THE MYOCARDIUM IN YELLOW FEVER

I. The Myocardial Function in Experimental Yellow Fever

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I. The Myocardial Function in Experimental Yellow Fever*

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INTRODUCTION

AMONG the changes in myocardial function occurring during the course of yellow fever, bradycardia has been noted most frequently by clinical observers. Although Delmas[14] in his treatise on yellow fever published in 1822 described this phenomenon, it remained for Charles Faget[20] to study accurately and to chart its behavior. He promulgated the law of a slowing heartbeat with a rising temperature in the early days of yellow fever, so that this seeming paradox became known as Faget's sign. It was confirmed by his confrere Touatre[62] and by later observers.[56, 12, 57, 5, 30, 21, 44, 43] Retardation of the heart rate in yellow fever has also been recorded with considerable constancy by most recent workers in this field. It has been described by Noguchi[48] and by Elliott[19] as existing in cases of the disease met with in Guayaquil, Ecuador, in 1918. Selwyn-Clarke[58] and Aitken,[1, 2, 3] as well as Mahaffy, Walcott, and Klotz,[28] observed the sign during the course of the disease in British West Africa in the years 1925 and 1926. The existence of this finding in the yellow fever of Senegal has been reported by Lasnet,[29] a French contemporary of these observers.

Investigation of the type and causation of the bradycardia occurring in yellow fever has been the basis of the experiments of several workers. In 1921 Cohn and Noguchi[10] first attempted to record and differentiate the type of bradycardia in experimental animals with the aid of electrocardiography. Unfortunately their results upon monkeys and guinea pigs inoculated with *Leptospira icteroides* and *Leptospira icterohaemorrhagiae*, in the light of our present knowledge, must be related to the functional pathology of Weil's disease rather than to that of yellow fever. Cannell,[6] in 1928, pointed out that bradycardia occurred in this disease independently of jaundice. The same author noted fatty degeneration in the auriculo-ventricular bundle and suggested that the occurrence of auriculo-ventricular dissociation might offer a possible explanation of the slow pulse rate in the disease. During the epidemic of yellow fever in Rio de Janeiro in 1928, Chagas[8] described a clinical picture occurring in from 10 to 15 per cent of his

*These studies have been performed under the tenure of a grant from the Banting Research Foundation. Their accomplishment has been possible because of the facilities made available in the Yellow Fever Laboratory of the International Health Division of the Rockefeller Foundation, at the Rockefeller Institute for Medical Research, and in the Physiological Laboratory of the Hospital of the Rockefeller Institute. The author is greatly indebted to the courtesy shown him by the directors of these laboratories, Dr. W. A. Sawyer and Dr. A. E. Cohn. During the absence of Dr. Cohn, Dr. H. J. Stewart kindly provided necessary facilities for the work.

From the Department of Pathology and Bacteriology of the University of Toronto.

patients, more frequently among those who recovered, which he termed a suprarenal syndrome of the disease. The symptoms which this observer ascribed to an adrenal origin were profound debility, peripheral vasodilatation with redness of the face, dermographism, frequent capillary hemorrhages, arterial hypotension, bradycardia, and less often dissociation of cardiac rhythm. The following year Chagas and de Freitas,[9] in electrocardiographic studies of human cases, reported the occurrence of bradycardia and rarely of auriculo-ventricular dissociation. This latter phenomenon was assumed to be due to the influence of the vagosympathetic system.

TECHNICAL METHODS

Graphic Methods of Investigation.—A series of twenty animals was employed, of which seventeen belonged to the species *Macacus rhesus* and three to the species *Macacus cynomolgus*. Electrocardiographic tracings were taken of the cardiac action in these animals before inoculation with yellow fever virus. After a period varying from one hour to forty-eight hours after the registration of the normal electrocardiograms for each monkey, the animal was inoculated intraperitoneally or subcutaneously with 0.5 c.c. of fresh infectious monkey blood (Asibi virus) withdrawn by cardiac puncture from an infected animal on the first day of fever. Upon frequent occasions, when virus in this form was not available, a quantity of desiccated blood, the preserved form of the Asibi virus,[55] equivalent to 0.5 c.c. of whole blood, was dissolved in Locke's solution and used for the inoculation. Electrocardiograms were obtained whenever possible upon these animals during the period of incubation, and upon successive days of the disease. Frequently during the latter days of the illness tracings were taken twice daily.

The monkeys were anesthetized in each instance five minutes before being electrocardiographed. In securing electrocardiograms upon the first four animals, sodium iso-amyl-ethyl barbiturate, administered in solution intraperitoneally, was used as an anesthetic. Since in these earlier experiments it was observed that, with the daily employment of this anesthetic, the experimental animals died at the end of a period of time twenty-four to forty-eight hours shorter than the average duration of illness in the monkey inoculated with Asibi virus, and before the development of well-marked yellow fever lesions in the viscera, it was abandoned to be replaced by ether. The dosage of the former drug used to produce anesthesia in an animal amounted to 0.05 gram per kilogram of body weight. All electrocardiograms were taken with the animals in a supine position with four points of the skeleton, the two scapular spines and the two ischial tuberosities, in the same horizontal plane.

The electrocardiograms were recorded from the three standard leads. In this place it may be noted that Lewis[35]: found no conspicuous differences between the levo- and dextrocardiograms in man and monkey. One animal, a *Macacus cynomolgus* which developed peritonitis during the course of the experiments, was subjected to electrocardiography on successive days of the disease preceding death. The electrocardiograms on this monkey, which did not receive yellow fever virus, are offered as controls. In all, 256 tracings were obtained upon this series. Of 19 animals inoculated with the virus, 17 died of yellow fever, while 2 recovered from the disease. Following the completion of each physiological experiment and the death of the animal, a post-mortem examination was made. The heart was removed, and its cavities were opened in such a manner as to preserve intact the sino-auricular node and the auriculo-ventricular bundle. The whole cardiac tissue was then fixed in Zenker's fluid. Sections were also taken of the liver, kidney, and spleen in each case for the purpose of verifying microscopically the existence of yellow fever lesions in these organs.

Surgical Methods of Investigation.—The hypothesis of vagus nerve stimulation as the cause of bradycardia, suggested by some writers,[9] obviously necessitated investigation. Two monkeys were obtained at death, and dissections were made of the cervical and thoracic portions of the vagus nerve in order to obtain a familiarity with its course and distribution in *Macacus rhesus*. Ten animals were then selected for the elucidation of the problem. Six of these monkeys had been infected with yellow fever virus and formed a group of a larger series in which the development of slow heart action had been noted. Electrocardiograms designed to record the existing bradycardia were taken on these animals before submitting them to the operation of bilateral vagus section. In one experiment electrocardiograms were recorded after the vagi had been isolated and were about to be cut. In all experiments vagus section was performed immediately after the preliminary recording of the electrical changes accompanying the heartbeat. Electrocardiograms were taken again directly after the vagus section operation, and frequently additional ones were obtained from ten to fifteen minutes later. The remaining four animals of the group of ten monkeys relegated to the study of the problem of vagus effects were monkeys in apparent health upon whom vagus section was performed for purposes of control. In this series as well, tracings were taken immediately antecedent and subsequent to vagus section. Both the surgical and electrocardiographic procedures were carried out under ether anesthesia. After the completion of each vagotomy experiment the animal was killed by the continued administration of ether.

