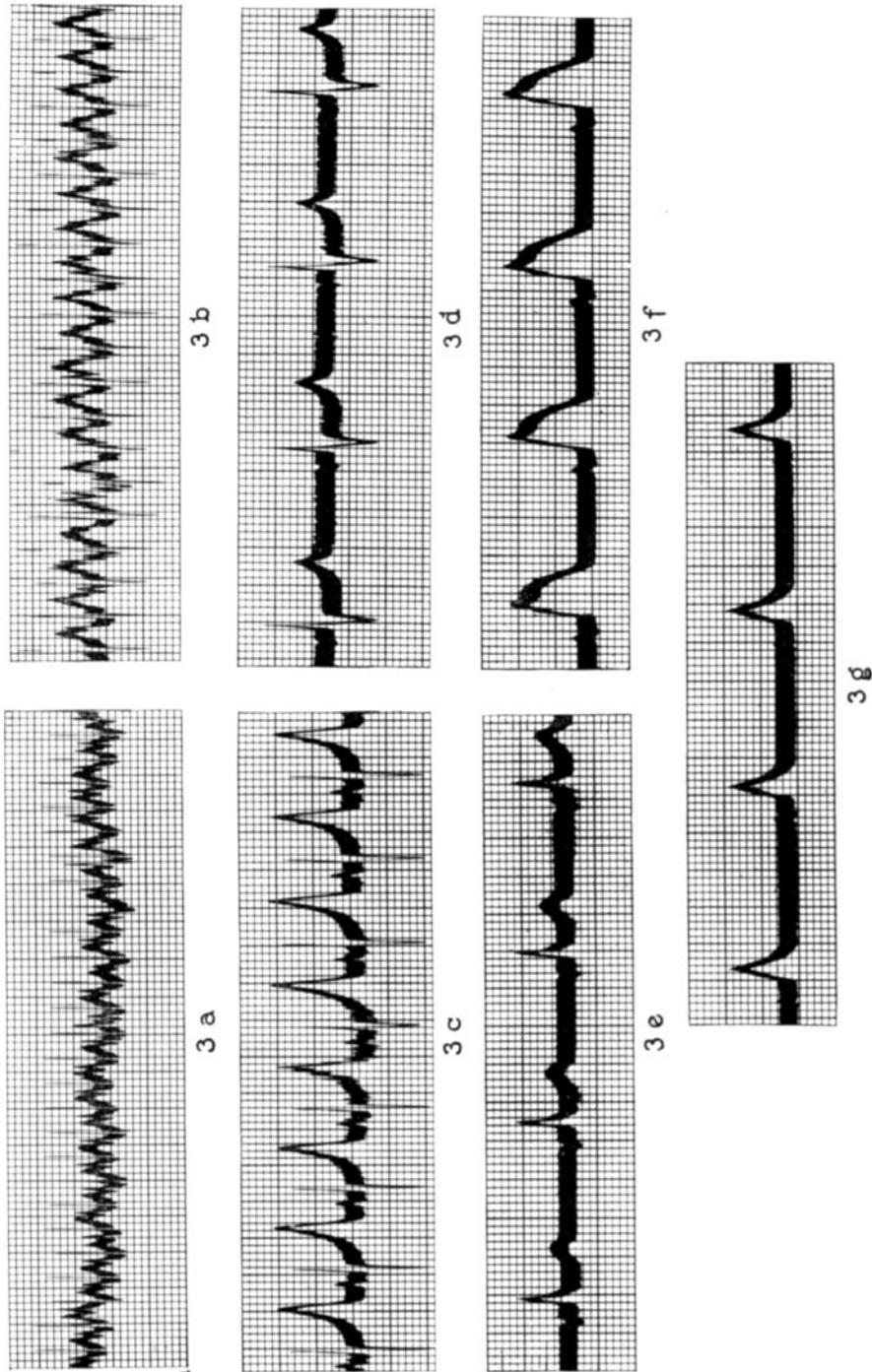
FIG. 2, *a* and *b*. Monkey 2. (*a*) April 21, 1919. Control curve. (*b*) April 30. Slowing, increase in height of R, S, and T waves, and increased auriculoventricular interval are seen.

PLATE 86.

FIG. 3, *a* to *g*. Monkey 3. (*a*) April 7, 1919. Control curve. (*b*) April 13. Day before death. S wave is increased. (*c*) April 14. Day of death. The R, S, and T waves are increased. The auriculoventricular interval is lengthened. (*d*, *e*, *f*, *g*) show increasing alteration in both auricular and ventricular parts of the curve. The ventricular alterations resemble those seen in dying hearts.



(Cohn and Noguchi: Etiology of yellow fever. XIII.)



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