The operation of vagus section was performed first on the right vagus nerve and then on the left. Section of the nerve was carried out at the point where the superior belly of the omohyoid muscle crossed the common carotid artery. In man, most of the rami cardiaci superiores arise from the vagus trunk below this level, while all the rami cardiaci inferiores arise either from the right vagus and recurrent laryngeal nerves or the left recurrent laryngeal nerve below this point.

However, this method of bilateral vagus section would not insure the cutting of those few fibers which may sometimes arise from the superior laryngeal nerve. I am unable to say whether such fibers exist in *Macacus rhesus*. The method of abrogating vagus function by section of the two main trunks was chosen in preference to the more usual one of atropinization, because it would seem to offer more certain and less controvertible results.

Following the completion of these physiological experiments, autopsies were performed upon the animals. The hearts were carefully excised from the bodies, so as to include the muscle at the junction of the superior vena cava with the right auricle. After removal of each heart, its cavities were opened, and the entire cardiac tissue was fixed in Zenker's fluid.

RESULTS

1. *Physiological observations upon the sino-atrial node and vagus nerve.*

The observations upon the cardiac rate demonstrated that bradycardia is a constant finding in experimental yellow fever in the monkey. It was absent in only one instance, that of *M. rhesus* 15, in which cardiac puncture and the attendant deprivation of blood had been instrumental in producing the early death of the animal. In *M. rhesus* 8, there existed normally a very slow heart rate. The rate increased markedly on the third day of the incubation period, after which it became retarded and continued so during the further course of the disease. The bradycardia was found to be for the most part a progressive one, the heart rate diminishing from day to day of the disease and even from morning to afternoon of the same day. Occasionally the

TABLE I

HEART RATE OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS

MONKEY NUMBER	NORMAL RATE	DAYS OF INCUBATION			FIRST DAY FEVER		SECOND DAY DISEASE		THIRD DAY DISEASE		FOURTH DAY DISEASE		FIFTH DAY DISEASE		RECOVERY PERIOD
		1	2	3	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	
1	189					177	205	136	D		150	D			
2	208								212						
3	188								D						
4	250				216	216	160	118	204	D					
5	202			167	177		189	D							
6	217				270		182								
7	200						233								
8	160			223	186		215						180	D	211
9		213					170								
10	210						193								
11	223						218								
12	205								162	D	D				
13	191								197	147	152				191
14	213						173		160		80	D			
15	221					230*	D		168						
16	232								D	144	D				
17	226								174	D					
18	228	226					204		34†	D					
19									150	D					
20	171					228	222	186	162	D					
Control									D						

*Bled from heart, animal died.
†Animal died during inscription of Lead III.
D—Animal dead.

rate was rapid during the early days of the fever, but it was never accelerated in the end stages. When recovery took place, the heart rate regained its normal frequency. Bradycardia was absent in the severe infection of the peritoneum which killed the previously mentioned *M. cynomolgus* after a period equal to the average length of illness of monkeys dying as a result of infection with the Asibi virus.

It was characteristic of the course of experimental yellow fever in this series of animals that the heartbeat remained regular in its occurrence. Only twice was disturbance of rhythm met with during the course of the disease. An irregular cardiac function was observed in the dying heart of *M. rhesus* 17, in which animal the heart stopped beating during registration from the third electrocardiographic lead. In *M. rhesus* 12, on the morning of the fourth and last day of the disease, when the heart rate had become slowed from the normal of 205 beats per minute to 80 beats per minute, the rhythm became a little

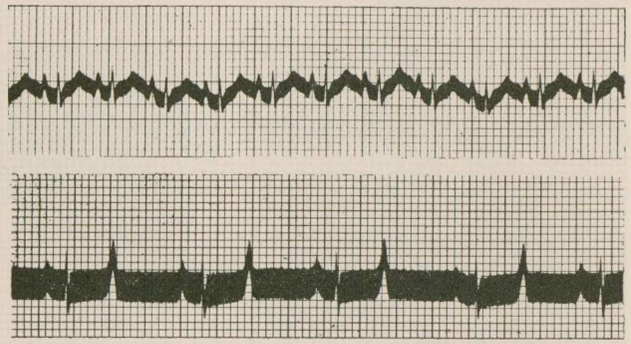


Fig. 1.—Bradycardia of yellow fever. Upper tracing shows the heart rate and the duration of the P-R period in *M. rhesus* 12 before inoculation with the virus. Lower tracing represents the degree of bradycardia and the lengthened P-R interval in the same animal on the morning of the fourth day of the disease (Lead II).

irregular. So slight was this change that it could not have been detected except by graphic methods of registration; the variations in the intersystolic periods were never greater than 0.08 of a second. The difference in length between intersystolic periods in the rhythm of this heart ranged from 0.04 to 0.08 of a second. Table I which presents the variations in cardiac rate from day to day of the disease, as measured by electrocardiography, and Fig. 2 which presents the same data in graphic form, give a better conception of these changes than could be obtained from further description. Recourse may also be taken to the serial cardiographic tracings (Figs. 7 and 8) which depict among other occurrences the lengthening of the intersystolic period in some of these animals during the later course of the disease. The slowed heart rate, as compared with the normal, is also well shown in Fig. 1.

The effect upon the existing bradycardia of cutting the vagi is of peculiar interest. The results of the experiments in which this opera-

tion was performed demonstrate that the bradycardia occurring in rhesus monkeys during the course of their illness from yellow fever persists after bilateral section of the vagus nerves. In only one animal was vagus section followed by a heart rate more rapid than that existing before the operation; in this case a bradycardia of 80 beats per minute was replaced by one in which 104 cycles were recorded

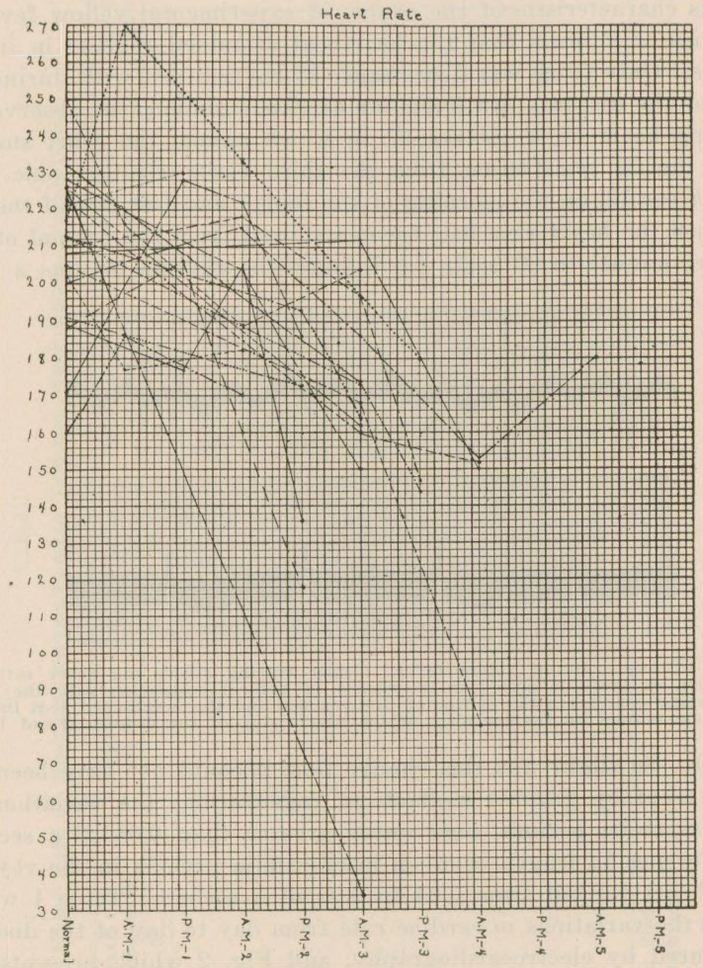


Fig. 2.—The heart rates of the various animals studied in the series of physiological experiments have been represented graphically from day to day of the disease. The abscissae represent the time of the disease measured at twelve-hour intervals; the ordinates represent the rates of heartbeat. The curve for each animal is drawn in a different type of solid or broken line. The progressive nature in the development of the bradycardia is well shown in the downward trend of most lines toward the later days of the disease.

during the same period. It should be borne in mind, however, that the later recorded rate of 104 was still half the original cardiac frequency and represented a most marked bradycardia. In one instance in this series the heart rate remained the same before and after vagus sec-

tion, while in the other four instances it was even less following the operation than previously. The explanation of this latter effect is problematical, but may possibly be related to a slower filling of the heart chambers associated with the very much slower respiratory rhythm. A slight lengthening of the conduction time, as represented by the P-R interval of the electrocardiogram, was noted in five of the ten experiments. This increase in the P-R period was never greater than 0.02 of a second. Its occurrence recalls the effect of vagal section or of atropinization in increasing the A-V block which follows rapid auricular action.[38] With regard to this consideration it may also be noted that in the dog's auricle in many circumstances in which the transmission intervals are long, vagal stimulation shortens these and, where actual block exists, partially or wholly relieves the condition.[37, 39, 36, 15, 16] In the remaining five experiments the conduction time was in one instance shortened, and in three instances unchanged, following the cutting of the vagi. The evidence of the control experi-

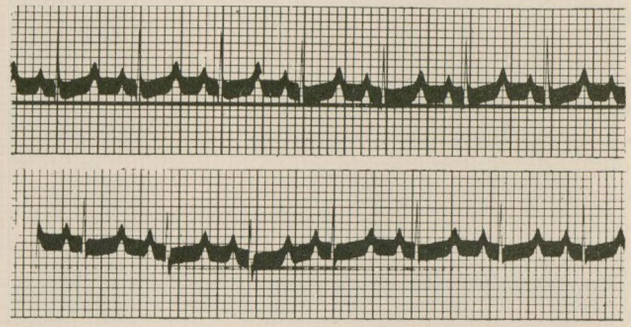


Fig. 3.—Independence of the bradycardia of yellow fever of vagus nerve influence. Upper tracing represents the heart rate in *M. rhesus* 2 before bilateral vagus section. Lower tracing shows the heart rate in the same animal following vagotomy.

ments suggests that even in normal monkeys the vagus nerve exerts little effect upon the heart rate during ether anesthesia. The latter suggestion is in keeping with the finding of Gold, Gryzwacz, and Nowicki[22] that ether by inhalation, in doses that do not paralyze respiration, depresses but does not completely paralyze the vagi. In these control animals the heart rate was in two instances unaltered, on one occasion slightly raised, and upon another slightly lowered, following bilateral vagus section. Vagus influence upon the heart rate is known to be very fluctuating.[46] It is very well marked in the dog and to a lesser degree in man.[17] Vagus tone varies from species to species,[59] from animal to animal within the same species, and from time to time within the same animal. As Wenckebach and Winterberg[63] have pointed out, the bradycardia of sino-atrial origin is different from that responsible to vagus influence in that the former is a regular one, while the latter is irregular in its rhythm. It may be noted that the slow heart rate of yellow fever persists during anesthesia induced by

sodium iso-amyl-ethyl barbiturate given intraperitoneally in a dosage of 0.05 gram per kilogram of body weight. This result was consistent in the four animals of this series on which the drug was used. The amount given to one animal frequently equalled 100 to 150 milligrams, depending upon its weight. Lieb and Mulinos[42] have shown that when 20 milligrams of sodium iso-amyl-ethyl barbiturate are

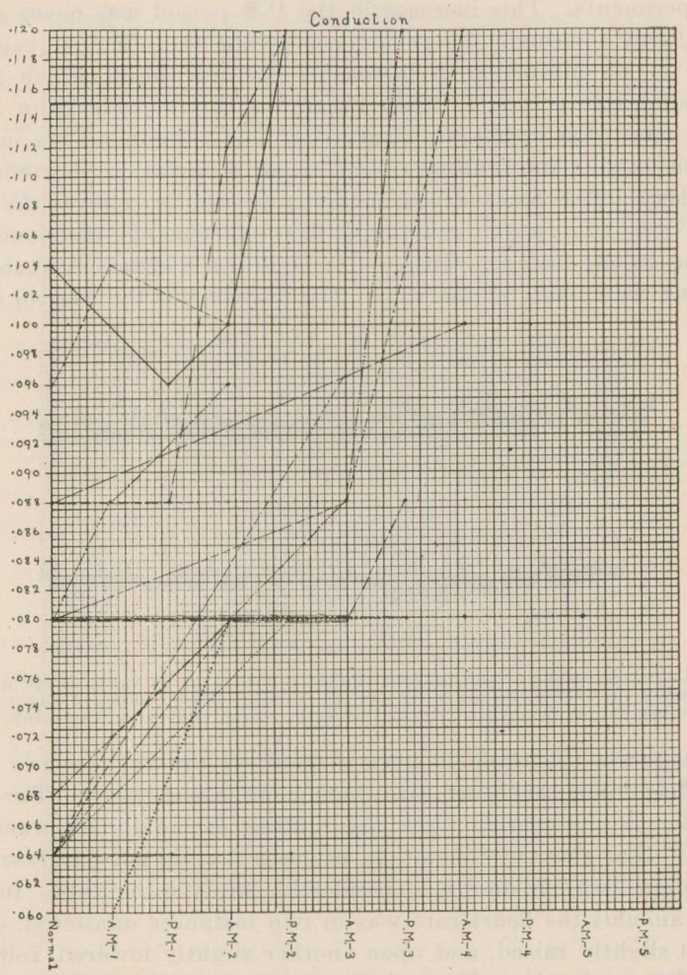


Fig. 4.—The conduction times, as measured by the P-R intervals of the electrocardiograms, of the various animals studied in the series of physiological experiments have been represented graphically from day to day of the disease. The abscissae indicate the time of the disease process measured at twelve-hour intervals; the ordinates represent the time values of the P-R intervals measured in decimals (thousandths) of a second. The curve for each animal is drawn in a different type of solid or broken line. A progressive but not a constant trend toward lengthening of the conduction time during the progress of the disease is well shown.

given intravenously to a cat, prolonged, but temporary, paralysis of the vagus fibers to the heart results. These considerations are cited because it is believed that the evidence points to the concept that the

Table II

Effect Vagus Section on Bradycardia of Monkeys Experimentally Infected With Yellow Fever Virus

Monkey Number	Before Vagus Section		After Vagus Section	
	Heart Rate*	Conduction† Time	Heart Rate	Conduction Time
6	180	0.08	156	0.088
2	150	0.10	150	0.104
16	174	0.08	158	0.10
7	180	0.08	172	0.08
9	135	0.08 0.096‡	120	0.08
12	80	0.12	104	0.14
21 C	222	0.08	225	0.08
22 C	246	0.056	234	0.06
23 C	202	0.12	235	0.10
24 C	252	0.08	252	0.08

*Heart rate recorded in beats per minute.
†Conduction time as indicated by P-R interval of the electrocardiogram, recorded in decimals of a second.
‡Traction on vagi.
C—Control experiment.

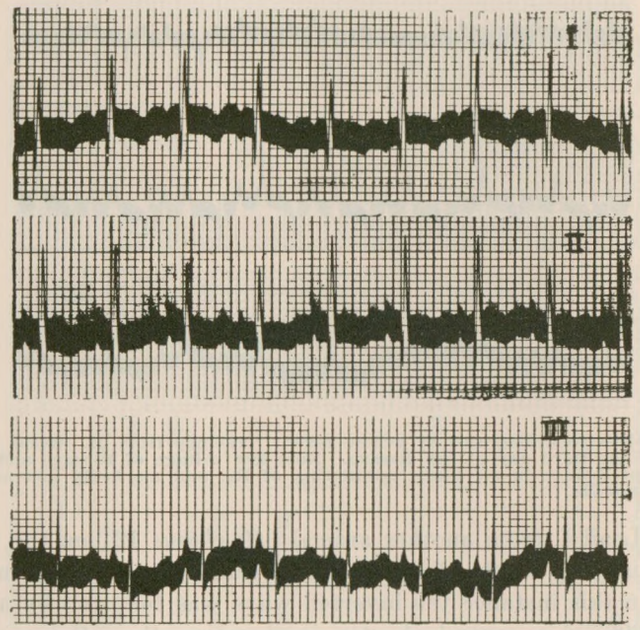


Fig. 5.—Electrocardiograms of yellow fever. Tracings from *M. rhesus* 12 on the morning of the third day of the disease. Note negative P_1 and T_1 deflections.

bradycardia of yellow fever is independent of vagus influence. Table II summarizes the results of the vagus section experiments; and in Fig. 3 electrocardiograms of the existing bradycardia in *M. rhesus* 2, before and after vagus section, are represented.

2. *Physiological observations upon the auricular muscle.*

Careful study of the character of the P-deflection during the course of the disease disclosed an infrequency of changes which could be

definitely recognized as abnormal. Nevertheless, in those infrequent instances when alterations in this wave were encountered, they were of the most profound kind. On two occasions in one animal (*M. rhesus* 4) the P-wave was reduplicated in Lead III during the first and second days of the disease. In another monkey (*M. rhesus* 6), it was found to be doubled in the tracing of Lead II, on the morning of the second day of the malady. In neither animal did these variations in the P-wave persist during the later progress of the infection. The reduplication of the P-deflection was in these instances inconstant from cycle to cycle, and frequently the second P-wave was observed to be negative in direction, thus imparting a diphasic character to the auricular tracing. Apart from these observations, purely negative P-waves occurred at one period of registration in the electrocardio-

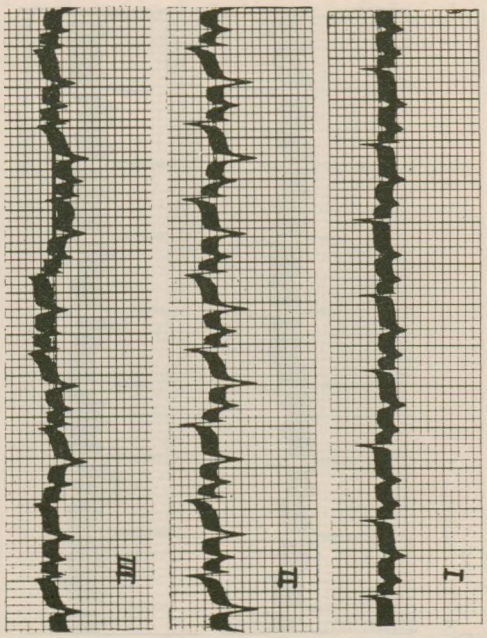


Fig. 6.—Electrocardiograms of yellow fever. Tracings from *M. rhesus* 19 on the morning of the third day of the disease. Note low voltage of R-wave and increased amplitude of S-wave in all leads: splintering of R_3; and markedly increased amplitude of T_2 and T_3.

gram of Lead I, from another animal (*M. rhesus* 12) on the morning of the third day of the disease. This event is well shown in Figs. 5 and 8. In this instance the inverted wave was followed by a P-R interval 0.008 of a second shorter in duration than the normal for that animal. This change was not found in the tracing from the same lead of the same animal on the following day. The monkey was one which showed the most marked bradycardia in the series as well as marked alterations in the T-deflection.

3. *Physiological observations upon the auriculo-ventricular bundle.*

In these experiments the time required for the conduction of the excitation wave along the A-V bundle has been an important consideration. Observations upon the P-R interval of the electrocardiogram showed that in sixteen of the nineteen animals infected with yellow

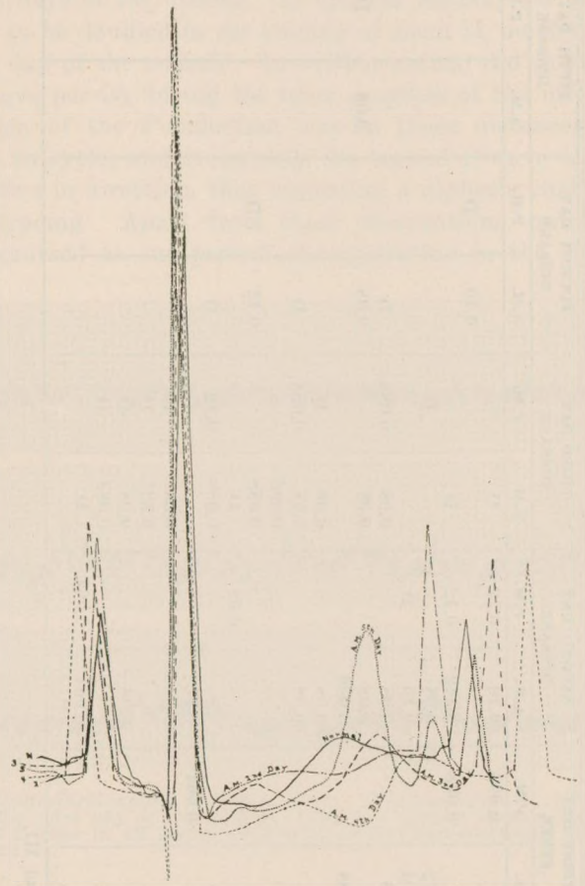
TABLE III

CONDUCTION TIME OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS‡

MONKEY NUMBER	NORMAL	DAYS OF INCUBATION		FIRST DAY FEVER		SECOND DAY DISEASE		THIRD DAY DISEASE		FOURTH DAY DISEASE		FIFTH DAY DISEASE		RECOVERY PERIOD
		1	3	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	
1	0.104				0.096	0.10	0.12	D						
2	0.088									0.10	D			
3	0.088				0.088	0.112	0.12	D						
4	0.064			0.072		0.08			D					
5	0.096		0.10	0.104		0.10	D							
6				0.06		0.08		0.08	0.08	D				
7	0.08					0.08		0.08		0.08		0.08	D	
8	0.08		0.08	0.088		0.096								
9		0.08				0.08		0.08	D					0.08
10	0.08					0.08		0.08	0.088	D				
11	0.064							0.096						
12	0.088							0.088		0.12	D			0.08
13	0.064						0.08	D						
14	0.068							0.088	0.12	D				
15	0.064				0.064*	D								
16	0.08							0.08	D					
17	0.08							0.32†	D					
18	0.064					0.08		0.08	D					
19		0.08						0.088	D					
20	0.064					0.064	0.064	D						
Control														

†Animal died during inscription of Lead III.
*Bled from heart, animal died.
‡As indicated by P-R interval of electrocardiogram recorded in decimals of a second.
D—Animal dead.

fever virus, there occurred prolongation of the conduction time, usually slight in degree. Moreover, with few exceptions the delay in conduction was progressive, increasing from day to day of the disease. In one of the two animals which recovered, the conduction period had



Figs. 7 and 8.—In each figure, outline drawings of a specific electrocardiographic lead from one animal are reproduced. The series of tracings composing a figure represents normal electrocardiograms and electrocardiograms taken at varying intervals during the course of the disease. The method of their preparation consisted in the projection upon a screen of lantern slide reproductions of the various electrocardiograms from a given animal. Employing always the same magnification, a representative cardiac cycle was selected in each lantern slide, and its outline was traced upon white paper. Succeeding cycles were so projected that the points of onset either of the Q- or R-waves of serial cycles were made to coincide. From this fixed point in each series the outlines were always traced. The time of annotation of each electrocardiogram is noted upon the figures. This method of illustration shows well the variations in the length of the entire cardiac cycle from day to day of the disease, variations in the duration of the P-R and R-T periods, and especially well the deformities of the R-T period and the T-wave during the course of the disease.

lessened during convalescence but at the last period of observation had not yet regained its normal time interval. It should, however, be noted that in this instance the last record was taken only four days

following the first appearance of fever. In the other recovered monkey the conduction time had returned to normal by the last day of observation. In this case the final registration was secured twenty-five days after the animal had first shown fever.

On one occasion the A-V conduction time was approximately doubled during the course of the disease. In three instances it was increased by approximately half its normal value. Just before death in one animal the P-R interval measured 0.32 of a second as contrasted with the normal period in the same animal of 0.08 of a second. Excluding from the series this one extreme value, the average greatest increase in the conduction period equalled 0.014 of a second. The

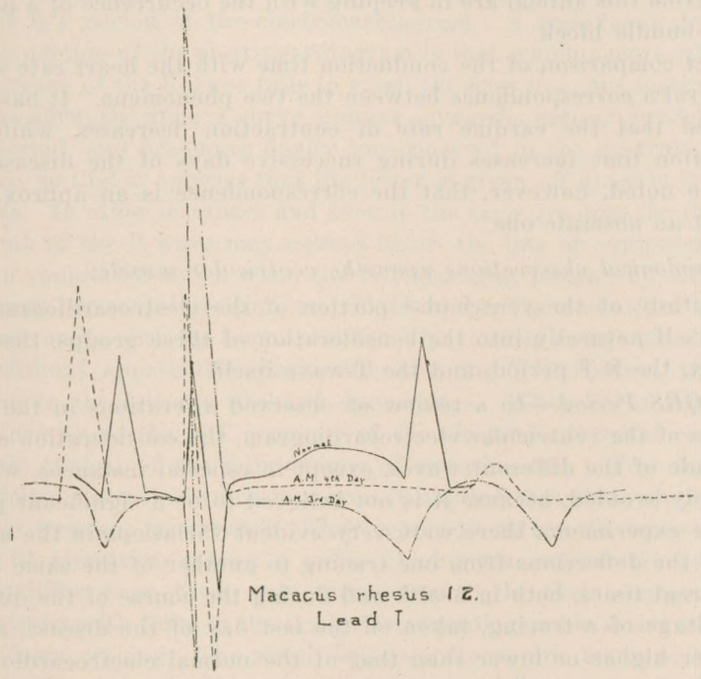


Fig. 8.

average normal value was 0.078 of a second, while the average longest period in each animal during the course of the disease was 0.092 of a second. The fact is significant that no increase in the P-R interval of the electrocardiogram occurred in the control animal dying from a peritoneal infection after a period equal in duration to the average course of yellow fever in the monkey. Table III epitomizes the detailed information regarding these variations. In Fig. 4 the P-R periods for the various animals have been plotted in graphic form, so that it may be possible to visualize the degree of the delay in conduction. The lengthening of the P-R interval on successive days of the disease is well shown in the serial cardiographic tracings (Figs. 7 and 8).

In these experiments the occurrence of altered and reduced con-

duction in the auriculo-ventricular bundle branches has been suggested in the occasional observance of definite widening of the base of the R-wave and, in one instance, of distinct notching of the apex of this deflection in a tracing taken from Lead III on the morning of the third day of the disease. That in this instance the evidence of a broadened base of R with notching of its apex is significant, is further rendered likely by the occurrence of a concurrent reversal of preponderance. At the same time T became of greatly increased height in a positive direction in all leads, while S assumed a considerably increased amplitude in Leads I and II, where it formed the most prominent "spikes" of the tracings. The several findings in the electrocardiograms from this animal are in keeping with the occurrence of a partial branch-bundle block.

Direct comparison of the conduction time with the heart rate shows in general a correspondence between the two phenomena. It has been observed that the cardiac rate of contraction decreases, while the conduction time increases during successive days of the disease. It must be noted, however, that the correspondence is an approximate and not an absolute one.

4. *Physiological observations upon the ventricular muscle.*

The study of the ventricular portion of the electrocardiogram divides itself naturally into the consideration of three groups, the QRS complex, the R-T period, and the T-wave itself.

The QRS Period.—In a review of observed alterations in the QRS portions of the ventricular electrocardiogram, the consideration of the amplitude of the different waves, except in especial instances, will be purposely avoided, because it is not believed to be a significant point. In these experiments there were very evident variations in the amplitude of the deflections from one tracing to another of the same heart at different times, both in health and during the course of the disease. The voltage of a tracing, taken on the last day of the disease, might be either higher or lower than that of the normal electrocardiogram of the same animal. That changes of amplitude of qualitative significance may occur, however, is supported by the appearance of certain alterations of unusual incidence associated with other and more significant changes. An S-wave, previously absent or poorly defined in Lead III, has during the course of the disease been observed to become of considerable amplitude, and in association with a diminution in the size of R, to assume the place of the most prominent "spike" in the tracings. Similarly S, a badly demarcated wave in Leads II and III of the electrocardiograms taken before inoculation of the animal with yellow fever virus, has been seen to become of marked amplitude with a diminution of the R-wave in the same leads on the later days of the disease (Fig. 6). Not infrequently a Q-wave barely discernible in Lead I of the normal tracing had attained so great an amplitude, in

later stages of the disease, as to appear as the most prominent "spike" in the electrocardiogram from the same lead. Changes in preponderance from day to day of the disease have been commonly noted. A splintering of the R-wave in Lead III has been found associated with variation in the amplitude of the associated deflections of the ventricular electrocardiogram (Fig. 6).

The R-T Period.—A much more definite change observed in the ventricular electrocardiogram during experimental yellow fever resembles changes of similar form described by Pardee[49] as evidence of blocking of a branch of the coronary artery, and by Cohn and Swift[11] as well as Rothschild, Sacks, and Libman,[54] as occurring in the acute phases of rheumatic fever. This change consists in deformity of the R-T or S-T period of the electrocardiogram. A significant deviation of this portion of the electrocardiogram is that which occurs when the downstroke of the R-wave fails to reach the base line, but instead commences abruptly upon a curve, convex upwards, occupying the entire R-T period, and becoming finally incorporated in the upstroke of the T-wave, so that it appears that the latter is given off directly from the R-wave. In other instances and even in the same tracing, the descending limb of the R-wave may extend below the line of equipotential to form a rounded S-wave, when the R-T segment, instead of occupying an almost horizontal position, may slope upward or downward to form an acute angle with the horizontal base line, and to merge itself gradually without appreciable distinction into the T deflection, thus imparting to the latter a diphasic appearance. While these two types of deformity of the R-T segment of the electrocardiogram represent changes typical of the later stages of experimental yellow fever, no specificity is attached to them, nor is it implied that these changes are of most frequent occurrence. They represent rather the more definite types of alteration among a series of changes comparable to them, which differ from them only unimportantly in their contours, and which exist with them in the same electrocardiographic series and even in the same tracing. The serial electrocardiographic tracings (Figs. 7 and 8) show clearly this pleomorphism in the contour of the R-T period in the electrocardiograms of yellow fever.

Observations upon the length of the R-T interval showed that in eighteen of the nineteen animals studied electrocardiographically during the course of infection with experimental yellow fever, an increase was noted in the duration of this period. The prolongation of the R-T interval was progressive in character and increased from day to day of the disease. There was in general a parallelism in the progressive increase in length of the R-T period with that of the R-R period, but the relation was by no means a constant one. While the ratios between the durations of the two periods showed in many instances an approximate correspondence, in others they presented wide divergence. In three experiments, lengthening of the period became so

marked that T encroached on the following P-wave or else the latter became superimposed on the T deflection. The control animal suffering from an infection of the peritoneum also presented a lengthening of the R-T period. The only animal in this series which did not show lengthening of the R-T interval recovered from the disease. The other recovered animal presented prolongation of this period during the course of the disease, with subsequent shortening during convalescence. In the light of our present knowledge of electrocardiography, it is impossible to determine the significance of the lengthened R-T period. The lengthening of the period is also shown in Figs. 7 and 8.

The T-wave.—The results of the study of the T-wave of the electrocardiogram in experimental yellow fever reveal certain observations which are significant because of their frequency and uniformity of occurrence. These changes warrant consideration. It has been noted that in fourteen of the nineteen animals infected with yellow fever virus, the character of the T-wave became altered in the end stages of the disease, becoming in one or more leads either diphasic, reduplicated, negative, or accentuated in its inscription. These deformities of the T-wave were independent of alterations in the initial ventricular deflections (QRS complexes). The normal upright terminal wave of the ventricular electrocardiogram was inconstantly replaced by a deflection either negative in direction, or diphasic in contour, the latter presenting either two waves above the line of equipotential or one positive and one negative wave in relation to the base line (Figs. 5, 7, 8). Exclusive of these types of deformity of the terminal deflection, an upright T-wave of increased height associated with other electrocardiographic changes has been a common finding (Fig. 6). An accentuated terminal deflection has, however, been observed upon two occasions in tracings from normal animals.

Two of the five animals (*M. rhesus* 8 and *M. cynomolgus* 11) which failed to show alterations in the T deflection recovered from the disease. The remaining three animals were not fairly representative of the course of the experiment, as each died prematurely of early or only moderately advanced yellow fever lesions, hastened in their death in two instances (*M. rhesus* 1 and 3) by the coma and subnormal temperature induced by the administration of sodium iso-amyl-ethyl-barbiturate, and in a third (*M. rhesus* 15) by the loss of blood following a cardiac bleeding. Nevertheless, even with these animals included in the series, the incidence of aberrant T deflections is a noteworthy one, occurring as it did in 74 per cent of the monkeys dying of yellow fever. A study of the time relationship of these changes to the course of yellow fever reveals the fact that the abnormal variations appeared most frequently on the latter days of the disease. In nine of the thirteen animals in which they were observed, these alterations were first noted on the day of death. In five of these nine cases it had been

possible to obtain tracings on the monkeys on the day previous to death; the electrocardiograms taken on this day showed normal T deflections. In two animals the abnormal waves were first inscribed on the day preceding death and in one they were first noted two days previous to the animal's death. In seven of the fourteen instances in which significant alterations in the T-waves existed, negative deflections were observed in either Lead I or Lead II, or in both of these leads (Fig. 5). This fact is pointed out not because it is believed that the negative variations were the most significant of those noted, but rather because in a purely empirical way we know most about this type of change in the T-wave. Before leaving the consideration of the terminal portion of the ventricular electrocardiogram in yellow fever, it is important to note the ephemeral character of any given deformity either of the R-T period or of the T-wave. These disturbances are transient, fleeting in nature, present in one tracing and not in another, one type of variation being inscribed upon one occasion, and a different deformity appearing during subsequent inscriptions. The variations of the T deflections and of the R-T period during the course of the disease are well represented in the serial electrocardiographic tracings (Figs. 7 and 8).

DISCUSSION

A perusal of the literature upon bradycardias of sino-atrial origin engenders the belief that those types of sino-auricular block which are invariably associated with irregular or inconstant forms of bradycardia, and which occur in relatively normal hearts, possess nothing in common with the retarded heart rate of yellow fever. That a relationship may exist between some types of the so-called sino-auricular block and the bradycardia of yellow fever, is, however, rendered problematical in view of the observations of Mackenzie[45] and Riebold.[50] The former author first described the condition as occurring in influenzal myocardial involvement, and suggested "that the heart symptoms in this case, and it may be in the slow irregular hearts in diphtherial cases, are due, not to vagus stimulation but to a poison acting like digitalis, directly on the heart itself." Riebold also expressed the belief of a relation of sino-auricular block to infectious diseases. More recently Cohn and Swift[11] have reported the occurrence of sino-atrial block in the course of rheumatic fever; and Smith[60] has recorded its incidence in diphtheria. A type of sinus bradycardia closely resembling that of experimental yellow fever, has been reported by Winternitz and Selye[68] as a result of thrombosis of the artery to the sino-atrial node.

In the consideration of the relation of jaundice to the slow cardiac rhythm of yellow fever, certain observations are of value. The fact is so well known that bradycardia is frequently a concomitant manifestation of the icteric state that a second fact needs to be empha-

sized, namely, that the association is by no means a universal one.[51, 67, 6] Every experienced observer has seen numerous cases in which the most marked degrees of jaundice were accompanied by a rapid pulse. The facts that a retarded cardiac rate is a constant phenomenon in experimental yellow fever, and that jaundice is very inconstantly associated with slow heart action, offer an inconsistency which militates against the possibility of a causal relationship of the icterus to the bradycardia in this disease. The bradycardia associated with icterus is of an irregular type,[67] whereas that of yellow fever is a regular one. Moreover, in yellow fever bradycardia may occur independently of jaundice, and in the presence of a normal bilirubin content of the serum.[4]

The hypothesis which Chagas has advanced that the bradycardia of yellow fever is a part of a "suprarenal syndrome" fails to attain credence in consideration of the fact that in the two cases in his series in which suprarenal lesions were found at autopsy the degeneration was confined to the cortical zones.[61]

In the auricular electrocardiograms of yellow fever, the occurrences of reduplicated and more especially of inverted P-waves, though infrequent, are of importance. A negative P-wave has been regarded by many workers[31, 32, 52, 47, 25, 65, 66, 7, 23, 13] as indicating a shifting of the pacemaker from its normal position in the upper extremity[40] of the S-A node to a lower functional level in the sinus node, auricle or A-V node. Negative P-waves can be produced experimentally in the tracings taken from animals during vagus stimulation, in which instance they may be abolished by atropine.[27, 17, 24, 26, 18] In some cases, however, negative P-waves persist after atropinization, and do not change on compression of the vagus nerve in the neck.[7] Wiggers[64] believes that in these instances, the sino-atrial node should not be thought to be the seat of disease, unless the inverted waves are associated with a reduced or a reversed P-R interval, or are accompanied by auricular extrasystoles or periodically give rise to tachycardia.

The lengthening of the P-R interval of the electrocardiogram, moderate in degree, which has been observed with considerable constancy during the course of experimental yellow fever, is indicative of an impairment of function in the auriculo-ventricular bundle.

In experimental yellow fever the changes in the ventricular electrocardiogram are of especial interest. Because of the considerable amount of evidence which has been obtained in recent years relating to alterations in the T-wave of the electrocardiogram, which have been observed during the course of many disease conditions provocative of damage to heart muscle, it is important that we should consider the changes in the terminal deflections which have been so frequently encountered during the course of experimental yellow fever. The observations on the latter disease are of singular significance in that in this instance the opportunity has been afforded of correlating these functional aberrations with the findings of histopathology in the precise muscular tissue in which they were produced only a few hours antecedent to the fixation of the tissue. This privilege obtains only in a few diseases, and in still fewer may the study be conducted under the more readily controlled methods of animal experimentation. Observations relating to the histopathological changes in the myocardial tissues in this series of animals will be published in another paper.

General acceptance is accorded the view that the initial portion of the ventricular electrocardiogram, the QRS complex, represents a composite tracing of the differences in electrical potential set up in the plane of the lead by the wave of excitation passing throughout both ventricles.[41, 33, 34] The period between R and T or between S and T, which in the normal electrocardiogram usually follows the base line, indicates an electrical equilibrium in the cardiac musculature in the plane of the lead at that time, and implies that a state of excitation exists throughout the ventricles. The frequent divergence of this portion of the curve in yellow fever suggests a disturbance of those stresses which normally during this period repose in equilibrium.

In view of our present information upon this subject, no justification exists for attaching a specific significance to a single form of alteration in the contour of the end deflection. The occurrence of one type of deformity of the T-wave at the time of registration of a given lead, and of another deformity in the same lead at another time of recording during the progress of the disease, suggests a common basis for these aberrations and an existing relationship between them. Rosnowski[53] has noted the occurrence of changes in the end deflection in the course of intoxications which, like yellow fever, result in diastolic arrest of the ventricles. The common observance of the markedly accentuated T-wave with a high, sharply vertical summit during the later days of the disease may, with caution, be tentatively accepted as a deformity of the terminal deflection of undetermined significance. There is no evidence of a different pathological interpretation of a T-curve which is diphasic in contour from one solely negative in direction. The incidence of abnormal deflections in more than one lead from the same animal, and their occurrence in the first and second leads, would seem to be more important than a solitary incidence of the change, especially if the latter presented itself in Lead III alone. In the extent of existing knowledge it is only justifiable to attribute to these T deflections of proved altered and abnormal contour, whether they be inverted, diphasic, or doubly positive in direction, the general significance of an abnormal retreat of the excitation process. They are signs that the myocardium is not behaving normally.

The consideration which the presented observations make desirable of emphasis is that well-marked deformities of the T-wave, such as are never observed in the healthy animal under the conditions of the experiment, are recorded with considerable constancy of occurrence

on the latter days of the disease, at a time at which subsequent observations have shown that advancing myocardial degeneration is taking place in the ventricles. For these reasons the suggestion is advanced that alteration in the end deflection of the electrocardiogram may afford valuable information of functional injury to the ventricular muscle. This concept is further supported by the fact that alterations in the T deflection were absent in the two animals in the series studied which recovered from the disease, while they were present in all the monkeys which died, with uncomplicated lesions of yellow fever, at the end of a complete course of the infection. The deformities of the T-wave were also not observed in the animal dying from peritonitis at the end of a comparable period.

SUMMARY

1. Bradycardia, regular in rhythm, absolute in degree, and progressively more marked on succeeding days of the disease, has been a constant finding in experimental yellow fever in the monkey; the phenomenon persisted independently of ether anesthesia, sodium isoamyl-ethyl barbiturate anesthesia, and bilateral section of the vagus nerves.

2. Reduplication of the P-wave of the electrocardiogram was occasionally observed in experimental yellow fever; more rarely this deflection was seen to be inverted.

3. Prolongation of the conduction time of the auriculo-ventricular bundle was observed in slight or moderate degree in 84 per cent of cases.

4. Among electrocardiographic alterations referable to the ventricular muscle during the course of the disease, changes in ventricular preponderance were commonly observed. The R-T period was lengthened in 94 per cent of cases; and frequently it was deformed. The normal upright T-wave was replaced in 74 per cent of cases by a deflection either negative in direction, diphasic in contour, or increased in height.

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REFERENCES

1. Aitken, Connal, Gray, and Smith: Tr. Roy. Soc. Trop. Med. & Hyg. **20**: 166, 1926.
2. Aitken and Smith: Tr. Roy. Soc. Trop. Med. & Hyg. **20**: 530, 1927.
3. Aitken and Smith: Conférence Africaine de la Fièvre Jaune. Dakar. Avril, 1928, pp. 60, 67, Imprimerie Militaire Universelle L. Fournier, Paris, 1929.
4. Berry and Kitchen: Personal communication.
5. Boyce: Yellow Fever and Its Prevention, London, 1911, John Murray.
6. Cannell: Am. J. Path. **4**: 431, 1928.
7. Carter and Wedd: Arch. Int. Med. **23**: 1, 1919.
8. Chagas: Compt. rend. Soc. de biol. **99**: 1664, 1928.
9. Chagas and de Freitas: Mem. do Inst. Oswaldo Cruz **7**: 72, 1929.
10. Cohn and Noguchi: J. Exper. Med. **33**: 683, 1921.
11. Cohn and Swift: J. Exper. Med. **39**: 1, 1924.

12. Coll y Toste: An. méd. Puerto Rico, San Juan **1**: 43, 1912.
13. Cowan and Fleming: Lancet **213**: 1064, 1927.
14. Delmas: Quoted by Touatre, New Orleans M. & S. J., 1898.
15. Drury and Andrus: Heart **11**: 389, 1924.
16. Drury and Andrus: J. Physiol. **59**: 41, 1924-25.
17. Einthoven: Arch. f. d. ges. Physiol. **122**: 517, 1908.
18. Einthoven, Fahr, and De Waart: Arch. f. d. ges. Physiol. **150**: 275, 1913.
19. Elliott: Arch. Int. Med. **25**: 174, 1920.
20. Faget: Monographie sur le type et la spécificité de la fièvre jaune établis avec l'aide de la montre et du thermomètre, Paris, 1875, J. B. Baillière et Fils.
21. Fowler, Simpson, Ross, and Leishman: Second Report of the Yellow Fever Commission (West Africa), London, 1914, Waterlow and Sons.
22. Gold, Gryzwacz, and Nowicki: Am. Heart J. **4**: 336, 1929.
23. Hamburger: Arch. Int. Med. **26**: 232, 1920.
24. Hering: Arch. f. d. ges. Physiol. **127**: 155, 1909.
25. Hering: München. med. Wchnschr. **61**: 2057, 1914.
26. Von Hoesslin: Deutsche Arch. f. klin. Med. **113**: 537, 1914.
27. Kahn: Arch. f. d. ges. Physiol. **140**: 627, 1911.
28. Klotz: Personal communication.
29. Lasnet: Conférence Africaine de la Fièvre Jaune. Dakar. Avril, 1928, page 32, Imprimerie Militaire Universelle L. Fournier, Paris, 1929.
30. Lebredo: Yellow Fever Bur. Bull. **1**: 294, 1911.
31. Lewis: Brit. M. J. **1**: 750, 1910.
32. Lewis: Heart **2**: 23, 1910-11.
33. Lewis: Phil. Tr. Roy. Soc., London, series "B," **207**: 221, 1916.
34. Lewis: Arch. Int. Med. **30**: 269, 1922.
35. Lewis: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, ed. 3, page 131, Shaw and Sons.
36. Lewis and Drury: Heart **10**: 179, 1923.
37. Lewis, Drury, and Bulger: Heart **8**: 83, 1921-22.
38. Lewis, Drury, and Iliescu: Heart **9**: 21, 1921-22.
39. Lewis, Drury, Iliescu, and Wedd: Heart **9**: 55, 1921-22.
40. Lewis, Oppenheimer, and Oppenheimer: Heart **2**: 147, 1910-11.
41. Lewis and Rothschild: Phil. Tr. Roy. Soc., London, series "B," **206**: 181, 1914-15.
42. Lieb and Mulinos: Proc. Soc. Exper. Biol. & Med. **26**: 709, 1929.
43. Lins: a Folha med. **9**: 218, 1928.
44. Macfie and Johnston: Yellow Fever Bur. Bull. **3**: 121, 1913-1915.
45. Mackenzie: Brit. M. J. **2**: 1411, 1902.
46. Macleod: Physiology and Biochemistry in Modern Medicine, ed. 5, p. 440, St. Louis, 1926, The C. V. Mosby Co.
47. Meek and Eyster: Heart **5**: 227, 1913-14.
48. Noguchi: J. Exper. Med. **29**: 547, 1919.
49. Pardee: Arch. Int. Med. **26**: 244, 1920.
50. Riebold: Ztschr. f. klin. Med. **73**: 1, 1911.
51. Riegel: Ztschr. f. klin. Med. **17**: 221, 1890.
52. Ritchie: Quart. J. Med. **6**: 47, 1912-13.
53. Rosnowski: Compt. rend. Soc. de Biol. **100**: 211, 1929.
54. Rothschild, Sacks, and Libman: Am. Heart J. **2**: 356, 1927.
55. Sawyer, Lloyd, and Kitchen: J. Exper. Med. **50**: 1, 1929.
56. Seidelin: Berl. klin Wchnschr. **46**: 821, 1909.
57. Seidelin: Yellow Fever Bur. Bull. **1**: 134, 1911.
58. Selwyn-Clarke: Conférence Africaine de la Fièvre Jaune. Dakar. Avril, 1928, p. 138, Imprimerie Militaire Universelle L. Fournier, Paris, 1929.
59. Smirnow and Olefirenko: Ztschr. f. d. ges. exper. Med. **57**: 559, 1927.
60. Smith: J. A. M. A. **77**: 765, 1921.
61. Torres and Azevedo: Compt. rend. Soc. de Biol. **99**: 1673, 1928.
62. Touatre: Yellow Fever—Clinical notes, translated from the French by Charles Chassaignac, New Orleans M. & S. J., 1898.
63. Wenckebach and Winterberg: Die unregelmässige Herztätigkeit, Textband, Leipzig, 1927, p. 132, Wilhelm Engelmann.
64. Wiggers: Modern Aspects of the Circulation in Health and Disease, ed. 2, p. 285, Philadelphia and New York, 1923, Lea & Febiger.
65. Wilson: Arch. Int. Med. **16**: 86, 1915.
66. Wilson and Robinson: Arch. Int. Med. **21**: 166, 1918.
67. Windle: Brit. M. J. **1**: 123, 1916.
68. Winternitz and Selye: Wien. Arch. f. inn. Med. **16**: 377, 1929.